Physical and psychological consequences of primary postpartum haemorrhage

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This thesis is dedicated to my mother and my grandpa, who passed away during my DPhil. They have always been the two great pillars of my life who always wanted the best for me, and they made me who I am today. I hope this will make up partially for my absence in their final moments. Their love, kindness, and sacrifices for me will be missed.

Abstract

Background

Primary postpartum haemorrhage is characterised by excessive bleeding in the first 24 hours after childbirth. Compared with immediate physical and psychological outcomes, there are relatively fewer studies that have investigated longer-term physical and psychological outcomes of PPH, leading to a significant knowledge gap. The existing literature suggests that cardiovascular disease and mental illness may be longer-term health outcomes of potential importance following PPH.

Aim

The overall aim of the research carried out for this thesis was to provide high quality evidence about longer-term physical and psychological consequences of primary PPH in a high-income setting and, in particular, to investigate potential associations between PPH and cardiovascular disease and longer-term mental illness.

Methods

A mixed-methods systematic review was conducted to synthesise the existing evidence about longer-term health outcomes of PPH. This review also helped determine the outcomes to be investigated in two retrospective record-linked cohort studies using Scottish health administrative datasets. The first of these used data for 32 years to investigate the association between PPH and cardiovascular disease. The second used data for 10 years to investigate the association between PPH and longer-term mental illness.

Findings

The mixed-methods systematic review screened 7,068 papers, included 21 studies from nine different countries and demonstrated that there was limited research about the longer-term health consequences of PPH. Prevalence studies suggested a higher proportion of women with physical health problems including CVD, low general health score, breastfeeding problems, and mental health problems such as postpartum depression and posttraumatic stress disorder, following PPH. Evidence to support a causal association was limited due to a lack of comparison groups and adjustment for potential confounding.

The retrospective cohort study of 70,904 women in Aberdeen, Scotland who gave birth between 1986 and 2016 showed that women who had at least one PPH in this period were at a higher risk of developing CVD in later life, compared with women who had not had a PPH. The risk of CVD was almost doubled for such women in the first postnatal year, with the excess risk continuing up to 15 years after PPH, but with no evidence of an excess risk beyond 15 years.

In a second retrospective cohort study, analysis of data about 18,798 women in the same geographical area, who gave birth between 2008 and 2016, showed that there was no evidence of an association between PPH and longer-term mental illness following the first postnatal year, irrespective of severity of PPH or mode of birth whereas the prevalence of pre-existing mental illness was associated with a ten fold risk of longer-term mental illness.

Conclusions

Primary PPH is associated with an increased risk of subsequent CVD, particularly in the first postnatal year. Further population-based prospective cohort studies are required to assess

causality and to understand the underlying mechanisms behind the observed association. The six-week check and regular follow up within the first postnatal year should be considered as an opportunity for women who have had a PPH, for primary prevention, and early identification for CVD in affected women.

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List of publications

1. Latt SM, Alderdice F, Elkington M, Awng Shar M, Kurinczuk JJ, et al. (2023) Primary postpartum haemorrhage and longer-term physical, psychological, and psychosocial health outcomes for women and their partners in high income countries: A mixed-methods systematic review. PLOS ONE 18(6): e0274041. https://doi.org/10.1371/journal.pone.0274041

2. Latt SM, Opondo C, Alderdice F, Kurinczuk JJ,et.al. Postpartum haemorrhage and risk of cardiovascular disease in later life: A Scottish population-based record linkage cohort study (Oral poster, 42) reported in 'Abstracts of the 2022 BMFMS meeting. (2023). BJOG : An International Journal of Obstetrics and Gynaecology, 130(S1), 4-129.'

Abbreviations and key terms

aHR	Adjusted hazards ratio
AMND	Aberdeen Maternal and Neonatal Databank
aOR	Adjusted odds ratio
APH	Antepartum Haemorrhage
ARF	Acute renal failure
aRR	Adjusted risk ratio
BMI	Body Mass Index
BNF	British National Formulary
CAPS-5	Clinician administered PTSD scale
CASP	Critical Appraisal Skills Programme
CHI	Community Health Index
CI	Confidence interval
CVD	Cardiovascular disease
DaSH	Grampian data Safe Haven
DIC	Disseminated intravascular coagulation
EBL	Estimated blood loss
ENTREQ	Enhancing transparency in reporting the synthesis of qualitative research
EPDS	Edinburgh Postnatal Depression Scale
EPH	Emergency peripartum hysterectomy
EPPI	Evidence for policy and practice information centre
HADS	Hospital Anxiety and Depression Scale
HDP	Hypertensive disorders of pregnancy
HICs	High income countries
HIV	Human immunodeficiency virus
ICD	International classification of disease
ICU	Intensive care unit
IESR	Impact of Event Scale
IQR	Interquartile range
JBI	Joanna Briggs Institute
kg	Kilograms
MIBS	Mother infant bonding scale
ml	Millilitres
MOH	Major obstetric haemorrhage
NHS	National Health Services
NICE	National Institute of Health and Clinical Excellence
NRS	National Records of Scotland
OR	Odds ratio
PIS	Prescription Information System
PPD	Postpartum depression
PPH	Postpartum haemorrhage

PPROM	Preterm pre-labour rupture of membranes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols
PROM	Pre labour rupture of membranes
PROSPERO	International Prospective Register of Systematic Reviews
PTSD	Post-traumatic stress disorder
RCOG	Royal College of Obstetricians and Gynaecologists
RoB	Risk of bias
ROBANS	Risk of bias assessment for non-randomised studies
SF 36	The 36-item short form
SIMD	Scottish index of multiple deprivation
SMR	Scottish Morbidity Record
STAI	Spielberger State-Trait Anxiety Inventory score
TSQ	Trauma Screening Questionnaire Score
TVC	Time varying covariate
UK	United Kingdom
VTE	Venous thromboembolism
WHO	World Health Organization

Chapter 1. Introduction

1.1 Topic overview

Postpartum haemorrhage (PPH), excessive bleeding after childbirth, is the leading direct cause of maternal morbidity and mortality worldwide, and accounts for one quarter of all maternal deaths, estimated to be around 100,000 deaths every year. (1, 2) The number of women who experience PPH is increasing across the world, especially in high-income counties (HICs). (3) Although most women who experience PPH after childbirth do not die in HICs, there can be substantial impact of PPH resulting in severe morbidity. (4) Only the short-term implications of excessive bleeding after childbirth were well-established in the literature at the inception of this research. There was a need to explore the longer-term impacts of PPH on maternal physical and mental health. The research presented in this thesis, comprising a systematic review and two analyses of linked Scottish routine datasets, investigated the longer-term outcomes of PPH.

1.2 Background

1.2.1 Definitions and measurement of postpartum hemorrhage

Different institutions and guidelines apply different 'cut offs' for the volume of blood loss used to define PPH. For example, the World Health Organization (WHO), the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, all define primary PPH as an estimated blood loss of more than 500ml from the genital tract within 24 hours of birth, regardless of the mode of birth. (5-7) Some organisations apply different cut-off points, depending upon the

mode of birth. (3, 5, 8) For example, the International Federation of Gynaecology and Obstetrics and the Society of Obstetricians and Gynaecologists of Canada defined PPH as loss of at least 500ml for a vaginal birth and 1000ml for a caesarean birth. (7) There is also no uniform agreement on the amount of blood loss that can be considered as a major or severe PPH, which increases the difficulty further. Markers of severity of PPH range from the units of blood transfused, haematocrit level, fall in haemoglobin level, intervention, and management indicators such as arterial embolisation and emergency peripartum hysterectomy (EPH). (5, 9)

In the UK, if postpartum blood loss occurs outside the operating theatre, the amount of blood loss is typically estimated visually by the clinician providing care, usually a midwife. However, some hospitals may use quantitative blood loss measurements such as gravimetric measurement by weighing all blood-soaked swabs and under-buttocks incontinence bed pads and subtracting their known dry weight. (10) In the operating theatre, the amount of blood loss is usually calculated based on the volume of blood loss collected in suction containers, accounting for the subtraction of amniotic fluid and weighing blood-soaked swabs. Visual estimation is known to be inaccurate in comparison to other methods such as gravimetric or weight-based methods, resulting in underestimations of 30- 50%. (11-13) Inaccurate estimation of blood loss can result in delayed recognition of PPH and subsequently poor outcomes. (5, 10) Inaccuracies in the estimation and measurement of blood loss, in combination with varied definitions of PPH, can also make it challenging to compare research related to PPH carried out in different settings or countries. (3, 7)

1.2.2 Causes, risk factors and management of PPH

Primary PPH, the focus of the research reported here, is characterized by excessive bleeding in the first 24 hours after childbirth. (14) Uterine atony, defined as the failure of adequate uterine contraction, is the cause of more than 70% of primary PPH. (15) Other causes include inherited or acquired coagulation defects, placenta accrete, retained placenta, uterine inversion, genital tract trauma and lacerations. (15, 16)

PPH can be unpredictable and can occur in women with straightforward pregnancies without the presence of known risk factors. (17) Some pre-existing maternal and clinical characteristics, for which there is strong evidence as a risk factor for PPH include previous PPH, placenta praevia, hypertensive disorders of pregnancy (HDP), late gestational age, and multiple gestation. (18, 19) There is some indication that advanced maternal age ≥35 years and maternal obesity are associated with PPH, but the evidence is inconsistent. (20-22) Other risk factors of importance, during labour and birth, include induction of labour, instrumental or caesarean birth, macrosomia, uterine rupture and prolonged third stage of labour. (15, 23)

Awareness of risk factors for PPH can alert clinicians to increased individual risk and inform choices about planned place of birth. Although PPH cannot be fully prevented, primary prevention such as the active management of the third stage of labour, including the administration of oxytocin, can reduce the overall risk of PPH. (1, 23) The WHO recommends the administration of oxytocin or other alternative uterotonics such as misoprostol in the third stage of labour. (24) The management of PPH, once it has occurred, involves a multidisciplinary team and includes an initial identification of the cause of PPH to inform further management that may range from the administration of IV oxytocin and blood

transfusion to more intensive interventions such as blood transfusion, and surgical or radiologically guided invasive procedures in the case of persistent blood loss. (23, 25)

1.3 Research rationale

1.3.1 Increasing incidence of primary PPH

Population-based studies demonstrate that the incidence of PPH has increased in many HIC countries over recent decades. (3, 26-29) A retrospective analysis of hospital births in Canada between 1991 and 2004 reported that rates of atonic PPH increased by 34% over that period. (30) In Switzerland the incidence of PPH is reported to have almost doubled, affecting 4.5% of births in 2014 compared with 2.5% of births in 1993 ($p < 0.001$). (29) An analysis of over 600,000 births from 1999-2009 in Ireland showed a three-fold increase in incidence over the study period. (26) NHS maternity statistics in England indicate that in 2018-2019, when the research reported in this thesis was started, 21% of all women giving birth in NHS hospitals experienced a PPH, (31) compared with 13% in 2011-2012. (32) As increasing numbers of women experience PPH it becomes increasingly important to investigate the potential physical and psychological consequences of PPH, with a view to improving care for individual women who experienced PPH, and for planning follow-up services for the longer-term adverse consequences of PPH.

1.3.2 PPH and maternal mortality

Globally, PPH accounts for one quarter of all maternal deaths, with one woman dying every four minutes due to PPH, resulting in about 70,000 maternal deaths each year. (1, 2, 25) Most PPH-related deaths globally occur in low resource settings such as sub-Saharan Africa, with an estimated mortality rate of 150 per 100,000 maternities. (33) In comparison, in HICs such

as the UK, maternal death due to PPH is rare. According to the latest maternal deaths surveillance in the UK, maternal deaths from direct obstetric causes have declined in the UK from 143 deaths in 2003-2005 to 109 deaths in 2018-2020, and in the latter period haemorrhage accounted for 18 maternal deaths, with a mortality rate of 0.76 per 100,000 maternities. (34)

1.3.3 PPH and acute maternal morbidity

The increasing incidence of PPH in HICs means that PPH remains a significant issue for maternal morbidity. (3, 26, 29, 35) According to the Scottish national audit of severe maternity morbidity report, major obstetric haemorrhage (MOH), with blood loss of ≥2,500ml, was the most common cause of severe maternal morbidity between 2003 and 2012, affecting 2,727 women. (36) Among 339 women with MOH in 2012, 20 women (6%) required peripartum hysterectomy, and 36 women (11%) required an intensive care admission. (37, 38)

The association between PPH and acute physical complications such as hypovolaemic shock, sepsis and disseminated intravascular coagulation is well-established. (39, 40) There is some evidence suggesting a higher incidence of myocardial ischaemia and acute renal failure (ARF) among women who had a severe PPH. (41-46) In one case study, 28 out of 55 (51%) women with severe PPH who were referred for intensive care in France had elevated serum levels of the cardiac enzyme associated with cardiac ischaemia. (43) A retrospective multicentre study from maternity wards in the north of France that analysed all postpartum ICU complications between 2008 and 2012 found that 43 out of 68 postpartum women who had ARF had a PPH,

and the authors concluded that HELLP syndrome combined with PPH was the only independent factor associated with ARF complications in ICU. (42)

Furthermore, women who have experienced PPH have an increased risk of uterine infection, and are also less likely to exclusively breastfeed their baby. (47-49) One recent study found that PPH is a significant risk factor for subsequent maternal readmission (adjusted risk ratio=5.26, 95% CI=4.94, 5.59). (50) In addition to these physical consequences, a birth with PPH can be traumatic and women may experience anxiety, postpartum depression (PPD) and post-traumatic stress disorder (PTSD) following a birth affected by PPH. (51, 52)

1.3.4 Longer-term physical and psychological consequences of PPH

Compared with the immediate physical and psychological outcomes of PPH, there are relatively fewer studies that have investigated longer-term physical and psychological outcomes, leading to a significant knowledge gap. (16, 45, 47, 49, 53-55) A systematic review of the consequences of PPH carried out in 2016 confirmed the scarcity of high-quality studies investigating the longer-term impact of primary PPH. (56) The review concluded that there were persistent maternal morbidities between three and six months after PPH, including postnatal depression (13%), PTSD (3%), and health status “much worse than one year ago” (6%), but that there was insufficient evidence for a casual association. (56) Another systematic review of the association between PPH and PTSD conducted in 2018 also concluded that the number of studies about the longer-term consequences was limited and evidence to support an association between PPH and PTSD was limited. (57)

Longer-term health outcomes following PPH may have implications for policy and clinical care. These could include, for example, increased awareness and advocacy for improved

quality of care and follow-up of women who experienced a PPH, and the opportunity for early identification and intervention for any chronic diseases found to be associated with PPH. For example, the association between HDP and subsequent cardiovascular disease (CVD) is well-established, and pre-eclampsia is now considered to be a female-specific risk factor for CVD risk management. (58, 59)

Chapter 2. Aims and objectives

At the start of this research, the overarching aim was to provide high quality evidence about longer-term physical and psychological consequences of primary PPH in a high-income setting. The first step in addressing this aim was to conduct a comprehensive mixed-methods systematic review to synthesize the qualitative and quantitative evidence about longer-term physical and psychological consequences of primary PPH for women and their partners. The findings of this review, and two existing reviews about PPH, (56, 57) were then used to refine the scope of the research and define further objectives, including identifying the specific longer-term outcomes for investigation.

2.1 Refining the scope of the research

The mixed-methods systematic review reported in Chapter 3, and two previous reviews about the consequences of PPH, (56, 57) confirmed the relative scarcity of high quality studies investigating the longer-term impact of primary PPH, but also informed decision-making about specific longer-term outcomes to be investigated in the further research for this thesis. Based on the availability of reliable data about PPH and longer-term outcomes, it was planned to use Scottish routine health administrative data to carry out retrospective cohort studies investigating selected longer-term health outcomes. In order to help select outcomes for investigation, attention was given to the global burden of chronic disease and, given that the routine data sources for analysis were from the Grampian region of Scotland, to the specific burden of disease in Scotland. The five main leading causes of health burden in Scotland in 2016 were cancers, followed by mental health and substance use disorders, CVD, neurological disorder and musculoskeletal diseases, which in combination accounted for approximately

72% of the overall health burden in Scotland. (60, 61) Plausible causal pathways between PPH and these major chronic diseases were initially considered, based on the possibility of residual impact on the major organs (heart, kidneys, lungs, brain) following excessive blood loss after childbirth.

The findings of the mixed-methods review suggested that CVD, including venous thromboembolism (VTE), was a health outcome of potential longer-term relevance follows PPH, with population-based cohort studies in England and South Korea suggesting that women who had a severe PPH which required a transfusion were at a higher risk of developing CVD in later life. (62, 63) While the evidence was limited, there was biological plausibility for the potential impact of PPH on the cardiovascular system which could potentially result from acute heart failure, and myocardial ischaemia following severe haemorrhage. (43, 64) It was hypothesised that, with timely treatment, myocardial ischemia and infarction could be averted, but extreme blood loss might leave a permanent damage to cardiovascular functioning which might in turn result in an increased risk of CVD in later life. A 2019 American study suggested that compared with chronic myocardial infarct patients, acute myocardial infarct was associated with an increased risk of death and other ischaemic events, with a higher recurrent cardiovascular event rate in the first three months of acute myocardial infarct. (65) Therefore, it seemed biologically plausible that birth complications such as PPH may increase the risk of CVD by exposing women to acute myocardial ischaemia.

Both quantitative studies and qualitative studies included in the mixed-methods systematic review investigated a wide range of potential psychological and psychosocial impacts of PPH, including anxiety, PPD, and symptoms of posttraumatic stress disorder (PTSD) including

flashbacks, and mother infant bonding. (51, 66-71) The findings indicated a higher prevalence of mild to moderate anxiety and symptoms of PTSD among women who had a PPH, particularly severe PPH, compared with women who did not have a PPH, (67, 70) with some supporting qualitative evidence from women's self-report and narratives suggesting symptoms of anxiety and PTSD followed PPH. (52, 67) However, evidence about an association between PPH and mental illness was conflicting, with different studies reporting different effect sizes and directions for the association between PPH and mental illness. (68-71) While it was unclear whether the presence of anxiety or PTSD among women who had experienced PPH was specifically related to PPH itself, or as a result of birth-related trauma, it was considered that PPH and its potential association with longer-term mental illness was worthy of further research.

Based on this rationale, the outcomes selected for the further research reported in this thesis were cardiovascular disease and longer-term mental illness.

2.2 Research aim and objectives

The overall aim of the research presented in this thesis was to provide high quality evidence about longer-term physical and psychological consequences of primary PPH in a high-income setting. The specific objectives were:

1) To identify, critically appraise and summarize the existing evidence about longer-term physical, psychological and psychosocial consequences of primary PPH for women and their partners following PPH, including their experiences of care, in HICs.

2) To investigate the association between primary PPH and cardiovascular disease.

3) To investigate the association between primary PPH and longer-term mental illness.

4) To investigate whether mode of birth or HDP modify the association between primary PPH and cardiovascular disease, or the association between primary PPH and longer-term mental illness.

2.3 Component studies and structure of the thesis

This overall research aim and objectives were addressed in three component studies conducted between 2019 and 2022:

Study 1: A mixed-methods systematic review (Objective 1, reported in Chapter 3)

Study 2: A retrospective cohort study to investigate the association between PPH and CVD using data from the Aberdeen Maternity and Neonatal Databank (AMND) linked with other routine health datasets from the Grampian region of Scotland (Objectives 2 and 4, reported in Chapter 4)

Study 3: A retrospective cohort study to investigate the association between PPH and longer-term mental illness using data from the AMND and other routine health datasets from the Grampian region of Scotland (Objectives 3 and 4, reported in Chapter 5)

This thesis is presented in six chapters. The findings of each individual study, and the strengths and limitations specific to each study, are discussed in each Chapter 3, Chapter 4, and Chapter 5. In Chapter 6, the findings of all three studies are summarised and discussed against the background of other relevant research to address the overarching thesis aims and

objectives. The overall strengths and limitations and the implications for clinical practice and policy are discussed, together with future research recommendations.

Chapter 3. Primary PPH and physical, psychological, and psychosocial health outcomes: mixed-methods systematic review

3.1 Introduction

A systematic review conducted in 2016 investigated the prevalence of women's emotional and physical health problems following PPH and included six quantitative studies. (56) Several articles investigating potential physical or psychological consequences of PPH were published since the last systematic search conducted for that review, in April 2015. (69, 70, 72) A further systematic review reported a potential association between PPH and PTSD, but this conclusion was limited by the small number of studies investigating this association. (57) Despite a lack of strong conclusions in these reviews, they provided some evidence of persistent physical and psychological problems up to six-months following PPH.

Differences in quality of care might explain some of the heterogeneity in the direction and size of associations found by studies included in these previous reviews, on the basis that quality of care might impact on prognosis of PPH and associated acute morbidities, and inadequate care might exacerbate the effects of initial haemorrhage. (73, 74) Understanding women's and partners' experience of PPH and their care experiences might therefore help to understand variations in outcomes. Neither of the previous reviews included qualitative research exploring women's experience of PPH, suggesting a comprehensive systematic review using an integrated mixed-methods approach would be valuable. (75) A mixed-methods systematic

review was therefore conducted to synthesize the existing evidence about the physical and psychological consequences of PPH for women and their partners.

3.2 Aims and objectives

The aim of this systematic review was to identify, critically appraise, and summarise the evidence about the physical and psychological consequences of PPH for women and their partners. The specific objectives were:

1) To investigate the longer-term physical, psychological and psychosocial health consequences of PPH for women
2) To investigate the psychological consequences of PPH for their partners
3) To explore women's and partners' experiences of PPH, including care around the time of the PPH, follow-up care and longer-term impacts of PPH
4) To identify the gaps in the current evidence around the longer-term consequences of PPH

3.2.1 Definitions/terms

The following definitions were applied in the context of this systematic review.

Physical health outcomes: any non-immediate non-immediately fatal physical health outcomes including: for example: venous thromboembolism; chronic heart, respiratory, and renal diseases; breastfeeding problems; decline in general health status. This excludes: immediate outcomes during the initial birth admission such as maternal death, sepsis or acute organ failure; any physical health related problems or diagnoses that were interventions (e.g.,

hysterectomy, ICU admission, blood transfusion, etc.); pregnancy-related outcomes (e.g., recurrence of PPH).

Psychological health outcomes: any mental health problem including presence of symptoms and diagnosed disorders such as anxiety, depression and posttraumatic stress disorder, excluding acute mental health illness during the initial birth admission.

Psychosocial health outcomes: outcomes that are a combined influence of psychological factors and the surrounding social environment, for example, relationships, maternal self-efficacy, etc.

Longer-term: One challenge to the understanding about longer-term outcomes is the lack an agreed definition of what health outcomes should be considered as 'longer-term' consequences of PPH. In the absence of any universally agreed definition of what is considered to be a 'longer-term' outcome, and to maximise inclusion of post-discharge outcomes that might have an impact on longer-term wellbeing, all eligible physical, psychological and psychosocial health outcomes following PPH after discharge from the hospital were included.

3.3 Methods

The mixed-methods systematic review was based on the Joanna Briggs Institute (JBI) methodology, with modifications for the data extraction and quality assessment tools. (76) The JBI approach describes three main methodological approaches for conducting a mixed-methods systematic review: sequential, convergent integrated and convergent segregated. In the sequential approach the synthesis occurs consecutively whereas in the convergent

approach the synthesis occurs simultaneously. The convergent integrated approach involves data transformation (for example, quantifying the qualitative data) so that reviewers can combine quantitative and qualitative data. This review used the convergent segregated approach, involving separate analysis of quantitative and qualitative evidence, followed by integration of both sets of evidence. (75) The convergent segregated approach was chosen because the research questions of this review focused on different outcomes following PPH, including care experiences. Although the physical and psychological health outcomes were objectively measured through quantitative research, the experience of PPH and care for women and their partners were assessed using qualitative evidence.

The findings are reported according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement (77, 78) together with its elaboration and explanation paper. (79) In addition to the PRISMA checklist (Appendix 1), the enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement developed by Tong (80) was also applied (Appendix 2).

The protocol was developed before conducting the searches and registered with the International Prospective Register of Systematic Reviews (PROSPERO), Registration Number- CRD42020161144.

3.3.1 Eligibility criteria

Inclusion criteria

Studies were included in the review if they met the following inclusion criteria.

3.3.1.1 Population

The population of interest in this review was women who gave birth after a minimum of 24 weeks' gestation and had a PPH, and/or their partners.

3.3.1.2 Exposure

Studies were included if their primary exposure of interest was primary PPH. The following definition of PPH was used to allow maximum sensitivity and allow for variation in the definition of PPH used in different studies:

> Bleeding from the genital tract, within 24 hours of giving birth, with an estimated blood loss of >500ml and/or blood transfusion within 24 hours of giving birth, and/or having emergency peripartum hysterectomy (EPH) or arterial embolisation following PPH, and/or peripartum fall in haemoglobin concentration of > 2g/dl.

3.3.1.3 Comparison

Studies with or without a control or comparison group, comprising participants who did not experience a PPH, were included.

3.3.1.4 Outcomes

This review included quantitative studies investigating any non-immediate and non-immediately fatal physical, psychological or psychosocial health outcomes for women and their partners after PPH including, for example: venous thromboembolism; chronic heart, respiratory, and renal diseases; breastfeeding problems, including breast infections such as mastitis; decline in general health status; and psychological or psychosocial wellbeing, including anxiety, depression and PTSD.

Furthermore, with a view to understanding how postpartum experiences of PPH and quality of care might influence the longer-term impact of PPH, this review included qualitative studies that explored the following: women's and/or partners' experiences of care and/or of seeking care around the time of PPH and during the postpartum period, and women's and/or partners' knowledge and perceptions about the health outcomes of PPH.

3.3.1.5 Time period of follow-up

Quantitative studies with any follow-up duration after hospital discharge following PPH were included. Qualitative studies were included regardless of their follow-up duration.

3.3.1.6 Setting

Studies that were conducted in HICs as defined by the World Bank (81) at the time of the study were included.

3.3.1.7 Study design

Both quantitative and qualitative study designs, including mixed-methods studies, were included. These included:

- Quantitative cohort, case-control, cross-sectional, or case series studies.
- Qualitative studies including analysis of interviews, free text boxes or open-ended survey questions which explored women's and partners' experiences of care or seeking care and information following PPH, and/or their perceptions about the physical, psychological and psychosocial impact of PPH.
- Mixed-methods studies with an eligible qualitative or quantitative component.

Exclusion criteria

Studies were excluded from the review according to the following criteria.

3.3.1.8 Population

Studies that included women who had PPH and/or their partners as a subset of participants (e.g. PPH participants as a subset of women with a range of maternal morbidities) were excluded, unless separate data from women who had a PPH could be retrieved.

3.3.1.9 Exposure

Quantitative studies where PPH was not the primary exposure of interest or in which PPH was not well-defined and measured by one of the criteria described above were excluded.

3.3.1.10 Outcome

Studies with immediate outcomes, including maternal death following PPH, acute organ failure, sepsis, shock, and interventions such as hysterectomy, intensive care admission, blood transfusion during initial birth admission were excluded, as were studies reporting pregnancy-related outcomes including secondary PPH, or recurrence of PPH in subsequent pregnancies.

3.3.1.11 Setting

Studies that were not conducted in HICs as defined by the World Bank (81) at the time of the study were excluded.

3.3.1.12 Study design

Intervention studies including randomised control trials were excluded, as were conference abstracts, protocols, case reports, reviews, protocols, editorials and opinion papers.

3.3.1.13 Language

Papers that were not written in English were excluded.

3.3.2 Search strategy

Searches were conducted in five electronic databases, Medline (Ovid), Embase, Web of Science, CINAHL and PsycINFO, on 16th December 2019. Search strategies were developed for each database using a combination of controlled vocabulary (e.g., 'post-partum/post-natal/peri-partum haemorrhage', "postpartum/postnatal/peripartum haemorrhage", "obstetric haemorrhage", 'maternal morbidity', 'post-natal/postnatal/post-partum/postpartum/peripartum/peri-partum bleeding"), keywords (e.g. "massive bleeding", "transfusion" "hysterectomy") and tested search filters for study designs. The detailed search strategy (Appendix 3) was created in consultation with a senior outreach librarian at the University of Oxford Bodleian Health care libraries, Ms. Nia Roberts who has expertise in literature searching for systematic reviews.

The search was undertaken from the inception of each database to 16th December 2019, and then updated on 6th January 2021. For the purposes of the searches, no restrictions were made on language, year of publication or year of study. Reference lists from all included full text articles were hand searched. Due to resource limitations, a grey literature search was not included.

3.3.3 Screening and study selection

Search results were imported into the reference management software Endnote,version X8.2 and duplicates were removed. (82) After removing duplicates in Endnote, search results were imported into Covidence software for screening and data extraction. (83) Screening was

carried out by the author (first reviewer), Dr Mahkawnghta Awng Shar: an independent researcher from Myanmar ('second reviewer 1'), and Madeline Elkington: a doctoral research student from Oxford Population Health ('second reviewer 2'). The title and abstract of all articles identified were screened by the author and second reviewer 1 against inclusion criteria, followed by the screening of full text articles using a pre-developed eligibility checklist. Full text screening was conducted independently by the author, and second reviewer 2 (Appendix 4). Any disagreements were resolved by consensus between reviewers and the supervisory team was involved when necessary.

3.3.4 Data extraction

Study characteristics and outcome information were extracted for both quantitative and qualitative studies using bespoke data extractions forms developed and pilot-tested for this review (Appendix 5, Appendix 6). For the qualitative studies, all the text and themes reported under findings or results from the studies included were imported into NVivo software (84) and treated as primary textual data source for analysis.

Data extraction was performed independently by three reviewers. The author extracted the data from all studies, with the two second reviewers each extracting data from half of the studies.

3.3.5 Risk of bias and quality assessment

Included quantitative studies (and the quantitative component of mixed-methods studies) were assessed using the risk of bias assessment for non-randomized studies (ROBANS) tool, with additional guidance specifically developed for this review (Appendix 7). (85) ROBANS is a domain-based assessment tool which assesses six methodological domains: participant

selection, confounding, measurement of exposure, outcome ascertainment and blinding, incomplete data, and selective reporting. In the modified version, the first four domains for participant selection, confounding and exposure and outcome measurement were tailored on the basic of review questions and definitions for PPH. Additionally, potential confounders were included in the guidance note. These modifications allowed the author and second reviewers to provide consistent assessment using tailored criteria for this review (Appendix 5).

Quality assessment for qualitative studies was conducted using the Critical Appraisal Skills Programme (CASP) tool. (86) This includes 10 items covering research aims, appropriateness of qualitative study design, recruitment method, sampling, data collection and analysis, adequate consideration for ethics and reflexivity of the researchers' role (Q 1-9), and the overall value of the research (Q10). The response options for Questions 1-9 were modified from yes/no/unclear to include the option to respond 'partly' where a paper addressed some items in the checklist associated with the question, but not all.

Studies were not excluded based on the risk of bias and quality assessment, but the assessments were used to inform the synthesis of study findings. Risk of bias and quality assessment for the studies included was conducted by all three reviewers, (SM, MK, MA) with at least two independent reviewers for each study. A similar approach to data extraction was applied, with any disagreements resolved by consensus.

3.3.6 Data synthesis

Quantitative synthesis

Since the quantitative studies were not homogeneous in terms of study design and outcome measurements, a meta-analysis was not conducted. Although some outcomes (e.g., PPD and

PTSD) were reported by more than two studies, it was not possible to pool the outcome and undertake a meaningful meta-analysis of effect estimates since the time points assessed, the tools used for the outcomes, and the measures of effect used varied. Hence, a narrative synthesis was considered most appropriate and conducted for the quantitative studies. (87) First, preliminary synthesis of the findings of included studies was undertaken. Second, the relationships within and between studies were explored. Finally, the robustness of the synthesis was assessed. The results were grouped and presented in narrative synthesis tables separately for (i) physical health outcomes, and (ii) psychological health outcomes.

Qualitative synthesis

Qualitative studies were synthesised using thematic synthesis following the approach described by Thomas and Harden, and developed by the EPPI-Centre. (88-90) This synthesis involved three steps: 1) free line-by-line coding of the findings of primary studies; 2) the organization of codes in related areas to construct 'descriptive' themes; and 3) the development of 'analytical' themes to answer the research questions. (88-90) This approach was suitable for this review because (i) there was no prior framework to support the analysis for the research questions in this review, and (ii) there were limited studies that directly addressed the impacts of PPH and this approach allowed for translation of key concepts from existing studies, but also allowed for the generation of new concepts and explanation. (88)

First, the findings of the qualitative studies were imported into NVivo and line by line coding was conducted. (84) Although it was originally planned to start coding the findings from studies included according to the original research questions (i.e., longer-term physical and psychological health consequences of PPH), only two studies directly addressed the

impact/implications of PPH in the findings. (67, 91) The findings of the remaining studies were structured around life threatening experiences of PPH and care experiences, including information and communication. Therefore, an inductive coding approach was applied to capture the broad range of women's and partners experiences following PPH, without attempting to answer the research questions directly at this step. After coding for each study, the list of codes was reviewed in NVivo for their consistency and interpretations. The codes from each study were iteratively compiled, generating new codes and refining existing codes throughout the process.

Second, all qualitative data from the included studies were reviewed to ensure that at least one code was assigned, except where the data were not relevant to this review. For example, quotes from health care professionals that did not relate to women's experience or outcomes were not coded. After coding all qualitative data in this way, the codes were reviewed again to ensure that they captured all the information from the primary studies. A further level of coding was added at this point where necessary. For example, additional coding levels were applied for psychological aspects of women experiences, based on whether women's expressed views were associated with the women themselves, their babies, or their family/partners. Codes were also organised separately for women and partners at this stage.

Finally, the descriptive codes from each study were compiled to describe women's and partners experiences of PPH overall. Descriptive codes were merged together into a smaller number of descriptive themes based on their meaning/similarity. To enable interpretation of these themes beyond the content of the primary studies, the original research questions about the consequences of PPH were again brought into consideration. Analytical themes were generated by inferring the descriptive themes as the potential physical, psychological, and

psychosocial impact of PPH and care experiences. These themes were reviewed and refined throughout the process of writing and were finally reported under different time periods in reference to childbirth. This intuitive process of refining the analytical themes and amending the writing to reflect changes continued until it fully captured all relevant aspects of women and their partners' experiences relating to the research questions for this review.

Integration of qualitative and quantitative evidence

The findings of the quantitative and qualitative synthesis were integrated according to the JBI convergent segregated approach and integration for mixed methods systematic reviews. (76) Following separate analysis of the quantitative and qualitative evidence, the similarities and differences in findings were compared to produce a narrative summary. Women's experiences from the qualitative synthesis were explored as a potential explanation for the casual pathway between PPH and the health outcomes investigated in the quantitative studies.

The JBI guidance for the integration of findings using the convergent segregated approach focuses on reviews of effectiveness. (76) The author therefore applied the modifications to the guidance questions shown in Table 3.1.

Table 3.1 Guidance questions for integration of quantitative and qualitative findings

Original JBI guidance	Modifications used in this review
• Are the results/findings from individual synthesis supportive or contradictory?	• What are the common health outcomes explored by both quantitative and qualitative evidence? • Are the results/findings from individual synthesis supportive or contradictory?
• Does the qualitative evidence explain why the intervention is or is not effective?	• Does the qualitative evidence explain why the exposed group (women with PPH) have certain health outcomes identified in the quantitative findings?
• Does the qualitative evidence help explain differences in the direction and size of effect across the included quantitative studies	• Does the qualitative evidence help explain differences in the direction and size of physical and psychological health outcomes across the included quantitative studies?
• Which aspects of the quantitative evidence are/are not explored in the qualitative studies?	• Unchanged
• Which aspects of the qualitative evidence are/are not tested in the quantitative evidence?	• Unchanged

3.4 Results

The systematic search yielded 14,036 articles, and 5 additional articles were identified from other sources (Figure 3.1).

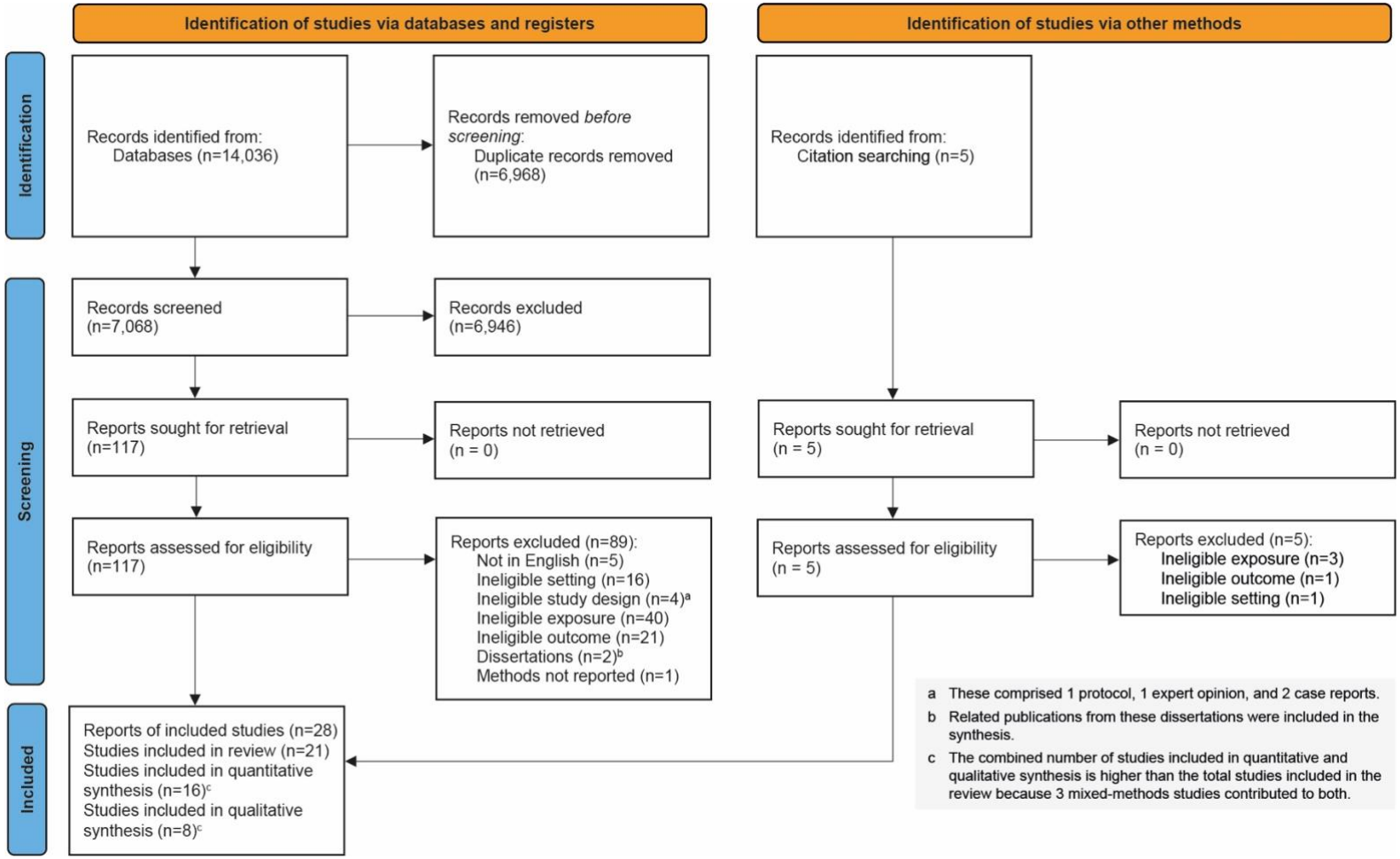


Figure 3.1 Prisma flow chart for study selection (78)

After removing duplicates, a total of 7068 references remained, of which 6946 were excluded after title and abstract review. A total of 122 full text articles (117 from databases and five identified from citations searches) were included for full text review. Of these, 94 articles (89 from databases and five from other sources) were excluded according to the exclusion criteria listed. The main exclusion criterion was ineligible exposure. After exclusions, 28 articles reporting a total of 21 studies, were included in the review.

3.4.1 Characteristics of included studies

The characteristics of studies included are summarised in Table 3.2. Studies were conducted in Australia, New Zealand, France, the Netherlands, Sweden, South Korea, Canada, the UK and the United States, between 2005 and 2020. There were 13 quantitative, five qualitative, and three mixed-methods studies. Sixteen studies explored the consequences of primary PPH as a main focus, while five studies assessed the consequences of primary PPH followed by emergency peripartum hysterectomy (EPH). Study sample sizes ranged from 40 to 1,224,975 in quantitative studies, and from 12 to 21 participants in qualitative studies. Participants were interviewed and their outcomes were assessed at different time points, ranging from immediately after hospital discharge to up to 29 years after having a PPH.

Table 3.2 Summary characteristics of included studies

Study characteristics	No. of studies (N=21)
Year	
2005-2014	6
2015-2020	15
Location	
Australia/New Zealand	4
France	4
Netherlands	3
Sweden	2
United States	2
United Kingdom	4
Canada	1
South Korea	1
Setting	
Single or two centres	8
Multi-centre	5
Population-based	8
Study design	
Quantitative	13
Qualitative	5
Mixed-methods	3
Methods	
Case-control study	1
Prospective cohort study	5
Retrospective cohort study	10
Semi-structured interviews	5
Participants	
Both women and partners	5
Women only	16
Outcomes	
Physical health	4
Psychological health	10
Both	7
Outcome measurements	
Self-reported tools/questionnaires	9
Hospital records	5
Objective/clinical measurements	2
Not applicable (i.e., qualitative)	5
Comparison group	
Yes	12
No	5
Not applicable	4
Maximum follow-up time	
Up to 6 weeks postpartum	7
>6 weeks to 1 year	3
2-5 years	3
>5 years	7
Not mentioned	1

The definitions for PPH and severe PPH used in the quantitative studies varied widely **(**Table 3.3**).** In studies defining PPH according to blood loss volume, this varied from 500ml to 1000ml for vaginal birth and from 750ml to 1500ml for caesarean birth. In two studies, PPH was identified by using ICD-10 codes recorded in hospital or insurance databases. (63, 92) Definitions for severe PPH also varied widely, from >1000ml to >2000ml. In five studies where the exposure was severe PPH, severity was also indicated by combining blood loss volume with interventions such as peripartum hysterectomy and/or arterial embolisation following PPH. (66-68, 93, 94)

The physical outcomes investigated included general health status, breastfeeding, venous thromboembolism, and symptoms of physical limitation such as pain, tiredness and fatigue, and difficulty in sexual intercourse **(**Table 3.3**).** The psychological outcomes investigated by the studies included were anxiety, depression, PTSD, mother-infant bonding and other symptoms of emotional distress. Most quantitative studies (n=9) used self-report tools or questionnaires for outcome assessments. Two studies used retrospective analysis of hospital records using ICD codes, and two studies used objective or laboratory confirmation to assess physical outcomes.

Table 3.3 Characteristics of included quantitative studies

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Outcome(s)
Cho 2021 (63) South Korea 2007-2015	Merged databases of the South Korean insurance claim and health screening programme	To determine whether PPH is associated with cardiovascular disease (CVD) beyond the peripartum period.	Women who gave birth in 2007 N= 150,381	Retrospective cohort Population-based study	PPH with or without blood transfusion, defined using ICD-10 codes	Newly diagnosed CVD and/or ischemic heart disease
Chauleur 2008 (95) France 1999-2004	University of Nimes Hospital	To explore the effect of severe PPH and its related treatments on postpartum venous thromboembolic risk	Women in their first intended pregnancy N=32,463	Prospective cohort Population-based study	Severe PPH PPH, defined as bleeding occurring in the first 24 hours after birth, persisting after manual exploration of the uterine cavity and requiring I.V prostaglandin administration	Superficial venous thrombosis
De la Cruz 2016 (68) United States Year of study not reported	Online community with 1.7 million registered users	To explore if women who had EPH are positive for post-traumatic stress disorder (PTSD) compared with women who did not have EPH more likely to screen	Women from online communities N= 409	Retrospective cohort	PPH defined as women who gave birth and had an EPH following PPH	PTSD, postpartum depression (PPD), both PTSD and PPD

Study **Country** **Year of study**	**Setting**	**Aims**	**Population** **Sample size**	**Study design**	**Exposure and definition if provided**	**Outcome(s)**
Chessman 2018 (96) Australia Records from 2007-2010	New South Wales public hospital	To determine the association between red blood cell transfusion and breastfeeding among women who had a PPH at birth taking into account postpartum haemoglobin concentrations	Women who had a PPH and had a red blood cell transfusion following a singleton birth of at least 37weeks' gestation. N= 15,451	Retrospective cohort Population-based study	PPH with transfusion, defined as blood loss of ≥500ml post-vaginal birth and of ≥ 750ml post-caesarean birth	Any breastfeeding at hospital discharge
Drayton 2016 (97) Australia Records from 2007-2012	All New South Wales hospitals	To determine the association between red blood cell transfusion and breastfeeding at discharge among women who had a PPH during their birth admission	All women giving birth in New South Wales, Australia N= 40,149	Retrospective cohort Population-based study	PPH and blood transfusion records were identified using diagnosis or procedure codes from the hospital records. Applied ICD-10-AM 8th Edition	Exclusive, partial and any breastfeeding
Eckerdal 2016 (69) Sweden 2006-2012	Uppsala University hospital	To explore the association between PPH and PPD	Women who gave birth at University Hospital in Uppsala N=446	Prospective cohort Population-based study	PPH, defined as bleeding of ≥1000ml within 24 hours after birth.	PPD

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Outcome(s)
Feinberg 2005 (98) United States Records from 1998-2002	A tertiary hospital in Chicago	To determine the incidence of Sheehan's syndrome among patients with obstetric haemorrhage	Women who gave birth at North-western Memorial Hospital with obstetric haemorrhage N=109	Retrospective cohort Hospital-based study	PPH, defined as >1000ml blood loss for a vaginal birth or >1500ml for a caesarean birth	Symptoms of Sheehan's syndrome
Knight 2016 (67) UK 2013 using records from 2005-2006	111 UK hospitals with consultant-led maternity units	To explore the longer-term health outcomes of women following EPH to control haemorrhage and to see how these differ from longer-term health outcomes in women who gave birth without EPH	Women who gave birth and had EPH in UK hospitals N=78	Case-control Population-based study	PPH with EPH, defined as any woman giving birth and undergoing a hysterectomy in the same clinical episode.	Pain, depression, anxiety, difficulty in sexual intercourse, severe tiredness, menopausal symptoms, flashbacks, difficulty in concentration

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Outcome(s)
Michelet 2015 (66) France 2012 using records from 2004-2011	Lariboisiere Hospital in France	To investigate the psychological impact of EPH	Women admitted with PPH who underwent EPH. N=869	Retrospective cohort Hospital-based study	PPH with EPH, identified by hospital records of postpartum hysterectomy among PPH patients. PPH was coded as "postpartum complication, haemorrhage shock, or acute anaemia or shock"	PTSD, anxiety, PPD
Ricbourg 2015 (70) France 2010-2011	Lariboisiere Hospital in France	To investigate the psychological impact of PPH on women and their partners, including its impacts on PTSD, PPD, and the mother/child relationship	Women admitted with PPH N=40 women, 26 partners	Prospective cohort Hospital-based study	PPH: Women admitted for PPH with a blood loss of ≥500ml, and their partners	PTSD, PPD, mother and infant bonding

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Outcome(s)
Sentilhes 2011 (94) France 2009 using records from 1994-2007	University affiliated tertiary referral centre at Rouen University Hospital in France	To estimate the longer-term psychological impact of severe PPH	Women with PPH who underwent pelvic arterial embolisation at the tertiary obstetric centre N=68	Retrospective cohort Hospital- based study	Severe PPH, defined as women who underwent arterial embolisation due to PPH.	Psychological symptoms including negative memories
Thompson 2010; Thompson 2011 (49, 51) Australia and New Zealand 2006-2007	17 hospitals across Australia and New Zealand	To explore the physical and psychological health outcomes and breastfeeding outcomes for women following PPH	Women who had primary PPH in Australia and New Zealand N=206	Prospective cohort Population-based study	Severe PPH, defined as an estimated blood loss of ≥1,500ml in the 24 hours after child birth, and/or a peripartum fall in haemoglobin concentration	Range of physical and psychological outcomes
Thurn 2018 (92) Sweden 2016 using records from 1999-2002	Tertiary hospitals in Sweden	To investigate postpartum blood transfusion and PPH as potential risk factors for postpartum venous thromboembolism (VTE)	Women who gave birth in Stockholm N=82,376	Retrospective cohort Population-based study	PPH, defined as an estimated blood loss of > 1000ml within 24 hour after birth	VTE

Study **Country** **Year of study**	**Setting**	**Aims**	**Population** **Sample size**	**Study design**	**Exposure and definition if provided**	**Outcome(s)**
Ukah 2020 (62) Canada Records from 1989-2016	Registry containing all hospital discharges in Quebec, Canada	To investigate the association between obstetric haemorrhage and CVD up to three decades after birth	Women who gave birth in Quebec, Canada N=1,224,975	Retrospective cohort Population-based study	PPH with or without transfusion , defined using ICD-9 and ICD-10 codes and procedural codes for blood transfusion	Hospitalisation for CVD
Van Steijn 2019; Van Steijn 2020 (71, 72) Netherlands 2015-2017	8 hospitals in Amsterdam, Netherlands	To evaluate whether (i) severe PPH is a risk factor for PTSD in women and (ii) witnessing severe PPH is a risk factor for developing PTSD in partners	Women with ≥ 2000 ml of blood loss and their partners in Netherlands N= 308 women, 185 partners	Prospective cohort Population-based study	Severe PPH, defined as blood loss ≥ 2000 ml after birth	PTSD
Van Stralen 2018 (93) Netherlands 2012-2013	98 hospitals with a maternity unit in the Netherlands	To investigate quality of life and psychological impact of major obstetric haemorrhage on women and their partners	Women who experienced major obstetric haemorrhage and had hysterectomy and arterial embolisation in the Netherlands N=58 women, 49 partners	Retrospective cohort Population-based study	PPH with EPH or embolisation, defined as peripartum hysterectomy or embolisation after a minimum gestational age of 24 completed weeks	General health status and psychological outcomes

In the qualitative studies, PPH was defined according to blood loss volume varying from 500ml to 1000ml for vaginal birth and a blood loss of more than 1500ml for severe PPH. In three studies, PPH was indicated by interventions, such as having EPH, following PPH. In the remaining two studies, PPH was not well-defined. All of these qualitative studies were included regardless of the definitions used as this was not part of the eligibility criteria for qualitative studies (Table 3.4).

The outcome categories explored by included qualitative studies were related to previously mentioned physical and psychological health outcomes explored by quantitative studies. Additionally, the themes covered ‘psychosocial' health outcomes related to experiences of early motherhood, and relationship with their partners and family, etc. Health care experiences of women and partners were also explored. Most qualitative studies used semi-structured interviews (n= 6), while two of the mixed-methods studies used open-ended self-completed survey questions. (55, 67) Seven out of eight studies applied thematic analysis and one study used framework analysis (Table 3.4).

Table 3.4 Characteristics of included qualitative studies

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Themes reported
Briley, 2020 (99) United Kingdom Not reported	Postnatal wards in two South London NHS Trusts	To investigate the experience of PPH, for women, birth partners, and health care professionals	Women who had experienced PPH and their partners N=9 women, 4 partners	Qualitative in-depth-interview study Maximum variation purposive sampling, semi-structured face to face interviews, thematic analysis	PPH, definition not provided	Knowledge specific to PPH, effective and appropriate responses to PPH, communication of risk factors, and quantifying blood loss
De La Cruz 2013 (100) United States Not reported	Online/internet group	To explore women's peripartum experiences of EPH to make recommendations for care	EPH survivors from an English-speaking international internet support group N=15	Qualitative interview study using grounded theory Purposive sampling, semi-structured telephone interviews, constant comparative thematic analysis	PPH defined as women who gave birth and had an EPH following PPH	Death/dying, pain, fear, bonding, numbness/ delayed emotional response, communication

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Themes reported
Dunning 2016 (91) United Kingdom 2013-2014	One teaching hospital in London	To investigate the experiences of women who have had a primary PPH and the experiences of birth partners who witnessed the PPH	Women who had an estimated blood loss of ≥500ml within 24 hours after vaginal birth and their partners who were present at the time of the PPH N=11 women, 6 partners	Qualitative interview study Maximum variation sampling, explanatory, semi-structured face to face interviews, thematic analysis	PPH, defined as an estimated blood loss of >500ml within the first 24 hour of vaginal birth	Control, communication, consequence (physical and psychological impact), competence
Elmir 2012a; Elmir 2012b; Elmir 2012c; Elmir 2014 (52, 101-103) Australia	University campuses and public places such as pharmacies and child care centres	To describe women's experiences of having an EPH following a severe PPH including impacts on early mothering experiences and to explore the way that women find meaning and positivity in their lives	Women who had an EPH following a severe PPH. N=21	Qualitative interview study using naturalistic inquiry approach Purposive snowball	Severe PPH and emergency hysterectomy, definition not provided	Between life and death, loss of normality, early mothering experiences, moving forward

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Themes reported
2009				sampling, semi-structured face to face/telephone/e-mail/internet interviews, thematic analysis using inductive method		
Knight 2016 (67) United Kingdom 2013	111 UK hospitals with maternity units	To explore the longer-term health outcomes of women following an EPH to control haemorrhage	Women who had an EPH to control haemorrhage N=78	Mixed method study using open-ended survey questions Purposive sampling, free text questions at the end of follow-up questionnaire, thematic analysis	PPH with EPH, defined as any woman giving birth and undergoing a hysterectomy in the same clinical episode.	The staff providing care, organization / structure of care, longer-term impact of birth experiences

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Themes reported
Snowdon 2012 (104) United Kingdom 2006-2007	Two hospitals in UK	To explore women's and partners' experiences of severe PPH and its management	Women who had experienced severe PPH and their partners N=9 women, 6 partners	Qualitative interview study using interpretative phenomenological approach Purposive sampling, semi-structured face to face interviews, thematic analysis	Severe PPH, defined by interventions received (uterine tamponade, embolisation, laparotomy after vaginal delivery, suture, vessel ligation, or hysterectomy)	Confidence vs fear, trust vs mistrust, satisfaction/ dissatisfaction, communication difficulties
Thompson, 2010; Thompson, 2011 (49, 55) Australia and New Zealand 2006-2007	17 hospitals with maternity services in Australia and New Zealand	To identify sources of distress for women and gaps in service provision, particularly their informational needs	Women who had severe PPH N=206	Mixed-method study using open-ended survey questions Purposive sampling, open-ended self-completed survey questions, thematic analysis	Severe PPH, defined as an estimated blood loss of ≥1,500ml in the 24 hours after child birth, and/or a peripartum fall in haemoglobin concentration	Adequacy of care, emotional responses to the experience, implications for the future, and concerns for their baby

Study Country Year of study	Setting	Aims	Population Sample size	Study design	Exposure and definition if provided	Themes reported
Woiski 2015 (105) Netherlands Not reported	3 University Hospitals in Netherlands, and childbirth forums on internet	To identify obstacles and facilitators for providing high quality PPH care, from both patient and professional perspectives	Women who gave birth and lost more than 1000ml of blood after birth N=12	Qualitative interview study Purposive maximum variation sampling, semi-structured face to face/ telephone interviews with patients, framework analysis	PPH, defined as a blood loss of >1000ml following childbirth	Influencing factors from patient perspectives, professional factors and organizational factors

3.4.2 Risk of bias assessment for quantitative studies

The results of the risk of bias assessment for the quantitative studies is presented in Table 3.5. Most studies (n=13) had a low risk of bias (i.e., low risk of bias in most domains assessed). However, three studies had a high risk of bias in two or more areas of domains assessed with the main sources of bias being participant selection, outcome measurement and incomplete data. (66, 68, 93) Four studies had a high risk of bias in participant selection which originated from inappropriate selection or lack of a comparison group, potentially leading to selection bias. Six out of 16 studies had an unclear or high risk of bias for outcome measurement. The most common sources of bias for blinding and outcome measurement were using unvalidated outcome tools or assessments and using subjective measurements such as self-report questionnaires. Almost two-thirds of the studies were rated high risk of bias or unclear for the incomplete data domain because of potential differential loss to follow up and lack of appropriate handling of missing data.

Table 3.5 Risk of bias for quantitative studies using adapted version of ROBANS (85)

Study	Participant selection	Exposure measurement	Confounding	Outcome measurement	Incomplete data	Selective reporting
Chauleur 2008 (95)	+	+	+	+	?	+
Chessman 2018 (96)	+	+	+	+	?	+
Cho 2021 (63)	+	+	+	+	+	+
De la Cruz 2016 (68)	−	?	+	−	+	+
Drayton 2016 (97)	+	+	+	−	+	+
Eckerdal 2016 (69)	+	+	+	+	?	+
Feinberg 2005 (98)	+	+	+	+	−	+
Knight 2016 (67)	+	+	+	+	−	+
Michelet 2015 (66)	−	+	−	−	+	+
Ricbourg 2015 (70)	+	+	+	+	−	+
Sentilhes 2011 (94)	−	+	+	−	+	+
Thompson 2010; Thompson 2011(49, 51)	+	+	+	+	+	+
Thurn 2018 (92)	+	+	+	+	?	+
Ukah 2020 (62)	+	+	+	+	?	+
Van Steijn 2019; Van Steijn 2020 (71, 72)	+	+	+	?	−	+
Van Stralen 2018 (93)	−	−	−	?	−	+
	+ Low risk of bias , ? Unclear, − High risk of bias					

3.4.3 Results of quantitative synthesis for women and partners

Quantitative findings were summarised separately for physical and psychological health outcomes for women and their partners in Table 3.6.

Table 3.6 Physical and psychological health outcomes investigated by included quantitative studies

Study	Sample size (N)	Time since PPH	Outcome	Outcome assessment	Percentage or median/mean (IQR/SD) PPH	Percentage or median/mean (IQR/SD) No PPH	Risk ratio (RR) or Odds ratio (OR) or Hazard ratio (HR) (95% CI; p value)
Physical health outcomes							
Thompson 2011 (51)	206	2 months	General Health	Median SF36	75 (60–80)	NC	NC
		4 months			72.5 (60–80)	NC	NC
Van Stralen 2018 (93)	58	6-9 years		Mean SF36	70 (23.7)	71.5 SF36 reference group	NR (p=0.23)
Drayton 2016 (97)	40,149	Hospital Discharge	Exclusive breastfeeding	Perinatal database	81% (PPH only)	83%	NR
					71% (PPH with transfusion)		
Chessman 2018 (96)	15,451	Hospital discharge		Perinatal database	67% (Hb >90g/L)	79%	NR
					71% (Hb 70-90g/L)		
					65% (Hb<70 g/L)		
Knight 2016 (67)	78	7 days		Health questionnaire	39%	60%	NR (p=0.089)
		1.5 months			14%	40%	NR (p=0.018)
		6 months			12%	19%	NR (p=0.519)
Thompson 2010 (49)	206	7 days		Health questionnaire	63%	NC	NC
		2 months			58%	NC	NC

Study	Sample size (N)	Time since PPH	Outcome	Outcome assessment	Percentage or median/mean (IQR/SD) PPH	Percentage or median/mean (IQR/SD) No PPH	Risk ratio (RR) or Odds ratio (OR) or Hazard ratio (HR) (95% CI; p value)
		4 months			45%	NC	NC
Chauleur 2008 (95)	32,463	1.5 months	VTE	Colour duplex ultrasound	NR	NR	RR=5.4 (1.68, 17; p=0.0047) aRR=5.3 (1.6, 17; p=0.005)
Thurn 2018 (92)	82,376	1.5 months	VTE	ICD-10 diagnostic codes	NR	NR	OR=2.85 (1.47, 1.55; p=0.001) aOR=2.7 (1.4, 5.2) aOR=1.4 (0.5, 3.5) Further adjusted for blood transfusion
Cho 2021 (63)	150,381	Up to 8 years	CVD	ICD-10 diagnostic codes	4.5% (PPH) 6.9% (PPH with transfusion)	4.6%	aHR=0.96 (0.86, 1.07) (PPH) aHR=1.60 (1.25, 2.06) (PPH with transfusion)
Ukah 2020 (62)	1,224,975	Up to 29 years	CVD	ICD-10 diagnostic codes	NR	NR	aHR=1.00 (0.95, 1.06) (PPH) aHR=1.38 (1.13, 1.68) (PPH with transfusion)

Study	Sample size (N)	Time since PPH	Outcome	Outcome assessment	Percentage or median/mean (IQR/SD) PPH	Percentage or median/mean (IQR/SD) No PPH	Risk ratio (RR) or Odds ratio (OR) or Hazard ratio (HR) (95% CI; p value)
Feinberg 2005 (98)	109	12-40 months	Sheehan's Syndrome	Two or more symptoms in questionnaire	25%	7%	NR
Knight 2016 (67)	78	12 months	Difficulty in sexual intercourse	Health questionnaire	27%	6%	NR
		8.1 years			13%	8%	NR
Knight 2016 (67)	78	12 months	Menopausal symptoms	Health questionnaire	17%	0%	NR
		8.1 years			33%	13%	NR
Knight 2016 (67)	78	12 months	Pain	Health questionnaire	43%	19%	NR
		8.1 years			10%	10%	NR
Knight 2016 (67)	78	12 months	Severe tiredness and Fatigue	Health questionnaire	33%	13%	NR
		8.1 years			17%	21%	NR
Thompson 2011 (51)	206	2 months	Postpartum fatigue	Median Milligan score	17 (15-18)	NC	NC
		4 months			15 (14-17)	NC	NC
Thompson 2011 (51)	206	2 months	Mastitis	Health questionnaire	22%	NC	NC
		4 months			14%	NC	NC
Van Stralen 2018 (93)	58	6-9 years	Patient Perception-Consequences	Mean B-IPQ	7.5 (2.6)	NC	NC

Study	Sample size (N)	Time since PPH	Outcome	Outcome assessment	Percentage or median/mean (IQR/SD) PPH	Percentage or median/mean (IQR/SD) No PPH	Risk ratio (RR) or Odds ratio (OR) or Hazard ratio (HR) (95% CI; p value)
Psychological health outcomes							
Michelet 2015 (66)	869	26.5 months	Anxiety	Median HADS	10 (8-12)	NC	NC
Thompson 2011 (51)	206	2 months		Median STAI scale (State subscale)	10 (9-11)	NC	NC
		4 months			10 (9-11)	NC	NC
Knight 2016 (67)	78	12 months		Health and wellbeing questionnaire	27%	10%	NR
		8.1 years			17%	17%	NR
Michelet 2015 (66)	869	26.5months	Depression	Median HADS scale	6 (2-8)	NC	NC
Knight 2016 (67)	78	12 months		Health and wellbeing questionnaire	33%	8%	NR
		8.1 years			13%	19%	NR
Delacruz 2016 (68)	409	6 months		EPDS (score ≥12)	6%	9%	NR
		36 months			0%	4%	NR
Eckerdal 2016 (69)	446	1.5 months		EPDS (score ≥12)	14%	10%	aOR=1.81 (0.91, 3.57)
Ricbourg 2015 (70)	40	1 months		EPDS (score ≥12)	35%	15%	NR
		3 months			11%	0%	NR
Thompson 2011 (51)	206	2 months		EPDS (score ≥12)	11%	NC	NC
		4 months			13%	NC	NC

Study	Sample size (N)	Time since PPH	Outcome	Outcome assessment	Percentage or median/mean (IQR/SD) PPH	Percentage or median/mean (IQR/SD) No PPH	Risk ratio (RR) or Odds ratio (OR) or Hazard ratio (HR) (95% CI; p value)
De la cruz 2016 (68)	409	6 months	Post-traumatic stress disorder	PSS score (≥15)	9%	1%	aOR=2.46 (1.92, 3.16)
		36 months		PSS score (≥15)	24%	5%	aOR=1.90 (1.57, 2.30)
Michelet 2015 (66)	869	26.5 months		IESR (≥30)	64%	NC	NC
Ricbourg 2015 (70)	40	1 months		IESR (≥30)	45%	21%	NR
		3 months			24%	13%	NR
Thompson 2011 (51)	206	2 months		PCL (>44)	5%	NC	NC
		4 months			3%	NC	NC
Van Steijn 2020 (71)	308	1-1.5 months		PCL-5 ≥32)	7%	1.7%	RR=4.45 (0.99, 20.06; p=0.035)
		1.5 months		CAPS-5	5.60%	0%	NR, (p=0.007)
Ricbourg 2015 (70)	40	1 months	Mother-infant bonding	Median Mother Infant Bonding Scale (MIBS)	1 (0-2)	0 (0-2)	NR
		3 months			1 (0-1)	0 (0-2)	NR
Thompson 2011 (51)	206	2 months	General mental health	Median SF36	80 (70–80)	NC	NC
		4 months			80 (70–90)	NC	NC
Van Stralen 2018 (93)	58	6 -9 years		Mean SF36	75 (17.4)	75.5	NR (p=0.85)
Knight 2016 (67)	78	12 months	Difficulty in concentrating	Health questionnaire	23%	2%	NR
		8.1 years			23%	17%	NR
Knight 2016 (67)		12 months	Flashbacks to labour or birth	Health questionnaire	33%	6%	NR
		8.1 years			17%	2%	NR
Sentilhes 2011 (94)	68	1-15 years	Negative memories of PPH	Survey question	68%	NC	NC

Study	Sample size (N)	Time since PPH	Outcome	Outcome assessment	Percentage or median/mean (IQR/SD) PPH	Percentage or median/mean (IQR/SD) No PPH	Risk ratio (RR) or Odds ratio (OR) or Hazard ratio (HR) (95% CI; p value)
Sentilhes 2011 (94)		1-15 years	Suggestion by hospital staff of a visit to psychologist	Survey question	66%	NC	NC

aRR= adjusted risk ratio, aOR= adjusted odds ratio, aHR=adjusted hazard ratio
NC= No comparison group
NR= Not reported
Outcome measurements:
SF 36 (Short form health survey): Scores 0-100 with a higher score reflecting better outcomes
Milligan score: Scores 10–14 'no/low' postpartum fatigue, 15–20 'medium', and 21–40 'high' postpartum fatigue
B-IPQ (Brief Illness Perception Questionnaire): Scores 0-80 with higher scores reflecting a greater perceived burden of a disease and lower scores reflecting better outcomes
HADS (Hospital Anxiety and Depression Scale): Scores 0-21 with 0-7 normal, 8-10 borderline abnormal, 11-21- abnormal
STAI (Spielberger State-Trait Anxiety Inventory): Scores 6-24 with >12 indicating high anxiety
EPDS (Edinburgh Postnatal Depression Scale): Scores 0-30 with >12 indicating postnatal depression.
PSS Scale (Post-traumatic stress disorder symptom scale): 17 item checklist with ≥15 indicating PTSD
IESR Scale (Impact of Events Scale): Scores 0-88 with ≥30 indicating PTSD
PCL scale (17 item checklist): Scores 17-85 with >44 indicating PTSD
PCL-5 score (20 item self-report tool): Scores 0-80 with ≥ 32 indicating PTSD
CAPS-5 score (Gold standard to diagnose PTSD using criterion A, B-E, F, G): Having at least one B Criterion symptom, one C Criterion symptom, two D Criterion symptoms and two E Criterion symptoms indicates PTSD.
TSQ (Trauma Screening Questionnaire): Score 0-10 with ≥7 indicating PTSD
Mother Infant Bonding Scale: Scores 0-27 with a high score indicating a disorder related to mother-child bonding.

3.4.3.1 Physical health outcomes for women

Two studies reported on general health status in women following PPH, both using the 36-item short form (SF36) general health survey to assess general health status. The first found a decline in general health status at two months (SF score median 75; IQR 60-80) and four months (SF score median 72.5; IQR 60-80) following the PPH, with 35% of women having a lower SF36 score compared with one year previously. (51) The second study found no difference in SF36 score for women following PPH compared with SF36 reference group values (SF score mean 70 vs 71.5). (93) Neither study collected data from an appropriate comparison group.

Four studies explored breastfeeding as an outcome to investigate women who experienced a PPH were less likely to breastfeed their babies, compared with women who did not have a PPH. (51, 67, 96, 97) Data about breastfeeding status at hospital discharge were extracted from birth records in a perinatal database in two studies, while women were asked to self-report their feeding practices using a health questionnaire in two other studies. One study reported the percentage of fully breastfeeding, partial breastfeeding and bottle feeding using the WHO's definition of 'fully breastfeeding' (i.e. exclusively breastfeeding which means only giving an infant breastmilk and giving no other food or drink, or predominantly breastfeeding which includes breastmilk, drops, syrups and certain liquids). (49) Other studies reported the percentage of exclusive breastfeeding and/or partial breastfeeding (breastmilk and infant formula feeding) and/or any breastmilk feeding. (67, 96, 97) One study, of 40,149 birth records of women who gave birth in New South Wales, Australia between 2007 to 2012, found that there was no significant difference in the proportion of exclusive breastfeeding among mothers who had a PPH compared with mothers who did not have a PPH, although,

the proportion of women who reported breastfeeding was slightly lower among mothers who received a blood transfusion following PPH. (97) A second study, that included 15,451 birth records of women from the same Australian cohort who gave birth between 2007 to 2010, reported that a low Hb level was associated with a lower proportion of exclusive breastfeeding among mothers who had a PPH and a blood transfusion. (96) The other two studies investigating breastfeeding after PPH reported similar findings. In a study of 78 women investigating longer-term health outcomes following peripartum hysterectomy, women who had a peripartum hysterectomy after PPH were less likely to report exclusive breastfeeding (i.e. breast milk only) in the first week, six weeks, and six months after birth compared with women who did not have a hysterectomy (14% vs 40% at six weeks after birth). (67) Finally, in a study of 206 women from hospitals across Australia and New Zealand, women who had a PPH were asked to self-report infant feeding methods. (49) Exclusive breastfeeding in this group was 63% in the first postpartum week, 58% at two months and 45% at four months postpartum. However, this study did not have a comparison group of women who did not have a PPH. (49)

Two studies explored the potential association between PPH and venous thromboembolism (VTE) at six weeks postpartum. (45, 92) In one study of 32,463 women in France, severe PPH was strongly associated with the occurrence of VTE in the first six weeks after birth, after adjusting for caesarean birth, and low molecular weight heparin use after birth (OR= 5.3, 95% CI= 1.6-17, p=0.005). (45) Outcome assessments were confirmed using an exhaustive, bilateral, comparative colour duplex ultrasound investigation to validate the diagnosis. In a second Swedish study, that included 82,376 birth records of women who gave birth between 1999 to 2002 in Stockholm , there was a statistically significant association between PPH and

the risk of VTE at six weeks postpartum (OR= 2.7, 95% CI= 1.4-5.2) after adjusting for age, BMI, multiple pregnancy and blood group. (92) However, after further adjustment for caesarean birth, placental retention, pre-eclampsia, and blood transfusion the association was no longer statistically significant and the authors concluded that PPH was not a major risk factor for VTE unless there was an associated blood transfusion following the PPH. (92)

Two studies explored the potential association between PPH and the risk of CVD. (62, 63) In both studies, diagnostic codes were used to retrospectively identify cardiovascular related morbidities, one using a health insurance database and the other hospital registry data. Both studies found no difference in the risk of hospitalisation from CVD between women who experienced PPH without transfusion and women who did not experience PPH. However, both studies suggested that women with a PPH requiring blood transfusion had a higher risk of hospitalisation for CVD (aHR= 1.60, 95% CI= 1.25-2.06; and aHR= 1.38, 95% CI= 1.13-1.68) compared with women without PPH after adjusting for potential confounders. (62, 63)

Other physical outcomes investigated included Sheehan's syndrome (damage to the pituitary gland following major haemorrhage), (98) difficulty in sexual intercourse, (67) menopausal symptoms, pain, severe tiredness and fatigue, (67) and mastitis. (51) A higher proportion of women reported these symptoms in severe PPH or EPH groups compared with women who did not have a PPH or EPH. The percentage of those symptoms among women after PPH in each study are summarised in Table 3.6.

3.4.3.2 Psychological health outcomes for women

Three studies reported the prevalence of anxiety following PPH at different time points. (51, 66, 67) The exposed group in all studies was women who had a severe PPH or EPH following

PPH, and the follow-up time ranged from two months to eight years after birth. The first study of 869 French women who had EPH, used the Hospital Anxiety and Depression Scale (HADS) to measure anxiety. HADS scores ranged from 1 to 21, with higher scores reflecting greater anxiety. The median score for HADS among women who underwent EPH following PPH was 10, which reflects moderate anxiety. (66) In the second study, anxiety was assessed at two and four months after birth using the six-item short form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). At both two and four months after birth women who had a PPH demonstrated mild anxiety. (51) Neither of these studies had comparison groups. Finally, a third study from the UK used self-reported questionnaires that included a range of experiences of health and well-being problems 1) in the first year after childbirth and 2) at the time of survey (median 8.1 years of follow up after childbirth) among women who had EPH compared with women who did not have EPH. (67) Women who had a hysterectomy were more likely to report anxiety or 'nerves' (27%) in the first 12 months after birth than women who did not have a PPH (10%), but there was no difference between the two groups at the time of data collection, around seven to nine years after birth. (67) Overall, there was no clear evidence of association between PPH and anxiety symptoms in these studies, although women in three prevalence studies reported mild anxiety symptoms up to about two years after childbirth, and only one study had a comparison group.

Six studies explored potential associations between PPH and depression with a follow up ranging from one month to eight years after childbirth. (51, 66-70) Sample sizes of the studies ranged from 40 to 869. These studies reported conflicting findings with different directions of association between PPH and depression. Four studies conducted in United States, Sweden, France, and Australia and New Zealand used the Edinburgh Postnatal Depression Scale

(EPDS) to measure PPD. (51, 68-70) For the EPDS, scores can range from 0 to 30, with a score of at least 12 suggesting PPD. One study conducted in France with women admitted with PPH and who underwent EPH between 2004 to 2011, used the HADS scale to measure depression. HADS scores range from 0 to 21, with higher scores reflecting greater depression. A study in the UK used a health and wellbeing questionnaire with 78 women who had EPH to explore to self-report health and well-being problems, including depression. (66, 67)

Three of these studies reported a slightly higher prevalence of depression in women who had a PPH compared with women who had not had a PPH, at one, three and 12 months after birth. (67, 69, 70) However, only one of these studies adjusted for potential confounders and reported that there was no statistically significant association between PPH and PPD at six weeks postpartum in the adjusted model. (69) Conversely, one study in United States, that explored 409 women from two groups of mothers recruited from an online communities, reported a slightly higher prevalence of PPD among women who did not have an EPH (9%) compared with women who had an EPH (6%) at six months after birth. Two further studies reported depression scores but did not have appropriate comparison groups. The French study reported HADS scores within the normal range (HADS score =6) among 869 women who underwent EPH following a PPH, (66) while the second study, carried out in Australia and New Zealand, reported 11% prevalence of PPD at two months and 13% at four months after birth among 206 women who had experienced PPH. (51) Taken together, there was no convincing evidence from these studies of an association between PPH and subsequent PPD, with five of the studies providing contrasting results for the higher proportions of PPD following PPH, and one study with an appropriate adjustment for confounder suggesting no association.

Five studies explored the association between PPH and PTSD at different time points ranging from one month to three years after birth. (51, 66, 68, 70, 71) The exposed group in four of these studies was women who had a severe PPH or EPH following PPH. In the remaining study the exposed group was women who had a PPH, with no clear definition of PPH reported. (70) One study used the PTSD symptom scale (PSS) to measure PTSD, which is a 17-item checklist with a score of ≥15 indicative of PTSD. (68) Two studies used the Impact of Event Scale (IESR) which indicates the prevalence of PTSD symptoms with a threshold score of 30 points, (66, 70) and the remaining two studies used the DSM-5 (PCL-5) scale which is a 20-item self-report tool to assess PTSD symptoms. (51, 71) Only three studies had a comparison group. (68, 70, 71) All three of these studies suggested a higher risk of PTSD among women who had a severe PPH and/or EPH compared with women who did not experience a PPH. Two of these studies also reported adjusted risk ratios and both studies suggested a significant association between PPH and PTSD (RR 4.45 at 1.5 months, 2.46 at six months after birth). (68, 71) Two studies that did not have comparison groups reported 5% prevalence of PTSD among women who had a PPH at two months after childbirth (51) and 64% prevalence of PTSD among women who had an EPH at the median follow up of 26.5 months after childbirth. (66) Overall, conclusions were limited by the lack of comparison groups and lack of adjustment for confounders in three studies, but adjusted hazard ratios from two studies with comparison groups were suggestive of a higher proportion of PTSD in women following PPH, albeit with one study having wide 95% CI.

Other psychological health outcomes investigated included mother infant bonding, (70) a general mental health score, (51, 93) difficulty in concentrating, (67) flashbacks to labour, (67) negative memories of PPH, (94) and suggestion by hospital staff of a visit to a

psychologist. (94) Results from these studies indicated that a higher proportion of women in severe PPH or EPH groups reported having difficulties in bonding with their infants, difficulties in concentration, and flashbacks, compared with women who did not have a PPH or an EPH.

3.4.3.3 Physical and psychological health outcomes for partners

No studies reported on physical health outcomes among partners of women who had experienced PPH. Two quantitative studies reported on the prevalence of psychological health outcomes among partners. The percentage or mean estimates of those psychological outcomes among partners in each study are summarised in Table 3.7. The first Dutch study, of 185 partners who witnessed their partners having a severe PPH, reported that there was no strong association between witnessing PPH and a subsequent PTSD diagnosis among partners, according to a self-report tool. (72) The second Dutch study explored the quality of life of 49 partners of women who had experienced severe PPH between 2012 and 2013, using SF-36 general health survey tools. (93) The results indicated that partners of women who had a severe PPH had better scores overall compared with the reference group's scores from myocardial infarct and systemic lupus erythematosus patients. However, the study authors reported that these reference values were not applicable for partners. Overall, there was no clear evidence of an association between witnessing PPH and the development of PTSD among partners of women.

Table 3.7 Psychological health outcomes for partners investigated by included quantitative studies

Study	Outcome	Outcome assessment	Sample size (N)	Time since PPH	% or mean (SD) in PPH partners	% or mean (SD) in control partners/ reference
Van Steijn 2019 (72)	Probable PTSD	PCL5 (≥32)	185	1-1.5 months	5.7%	0
	PTSD	CAPS-5		1.5 months	0	0
Van Stralen 2018 (93)	General health	SF36	47-49	6-9 years	79 (19.6)	NR
	Mental health	SF36		6-9 years	80.6 (14.7)	NR
	Patient perception consequences	B-IPQ		6-9 years	5.7 (2.8)	NR

NR= Not reported
PCL-5 score (20 item self-report tool): Scores 0-80 with ≥ 32 indicating PTSD
CAPS-5 score (Gold standard to diagnose PTSD using criterion A, B-E, F, G): Having at least one B Criterion symptom, one C Criterion symptom, two D Criterion symptoms and two E Criterion symptoms indicates PTSD.
SF 36 (Short form health survey): Scores 0-100 with a higher score reflecting better outcomes
B-IPQ (Brief Illness Perception Questionnaire): Scores 0-80 with higher scores reflecting a greater perceived burden of a disease and lower scores reflecting better outcomes

3.4.4 Quality assessment for qualitative studies

The results of the quality assessment for the eight qualitative studies included are presented in Table 3.8. The qualitative studies with "yes" for at least seven of the questions assessed using the CASP tool were considered "high quality", and those with "yes" for at least five of these questions were considered "moderate" quality. Overall the quality of the included qualitative studies ranged from moderate (n=1) to high (n=7).

All the qualitative studies included had clear aims and justified the choice of research design and methods to explore women's experiences of PPH and/or EPH. The methods of data collection were fully justified in most studies (n=6), with two studies that did not report how data saturation was judged to be reached. (55, 67) Most studies included had an overall low quality assessment for reporting about the relationship between researchers and participants with all but two (91, 104) not reporting this clearly, so it was not possible to assess how the roles of the researchers may have had an impact on the research study and interpretation of the findings. The final question of the CASP tool assessed the value of each individual study to the knowledge area of the research with all but one study judged to be of moderate to high value.

Table 3.8 Quality assessment for qualitative studies using the CASP tool (86)

Study	1.Clear statement of aims	2.Qualitative methodology appropriate?	3. Research design appropriate for the aims?	4.Recruitment strategy appropriate ?	5. Data Collection addressed the research issue?	6.Relationship between researcher and participants adequately considered?	7.Ethical consideration	8.Data analysis rigorous?	9. A clear statement of findings?	10. How valuable is the research?
Briley 2020 (99)	+	+	+	+	+	?	+	+	+	Moderate
De La Cruz 2013 (100)	+	+	+	+	+	?	+	+	+	Moderate
Dunning 2016 (91)	+	+	+	+	+	+	+	+	+	High
Elmir 2012a; Elmir 2012b; Elmir 2012c; Elmir 2014 (52, 101-103)	+	+	+	+	+	?	+		+	Moderate
Knight 2016 (67)	+	+	+	+	+	?	+	+	+	Moderate
Snowdon 2012 (104)	+	+	+	+	+	+	+	+	+	High
Thompson 2010; Thompson 2011 (49, 55)	+	+	+	+	+	?	+	+	+	High
Woiski 2015 (49, 55, 105)	+	+	+	+	+	?	+	+	+	Low
	Items 1-9 scored as Yes +, Partially +, Can't tell ?, No − Item 10 scored as low, moderate, or high value									

3.4.5 Results of the qualitative synthesis for women and partners

In relation to the research questions, ten analytical themes about the impact of PPH were identified from the synthesis of the qualitative studies included in this review. These themes were organised under four categories based on the research questions of this review, namely 'physical impact', 'psychological impact', 'psychosocial impact', and 'experiences of care'. Figure 3.2 presents the overall structure of the themes arising from the synthesis, organised into four key time periods: 'during emergency'; 'hospital recovery', up to one week after birth; 'postnatal', up to 12 months after birth, and 'longer term'.

Three qualitative studies also included partners of women as participants. (91, 99, 104) Three themes were identified from partners' accounts of PPH: 'brush with death', 'adequacy of care' and 'communication gaps and information needs'. Because these were complementary to those identified from women's experience these are discussed and reported alongside women's experience below. All quotes reported in the findings are extracted from studies included.

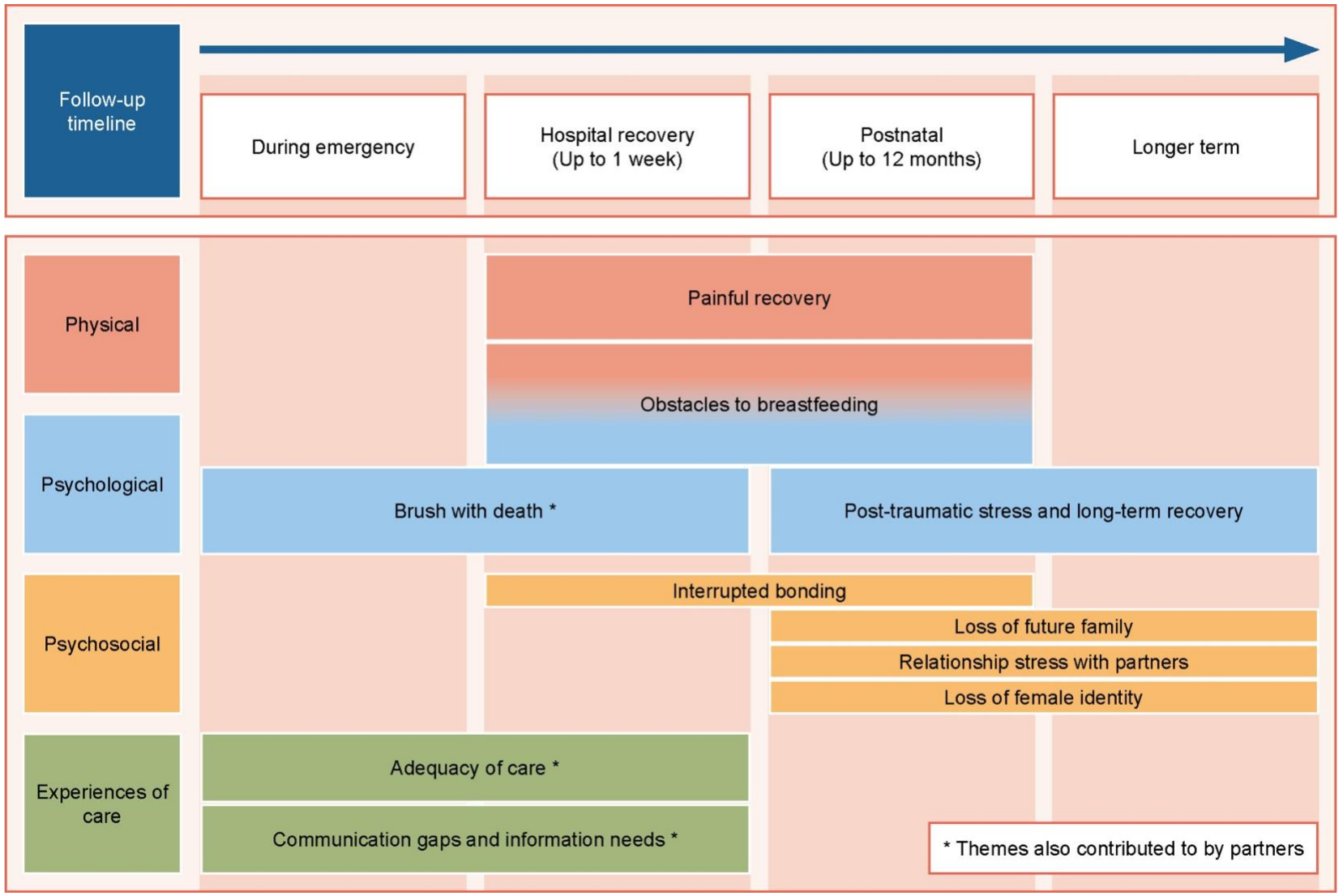


Figure 3.2 Summary of analytic themes from thematic synthesis of qualitative studies (n=8)

3.4.5.1 Physical impact

These themes reflect the impact of PPH on women's physical health. 'Painful recovery' was the main theme and another theme, 'obstacles to breastfeeding', which also crosses over into the 'psychological impact' category, is also presented here.

Painful recovery

This theme was contributed to by five studies and encompasses women's experiences of pain at the time of the PPH and for up to a year afterwards. (52, 55, 67, 91, 100) During the emergency episode women described "horrible" and "traumatising" pain from, for example, manual removal of their placenta or "pounding with the fists" on them. (100) Physical limitations during the immediate postnatal period and beyond (months after birth) were consistently reported by women across five studies. (52, 55, 67, 91, 100) Their descriptions indicated that pain prevented them from performing simple day-to-day activities such as walking and cooking dinner, and women also reported their inability to fully function due to insomnia and disrupted sleep patterns. (52, 91) One particular concern raised by women in two studies was that they were not able to take proper care of their babies as they were not physically strong enough or were not fully recovered from pain. (55) In the longer term, one woman who experienced an EPH reported that it took a year for her to physically recover. (67)

"And I was trying to kind of go for walks and stuff but it was just exhausting for me to go for a stroll or something" (Dunning 2016, page 6)

"With the operation and blood loss, it has been difficult to look after baby properly. I just haven't been feeling well enough to be able to provide continued care for baby." (Thompson 2011, page 333)

"… I spent 15 hours in theatre and a year to recover. Still physical and mentally affected by it. It had a great impact on my life and always will. I am not the same person anymore." (Knight 2016, page 127)

Obstacles to breastfeeding

This theme was contributed to by three studies (49, 100, 102) and describes the challenges encountered by women in initiating and continuing breastfeeding during the immediate recovery and subsequent postnatal period following a PPH. The immediate impacts of PPH, including separation from their baby, pain, and physical recovery, affected women's ability to breastfeed. Women reported how their capacity to breastfeed, in turn, resulted in feelings of failure as a mother and how this contributed towards interrupted bonding which is discussed below as a separate theme under 'psychosocial impact'.

During their immediate hospital recovery, women reflected that their initial separation from their baby when they were admitted to intensive care was one of the key barriers to initiating breastfeeding. (49, 102) Other key obstacles reported by women included pain, fatigue, limited mobility and posture problems, and delayed milk production. (49, 102) Delayed physical recovery was also reported as a major challenge to maintaining exclusive breastfeeding during the postpartum period. In one study for example, women reported stopping breastfeeding after a few months despite their willingness to continue as they had "insufficient milk supply" resulting from "large amount of blood loss" and "trauma they had endured" from PPH. (102)

"Separation from baby one and a half hours after birth and for about three plus hours whilst in theatre. Delay with getting breastfeeding underway." (Thompson 2010, page 7)

“I wanted to breastfeed my child for the first 12 months, as it was with my first child. Unfortunately, I had to give it up after a few months because my body could not cope and supply enough milk for my baby.” (Elmir 2010, page 1123)

Women’s experiences revealed the role of breastfeeding in initial bonding with their newborn babies. Women expressed feelings of failure and distance from their babies for not being able to breastfeed and described feeling anxious about not having enough energy to breastfeed after having PPH, or not being able to produce enough milk. (49, 102)

Women also talked about how their efforts and willingness to breastfeed after PPH were not sufficiently supported by health care professionals, including for example being told that they should not be bothered to breastfeed after a traumatic childbirth. (49) The lack of adequate support for breastfeeding and a lack of information about breastfeeding and the potential impact of PPH on milk production was evident in all three studies.

“Breastfeeding was VERY important to me…. I felt I had failed my newborn in not being immediately available to him for that first feed straight after birth…. I felt very guilty for not being there in the initial phase, post birth, to breastfeed him and bond with him. I initially felt a sort of distance between us because of this.”(Elmir 2011, page 1123)

"My dream of breastfeeding has been shattered due to no energy because of the PPH so have started feeling quite down." (Thompson 2011, page 9).

“In the maternity ward the one thing that really, really bothered me the most was that they didn’t give me enough information about breastfeeding and they kind of tried to steer me away from breastfeeding, “Oh you shouldn’t bother breastfeeding you’ve gone through so much trauma. It’s not going to work and blah blah blah.” I just wish they would have just listened to my wishes and helped me out a little bit more. And I know they thought it was bad for me, but it wasn’t, emotionally anyway.” (De la Cruz 2013, page 260)

"..... that mothers suffering PPH be advised of its potential impact on milk supply and be offered feeding support earlier rather than later." (Thompson 2010, page 8)

3.4.5.2 Psychological impact

The themes presented under this category encompass the negative psychological consequences of experiencing a PPH. This includes the impact of an immediate life-threatening event on women's and their partners' psychological wellbeing and expressed symptoms of PTSD.

Brush with death

This theme was contributed to by three studies and encompasses women's and partners' acute psychological distress as a result of an unexpected encounter with an emerging life-threatening event. (52, 91, 100)

Women

Being so close to death was traumatic and frightening particularly when women did not anticipate that death was a possibility. (52, 100) Their, overwhelmingly negative, emotional responses to this were described as varying from "shock", to having a "major anxiety attack" or having an "out of body experience". (52, 100) Elmir et al. (2012) also highlighted that women were afraid of "leaving their young children behind to the unknown" and not knowing "whether or not they would cope without a mother". (52)

"... I'm going in and out of consciousness, and I'm having a hard time staying earth-bound…I'm just talking to my husband and telling him, "Please make sure that you take care of our kids and let him [newborn] know that I loved him very much if I don't make it through all of this." I remember kind of losing it before I went into surgery, almost like leaving earth, like having an out-of-body experience. (De la Cruz 2013, page 40)

"I had a major anxiety attack.. I think I made the connection between feeling really cold [due] to the blood loss and the shock that I was going into, and the fact, you know, how close to death people can be in those times. I felt like I was kind of having a bit of an out of body experience. I was disassociating from it…" (Elmir 2012, page 31)

In one study, (91) the author identified "control" as a main theme to reflect how women felt about the emergency situation at the time of PPH. Most women felt in control for the care they had received, however, two women who had moderate PPH of blood loss between 1000ml-2000ml expressed losing control as they were not sure "whether the health care professionals were going to be able to deal with the issue". Women who had a PPH, irrespective of severity of blood loss consistently reported "dissociation" and a feeling of "distortion of time".

"Everything for me went by so quickly, and then when I was in the hands of their care I felt OK."– (Dunning 2016, page 3)

"I couldn't tell anything, I was knocked out completely" (Dunning 2016, page 4)

"I mean I was so out of it. I was so out of it" (Dunning 2016, page 4)

Partners

The theme of 'brush with death' was also contributed to by two studies that reported on partners' experiences of PPH, from the acute emergency to the postnatal period. (91, 104) These showed that, while women were facing life and death situations, their partners also experienced psychological distress from witnessing this. One partner described himself as "desperate" at being left alone with his baby without support or communication about what had happened to the baby's mother when she was suddenly taken to the theatre. (104) This

was also echoed by others as “distressing”, and one partner reported seeking help from the GP and counselling services in the months after witnessing such a traumatic birth. (91) Partners talked about feeling “forgotten” and “upset” at not receiving updates about women’s wellbeing during the immediate events. (91, 104)

“[I was] almost forgotten about, not entirely forgotten about, obviously there’s a lot going on in a hospital and everyone’s busy. y [I]t was easier to stick me in a quiet corner.”(Snowdon 2012, page 795)

“... definitely I felt numb, just ...yeah, emotionally I think it did affect me more than her, um, because ... all, yeah, and it did so for a number of, definitely, six weeks and even beyond ... I felt a different person, it was like I had changed and I just felt like ... um ... yeah because it just was there in front of you for such a long period and it kind of, the shock and the ... and me and (W10) were talking and she’d say, ‘Maybe you should go and get some counselling or ... that would be helpful” (Dunning 2016, page 6)

“...they rushed her off and just left me with the baby, um, and I was asking what was wrong and all they could say was, ‘She’s lost a lot of blood, we don’t know why, we can’t stop the bleeding.’ Um ... and ... yeah, so I was left with the baby and in ... yeah, just in a daze really.” (Dunning 2016, page 4)

Symptoms of posttraumatic stress and long term recovery

This theme was contributed to by five studies and describes women’s experiences of PTSD symptoms following PPH. (52, 55, 67, 91, 100) PTSD is characterised by four key symptoms: reliving experiences, avoidance of reminders of trauma, negative thoughts and mood, and hyperarousal. (56) Women’s descriptions of their symptoms in the postnatal period were strongly indicative of PTSD. (52, 55, 67, 91, 100) Data from two studies, which investigated women’s experience after hysterectomy as a consequence of PPH, (52, 67) indicated that

some women continued to experience these symptoms years after hysterectomy, whereas in the other three studies symptoms were reported up to six months after childbirth. (55, 91, 100)

Women described re-experiencing their traumatic birth in the form of vivid memories, flashbacks and nightmares. (52, 55) Triggers for flashbacks included seeing other pregnant women, being in a hospital environment or seeing stories in the media about giving birth. (52)

"Every time I close my eyes, I relive the labour and birth." (Thompson 2011, page 331)

"It's once I start thinking about it, it like … kind of brings the whole thing back." (Dunning 2016, page 6)

"It definitely brings back memories when you watch something on television that mentions hysterectomy, but yet you don't hear about hysterectomy following childbirth that often." (Elmir 2012, page 232)

"The nightmares usually revolve around the part where I am begging for help, it's really horrible. Because the pain is unbearable, I have nightmares where I am trying to see people's faces, cause I remember gasping for breath…In the nightmare, I don't remember pain, I always remember I am about to die. So the nightmares are about me about to die after giving birth…" (Elmir 2012, page 232)

Women also talked about avoiding reminders of trauma. One woman, for example, said that she avoided hospital environments, while another talked about avoiding sharing her experience with anyone else as they would not understand the situation. (52)

"I don't like going to the hospital or the doctors, like my daughter is 15mths, I didn't take her to see the doctor until I had to and she was really bad, she had tonsillitis and needed an operation." (Elmir 2012, page 232)

Women reported feeling “numb” after learning about their hysterectomy and feeling “guilt” and “anger” after they have been discharged from hospital. (100) For some women, reported in two studies, these symptoms were severe, including having suicidal thoughts. (67, 103) Women from these studies reported that it took years to fully recover from their hysterectomy and eventually being reconciled to the event and its impact. (67, 103)

“I have felt so unbearably sad and unfairly treated by life. I have had suicidal feelings which I have never disclosed to anyone.” (Elmir 2012, page 233)

“I suffered the most awful postnatal depression and there is a distinct lack of mental health support. This needs to be addressed as I had suicidal thoughts often in the two-three years after the birth of my son.”(Knight 2016, page 126)

While the overwhelming majority of women’s observations from most studies were negative, women from one study reflected on being able to take something positive from their experiences, talking about how it helped them find some perspectives and resilience. (101)

“I try to seek a positive out of my experience and think well at least we don’t have to use contraception.” (Elmir 2014, page 513)

“I actually quite enjoy not getting my periods, I have to say. Really it’s actually heaven…..” (Elmir 2014, page 513)

“*Having a hysterectomy allowed me to not stress about silly little things, just worry about what counts. I never used to be like that, it wasn’t until you are put in a life and death situation that you start to think about what really counts.”(Elmir 2014, page 512)*

3.4.5.3 Psychosocial impact

Themes presented under this category encompass women's reflections about loss of identity, including potential future relationships, social relationships with their babies and their partners during their immediate recovery, as well as the postpartum period and beyond. These themes also highlight how these interpersonal dynamics shaped women's psychological and social well-being. The four themes identified were 'interrupted bonding', 'loss of future family relationships', 'relationships stress with partners' and 'loss of female identity'.

Interrupted bonding

This theme was contributed to by three studies and reflects women's perceptions of bonding with their infants and their role as a mother during their recovery in hospital and in the postnatal period. (49, 100, 102) This theme is interlinked with the theme 'obstacles to breastfeeding'.

During the immediate postpartum period, women in two studies reported feeling that bonding with their babies was disrupted by physical separation because of admission to intensive care or neonatal care. Women talked about having concerns for their baby's wellbeing and not knowing if they were okay. (49, 102) Women reflected that this initial separation prevented them from holding, touching and breastfeeding their baby, and many felt that this was a key barrier to establishing a close relationship with their baby.

Women's reports in these studies showed that this initial interrupted bonding during their immediate recovery could continue in the weeks following hospital discharge, with some women experiencing extreme tiredness, continuing for up to a year after childbirth. Some women in one study talked about feeling "upset" and "guilty" when their caring

responsibilities were taken away by their family members and partners. (102) The authors also argued that many women considered caring responsibilities for their baby and taking care of the family as an important chapter in their life as a mother.

"My biggest concern in ICU, I needed to get to my baby. I didn't know what they (nurses were doing with her or what they were giving, and I needed to get to her." (Elmir 2011, page 1122)

"I was really worried because I'd not seen him [newborn] for so long—I'd not even held him—that I'd struggle to bond with him and I wouldn't be able to feed him, and not only would I not be able to have the delivery I wanted, I also wouldn't be able to feed him myself… I just couldn't wait to hold him, almost frantic… I was worried and I feared that I wouldn't be able to bond with him very well." (De la Cruz 2013, page 259)

"I feel the bond with my son weekened significantly due to my postpartum recovery." (Thompson 2011, page 333)

"I had lost that bond with her [baby] until she was one… I came so close to strangling the kid while she was asleep, it got to a point where my husband would say stay in bed, I'll go get her because he just knew I was cracking." (Elmir 2011, page 1124)

Loss of future family

This theme was contributed by two studies and encompasses women's feelings of loss in relation to future childbearing following PPH. (49, 55, 67) At four months after childbirth, some women talked about feeling worried about having a PPH in any future births and losing their confidence in their ability to go through birth again. (55) Traumatic birth experiences convinced some women not to have more children. (55) On the other hand, women who had a hysterectomy following PPH talked about their regret at not being able to have more children. (67)

"I must admit that the thought of going through labour again scares the wits out of me. I almost feel like I cheated death once and don't want to tempt fate." (Thompson 2011, page 332)

"I cannot forget how traumatic it was, neither does my husband. As a result of the experience we have decided to not have any more children." (Thompson 2011, page 333)

"It is a shame the condition was not picked up earlier as I would have liked to have had more children." (Knight 2016, page 127)

"We adopted a second son to complete our family." (Knight 2016, page 127)

Relationship stress with their partners

This theme was contributed to by three studies and reflects women's perceptions of their relationships with their partners following PPH and/or hysterectomy, in the immediate postnatal period and up to a year after birth. (67, 91, 103) In one study, one woman who had a PPH described having a relationship breakdown with her partner following a traumatic birth. (91) Women who had a hysterectomy following PPH talked about sexual tension and intimacy issues with their partners. (67, 103) For instance, a woman in one study mentioned loss of libido and avoidance of physical contact with her partner, (67) with this lack of sexual desire and "fear for intimacy" also being echoed by women in a second study. (103)

Elmir et al. discussed that the function of sexual intimacy was seen by many women as a way to reproduce, which constantly reminded them about their lack of uterus and their inability to have more babies. (103) Women from this study described how their partners were understanding and patient about re-initiating sexual intimacy, but that they felt "guilty",

"anxious", and "fear" that their partners might leave them. Women also reported developing insecurities over time, causing a strain in their marriage. (103)

"No, I'm not with … I think maybe it was too much for him." Woman with moderate PPH speaking about her relationship with her partner following the birth (Dunning 2016, page 6)

"When my husband and I started to have sex again, I'd cry afterwards because I would think, no I'll never, you know, I don't know, I guess that's what sex is for is to create life. I'd never have another child again so … He was very patient. He knew I just needed time … he was very understanding." (Elmir 2012, page 57)

"I'm very lucky in my husband because one of the hardest things afterwards for me was thinking, I can't give him children. Well not anymore. And for some reason I minded that more for him than I did for me I think because he could choose to go and have a child with another woman and that's not something I could choose. But he has just taken it in his stride … we had intended to have more children. It was something that was important to us…" (Elmir 2012, page 57)

"… My libido has all but vanished and this has put a strain on my marriage to a degree." (Knight 2016, page 127)

Loss of female identity

This theme was contributed to by two studies and covers women's experiences of hysterectomy as a consequence of a PPH. (67, 103) In particular, this theme reveals how having a hysterectomy had changed their identity as a woman. Women expressed that they could not forget the whole experience of having to go through unplanned hysterectomy. Women's accounts reflected that the memories lingered with them for many years and this changed how they felt about themselves as a woman. (103)

Elmir et al. (2012) discussed how women perceived having a uterus as one of the "feminine" characteristics that distinguished women from men. (103) Therefore, women felt the lack of uterus was associated with their feelings of incompleteness and emptiness. This was also echoed by women in another study who talked about how hysterectomy made them feel like a different person and not like a "complete woman". (67)

"For me the uterus symbolizes fertility! Femininity! New life! Being female! Hope! Possibility! Wholeness! Without it, I feel incomplete, less feminine, less a female and hopelessly infertile." Elmir 2012, page 55)

"After the shock of losing my womb I felt very down and not like a complete woman any more. I would give anything to still have my womb and be having periods and then naturally gone into the menopause. Instead I went into the menopause at the age of 42. I feel old before my time and it still gets me down..." (Knight 2016, page 127)

3.4.5.4 Experiences of care

Themes reported under this category encompass the positive and negative care experiences of women and their partners in terms of competency of health care professionals, overall care experience, care setting/environment, and communication and information needs during and after experiencing a PPH. Two analytical themes were identified under experiences of care: 'adequacy of care', and 'communication and information needs'.

Adequacy of care

Women

This theme was contributed to by six studies and describes women's perceptions of care, around the time of their PPH and into the postnatal period, including the perceived

competency of health care staff, their overall satisfaction with the care they received, the care setting and environment, and their follow-up support needs. (55, 67, 91, 99, 100, 105)

Both positive and negative experiences of care were reported by women, but all demonstrated the crucial role of health care professionals play in helping women feel calm and supported in an emergency when they have established mutual trust. (55, 67, 91, 99, 105) Some women reflected that they appreciated it when the doctors and midwives appeared confident and calm, and took time to reassure afterwards. (91, 99) Other women described feeling unsupported when midwives were "impatient" towards them, "too busy" to explain things or did not "acknowledge" them while providing care.

Women's accounts also showed how the care environment could also affect their overall experiences. One woman, for example, reported that she was very pleased to be in the critical care unit compared to a busy ward. (67)

"... I'm not a clinician in anyway, but because I work in the health field I was probably more aware that something had, you know, that it hadn't gone well but I sort of felt that there was no panic and people knew what they were doing. The thing I really liked was the Midwife, who'd been with me before ... he was there, like when we went into theatre and stayed with me and talked and then came into HDU and stuff afterwards and that was really nice and I really liked that, that he was there throughout, really good." (Briley 2020, page 4)

"No, the care up to that point had been so good and everybody had been, um, so supportive, not that I'd expected otherwise but I was quite, um, pleased with the time they took just to reassure me and … that sort of personal touch, do you know what I mean, was really nice" (Dunning 2016, page 7)

"Midwives were too busy to explain things or offer reassurance." *(Thompson 2012, page 331)*

"I was moved to the critical care ward on the delivery suite where I was allowed to stay for 5 days until discharge, avoiding a busy ward." (Knight 2016, page 126, primiparous)

Non-verbal clues such as facial expression, body language or behaviours from health care professionals were important, (55, 67, 99, 105) for example women were scared when health care professionals went extremely "quiet". (99) Women from two studies expressed being "terrified" when midwives showed their "panic" or were "nervous" during the emergency. (55, 105) Some women talked about apparent clinical errors, including for example, a catheter that was not fitted correctly. (67)

" ... I just had a baby ... and she [Midwife] was very nervous, I remember thinking that wasn't a very nice face ... " (Briley 2020, page 6)

"But as she failed to hide her panic and she had never once assured me that I could trust her, I was terrified!!" (Thompson 2011, page 331)

"I also had a catheter fitted wrong which did not let urine pass and I ended up with tremendous pain in my kidneys. I could go on and on about the clinical errors!" (Knight 2016, page 122)

There were concerns raised about early discharge from hospital, unmet needs for breastfeeding support and psychological health services, and limited information about resources available during the postnatal period. In two studies women were concerned that they were discharged from hospitals too soon after a traumatic birth. (55, 105) Insufficient follow-up care and limited resources for psychological health during the postnatal period were identified in four studies. (55, 67, 99, 100) Women's accounts from three studies indicated that there was a need for psychological counselling and follow-up debrief during the postnatal

period. (55, 67, 100) Women also mentioned that patient information websites and support for breastfeeding would have been helpful for them. (55, 105)

"..because the hospital was full, they pushed me to go home when I didn't feel I was ready – was still fainting some of the time." (Thompson 2012, page 331)

"More needed about the emotional difficulties after experiencing such a traumatic birth. I wasn't prepared for this and suffered as a result." (Thompson 2011, page 332)

"I would have found it helpful to have spent some time at the breastfeeding clinic or have been encouraged to do so." (Thompson 2010, page 8).

"I suffered the most awful postnatal depression and there is a distinct lack of mental health support. This needs to be addressed as I had suicidal thoughts often in the two-three years after the birth of my son." (Knight 2016, page 126)

Partners

The theme of 'adequacy of care' was also contributed to by one study that reported on partners' experiences of care during the emergency and the immediate recovery period. (99) Similar to women's experiences, one partner appreciated when the doctors took time to reassure him afterwards. Conversely, one partner did not find it helpful when health care staff showed their panic or went quiet. (99)

"*Well it doesn't help anyone to panic ... " (Briley 2020, page 5)*

"I mean the anaesthetist was very good because he was very much like 'How are you feeling?' ... and asking a lot of questions and asking me 'Is she cold?' ... and had everything on hand ... that was good." (Briley 2020, page 5)

Theme: communication gaps and information needs

Women

This theme was contributed to by six studies and describes women's information and communication needs and preferences including their information seeking behaviours. (55, 67, 91, 99, 100, 104, 105)

Women appreciated when they were provided with thorough explanations and clear communication about their hysterectomy and its potential consequences. (67) Other accounts illustrated that a lack of information about their current condition could worsen psychological distress for women and their partners. (100, 104) One of the communication gaps reported by women who had a hysterectomy was that nurses were not aware of their complicated birth and women found it "unsettling" when they had to explain that they did not have a uterus for examination, and had no need for contraception. (100)

"There was a member of staff at the hospital who spent a good 20 minutes explaining to my husband about the hysterectomy I had (I was too ill). He was upset that I'd had to have it but she explained in great detail ... It was an informal chat that helped my husband enormously and he mentioned many times how grateful he was for her taking the time. He was so relieved and it took a lot of worry away." (Knight 2016, page 123)

"And a lot of the attitude toward the psychological aspect had been along the lines of "just get over it"… and "we did what we had to do to save your life"… "and you need to move on with yours now." They obviously think they were doing the right thing by me, and tried to convince me that I should enjoy my life with my daughter, and not worry about the past. They just… don't understand what it's like to have that taken away from you. They really don't." (De la Cruz, 2013, page 261)

Women expressed different information needs at different time periods. Before their childbirth, women preferred to receive information about the risk of birth complications including PPH and many women believed it would make them feel more prepared for an emergency. (67)

"My consultant had full and frank discussions with my husband and me when the pregnancy abnormalities were detected. So we were forewarned that the birth was likely to be premature with a high risk of major bleeding and potential for high dependency/intensive care post delivery. About a week after the birth my consultant talked me through the pregnancy and birth from the medical side, explaining every event and decision in detail, sparing no information. This was really helpful to me as it meant I had no gaps in knowledge and enabled me to quickly understand and accept what happened." (Knight 2016, page 123)

During the emergency, women felt appreciative about informed decision-making especially about hysterectomy, although they acknowledged the emergency nature of excessive bleeding. For instance, women in the study of De la Cruz et al. felt overwhelmed when they were rushed to decide to have hysterectomy. (100) Women from five studies consistently reported that they would like to know about all available treatment options and consequences of PPH including recovery time. (55, 91, 99, 100, 104)

"*Before I knew it, I had papers shoved in my face saying, "You do understand there's a great possibility of you needing to have a hysterectomy, we need you to sign on the bottom line… And I just remembered signing it thinking they're not even going to try to save my uterus… (De la Cruz 2013, page 260)*

During their immediate recovery, women's accounts demonstrated that many were unaware of their excessive blood loss. (91, 99) Additionally, women would have liked to have received information about what had happened to them, their current location (e.g. ICU or in a ward), and the condition of their babies in simple terms without the use of confusing technical words.

Women's descriptions showed that it was traumatising when they did not have access to that information following a traumatic birth. (55, 100, 104)

"I was really crying because I wanted like a human there to tell me what was going on but—but nobody was there… I honestly think that my intensive care stay that night was more traumatising than what happened before." (De la Cruz 2013, page 260)

"I didn't know I lost lots of blood, I actually asked the Midwife if I lost blood and she said no, and I was quite shocked that someone said that I lost 1200mLs, I was like, 'Oh, okay …' …" (Briley 2020, page 6)

The quotes from four studies consistently suggested that women's information needs extended into the postnatal period. (55, 91, 100, 105) The information needs reported by women across three studies included the implications of PPH for recovery time and impact on breastfeeding, and available support services. (55, 104, 105) The findings also suggested that women have different preferences about the timing and amount of the information they would like to receive. While women from one study said they would have liked to receive detailed information during their immediate recovery, (104) women from two other studies described being overwhelmed with an emergency for which they were unprepared and tried to understand their situation during the postpartum period and for years after childbirth. (91, 100)

"I would have been less disturbed if I had known that it takes longer to recover from PPH" (Woiski 2015, page 6)

"Perhaps information on what supplements/diet/exercise could be done to help quicken the recovery from the exhausting effects of (physically and emotionally) suffering from a haemorrhage." (Thompson 2011, page 331)

'So it wasn't until I was at home, it may have been a week or two afterwards that I Googled what it was, that I realised, and I hope my understanding is correct, I think at the time I thought it was something to do with the tear and the stitches, and then I realised it was actually more to do with the placenta, and it … So I was … until I Googled it myself I was completely unaware of what had actually happened.' (Dunning 2016, page 6)

Partners

Partners' information and communication needs and preferences around the time of the PPH, described in three studies, also contributed to this theme. (91, 99, 104) In contrast to women's experiences, partners' accounts also covered the emergency period. Partners' descriptions indicated that information gaps were not only applicable to women but also to their partners who were primary carers for women. Generally, partners would have liked more information about available treatment options and potential implications while waiting for women during the emergency (91, 104) Partners were frustrated when they were being asked to leave the emergency room without being fully informed what had happened to the women. (91, 104) However, in one study, one partner who was present in the labour room mentioned that more information might have made him confused and distressed.

"…they rushed her off and just left me with the baby, um, the baby, and I was asking what was wrong and all they could say was, 'She's lost a lot of blood, we don't know why, we can't stop the bleeding.' Um … and … yeah, so I was left with the baby and in … yeah, just in a daze really." (Dunning 2016, page 4)

"I would have liked more information about what … there were lots of things running through your head but the main thing immediately is, is she OK? What caused that? … What does that mean now for her immediate, immediate situation? Is she all right, what do we need to do to make it better? I didn't really get a lot of information on that" (Dunning 2016, page 5)

Partners' accounts also indicated that good communication could relieve their emotional distress from witnessing traumatic childbirth. For instance, partners in one study expressed that they felt "good" after reassurance from an anaesthetist. (99) However, others described feeling "forgotten" and anxious because they had not received any information about women for hours. (91, 104)

"Within half an hour [of leaving] I was wanting to find out. Some of the nurses and the midwives, it was almost as though they were irritated by an anxious relative! Everything was totally behind closed doors. I was completely on the outside, I didn't have a clue in terms of what options were available, what could happen, what is happening, what has happened, exactly where the blood's coming from, what the risks are? There was no conversations around that at all." (Snowdon 2012, page 794)

In the immediate postpartum period, partners in the study by Dunning et al. reported that they did not recognise that there had been more blood loss than normal and were not aware of them having a PPH. (91) This finding was consistent with the accounts of women who mentioned a lack of knowledge about PPH. One partner in the Snowdon et al. study said that a PPH information sheet would be helpful for partners and family members to be able to learn more about the situation. (104)

"'I didn't even know, I thought most women got, um, iron tablets so it wasn't a, it wasn't a big deal at that point. Um, I thought that was just the norm, all women lose blood and …" (Dunning 2016, page 5)

3.5 Discussion

3.5.1 Summary and interpretation of main findings

In this mixed-methods systematic review, the available evidence from HICs about physical, psychological and psychosocial health outcomes following primary PPH among women, and their partners, was critically appraised and the evidence gaps identified. A total of 21 studies with a mix of methodological quality ranging from weak to strong were included, with follow-up time ranging from hospital discharge following PPH to 29 years after childbirth. Among these, seven studies explored the longer-term impacts of primary PPH after five years, and just two quantitative studies (62, 94) and one qualitative study (52, 101-103) had a follow-up period longer than ten years. In comparison, the previous review conducted in 2017, with its focus on PPH and other outcomes, including near-miss mortality included 26 studies. (48) It is clear there is relatively limited research about longer-term health outcomes following primary PPH compared with the many studies that have investigated more acute morbidity and health outcomes. (48)

The review reported here provides evidence that women with PPH were more likely to have persistent physical and psychological health problems during the postpartum period compared with women who did not have a PPH. These differences were more pronounced for women who had some indication of severe PPH such as blood transfusion or an EPH. The quantitative findings suggest that women with a severe PPH were more likely to have a long recovery time, low general health score, symptoms of tiredness/fatigue, and were less likely to exclusively breastfeed. These quantitative findings were consistent with women's descriptions of their physical functioning and limitations in performing simple day-to-day activities and

women's experiences of challenges around initiating and maintaining breastfeeding found in the qualitative studies.

This review's findings build upon the findings of a previous review conducted in 2016 by including updated literature and by synthesizing available qualitative evidence about women's and partners' experiences of PPH, illuminating the different directions and size of effects in quantitative studies. (56) The findings reported here were similar to the results of the previous review in 2016 which found that women who experienced PPH had persistent morbidities between three and six months postpartum, including postnatal depression, PTSD and poor general health. (56)

Other studies that have investigated outcomes following major obstetric haemorrhage, including but not limited to PPH, provide some support for an association with longer-term negative impacts. For example, the results of a survey conducted among 372 women from the Netherlands who had a major obstetric haemorrhage, in which PPH was not distinguished from an antepartum haemorrhage, indicated that 28% of the participants experienced longer-term negative impacts up to six years after childbirth. (106) Major obstetric haemorrhage was found to have a negative impact on the partner and family, and on their work, and 25% of these women had an additional absence from work beyond maternity leave.

Bearing in mind the limitations identified in terms of the quantity and quality of the evidence, the findings of this current review support a conclusion that the physical and psychological health outcomes of PPH can be severe, and extend into motherhood and many years after childbirth. Of all the health outcomes explored by the studies included, there were two major outcomes that are likely to be of potential longer-term relevance. The first of these is PTSD.

Included studies suggested a high prevalence of PTS symptoms among women with PPH, ranging from 3% to 64%. Women's descriptions from qualitative studies, which included key symptoms of PTSD such as flashbacks and nightmares about having a PPH, were supportive of these quantitative findings. The PTSD symptoms were commonly present among women who had severe PPH and lasted for many years after childbirth. There is some support from other studies for this association. Qualitative studies have demonstrated that childbirth related PTSD can have severe and lasting effects on women and their relationships with their partners and their family. (107-109) In the general population, the mean prevalence of postpartum PTSD is 4%-6% and may be higher, with a mean prevalence of 19% among women with physical complications and mental health problems such as depression. (110, 111) One prospective cohort study in an English maternity unit investigated the relationship between severe maternal morbidity (including major obstetric haemorrhage, HDP, and ICU admission) and psychological health symptoms at 6-8 weeks postpartum and found that women who had experienced severe maternal morbidity had a higher prevalence of PTSD symptoms compared with women who had not. (112) While the findings of the review reported here indicated persistent PTSD symptoms among women who have had a primary PPH, years after childbirth, (68, 70, 71) the available evidence was limited to prevalence studies reporting percentages only. The lack of studies with appropriate comparison groups, testing for an association and adjustment for confounding, means that more evidence is required before making a conclusion that there is a causal association between PPH and PTSD.

The second health outcome of potential longer term relevance identified by this review was CVD, including VTE. Two included studies investigated the association between PPH and CVD, with findings suggesting that women who had a severe PPH that required a transfusion

were more likely to develop CVD in later life. Although there is limited evidence about this potential association, prior studies have shown that women with a severe PPH are at a higher risk of acute heart failure and myocardial ischaemia, resulting from haemorrhagic shock. (64, 113) Therefore, there is a potential that this acute failure may have longer-term consequences for the cardiovascular system which may in turn put women at higher risk of developing subsequent CVD in later life. Pregnancy-related factors, as a female-specific risk factor for CVD, are poorly researched. (64, 114) Studies have provided evidence for an association between obstetric complications such as pre-eclampsia, pre-term birth, maternal anaemia, and gestational diabetes and a subsequent increased risk of developing CVD. (115-118) Potential inter-relationships between these factors, PPH and CVD may also need to be considered before making any interpretation about a casual association between PPH and CVD.

Qualitative evidence included in this review indicated that whether women received adequate support during their immediate recovery and postnatal period can affect their acute psychological wellbeing and have an impact on longer-term psychological health outcomes after PPH. For example, women's accounts suggested that they received insufficient follow-up care and had unmet needs for breastfeeding support and psychological support services. Health care professionals and family members were crucial in helping women feel calm and supported. This was supported by qualitative studies conducted in Australia which have described how care providers' interactions and postnatal support from partners can affect women's experiences of trauma during childbirth. (119-121)

There was also limited evidence from this review to reach conclusions about health outcomes for partners witnessing women who had PPH, with only two quantitative studies without appropriate comparison groups. The evidence from both studies did not indicate any strong

associations with PTSD or general health status. However, partners' accounts in qualitative studies indicated that they experienced acute psychological stress and anxiety due to inadequate information when women were in the emergency room, and some of them required counselling services after witnessing the PPH. PPH may also have an impact on relationships between women and their partners. Witnessing their partner having a PPH and having relationship difficulties may affect partner's psychological wellbeing beyond the postnatal period. Qualitative studies into the experiences fathers when they witnessed birth trauma have identified that this can affect their mental health and relationships with friends and family long into the postnatal period. (122, 123) Studies have also found that men are more likely to cope with these traumatic experiences by avoidance, and may be reluctant to seek the necessary care which may lead to poor psychological health outcomes. (124, 125) Therefore, it is crucial to investigate the potential psychological impact among partners who have witnessed a PPH.

3.5.2 Strengths and limitations of the review

This mixed methods systematic review had several strengths. To the author's knowledge this is the first mixed-methods systematic review integrating quantitative and qualitative evidence to explore the potential longer-term physical and psychological consequences of primary PPH. It provides a comprehensive overview of current evidence on this topic. The inclusion of qualitative evidence about women's and partners' experiences helped illuminate the understanding of different directions and sizes of effect in the quantitative studies. For example, the qualitative evidence suggested that maternal care around the time of PPH could play an important role in how mothers perceived trauma related to PPH, which in turn might influence the development of acute mental illness such as PTSD.

A comprehensive and reproducible search strategy was conducted using five electronic databases and specific eligibility criteria were applied for the exposure (focused on primary PPH), setting (included only HICs), and outcomes (excluded immediate outcomes including maternal deaths). The review included 13 quantitative studies, five qualitative studies and three mixed-method studies and synthesized both quantitative and qualitative data from a large and diverse group of women from HICs.

There are a few limitations which need to be acknowledged, many of which reflect shortcomings of the studies included, while some related to the review process itself. First, there were some challenges to interpret or draw conclusions about associations between PPH and some health outcomes because of the limitations of the study designs of studies included. Some of the studies included did not have appropriate comparison groups and conclusions were reached from the prevalence or proportions among the exposed group without consideration of potential confounders. Most studies did not have sufficient follow-up time to observe longer-term outcomes. For most studies the follow-up time was less than five years. Most studies used self-reported health questionnaires to assess outcomes rather than objective measurements, such as a clinical diagnosis of disease.

The heterogeneity of studies, including different definitions of PPH, different follow-up time and variation in the outcomes investigated, meant that it was not possible to conduct a meaningful meta-analysis. Only a limited range of potential longer-term outcomes were investigated by the studies included. Hence, the number of studies designed to establish the potential longer-term impact of PPH was limited. The studies included were almost all conducted in Europe, America and Australia/New Zealand, so the findings of this review are really only applicable for those countries in the same high-income settings. Given the

significant contribution of PPH to maternal morbidity in low and middle-income countries, there would be value in a systematic review of longer-term outcomes in those settings although this was specifically not the intention of this review. Due to limitation of resources, five potentially eligible papers that were not written in English were not considered for inclusion. Furthermore, it was not possible to search the grey literature and reports from WHO, United Nations Population Fund, NHS maternity statistics as originally planned in the PROSPERO registered protocol due to resource limitations.

3.5.3 Evidence gaps and implications for future research

There is limited evidence about the longer-term impact of primary PPH and hence there is a need for further research in this area. This applies particularly to cohort studies with improved study designs, with particular consideration given to duration of follow up, sample size, comparison groups and outcome measurements.

Studies should be designed to have comparison groups from the same study population. Study designs with a long duration of follow-up for both exposed and unexposed groups, and sufficient sample size for relatively uncommon outcomes, are required to explore the association between PPH and long term health outcomes, including for example CVD.

Study designs could be improved by paying more attention to the tools used in outcome assessment. The gold standard tools (e.g., the Clinician Administered PTSD Scale for DSM-IV (CAPS-5) for PTSD diagnosis) or clinical diagnosis should be applied for outcome assessment, rather than self-reported non-standardised tools and recall of memories. Emphasis should be given to pre-defining and specifying the set of chronic diseases of interest, rather than using non-specific symptoms.

Furthermore, previous studies have not typically considered the frequency and cumulative impact of PPH throughout women's obstetric history. This is particularly important in multiparous women where they may have more than one primary PPH with the potential for more severe impact. There is room for further progress in determining how both the frequency and severity of PPH may modify the association between PPH and longer-term health outcomes.

As evidenced by qualitative studies, differences in the quality of health care (e.g., frequency of follow up, access to counselling and psychologist) should be also considered in any future prospective cohort studies in this area. Furthermore, the presence of other major obstetric complications such as pre-eclampsia, gestational diabetes, and women's pre-existing health status should also be considered when designing future studies.

In spite of increasing trends in PPH, women in HICs are less likely to experience adverse fatal outcomes due to better management and early identification of severe PPH compared with previous years. (27, 35) Globally, the research focus on other near-miss complications has shifted from maternal mortality to surveillance of the burden of severe maternal morbidity, including improvement in the quality of follow-up care. (3, 126) The same principle should be applied to future research on PPH to explore whether the trajectory of PPH and its acute morbidities is associated with subsequent risk of developing chronic diseases.

From the research to date it has been possible to demonstrate that PPH is associated with severe acute maternal morbidities, (48) including a higher incidence of ARF and acute heart failure following severe primary PPH. (42, 113, 127) However, the existence of potential casual pathways from these acute outcomes to chronic diseases, including severity and

potential effect modifiers and confounders for these pathways remains unanswered. As discussed above, further work is required to investigate the potential implications of PPH on the subsequent risks of developing CVD, and chronic renal diseases.

More research to investigate potential longer-term mental illness following PPH would also be of value. Evidence from this review is suggestive of persistent symptoms of PTSD after childbirth affected by PPH, and it remains unclear whether these symptoms are directly associated with the occurrence of PPH. Cohort studies should be carried out to assess mental health outcomes not only for women who have experienced PPH, but also among women who have not experienced PPH, with adjustment for potential confounders.

3.6 Conclusions

This mixed-methods systematic review about longer-term physical and psychological consequences among women who had a PPH in HICs showed that there is limited research in this area, but that women can have longer-term health problems associated with PPH beyond one year after childbirth. The extent of the impact of these health outcomes on women is poorly researched, and the direction and size of these outcomes may be influenced by the severity of PPH, the presence of other obstetric complications and the quality of care received. The relative lack of evidence focusing on longer-term consequences of primary PPH emphasises the need for further research in this area. Two particular potential outcomes of interest were CVD and longer-term mental illness.

Chapter 4. Primary PPH and cardiovascular disease (CVD): A Scottish population-based record-linked cohort study

4.1 Introduction

The potential association between PPH and subsequent risk of developing CVD remains unclear. Although death from extreme bleeding or hypovolaemic shock can be averted because of life-saving measures, this extreme blood loss from PPH may result in major haemodynamic instability leading to haemorrhagic shock or end-organ damage. (128, 129) Thus, there is the potential that PPH at childbirth might impair cardiac function which may lead to women being at higher risk of developing CVD, particularly ischaemic heart disease (IHD), in later life compared with women who have not experienced PPH.

The potential association between PPH and the establishment of CVD is relatively under-researched compared with the association between other obstetric complications, including preeclampsia, pre-term birth and maternal anaemia, and CVD. (115-117, 130) The systematic review's findings provided some evidence that PPH requiring blood transfusion may be associated with a higher risk of CVD, and given the high health burden relating to CVD in Scotland, the impact of PPH on CVD is worthy of further research. Therefore, a population-based record-linked cohort study was conducted to investigate the association between PPH and CVD in a Scottish population.

4.2 Aim and objectives

The primary aim of this study was to investigate the association between primary PPH and the development of CVD in the longer term. The specific research objectives were:

1) To estimate the incidence of CVD among women who had at least one PPH, including severe PPH, compared with women who never had a PPH.
2) To estimate the relative risk of CVD in women who had at least one PPH including severe PPH, compared with women who have never had a PPH.
3) To investigate whether any association between PPH and CVD is modified by mode of birth or HDP.

4.3 Methods

4.4 Study design

This study was a population-based retrospective cohort study using data from health record linkage.

4.4.1 Data sources

Data from the Aberdeen Maternity and Neonatal Databank (AMND) (131) were used to identify women who had (and did not have) a PPH and for data about maternal socio-demographic and clinical characteristics, labour and birth-related information and neonatal characteristics.

Data from AMND were linked to the following Scottish routine data sources for the Grampian region (including the Northern Isles): the Scottish Morbidity Record (SMR) 01, SMR04,

Prescribing Information System (PIS), National Records of Scotland's statistics of deaths (NRS deaths), and Trakcare (NHS Scotland's patient management system), for information about outcomes (Table 4.1). Data linkage was processed at the Grampian Data Safe Haven (DaSH) in Scotland by DaSH staff with honorary NHS contracts. Deterministic record linkage (132) was carried out using the Community Health Index (CHI) number , which uniquely identifies a patient within the NHS in Scotland, to generate the linked dataset. The data were pseudo-anonymised and transferred to the safe haven for the author to access. All analyses were conducted within the safe haven.

Table 4.1 Data sources

Data source	Description	Data availability[a]
Aberdeen Maternal and Neonatal Databank (AMND) (131)	AMND includes socio-demographic, pregnancy, labour-related, birth and neonatal data for all pregnancy events occurring in the Grampian Region from 1949 to the present day. Aberdeen Maternity Hospital is the only hospital providing tertiary level maternity care for the pregnant women in Aberdeen city and it also serves the wider Grampian region including the Northern Isles of Shetland and Orkney. The AMND coverage varies, ranging from 99% of all births in Aberdeen to 97% of births across the entire Grampian region. The validity of data is checked regularly by AMND staff conducting regular reviews of case notes and the completeness of the data entry is checked annually against NHS returns.	1986-2016
The Scottish Morbidity Record General/Acute Inpatient and Day Case Dataset (SMR01)[b] (133)	SMR01 contains sociodemographic and clinical management data about hospital inpatient and day case discharges from acute specialties from hospitals in Scotland. Details of the episode and management during the hospital stay are collected, including admission type, the patients' condition, and discharge information. These patient-level data have been collected continuously since 1960. The data are subjected to data quality checks and validation and are estimated to be 99% complete for the Grampian region.	1996-2018
The Scottish Morbidity Record Mental Health Inpatient and Day Case Dataset (SMR04)[b] (134)	SMR04 contains individual level data about patient characteristics, mental health diagnosis and length of stay, and previous psychiatric care for patients admitted to psychiatric hospitals at the time of admission and discharge. These data have been collected since the 1960s and are routinely available from 1997. These data are also estimated to be 99% complete in the Grampian region.	1996-2018
National Records of Scotland's statistics of deaths[b] (NRS deaths) (135)	National Records of Scotland's (NRS's) statistics of deaths includes all deaths occurring in Scotland, including the cause of death as recorded on death certificates, since 1974.	1986-2018
The Prescribing Information System (PIS)[b] (136)	PIS records all the medicines prescribed and dispensed in the community in Scotland and their related costs. These data have been collected since 1993 and CHI data for linkage has been recorded since April 2009.	2009-2018
Trakcare	Trakcare is part of NHS Scotland's Patient Management System. It was used with the CHI number to identify women who were lost to follow up (i.e. moved out of the Grampian region to other parts of Scotland) during the study period.	1986-2018

[a]Data availability at the time the data for this study were extracted.
[b]Records from NHS Grampian, including the Northern Isles, were included in the data linkage.

4.4.2 Setting

Aberdeen city is located in the north-east of Scotland and is Scotland's third most populated city, with an estimated population of 2.27 million in 2018. (137) Aberdeen Maternity Hospital is part of NHS Grampian and serves the area of Grampian and the islands of Shetland and Orkney. (131) UK citizens and residents have access to maternal healthcare from NHS Scotland's publicly funded universal healthcare system, including free treatment in public hospitals, outpatient services and subsidised access to prescription medicines.

4.4.3 Identification of eligible records

This study used pseudo-anonymised retrospective birth records from a cohort of women who gave birth after 24 or more completed weeks of gestation in Aberdeen Maternity Hospital, Scotland between 1st Jan 1986 and 31st Dec 2016. The following inclusion and exclusion criteria were applied to identify the eligible cohort of women.

4.4.3.1 Inclusion criteria

- Women who gave birth after 24 weeks of gestation between 1st January 1986 and 31st December 2016.
- Women for whom the first completed birth was recorded in AMND (i.e. parity at the first recorded antenatal visit in AMND was zero) and all of their subsequent births occurred in the Grampian region during the study period. The purpose was to minimise misclassification of exposure to PPH by excluding women who may have had one of her births elsewhere. Births occurring after the end of the study period (i.e. 31st Dec 2016) were not taken into account as no relevant data were available.
- Singletons and multiple births.

- Permanent registered patients with NHS Scotland (Patient category- NHS) to minimise loss to follow up of visitors.

4.4.3.2 Exclusion criteria

- Women whose first birth of more than 24 weeks of gestation was not recorded in AMND or was before 1st Jan 1986 (i.e. parity at the first recorded antenatal visit in AMND after 1st January 1986 was one or more).
- Women whose parity information was conflicting (for example, where parity was recorded as the same number for two different birth records of the same woman with >24 weeks of gestation).
- All birth records of women who had at least one birth outside of the Grampian region (i.e, where parity recorded for two different birth records of the same woman with >24 weeks of gestation was not consecutive).
- Birth records of women who had a CVD outcome (prescription or hospitalisation) occurring before their first birth or before their first PPH.
- Birth records occurring after the CVD outcome event.

4.4.4 Exposures of interest

The primary exposure of interest was primary PPH which was defined as blood loss of 500ml or more within 24 hours of childbirth. For births in which the blood loss volume was less than 500ml, but a procedure typically used for the management of PPH (Bakri ballooning, arterial embolisation, and emergency peripartum hysterectomy) was also recorded, a PPH was considered to have occurred. Other operative management, including data about compression sutures (Blynch sutures), were not available from AMND. Blood transfusion was not included

in the definition because the indications for blood transfusion can be non-specific, including other causes of anaemia which are not relevant to PPH. (138) Women who had a primary PPH in any of their birth records in AMND during the study period were the 'exposed' group, to be compared with women who did not have a PPH in any birth records, the 'unexposed' group.

The WHO definition of PPH as a blood loss of 500ml or more from the genital tract within 24 hours after birth was used. (24) Although there is some variation in the definition of PPH according to the mode of delivery, the UK international PPH collaborative group recommended the use of a unified definition of PPH regardless of the mode of birth since there is no difference in the physiological impact of blood loss. (3) This is also supported by recently published clinical opinion on the definition and diagnosis of PPH. (5)

The secondary exposure in this study was severe primary PPH. A combination of blood loss volume and intervention/treatment for PPH was used to define severe PPH because of the different types of definition and inaccuracy of estimated blood loss especially at higher amount of blood loss. (7) Severe PPH was defined as blood loss of 1500ml or more from the genital tract and/or Bakri ballooning and/or arterial embolisation and/or emergency peripartum hysterectomy. For analyses relating to severe PPH, women who had a severe PPH in any of their birth records in AMND during the study period were the 'exposed' group, compared with women who did not have a PPH in any birth records, the 'unexposed' group.

4.4.5 Outcomes and measurements

4.4.5.1 Rationale for a composite CVD outcome

The primary outcome for this study was a composite CVD outcome identified up to 32 years after childbirth. A composite outcome was used to capture a wide range of cardiovascular

diseases based on biological plausibility following a major blood loss. The definition of the composite outcome was pre-defined in the protocol to account for the relatively low prevalence of uncommon conditions such as pulmonary embolism and heart failure in this population and to exclude selected conditions, including arrhythmias, for which an association with blood loss was considered unlikely.

4.4.5.2 Operationalising the definition of CVD composite outcome

After defining the composite CVD outcome, individuals with outcome events were identified from three different data sources to assess CVD-related hospitalisation, prescription or death. Using prescription data meant that it was possible to take into account women who did not require hospitalisation from such diseases. Diagnostic codes for CVD were first identified based on the pre-defined CVD conditions, followed by a range of BNF sub-section codes for the selected CVDs. This composite CVD outcome was defined as the time to first occurrence of one of the following after the first birth:

- At least three prescriptions within any 365-day period of selected medications commonly used to treat CVD. This definition was used to identify regular medication for CVD and to exclude the prescription of such medication for other indications including, for example, a one-off prescription of a diuretic.
- Any CVD-related hospitalisation for selected CVDs, recorded as the main condition of diagnosis or in any other diagnostic fields.
- Death in which the main or secondary cause was CVD.

Table 4.2 shows how these outcome events were operationalised within each of the data sources used.

Table 4.2. Summary of the composite CVD outcome with operationalised definitions and data sources

CVD outcome event	Data Source	Definition
First prescribed date of selected CVD medications followed by at least two or more prescriptions of CVD medication within any 365-day period following the first PPH (exposed group) or following the first birth (unexposed group)	PIS	CVD medications in the following BNF sub-sections: 2.1 Positive inotropic drugs; 2.2 Diuretics, used to treat heart failure and/or hypertension; 2.4 Beta-receptor blocking drugs, mainly used to treat hypertension, ischaemic heart disease and/or heart failure; 2.5 Hypertension and heart failure, used to treat hypertension or heart failure; 2.6 Nitrates, calcium channel blockers, and other anti-anginal drugs, mainly used for ischaemic heart disease; 2.8 Anti-coagulants, mainly used for thrombosis; 2.9 Anti-platelets, used for prevention of clotting for a range of CVD; 2.10 Stable angina, acute coronary syndrome and fibrinolytics, mainly used for ischaemic heart diseases.
First date of CVD-related hospitalisation following the first PPH (exposed group) or following the first birth (unexposed group)	SMR01	Hospital discharge with any of the following ICD-10 diagnostic codes recorded as main condition of diagnosis or in any other diagnostic field: I20-I25 (Ischaemic heart diseases), I10-I13 (Hypertensive diseases), I50 (Heart failure), I26-I27 (Pulmonary hypertension and pulmonary embolism) and/or any of the following OPCS4 intervention codes recorded in any operative field: K40-44, K49.2, K50, K54, K75 for Coronary Artery Bypass Graft, Percutaneous Coronary Intervention and/or coronary angioplasty with stent insertion, for ischaemic heart disease.
Date of death from underlying CVD	NRS deaths	Death with any of the following ICD-10 codes recorded as the main or secondary cause: I20-I25 (ischemic heart diseases), I10-I13 (Hypertensive diseases), I50 (Heart failure), I26-27 (Pulmonary hypertension and pulmonary embolism).
Note: All the outcome data were identified from the PIS, SMR01, SMR04 and NRS deaths records from the Grampian region including Northern Isles, Scotland.		

4.4.6 Potential confounders and effect modifiers

A conceptual hierarchical framework approach, described in Table 4.3, was taken to identify potential confounding variables of the association between PPH and the CVD outcome using a causal diagram (Appendix 8). (139)

Table 4.3 Conceptual hierarchical framework

Sociodemographic characteristics, congenital diseases/genetic factors
Co-morbidity and past medical history
Obstetric characteristics
Obstetric complications during and after birth, baby's characteristics
Longer-term cardiovascular health (e.g. ischaemic heart diseases, hypertension, etc.)

Maternal sociodemographic and clinical characteristics such as maternal age at birth, year of birth, ethnicity, residence status, socioeconomic status, blood group, and BMI at first antenatal visit were explored in the analysis as potential confounders.

Maternal past medical history before childbirth were also considered as potential confounders. In order to identify and request access to a comprehensive range of data about potential co-variates from AMND, an inclusive approach was taken to identify the medical and obstetric conditions that are potentially associated with both PPH and CVD, with no strict criteria for p-values or size effects. The medical conditions that were found from the literature to be relevant as potential confounders were anaemia and bleeding disorders, diabetes, chronic renal disease, hepatitis, people living with HIV, chronic autoimmune disease, psychiatric and mental health disorder, congenital heart disease, CVD, uterine fibroids, gynaecological cancers. These past medical conditions were self-reported and recorded in AMND.

Additionally, obstetric characteristics (multiple gestation, parity and mode of birth) and other obstetric complications (gestational diabetes, antepartum haemorrhage, antenatal anaemia,

HDP, preterm premature rupture of membranes, premature rupture of membrane, puerperium infections) in any eligible birth, and baby's characteristics (gestational age at birth, birthweight of the baby, admission to neonatal unit, and APGAR score) were considered as potential confounders.

4.4.7 Duration of follow up

The follow up for each woman began on the date of her first birth recorded in the AMND during the study period, irrespective of whether she had a PPH in her first birth. This was pre-specified in the protocol and was based on two factors: (1) the lack of an 'index birth' in the unexposed group if follow-up was considered to begin at the date of the first PPH in the exposed group, and (2) the assumption that women were at some risk of CVD even before they entered the cohort and therefore follow-up time should begin at the first time they were under observation (i.e. the date of their first birth). The alternate approach of setting first PPH as the start of follow-up (T_0) in the exposed group and randomly assigning exposure dates (first proxy PPH date) to the unexposed group was also considered. However, this approach was not selected as it was considered that this might cause bias resulting from incomparable follow-up duration between the two groups not being comparable.

Data linkage for outcomes was completed for the period until 31st December 2018. The duration of follow-up therefore ranged from a minimum of two years for a woman whose first birth was in 2016 to a maximum of 32 years for a woman whose first birth was in 1986 **(**Figure 4.1**)**.

The follow up period for all women ended on:

- 31st December 2018 (the end date of the period covered by the data linkage),

  or

- The date the woman experienced the outcome event (censored),

  or

- The date the woman became lost to follow up (e.g. date of migration outside the Grampian region, as recorded in Trakcare) (censored),

  or

- The date of death (recorded in NRS deaths) (censored),

whichever occurred first **(**Figure 4.1**)**.

Figure 4.2 illustrates total follow-up duration for a woman with several birth records.

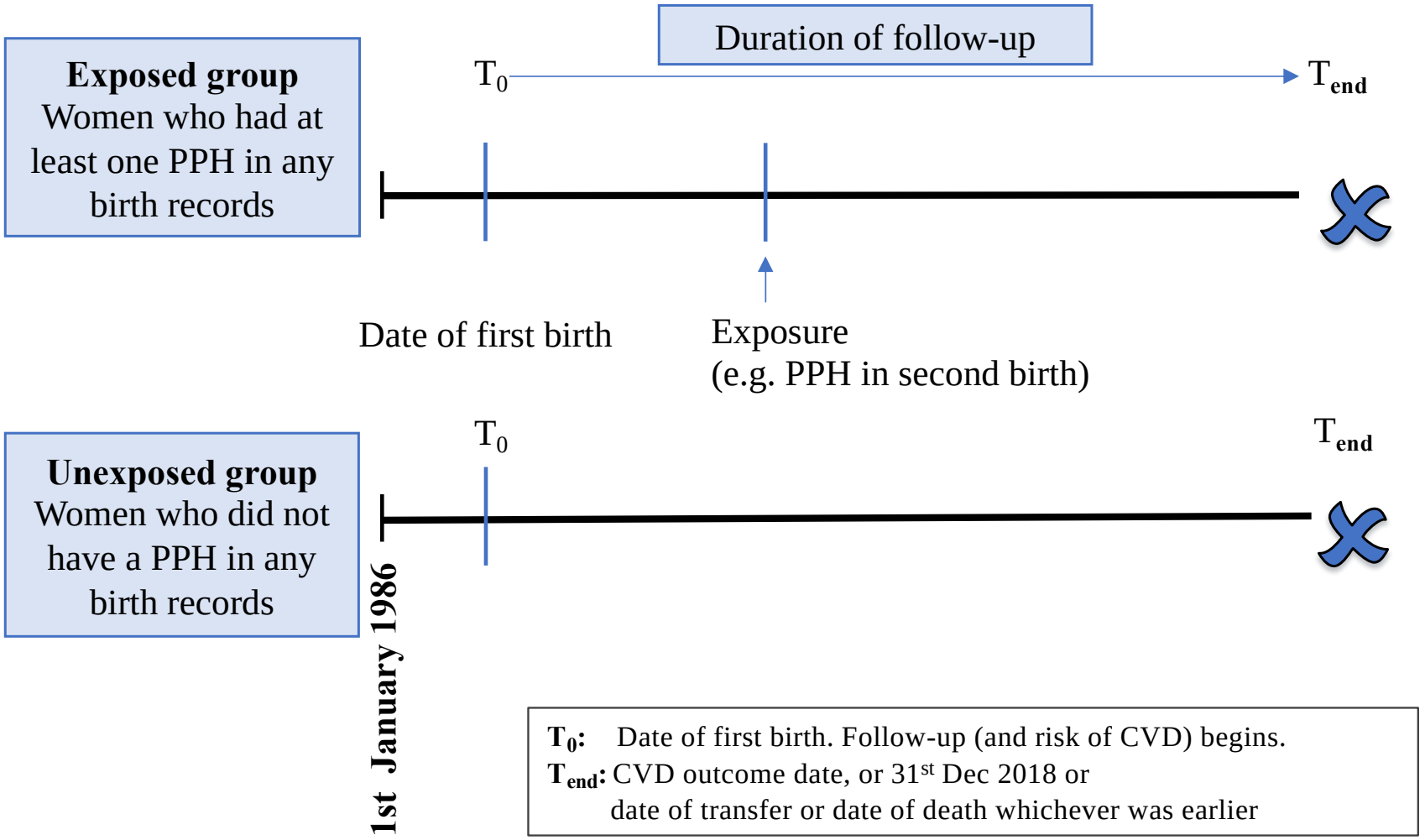


Figure 4.1 Follow up duration for women who had a PPH (exposed group) and women who did not have a PPH (unexposed group)

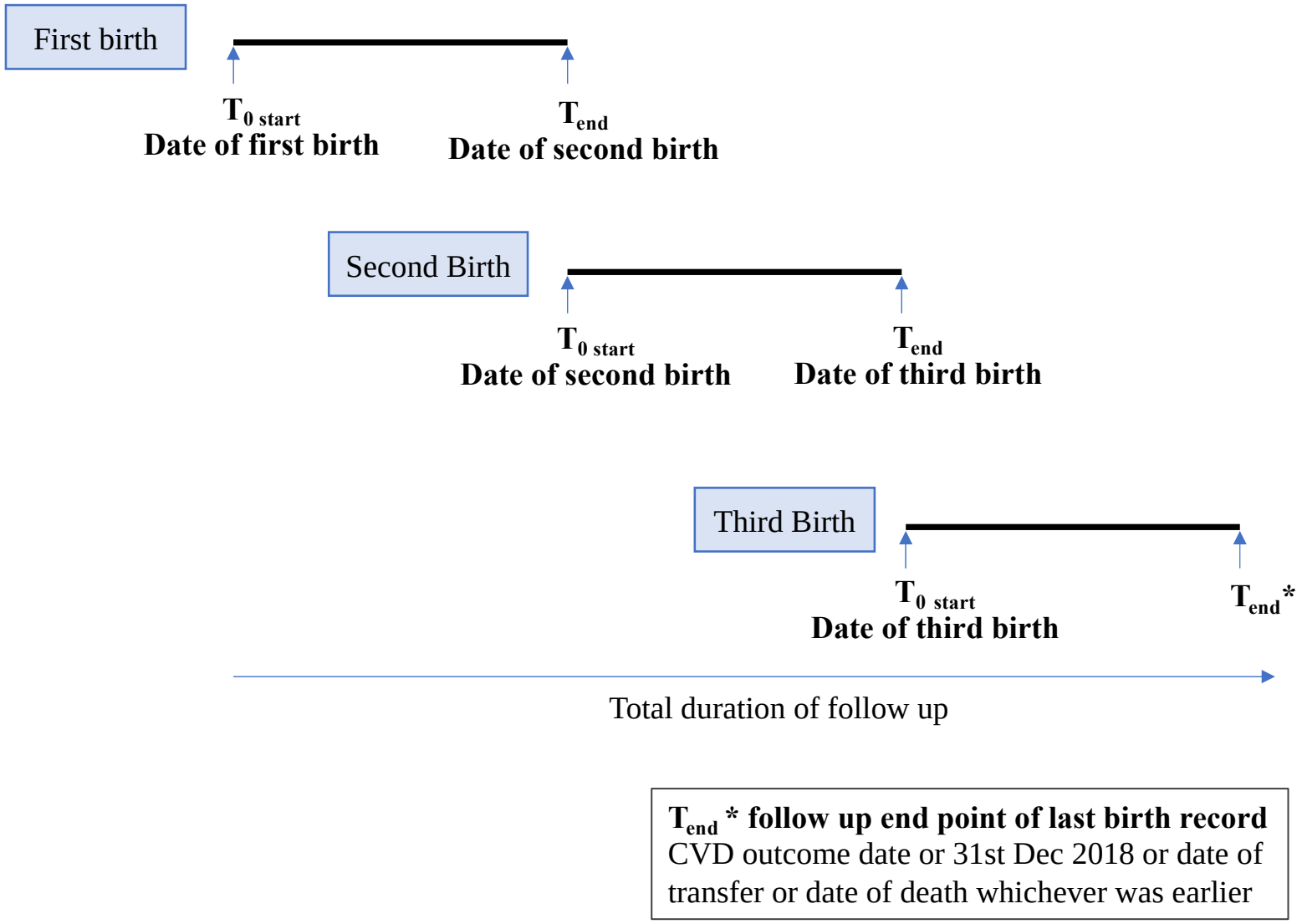


Figure 4.2 Example of follow-up time contribution for a woman who had three births

4.4.8 Ethical considerations

Approval for access to data from AMND for the analyses reported in this chapter and in Chapter 4 was applied in August 2020, and granted by the AMND Steering Committee in October 2020. Permissions from NHS Grampian R&D for the data linkage and access were granted in January 2021 (Project No. 2021OG001E, REC Ref: 21/NRS/0001**)** and a data processing agreement was signed between the University of Oxford as sponsor and NHS Grampian R&D. As a study involving secondary analysis of administrative data limited to previously collected non-identifiable information, research ethics approval was not required.

Extraction of eligible birth records from AMND was conducted by the AMND research coordinator. Initial linkage was processed at the Grampian Data Safe Haven (DaSH) by DaSH staff with honorary NHS contracts according to the DaSH project linkage plan customised for this project (Appendix 9). The data were pseudo-anonymised, released in eight different datafiles in July 2021, and accessible via a secure Virtual Private Network (VPN). All analyses were carried out on the DaSH platform, and raw data were never downloaded. Analysis generated tables and figures which were then assessed for risk of disclosure of patient identifiable information by a designated DaSH research coordinator before export from the DaSH.

4.4.9 Linking and merging data from different linked datasets

The AMND dataset formed the main dataset for this study, and the outcome platform files were merged by the author from five different data sources to this main dataset following the steps and specifications detailed below (Box 4.1, Figure 4.3**).**

Box 4.1 Data linkage and merging steps

Creating a composite cardiovascular disease (CVD) outcome platform file

(Steps 1 to 9)

Step 1: In the SMR01 data file (hospital discharge records), all records mentioning the relevant CVD outcome ICD-10 codes (Table 4.2) were tagged. A CVD hospitalisation variable 'cvsadm' was generated, and set to 1 for a tagged record and 0 for others. An indicator variable 'type' was created and set to 1 to indicate that these were hospitalisation records from SMR01.

Step 2: A sequence variable was created, numbering tagged records within each unique ID in ascending order of admission date. Only CVD-related hospitalisation records were retained and the file was saved as 'SMR01data2'. The admission date variable 'admdate' was renamed as date. Four variables: 'study ID', 'date', 'sequence', and 'type' were then kept to create the cut-down file 'SMR01cutdown'.

Step 3: In the PIS data file, all records mentioning the relevant CVD medication codes (Table 4.2) were tagged. A CVD prescription variable 'cvspresc' was generated, and set to 1 for a tagged record, and 0 for others.

For outcome ascertainment for CVD prescriptions, a 'year' variable was generated using the date of prescription. The time interval between subsequent prescriptions was calculated. A 'cvspresc3' variable was generated and set to 1 for women who had three or more eligible prescriptions within any 365-day period and 0 for women with less than three prescriptions.

An indicator variable ‘type’ was created and set to 2 to indicate that these were prescription records from PIS.

Step 4: A sequence variable was created, numbering tagged prescription records (i.e. those with three or more prescriptions in 365 days) within each unique ID. Only CVD-related prescription records were retained, the file was saved as ‘PISdata2’. The prescription date variable ‘presdate’ was renamed as ‘date’. Four variables ‘study ID’, ‘date’, ‘sequence’, and ‘type’ were then retained to create the cut-down file ‘PIScutdown’.

Step 5: In the NRS death data file, all death records mentioning CVD-related ICD codes (Table 4.2) as a primary or secondary cause of death were tagged. A CVD-related death variable ‘cvsdeaths’ was generated and set to 1 for a tagged record and 0 for others. An indicator variable ‘type’ was created and set to 3 to indicate that these were death records.

Step 6: Tagged records were retained, and the file was saved as ‘NRSdata2’. The date of death variable ‘DoD’ was renamed as date. Four variables ‘study ID’, ‘date’, ‘sequence’, and ‘type’ were then kept to create the cut-down file ‘NRSdthcutdown’.

Step 7: Files ‘SMR01cutdown’, ‘PIScutdown’ and ‘NRSdthcutdown’ were appended to create an antepenultimate CVD outcome file ’cvsantepenult’. A file sequence variable ‘fileseq’ was generated to number the sequence of all the records, and a morbidity sequence variable ‘morbseq’ was created to number the sequence of all the outcome records for each individual. For instance, if a woman had ten CVD outcome records, these were indexed from 1 to 10 sorted by their record date in ascending order.

Step 8: The first record of each outcome type (hospitalisation, prescription, death) was retained, new 'fileseq' and 'morbseq' variables were generated and a penultimate CVD outcome file 'cvspenult' was saved. This file contained the first record of hospitalisation, first record of prescription and death record if any against each individual ID. Therefore, any individual ID could have more than one outcome record in this file.

Step 9: For each individual ID the earliest outcome record was retained and a new 'fileseq' variable created. The file was saved as the ultimate CVD outcome file 'cvs_ultimate'. This contained the first record of either hospitalisation, prescription or death, whichever was the earliest. Therefore, in this file any individual ID could only have one outcome record.

Identifying the end date of follow up from vital statistics data file Trakcare

Step 10: In the vital statistics Trakcare data file 'vitalstats', variables containing the date of transfer 'DoT' and date of death 'DoD' were generated using information from the 'statusdate' variable which indicated the date of the event recorded in the 'status' variable. This file was saved as 'Vsdata2'.

Merging information from step 10 with the main birth record file and generating exit date

Step 11: The main birth records data file (AMND) was merged with 'Vsdata2' using a many-to-one match on 'study id'. A 'dead' variable was generated to indicate the records of women who had died, set to 1 if there was a date of death recorded, and 0 if there was no date of death recorded. An 'exit' variable was generated and set to date of death if the woman had died, the date of transfer if the woman had transferred out of the Grampian

region, and 31st December 2018 if there was no date of death or transfer recorded. This file was saved as 'Preg_VS'.

Merging the main birth record file with the CVD outcome platform file

Tagging CVD diagnosis and setting start and end date of follow up for each birth record

Step 12: The 'Preg_VS' file was merged with the CVD outcome platform file 'CVS_ultimate' using a many-to-one match on 'study id'. An indicator variable 'cvsdx' was generated for the CVD composite outcome and set to 1 if there was a record of CVD hospitalisation, prescription or death from the outcome platform file, and 0 if not. This linked file was saved as 'Preg_VS_CVS1'.

Birth records were reshaped from long form (one birth per row) into wide format (one woman per row) by linking observations using a pseudo ID and the parity sequence number. A 'start' variable was generated and set to the date of first birth. An 'end' variable was generated and set to the date of the next birth or the date of the outcome event if a CVD outcome event occurred between births, or the date of end of follow-up (i.e. end of data linkage) for the final birth record. This was to ensure that all birth records had a start and end date for follow up period and all the birth records of each woman contributed observation time to the analysis (Figure 4.2) The data were then reshaped into long format (one row per birth) and saved as 'follow-uptime'. The 'follow-uptime' file was merged with the linked data file 'Preg_VS_CVS1' and this file, including the start and end date of follow up for each birth record, was saved as 'Preg_VS_CVS2'.

Domain restriction and outcome ascertainment

Step 13: An indicator variable was generated to flag if the CVD event occurred after the date of first birth or the first PPH. All birth records of women who had a CVD event before their first birth or before their first PPH were excluded, as were the birth records after occurrence of the CVD outcome event. This file was saved as 'Preg_VS_CVS3'.

Generating key exposure variables

Step 14. A binary variable was generated to identify women who had at least one PPH recorded. Another binary variable was generated to identify women who had at least one severe PPH recorded. This final linked file was saved as 'PPH_VS_CVSfinal'.

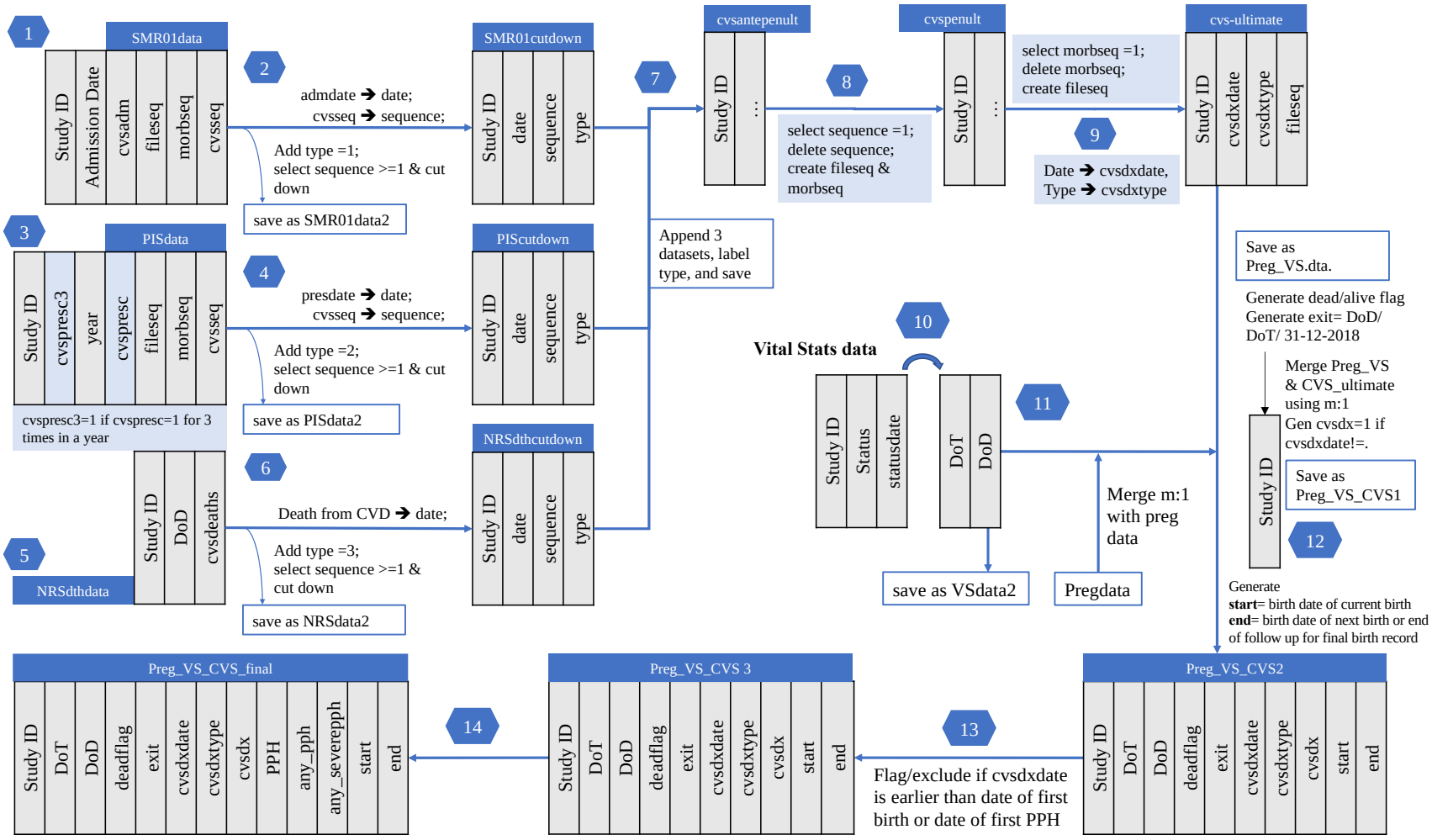


Figure 4.3 Data linkage flow diagram demonstrating the steps in generating the final linked dataset

4.4.9.1 Description of final linked dataset for CVD outcomes and derived variables

Table 4.4 summarises the key variables used in data analysis and, where applicable, how derived variables were generated.

Table 4.4 Data sources, codes, and database fields used to generate key variables

Variable	Data Source	Type	Database field/codes	Categories or units of measurements
Key exposure variables				
Any PPH	AMND	Categorical	Derived variable, generated using whether or not a woman had at least one record of PPH, including severe PPH, in any of her eligible birth records.	Yes; No
Any Severe PPH	AMND	Categorical	Derived variable, generated using whether or not a woman had at least one record of severe PPH in any of her eligible birth records.	Yes; No
Key outcome variables				
CVD outcome	PIS, SMR 01, NRS deaths	Categorical	First record of: at least three prescriptions within any 365-day period of selected CVD medications or CVD-related hospitalisation or death with CVD as underlying cause.	Yes; No
CVD outcome date	PIS, SMR 01, NRS deaths	Date	Date of CVD outcome	Date
Socio-demographic characteristics				
Year of birth[a]	AMND	Categorical	Derived from 'year of delivery' variable.	1986-1990; 1991-1995; 1996-2000; 2001-2005; 2006-2010; 2011-2016
Maternal age at childbirth[a]	AMND	Categorical	Derived from 'age at delivery variable.	<25; 25-29;30-34, ≥35
Ethnicity[a]	AMND	Categorical	Derived from 'ethnicity' variable. (Appendix 10)	Black; Asian; White; Other
Parity[b]	AMND	Categorical	'parity' variable.	1; 2; >3
SIMD[a]	AMND	Categorical	Derived quintiles from 'simd' deciles.	1; 2; 3; 4; 5

Variable	Data Source	Type	Database field/codes	Categories or units of measurements
BMI at first antenatal visit[a]	AMND	Categorical	Derived from maternal weight and height variables.	<18.5; 18.5-24; 25-29; ≥30
Maternal medical characteristics				
Anaemia and coagulation disorders[a]	AMND	Categorical	Derived using where past medical history codes indicated anaemia and coagulation disorders, which matched ICD-10 descriptions for D50-69.	Yes; No
Diabetes[a]	AMND	Categorical	Derived using where past medical history codes matched ICD-10 descriptions for O24, E08-E13	Yes; No
Psychiatric and mental health disorder[a]	AMND	Categorical	Derived using where past medical history codes matched ICD-10 descriptions for F01-F99	Yes; No
Cardiovascular disease[a]	AMND	Categorical	Derived using where past medical history codes matched ICD-10 descriptions for I00-I99	Yes; No
Congenital heart disease[a]	AMND	Categorical	Derived using where past medical history codes matched ICD-10 descriptions for Q20-Q26	Yes; No
Smoking[a]	AMND	Categorical	'smoking' variable	Non-smoker; Ex-smoker; Current smoker
Birth characteristics				
Mode of birth[a]	AMND	Categorical	Derived from 'mode of delivery of baby 1' variable. Coded as 'spontaneous vaginal' if mode of delivery was recorded as 'spontaneous vaginal delivery'; 'instrumental' if mode of delivery was recorded as 'Forceps', 'Kiellands forceps', 'Vacuum extraction', 'assisted breech', or	Spontaneous vaginal; Instrumental; Caesarean

Variable	Data Source	Type	Database field/codes	Categories or units of measurements
			'breech extraction'; 'caesarean section' if mode of delivery was recorded as 'caesarean section'.	
Multiple pregnancies[a]	AMND	Categorical	Derived from 'singleton' data variable.	Yes; No
Obstetric complications				
Gestational diabetes[a]	AMND	Categorical	'Gestation Diabetes mellitus during pregnancy' variable	Yes; No
HDP[a]	AMND	Categorical	Derived from 'hypertensive disorders' variable. Recoded as No for 'None', recoded as yes for 'gestational hypertension', or 'pre-eclampsia', or 'eclampsia', or 'other hypertension'	Yes; No
Any HDP	AMND	Categorical	Derived variable, generated using whether or not a woman has at least one record of HDP in any of her eligible birth records.	Yes; No
Antenatal anaemia[a]	AMND	Categorical	'Antenatal anaemia' variable	Yes; No
Pre labour rupture of membranes (PROM) or Preterm pre-labour rupture of membranes (PPROM)[a]	AMND	Categorical	Derived variable, generated using 'PROM' and 'PPROM' variables. Coded as 'yes' if either PROM or PPROM variable were coded as 'yes'.	Yes; No
Baby's characteristics				
Gestational age at birth (weeks)[a]	AMND	Categorical	Derived from 'gestation at delivery' variable	For descriptive analysis: <28; 28-31; 32-36; 37-38; 39-40; ≥41 For survival analysis: <37; 37-38; 39-40; ≥41

Variable	Data Source	Type	Database field/codes	Categories or units of measurements
Weight of the baby (grams)[a]	AMND	Categorical	Derived from 'birthweight' variable	<2500; 2500-3499; 3500-3999; >4000
Variables for time to event analysis				
Start	AMND	Date	'Date of delivery' variable	Date
End	AMND, SMR 01, PIS, Trak care, NRS deaths	Date	Derived variable, generated using date of next birth record, or 'CVD outcome date' if an outcome event occurs between two birth records, or end of follow-up if it is the final birth record during follow up period. *Note: Follow-up ended on 31 Dec 2018 or date of death, date of transfer or date of first outcome event whichever is earlier.*	Date

[a] For these variables, information from each birth was used when adjusting for confounding.
[b]Four missing values of parity were manually added by using parity information from previous birth and next birth.

4.4.10 Statistical analysis

The proposed approach to statistical analysis for the study was outlined in the clinical research protocol prepared for the purposes of obtaining research sponsorship from the University of Oxford, and data access approvals, for this study and the study described in Chapter 5 (IRAS 290656). This section of the protocol is reproduced in Appendix 11. Beyond this, there was no formal statistical analysis plan for this study.

4.4.10.1 Descriptive analysis

Maternal socio-demographic and clinical characteristics were summarised for women, and separately for births, by PPH status. Means with standard deviations were presented for continuous variables, and counts and proportions for categorical variables. The sequence of CVD outcome events was also explored and summarised in a flow diagram. This included: the number of each type (prescription, hospitalisation or death) of 'first occurrence' (i.e. primary outcome) of a CVD outcome event, followed by the number of 'second occurrence' CVD health events i.e. the number of women who had a CVD-related hospitalisation after having a CVD-related prescription, and the number of women with a CVD-related prescription after a CVD-related hospitalisation.

4.4.10.2 Univariable analysis

Univariable analysis was performed using Cox proportional hazard regression models to assess the association between PPH and CVD-free survival. (140, 141) This analysis was conducted at the level of the woman to take all births into account and to maximise the generalisability of the study.

Unadjusted incidence rates, the number of women with a CVD outcome event divided by follow-up time in person-years, were calculated separately for women with at least one record of PPH, women with at least one record of severe PPH and women with no record of PPH (unexposed group). Univariable Cox proportional regression was used to estimate hazard rate ratios (HRs) with 95% confidence intervals (Cis) for the CVD outcome in women who had a PPH, and in the sub-group of women who had a severe PPH, compared with women who did not have a PPH.

4.4.10.3 Investigating potential confounders

All the sociodemographic, clinical and birth-related characteristics described in section 4.4.6 were explored to assess their potential role as confounders in the association between PPH and the composite CVD outcome. A classical approach was taken to investigate whether the following three criteria are met for potential confounding variables. A variable was considered to be a potential confounder and was included in the model (i) if it was associated with PPH (exposure), (ii) if it increased the risk of CVD in the non-exposed, and (iii) if it was not an intermediate step in the causal pathway between PPH and CVD (for example, blood transfusion following PPH). (142) The first and second criteria were explored by fitting a logistic regression model between the potential confounder and PPH, and by fitting a Cox regression model between the potential confounder and the CVD outcome event. The conceptual framework diagram was applied for the third criterion to assess whether the variable was potentially on the causal pathway (Appendix 8).

Variables were included in the following multivariable models if they were considered likely to be confounders as described and they were not strongly correlated with other covariates in

the model. The potential confounding variables which were considered, and the variables included in the analysis are summarised in Table 4.5.

Table 4.5 Summary of potential confounding variables considered and then included in multivariable models

Characteristics	Potential confounding variables explored/considered in the analysis	Variables included in multivariable models[a]
Sociodemographic characteristics	• Ethnicity • Year of birth of baby • Residence status • Socioeconomic status (Social class, Deprivation category, Scottish index of multiple deprivation (SIMD)) • Blood group • Maternal age at birth • Body mass index (BMI) at first antenatal visit	• Ethnicity • Year of birth • SIMD • Maternal age at birth • BMI at first antenatal visit
Co-morbidity and past medical history	• Anaemia and bleeding disorders • Diabetes • Self-reported history of CVD • Congenital heart disease • Chronic renal disease • Hepatitis B and C • HIV • Chronic autoimmune disease • Psychiatric and mental disorder • History of alcohol and substance abuse/self-inflicted injury • Uterine fibroids • Gynaecological cancers • Smoking status	• Anaemia and bleeding disorders • Diabetes • Self-reported history of CVD • Congenital heart disease • Psychiatric and mental disorder • Smoking status
Obstetric characteristics	• Parity • Mode of birth • Multiple gestation	• Mode of birth
Obstetric complications	• Gestation diabetes • HDP • Antepartum haemorrhage • Antenatal Anaemia • Pre-labour rupture of membrane (PROM) or prolong pre-labour rupture of membrane (PPROM)	• Gestational diabetes • HDP • Antepartum haemorrhage • PROM or PPROM

Characteristics	Potential confounding variables explored/considered in the analysis	Variables included in multivariable models[a]
	• Postpartum complications including puerperium wounds and infections	
Baby's characteristics	• Gestational age at birth • APGAR score • Outcome of the baby • Weight of the baby • Admission to neonatal unit	• Gestational age at birth • Weight of the baby

[a]Variables were included in the multivariable models if they fully met all three criteria for the 'classical approach' to confounding and they were not strongly correlated with other covariates in the model. For these variables information from each birth was used when adjusting for confounding.

4.4.10.4 Multivariable Cox proportional regression models

Multivariable Cox proportional hazard regression models, estimating adjusted HRs, were fitted by sequentially adjusting for each category of potential confounder described in Table 4.5**.** The baseline model, and all subsequent models were adjusted for year of childbirth to account for potential confounding by unmeasured variables such as changes in management of labour, estimation of blood loss, etc. over time. Model 1 further adjusted for maternal age at birth, maternal ethnicity, BMI, and area deprivation. Model 2 was built on Model 1 by adding adjustment for past medical history (anaemia and bleeding disorders, diabetes, CVD, congenital heart disease, psychiatric and mental disorders) and smoking status. Finally, the fully adjusted model (model 3) was further adjusted for mode of birth, obstetric complications (gestational diabetes, HDP, antepartum haemorrhage, pre labour rupture of membrane (PROM) or prolonged pre-labour rupture of membrane (PPROM) and baby's characteristics (gestation age at birth and weight of the baby). For these variables information from each birth of an individual woman were used to adjust for confounding in the multivariable model.

4.4.10.5 Investigating the proportional hazards ratio assumption

The models described above assume that any association between the exposure, PPH/severe PPH, and the outcome, CVD, was constant over time (i.e. from 1986-2018), the 'proportional hazards assumption'. This assumption is violated (i) if the exposure variable in the model is a time varying covariate (TVC) or (ii) if the association between exposure and outcome changes over time. (143) In the analysis, the main exposure of interest was 'Any PPH', a binary variable indicating whether women had at least one record of PPH using all the birth records during the follow-up time to treat it as a time-independent covariate. This approach enabled the exposure variable 'Any PPH' not to be a TVC (assumption no. 1) by preventing women having different categories of PPH at different births if they had a PPH at one birth and did not have a PPH at another birth.

Log-log plots were used to assess whether the hazard ratio for the association between PPH/severe PPH and CVD was constant across follow-up time (assumption no. 2). A global proportional hazard test was also used to check the proportional hazards assumption for exposure variables and each confounder individually. Global test p-values <0.05 were interpreted as indicative of violation of the proportional hazards assumption, suggesting that the association between the exposure (PPH/severe PPH) and the CVD outcome, and/or the association between one or more confounding variables and the CVD outcome, were not constant over time.

4.4.10.6 Extended Cox regression models

Extended multivariable Cox regression analyses were conducted to address any identified interaction between the association between PPH/severe PPH and CVD, and time interval,

reporting adjusted hazard ratios for different follow-up time intervals. The total follow-up time (t) of each woman was split into four time periods after birth using the 'stsplit' command in Stata, splitting at three time points at one, five and 15 years after birth. After splitting time intervals, a covariate interaction term was then included between the exposure variables (i.e. any PPH, any severe PPH) and the time variable. The models were stratified by confounding variables which were found to be violating proportional hazard ratio assumptions. Adjusted HRs were calculated for different periods of follow-up time after birth: 'within 1 year', '2 to 5 years', '6-15 years' and 'more than 15 years' after birth. The 'proportional hazards assumption' was then tested again to ensure that it was satisfied within each follow-up period.

4.4.10.7 Investigating potential effect modification

Potential effect modification of the association between PPH/severe PPH and CVD was investigated for HDP, and mode of birth. HDP were explored due to the strong association with PPH found while exploring the variable as a potential confounder, and because of a well-established association with an increased risk of CVD. (144) Instrumental birth and caesarean section are important risk factors for primary PPH, and it was therefore explored whether having an instrumental or caesarean birth might be associated with a higher risk of CVD compared to women having a vaginal birth among women who had a PPH. (19) A new variable "Any HDP" was generated using whether or not a woman had at least one record of HDP in any of her eligible birth records. A new variable for mode of birth was also generated using whether or not a woman had at least one record of instrumental or caesarean birth in any of her eligible birth records. An interaction term was added between "Any PPH" and "Any HDP" variables in the final fully adjusted model (model3). Similarly, an interaction term was added between "Any PPH" and the newly generated mode of birth variable in the final model

(model 3). Likelihood ratio tests were used to assess the evidence of interaction in the final model.

4.4.10.8 Sensitivity analyses

Three sensitivity analyses were conducted using the fully adjusted model (model 3) for the association between PPH and the CVD composite outcome.

In the first sensitivity analysis, births to women with a self-reported history of CVD recorded in the 'past medical history' variable in AMND were excluded. Although women with the CVD outcome events (i.e., CVD prescriptions and hospitalisations) before first births were excluded from the analysis, self-reported CVD records were not excluded from the main analysis because AMND does not apply ICD-10 codes to record past medical conditions. Sensitivity analysis was conducted to see if any association between PPH and CVD was changed after removing births to women with self-reported CVD.

A second sensitivity analysis was performed by recoding missing values for PPH as having PPH. These values were originally coded as no PPH with the assumption that they were unlikely to be miscoded among women with PPH. The analysis was conducted for the fully adjusted model (model 3) to address any unintentional measurement errors of PPH by exploring if the association was changed after recoding.

A third sensitivity analysis was performed by restricting the outcome records to time to first CVD-related hospitalisation. The primary outcome was a composite CVD outcome which captured time to first occurrence of any CVD-related prescription, hospitalisation and death. As individuals were more likely to be prescribed with CVD medication before they experience hospitalisation from CVD, the main component of the CVD composite outcome was expected

to come from CVD- related prescriptions. Thus, a sensitivity analysis was conducted to explore if there was any change in the results for the more severe outcome, first occurrence of CVD-related hospitalisation. CVD-related death records were not included in this sensitivity analysis as the descriptive analysis had informed that there were only a very small number of deaths during the study period and it was considered beneficial in terms of ease of interpretation to investigate hospitalisations only rather than combined for both CVD hospitalisations and deaths.

4.4.11 Missing data

A 'missing' category was created for all other covariates with missing values to explore 'missingness'. The proportion and patterns of missingness for confounders were explored to determine the most suitable approach for handling missing data. Among variables with missing data, ethnicity, BMI at first antenatal visit, and mode of birth variables were missing in less than 3% of records, whereas smoking status and SIMD variables were missing in approximately 5%. Since the proportion of missing data was lower than 5% of the eligible births in this study and the missing variables were unlikely to be influenced by CVD events in the routine data, a complete case analysis was performed. (145)

Data were analysed using Stata software version 16. (146)

4.5 Results

4.5.1 Cohort characteristics

The linked dataset contained information about 125,022 birth records from 72,593 women who gave birth between 1986 and 2016, 124,795 of which were births after at least 24 weeks' gestation (Figure 4.4). After exclusions, the final cohort included data about 121,731 births to 70,904 women.

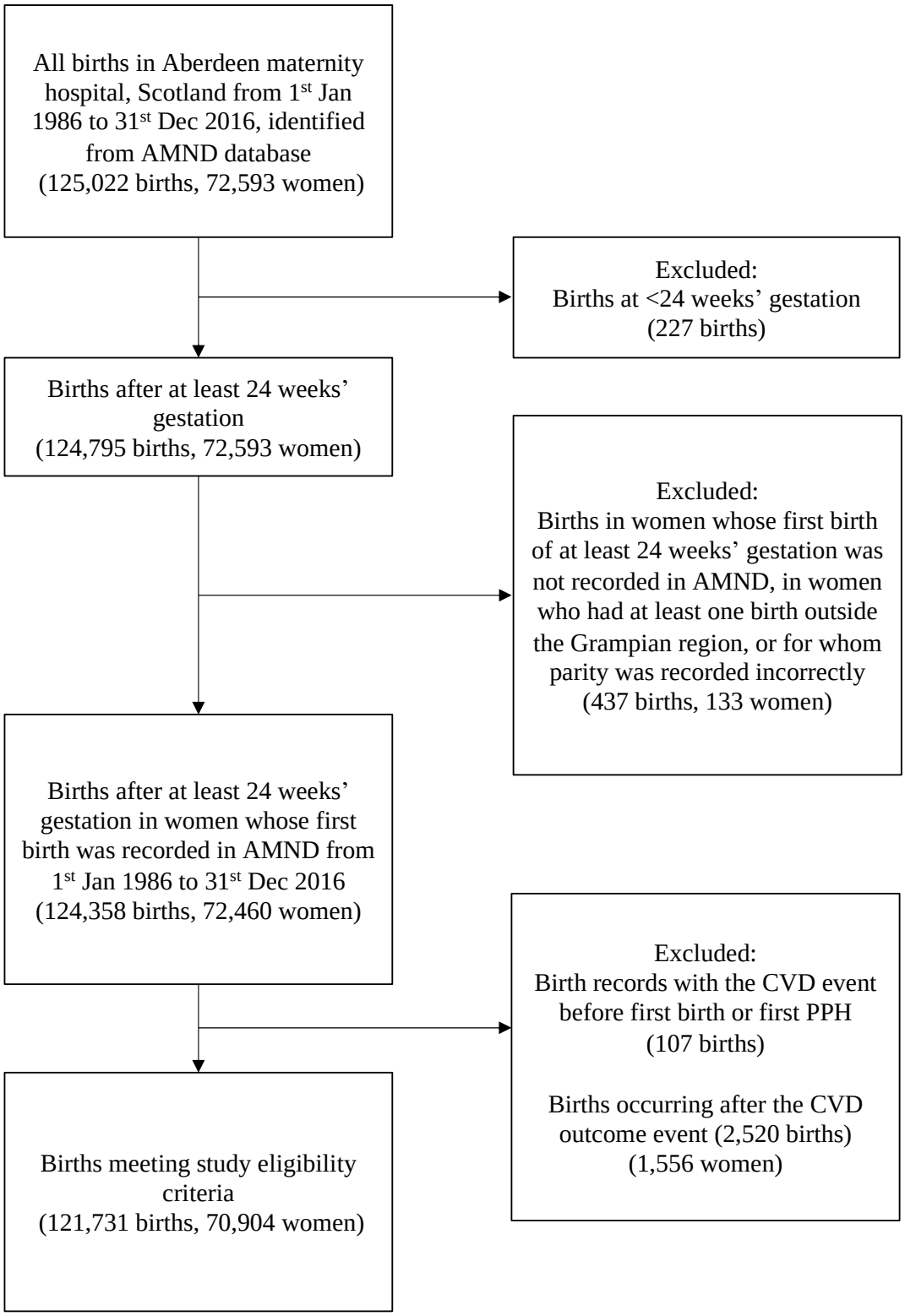


Figure 4.4 Cohort identification flow diagram

4.5.2 Characteristics of women

Of the eligible cohort of 70,904 women, 25,177 women (36%) had at least one primary PPH, including severe PPH, and 4,799 women (6%) had at least one severe PPH (Table 4.6). Among all eligible women, 45% of women (n=31,479) had one birth, 42% (29,893 women) had two births, and the remaining 13% had more than two births. On average, women in the cohort were aged 27 at their first birth, but women who had at least one PPH were on average older when they had their first birth compared with women who had never had a PPH.

Compared with women who had never had a PPH, women who had at least one PPH were more likely to be of Black, Asian or Other ethnic background and were more likely to have a higher BMI at their first antenatal visit. At their first birth, women who had at least one PPH were also more likely to have a past medical problem, including anaemia and coagulation disorders, diabetes, psychiatric and mental health problems, as well as CVD including congenital heart disease; they were more likely to be non-smokers; and were more likely to have a caesarean birth.

Among women who had at least one PPH, 20,416 (81%) had one PPH, 4,320 women (17%) had a PPH on two occasions and 441 women (2%) had a PPH at least three times.

Table 4.6 Maternal sociodemographic and clinical characteristics of women included in the study

Characteristics	Women without PPH[a] n= 45,727		Women with at least one PPH[b] n=25,177		Women with at least one severe PPH[c] n= 4,799		All women n=70,904	
	n	%	n	%	n	%	n	%
Year of first childbirth								
1986-1990	10,017	21.9	2,224	8.8	568	11.8	12,241	17.3
1991-1995	9,602	21.0	2,937	11.7	730	15.2	12,539	17.7
1996-2000	6,995	15.3	3,689	14.7	864	18.0	10,684	15.1
2001-2005	5,830	12.8	4,003	15.9	719	15.0	9,833	13.9
2006-2010	6,094	13.3	5,542	22.0	956	19.9	11,636	16.4
2011-2016	7,189	15.7	6,782	26.9	962	20.1	13,971	19.7
Age at first childbirth (mean,SD)	26.4	5.4	28.0	5.6	27.4	5.8	26.9	5.5
<25	17,316	37.9	6,893	27.4	1,530	31.9	24,209	34.1
25-29	15,321	33.5	8,152	32.4	1,501	31.3	23,473	33.1
30-34	9,736	21.3	7,004	27.8	1,228	25.6	16,740	23.6
≥35	3,354	7.3	3,128	12.4	540	11.3	6,482	9.1
Ethnicity								
Black	426	0.9	539	2.1	125	2.6	965	1.4
Asian	1,087	2.4	922	3.7	150	3.1	2,009	2.8
White	43,294	94.7	23,318	92.6	4,455	92.8	66,612	94.0
Other	208	0.5	190	0.8	25	0.5	398	0.6
Missing	712	1.6	208	0.8	44	0.9	920	1.3
Scottish Index of Multiple Deprivation quintile at first birth								
1 (Most deprived)	4,569	10.0	2,225	8.8	486	10.1	6,794	9.6
2	5,923	13.0	3,210	12.8	610	12.7	9,133	12.9
3	7,024	15.4	3,828	15.2	757	15.8	10,852	15.3
4	9,641	21.1	5,547	22.0	1,014	21.1	15,188	21.4
5 (Least deprived)	15,446	33.8	8,913	35.4	1,628	33.9	24,359	34.4
Missing	3,124	6.8	1,454	5.8	304	6.3	4,578	6.5

Characteristics	Women without PPH[a] n= 45,727		Women with at least one PPH[b] n=25,177		Women with at least one severe PPH[c] n= 4,799		All women n=70,904	
	n	%	n	%	n	%	n	%
No. of births								
1	21,269	46.5	10,210	40.6	1,601	33.4	31,479	45.2
2	18,737	41.0	11,156	44.3	2,227	46.4	29,893	41.6
3	4,521	9.9	2,954	11.7	721	15.0	7,475	10.4
4	943	2.1	649	2.6	185	3.9	1,592	2.2
≥5	257	0.6	208	0.8	65	1.4	465	0.6
BMI at first antenatal visit (kg/m2) at first birth								
<18.5	1,370	3.0	498	2.0	106	2.2	1,868	2.6
18.5-24	26,377	57.7	12,368	49.1	2,368	49.3	38,745	54.6
25-29	10,598	23.2	6,862	27.3	1,262	26.3	17,460	24.6
≥30	4,525	9.9	4,268	17.0	777	16.2	8,793	12.4
Missing	2,857	6.3	1,181	4.7	286	6.0	4,038	5.7
Past medical history before first birth								
Anaemia and coagulation disorders	312	0.7	237	0.9	44	0.9	549	0.8
Diabetes	151	0.3	240	1.0	45	0.9	391	0.6
Psychiatric and mental health disorder	4,188	9.2	2,828	11.2	500	10.4	7,016	9.9
Cardiovascular disease	888	1.9	695	2.8	132	2.8	1,583	2.2
Congenital heart disease	120	0.3	96	0.4	19	0.4	216	0.3
Smoking status at first birth								
Non-smoker	30,383	66.5	18,694	74.3	3,527	73.5	49,077	69.2
Smoker	10,212	22.3	3,815	15.2	755	15.7	14,027	19.8
Ex-smoker	4,072	8.9	2,184	8.7	377	7.9	6,256	8.8
Missing	1,060	2.3	484	1.9	140	2.9	1,544	2.2
Mode of birth at first birth								
Spontaneous vaginal	28,684	62.7	5,943	23.6	1,375	28.7	34,627	48.8
Instrumental	12,403	27.1	7,040	28.0	1,465	30.5	19,443	27.4
Caesarean	4,619	10.1	12,175	48.4	1,953	40.7	16,794	23.7
Missing	21	0.1	19	0.1	6	0.1	40	0.1

Characteristics	Women without PPH[a] n= 45,727		Women with at least one PPH[b] n=25,177		Women with at least one severe PPH[c] n= 4,799		All women n=70,904	
	n	%	n	%	n	%	n	%
Number of PPH per woman								
Never had a PPH	45,727	100	NA		NA		45,727	64.5
1	NA	NA	20,416	81.1	4,592	95.7	20,416	28.8
2	NA	NA	4,320	17.2	200	4.2	4,320	6.1
≥3	NA	NA	441	1.8	7	0.1	441	0.6

[a]Women who did not experience a PPH in any births recorded in AMND during 1986-2016

[b]Women who had at least one PPH in any relevant births recorded in AMND during 1986-2016 including women who had at least one severe PPH

[c]Women who had at least one severe PPH in any relevant births recorded in AMND during 1986-2016

4.5.3 Socio-demographic and clinical characteristics associated with births

Of all 121,731 births in the cohort, 30,417 (25%) were followed by a PPH, 5,013 of which (4% of all births) were followed by a severe PPH (Table 4.7). Overall, 19,975 births (66%) affected by PPH occurred following a first birth, 27% following a second birth, and the remaining 7.5% occurred following a third or subsequent birth. The 'row percentages' for the number and percentage of births with or without PPH (and severe PPH) for each five-year interval highlight the increasing incidence of primary PPH over time from 10.5% to 38.2% between 1986-1990 and 2011-2016, and of severe PPH from 2.3% to 5.1% over the same period (Table 4.7).

The overall mean maternal age at birth in the cohort was 28 years, with higher maternal age in births affected by PPH (30 years) compared with births unaffected by PPH (28 years). Compared with births not affected by PPH, a higher percentage of births affected by PPH and severe PPH were to women having a first baby. The overall distribution of age, BMI, smoking and past medical problems among births in the cohort was similar to the distribution of these variables at first birth among women in the cohort (Table 4.6). Area deprivation quintile (as measured by the SIMD) varied little between births affected and unaffected by PPH or severe PPH.

Compared with births unaffected by PPH, a higher percentage of births affected by PPH or by severe PPH were instrumental births or caesareans, multiple pregnancies, or were affected by other obstetric complications, including gestational diabetes, HDP, PROM or PPROM. Babies born in births affected by PPH or severe PPH were more likely to be either pre-term or post term (i.e., <37 or ≥41 weeks' gestation at birth respectively), and were more likely to weigh

less than 2500 grams or more than 4000 grams, compared with babies born in births unaffected by PPH.

Table 4.7 Maternal sociodemographic and clinical characteristics of births according to the presence and absence of PPH and severe PPH

Characteristics	Births without PPH		Births with PPH including severe PPH		Births with severe PPH		All births	
	n=91,314		n=30,417		n=5,013		n=121, 731	
	n	%	n	%	n	%	n	%
Year of childbirth (row %)								
1986-1990	14,060	89.5	1,643	10.5	369	2.3	15,703	100
1991-1995	19,004	87.0	2,832	13.0	638	2.9	21,836	100
1996-2000	15,535	76.7	4,212	21.3	902	4.6	19,747	100
2001-2005	13,278	72.9	4,927	27.1	764	4.2	18,205	100
2006-2010	13,708	65.9	7,086	34.1	1,043	5.0	20,794	100
2011-2016	15,729	61.8	9,717	38.2	1,297	5.1	25,446	100
Age at childbirth (mean, SD)	27.8	5.5	29.5	5.5	29.0	5.7	28.2	5.6
<25	26,344	28.9	5,834	19.2	1,102	22.0	32,178	26.4
25-29	29,728	32.6	9,122	30.0	1,525	30.4	38,850	31.9
30-34	24,745	27.1	9,831	32.3	1,501	29.9	34,576	28.4
≥35	10,497	11.5	5,630	18.5	885	17.7	16,127	13.3
Parity								
Primiparous	50,929	55.8	19,975	65.7	3,241	64.7	70,904	58.3
Parity 1	30,071	32.9	7,994	26.3	1,314	26.2	38,065	31.3
Parity 2	7,905	8.7	1,899	6.2	338	6.7	9,804	8.1
Parity ≥3	2,409	2.6	549	1.8	120	2.4	2,958	2.4
Scottish index of multiple deprivation								
1 (most deprived)	10,101	11.1	2,681	8.8	495	9.9	12,781	10.5
2	11,760	12.9	3,733	12.3	648	12.9	15,493	12.7
3	13,446	14.7	4,559	15.0	788	15.7	18,005	14.8
4	19,606	21.5	6,901	22.7	1,078	21.5	26,507	21.8
5 (least deprived)	31,662	34.7	10,850	35.7	1,687	33.7	42,512	34.9
Missing	4,740	5.2	1,693	5.6	317	6.3	6,433	5.3

Characteristics	Births without PPH		Births with PPH including severe PPH		Births with severe PPH		All births	
	n=91,314		n=30,417		n=5,013		n=121, 731	
	n	%	n	%	n	%	n	%
BMI at first antenatal visit (kg/m^2)								
<18.5	2,388	2.6	492	1.6	88	1.8	2,880	2.4
18.5-24	49,969	54.7	13,836	45.5	2,316	46.2	63,805	52.4
25-29	22,708	24.9	8,544	28.1	1,320	26.3	31,252	25.7
≥30	11,569	12.7	6,234	20.5	961	19.2	17,803	14.6
Missing	4,680	5.1	1,311	4.3	328	6.5	5,991	4.9
Past medical history								
Anaemia and coagulation disorders	451	0.5	246	0.8	38	0.7	687	0.6
Diabetes	243	0.3	241	0.8	36	0.7	484	0.4
Psychiatric and mental health disorder	8,374	9.2	3,501	11.5	562	11.2	11,875	9.8
Cardiovascular disease	1,253	1.4	736	2.4	130	2.6	1,989	1.6
Congenital heart disease	148	0.2	90	0.3	16	0.3	238	0.2
Smoking								
Non-smoker	62,865	68.9	23,390	76.9	3,781	75.4	86,255	70.9
Smoker	20,173	22.1	4,246	14.0	747	14.9	24,419	20.1
Ex-smoker	6,311	6.9	2,195	7.2	332	6.6	8,506	7.0
Missing	1,965	2.2	586	1.9	153	3.1	2,551	2.1
Mode of birth								
Spontaneous vaginal	64,804	71.0	6,246	20.5	1,346.0	26.9	71,050	58.4
Instrumental	16,265	17.8	6,342	20.9	1,179.0	23.5	22,607	18.6
Caesarean section	10,194	11.2	17,796	58.5	2,478.0	49.4	27,990	23.0
Missing	51	0.1	33	0.1	10.0	0.2	84	0.1
Multiple pregnancies	943	1.0	1,190	3.9	302	6.0	2,133	1.8

Characteristics	Births without PPH		Births with PPH including severe PPH		Births with severe PPH		All births	
	n=91,314		n=30,417		n=5,013		n=121, 731	
	n	%	n	%	n	%	n	%
Obstetric complications								
Gestational diabetes	1,103	1.2	711	2.3	120	2.4	1,814	1.5
Hypertensive disorders of pregnancy	13,994	15.3	6,387	21.0	1,236	24.7	20,381	16.7
Antenatal anaemia	10,619	11.6	3,604	11.8	856	17.1	14,223	11.7
PROM or PPROM	3,744	4.1	2,138	7.0	363	7.2	5,882	4.8
Gestational age at birth (weeks)								
<28	284	0.3	137	0.5	62	1.2	421	0.4
28-31	695	0.8	413	1.4	139	2.8	1,108	0.9
32-36	5,173	5.7	2,278	7.5	545	10.9	7,451	6.1
37-38	14,815	16.2	4,974	16.4	798	15.9	19,789	16.3
39-40	47,066	51.5	13,835	45.5	2,004	40.0	60,901	50.0
≥41	23,281	25.5	8,780	28.9	1,465	29.2	32,061	26.3
Weight of the baby (grams)								
<2500	5,786	6.3	2,351	7.7	600	12.0	8,137	6.7
2500-3499	48,824	53.5	12,320	40.5	1,857	37.0	61,144	50.2
3500-3999	27,298	29.9	10,047	33.0	1,525	30.4	37,345	30.7
>4000	9,406	10.3	5,699	18.7	1,031	20.6	15,105	12.4

4.5.4 Association between primary PPH and composite cardiovascular outcome

4.5.4.1 Components of CVD outcome and event-free survival

Among the 45,727 women who never had a PPH there were 6,111 (13%) first CVD events, compared with 3,070 (12%) events among the 25,177 women who had at least one PPH, which included 669 (14%) events in the subgroup of 4,799 women who had at least one severe PPH (Table 4.8**).** The distribution of the outcome events contributing to the composite CVD outcome is shown in Table 4.8. For all groups, prescription records accounted for the majority (~91%) of first CVD events identified by the composite outcome, with CVD-related hospitalisations accounting for 9% and death related to CVD accounting for less than 1% of first events (Table 4.8**).**

Table 4.8 Percentage contribution of individual outcome events to the composite cardiovascular outcome in each group

Outcome	**Women without PPH[a]** **n= 45,727**	**Women with at least one PPH[b]** **n=25,177**	**Women with at least one severe PPH[c]** **n= 4,799**	**All women** **n=70,904**
First record of prescription[d]	91%	91%	91%	91%
First record of hospitalisation[d]	9%	9%	9%	9%
Death record with CVD[d]	<1%	<1%	<1%	<1%
Number of women with first CVD event[d]	6,111	3,070	669	9,181

[a]Women who did not experience a PPH in any birth recorded in AMND
[b]Women who had at least one PPH in any relevant birth recorded in AMND, including women who had at least one severe PPH
[c]Women who had at least one severe PPH in any relevant birth recorded in AMND
[d]Numbers were compressed by the data provider due to the data privacy and confidentiality.

Among women who had a PPH, and those who did not, around 13% of those who had a prescription as their first CVD event had a subsequent CVD-related hospitalisation **(**Figure 4.5**)**. Over half of those who had a CVD-related hospitalisation as their first CVD event were subsequently prescribed CVD medication. Small numbers of CVD-related deaths were observed in both groups.

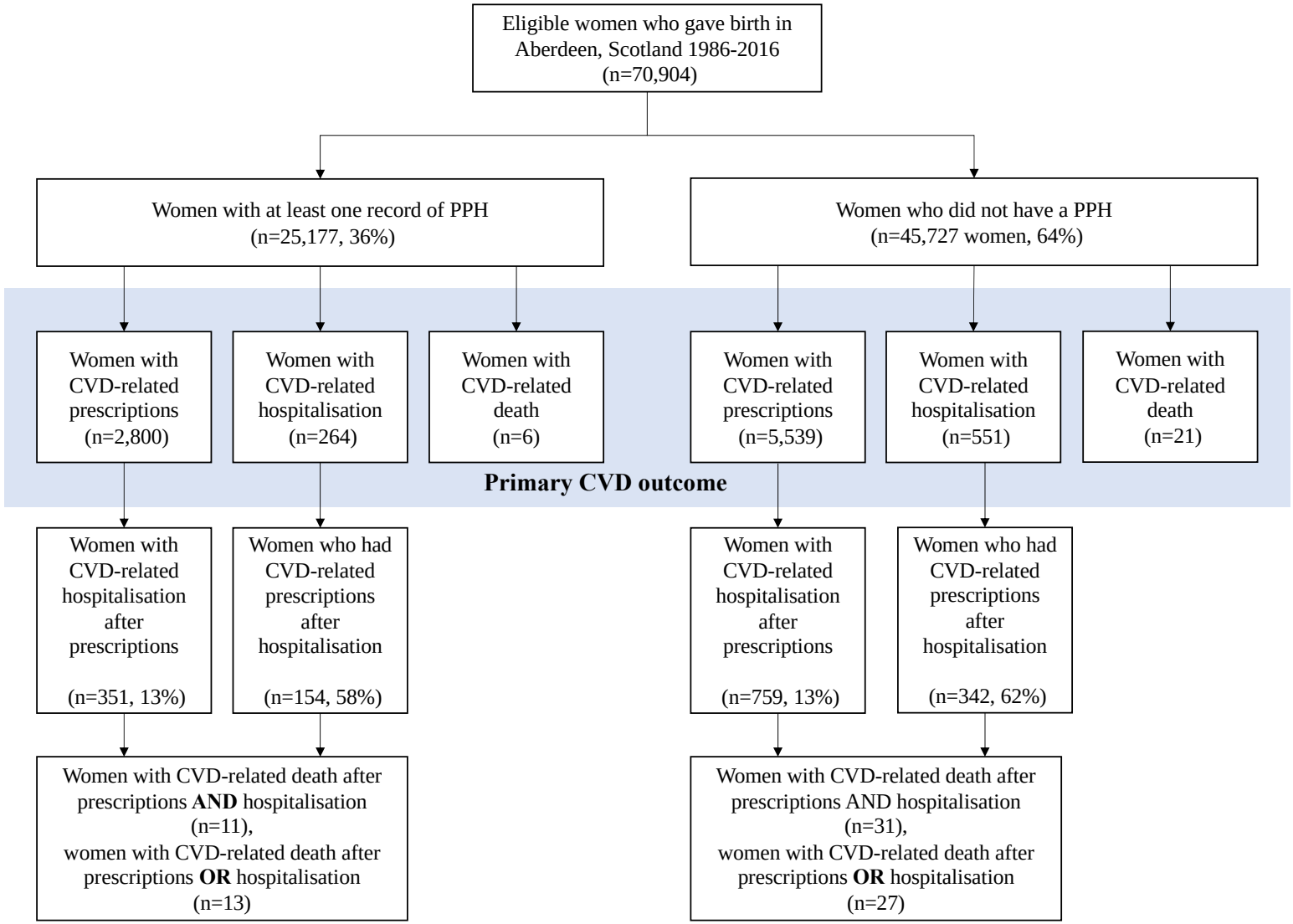


Figure 4.5 CVD outcomes in women with and without a PPH

The overall cardiovascular event-free survival for women who had at least one PPH, compared with women who did not have a PPH, is illustrated in Figure 4.6. Cardiovascular events occurred at a faster rate in the initial three years and then continued to occur at a slightly slower rate up to 30 years after birth in both groups. A similar pattern was observed in the subgroup analysis focusing on women who had at least one severe PPH compared with women who did not have a PPH (Appendix 12).

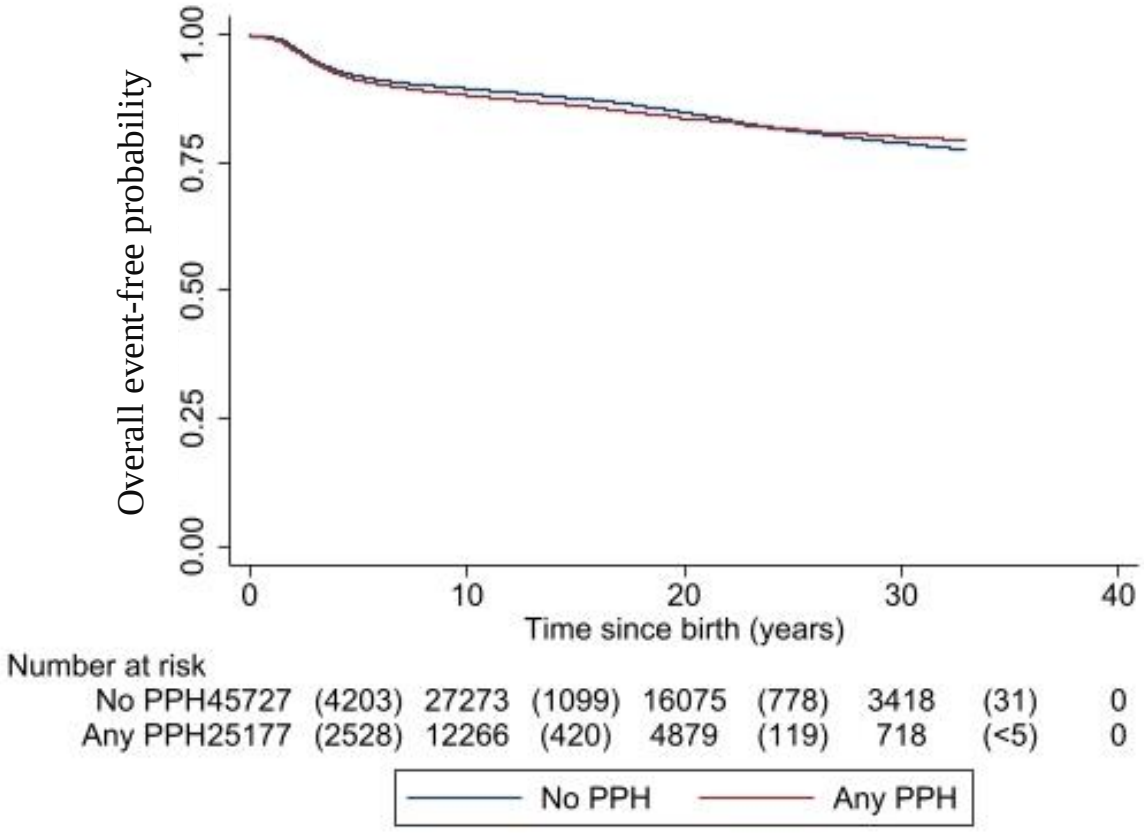


Figure 4.6 CVD event-free probability over time among women with at least one PPH and women with no PPH (n=70,904 women)

4.5.4.2 Univariable analysis, including incidence of composite CVD outcome

Compared with women who did not have a PPH (Incidence rate=90.2 per 10,000 person-years), women who had at least one PPH (Incidence rate=105.4) were 6% more likely to develop a CVD outcome event during the follow-up period (HR=1.06, 95% CI=1.02-1.11) (Table 4.9). Women who had at least one severe PPH (Incidence rate=107.3) were 14% more likely to develop a CVD outcome event during the follow-up period, compared with women who did not have a PPH (HR=1.14, 95% CI=1.05-1.23) (Table 4.10).

Table 4.9 Association between PPH and risk of cardiovascular composite outcome

Women with no PPH n=45,727			Women with at least one PPH n=25,177			Univariable model (Any PPH) n=70,904		
Women with CVD event	Total person-years (PY)	Incidence rate per 10,000 PY	Women with CVD event	Total person-years (PY)	Incidence rate per 10,000 PY	HR	95% CI	p-value
6,111	677,608	90.2	3,070	293,652	105.4	1.06	1.02-1.11	0.005

Table 4.10 Association between severe PPH and risk of cardiovascular composite outcome

Women with no PPH n=45,727			Women with at least one severe PPH n=4,799			Univariable model (Any severe PPH) n=50,526		
Women with CVD event	Total person-years (PY)	Incidence rate per 10,000 PY	Women with CVD event	Total person-years (PY)	Incidence rate per 10,000 PY	HR	95% CI	p-value
6,111	677,608	90.2	669	62,327	107.3	1.14	1.05-1.23	0.002

4.5.4.3 Multivariable Cox proportional hazards regression models

After adjusting for year of childbirth (baseline model), compared with women who did not have a PPH, women who had at least one PPH were 29% more likely to develop a CVD outcome event during the follow-up period (aHR=1.29, 95% CI= 1.23-1.35) (Table 4.11). There was a substantial change of HR from 1.06 to 1.29 after adjusting for the year of childbirth in the baseline model suggesting that 'year of childbirth' is a confounder of the association between PPH and CVD.

Further adjustment for sociodemographic factors (model 1) and past medical history (model 2) did not materially alter this association. Additional adjustment for childbirth-related factors, including the presence of other obstetric complications at birth, (model 3) resulted in attenuation of the association to 12%, which remained statistically significant (aHR=1.12, 95% CI= 1.06-1.18).

For severe PPH, the results were similar. In the baseline model, compared with women who did not have a PPH, women who had at least one severe PPH were 30% more likely to develop a CVD outcome event during the follow-up period (aHR=1.30, 95% CI= 1.18-1.44). After sequential adjustment, the strength of this association was somewhat reduced to 16%, but remained statistically significant (aHR=1.16, 95% CI= 1.06-1.27).

Table 4.11 Association between PPH and severe PPH and composite cardiovascular outcome, with sequential adjustment for potential confounders

Exposure	Base Model[a] (n=70,904, PPH) (n=50,526, severe PPH)		Model 1[b] (n=63,875, PPH) (n=45,107, severe PPH)		Model 2[c] (n=63,402, PPH) (n=44,743 severe PPH)		Model 3[d] (n=63,376, PPH) (n=44,726 severe PPH)	
	aHR (95% CI)	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
PPH	1.29 (1.23-1.35)	<0.0001	1.27 (1.21-1.33)	<0.0001	1.26(1.20-1.32)	<0.0001	1.12 (1.06-1.18)	<0.0001
Severe PPH	1.30 (1.18-1.44)	<0.0001	1.29 (1.19-1.41)	<0.0001	1.28 (1.17-1.39)	<0.0001	1.16 (1.06-1.27)	0.001

[a] Base model adjusted for year of birth only

[b] Model 1 adjusted for year of birth and sociodemographic factors (age at birth, BMI, ethnicity, Scottish index of multiple deprivation)

[c] Model 2 adjusted for variables in model 1, and additionally adjusted for past medical history (anaemia and coagulation disorders, diabetes, psychiatric and mental disorder, cardiovascular disease) and smoking status

[d] Model 3 adjusted for variables in model 2, and additionally adjusted for pregnancy-related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membranes, preterm pre-labour rupture of membranes, gestational diabetes, antenatal anaemia), gestational age at birth, baby's birthweight

4.5.4.4 Statistical tests and checks for proportional hazards (PH) assumption

The plots of hazard function against analysis time were convergent (Appendix 12). The p-value from the global test of the proportional hazards assumption was <0.001 suggesting that there was a violation of the assumption, indicating that the association between PPH and the CVD outcome, and also the association between several confounding variables (mode of birth, gestational age at birth, HDP, baby's birthweight) and the CVD outcome, were not constant over time.

4.5.4.5 Extended cox regression models for different time periods

Table 4.12 and Figure 4.7 present the results of the extended multivariable Cox regression models generating adjusted HRs (aHRs) for the association between PPH and the composite CVD outcome for different time intervals after childbirth.

During the first year after birth, in the fully adjusted model (model 3), compared with women who did not have a PPH, women who had at least one PPH were almost twice as likely to develop a cardiovascular outcome event (aHR=1.96, 95% CI= 1.51-2.53). Beyond the first year after birth, this association remained, but was attenuated over time (aHR=1.19 at 2-5 years, and aHR=1.17 at 6-15 years). Beyond 15 years after birth, women who had at least one PPH were 36% less likely to develop a cardiovascular event compared with women who did not have a PPH (aHR=0.64, 95% CI= 0.55-0.75).

Table 4.12 Association between PPH and composite CVD outcome for different time intervals after birth, with sequential adjustment for potential confounders

Time interval after birth	Base model[a] n=70,904		Model 1[b] n=63,875		Model 2[c] n=63,402		Model 3[d] n= 63,376	
	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
0-1 year	2.43 (1.95-3.02)	<0.0001	2.49 (1.98-3.11)	<0.0001	2.46 (1.95-3.02)	<0.0001	1.96 (1.51-2.53)	<0.0001
2-5 years	1.32 (1.25-1.40)	<0.0001	1.28 (1.21-1.36)	<0.0001	1.27 (1.19-1.35)	<0.0001	1.19 (1.11-1.30)	<0.0001
6-15 years	1.39 (1.27-1.53)	<0.0001	1.35 (1.22-1.48)	<0.0001	1.35 (1.23-1.49)	<0.0001	1.17 (1.05-1.30)	0.005
>15 years	0.88 (0.78-1.00)	0.042	0.87 (0.76-1.00)	0.058	0.87 (0.76-1.00)	0.057	0.64 (0.55-0.75)	<0.0001

[a] Base model adjusted for year of birth only
[b] Model 1 adjusted for year of birth and sociodemographic factors (age at birth, BMI, ethnicity, Scottish index of multiple deprivation)
[c] Model 2 adjusted for variables in model 1, and additionally adjusted for past medical history (anaemia and coagulation disorders, diabetes, psychiatric and mental disorder, cardiovascular disease) and smoking status
[d] Model 3 adjusted for variables in model 2, and additionally adjusted for pregnancy-related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membranes, preterm pre-labour rupture of membranes, gestational diabetes, antenatal anaemia), gestational age at birth, baby's birthweight

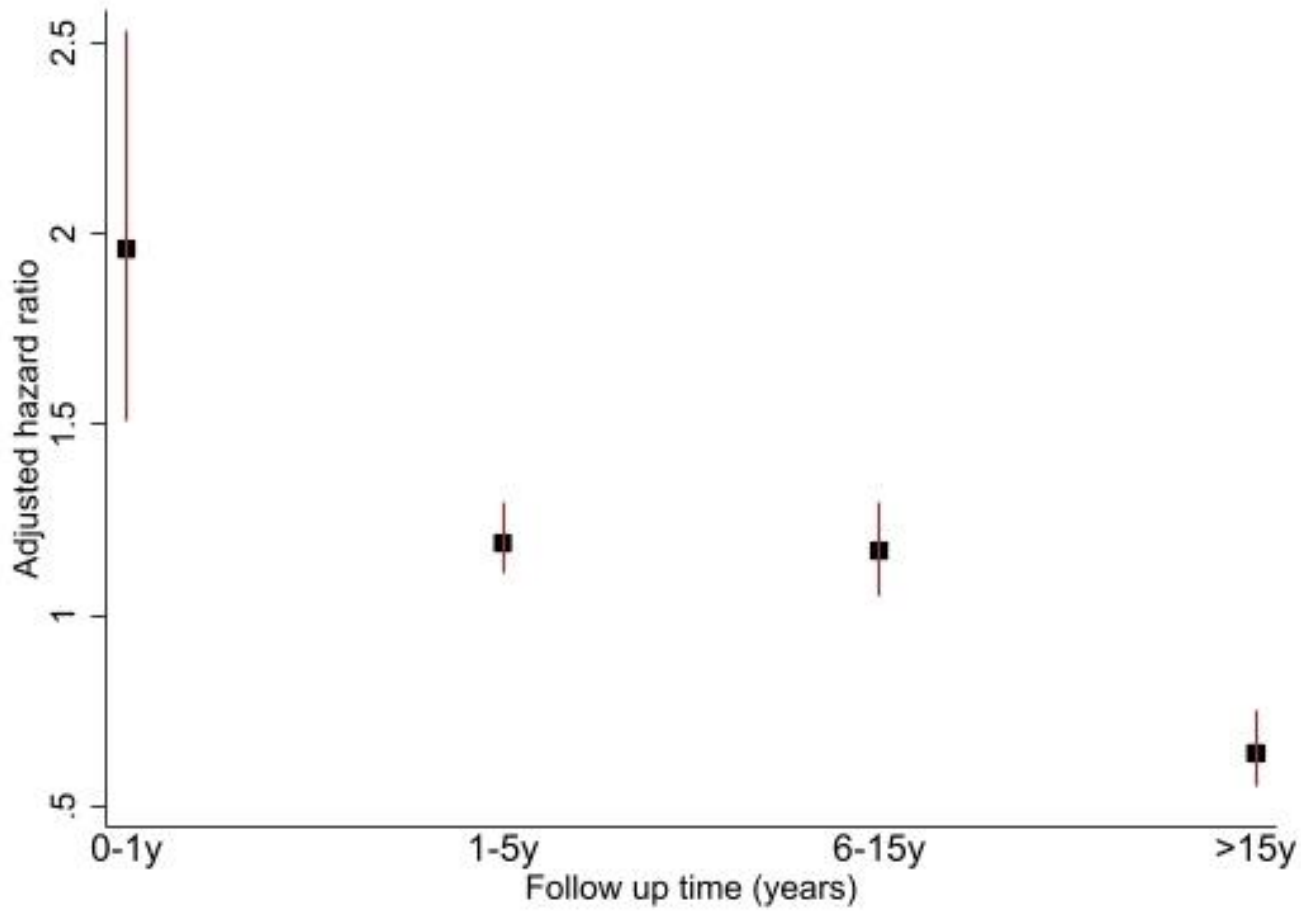


Figure 4.7 Adjusted hazard ratios for the association between PPH and CVD at different intervals after birth (model 3, n=63,376)

Models for the association between severe PPH and the CVD composite outcome over time are shown in Table 4.13 and Figure 4.8, with a similar pattern to the results for any PPH. During the first year after birth, in the fully adjusted model, compared with women who did not have a PPH, women who had at least one severe PPH were 86% more likely to develop a CVD outcome event (aHR=1.86, 95% CI= 1.25-2.80). This association was reduced over time (aHR=1.30 at 2-5 years, and aHR=1.21 at 6-15 years). Beyond 15 years after birth, there was an inverse association between having a severe PPH and the CVD composite outcome, suggesting that women who had at least one severe PPH were 50% less likely to develop a CVD outcome event compared with women who did not have a PPH (aHR=0.50, 95% CI= 0.37-0.69).

Table 4.13 Association between severe PPH and composite CVD outcome for different time intervals after birth, with sequential adjustment for potential confounders

Time interval	Base Model[a] (N=50,526)		Model 1[b] (N=45,107)		Model 2[c] (N=44,743)		Model 3[d] (N=44,726)	
	aHRs (95% CI)	p-value	aHRs (95% CI)	p-value	aHRs (95% CI)	p-value	aHRs (95% CI)	p-value
0-1 year	2.46 (1.71-3.53)	<0.0001	2.52 (1.74-3.68)	<0.0001	2.51 (1.72-3.65)	<0.0001	1.86 (1.25-2.80)	0.002
2-5 year	1.38 (1.24-1.53)	<0.0001	1.36 (1.22-1.51)	<0.0001	1.34 (1.20-1.49)	<0.0001	1.30 (1.16-1.46)	<0.0001
6-15 year	1.38 (1.18-1.63)	<0.0001	1.33 (1.21- 1.59)	0.001	1.34(1.13-1.60)	0.001	1.21 (1.00-1.46)	0.047
15+ year	0.71 (0.55-0.92)	0.009	0.71 (0.52-0.95)	0.021	0.69 (0.52-0.94	0.018	0.50 (0.37-0.69)	<0.0001

[a] Base model adjusted for year of birth only
[b] Model 1 adjusted for year of birth and sociodemographic factors (age at birth, BMI, ethnicity, Scottish index of multiple deprivation)
[c] Model 2 adjusted for variables in model 1, and additionally adjusted for past medical history (anaemia and coagulation disorders, diabetes, psychiatric and mental disorder, cardiovascular disease) and smoking status
[d] Model 3 adjusted for variables in model 2, and additionally adjusted for pregnancy-related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membranes, preterm pre-labour rupture of membranes, gestational diabetes, antenatal anaemia), gestational age at birth, baby's birthweight

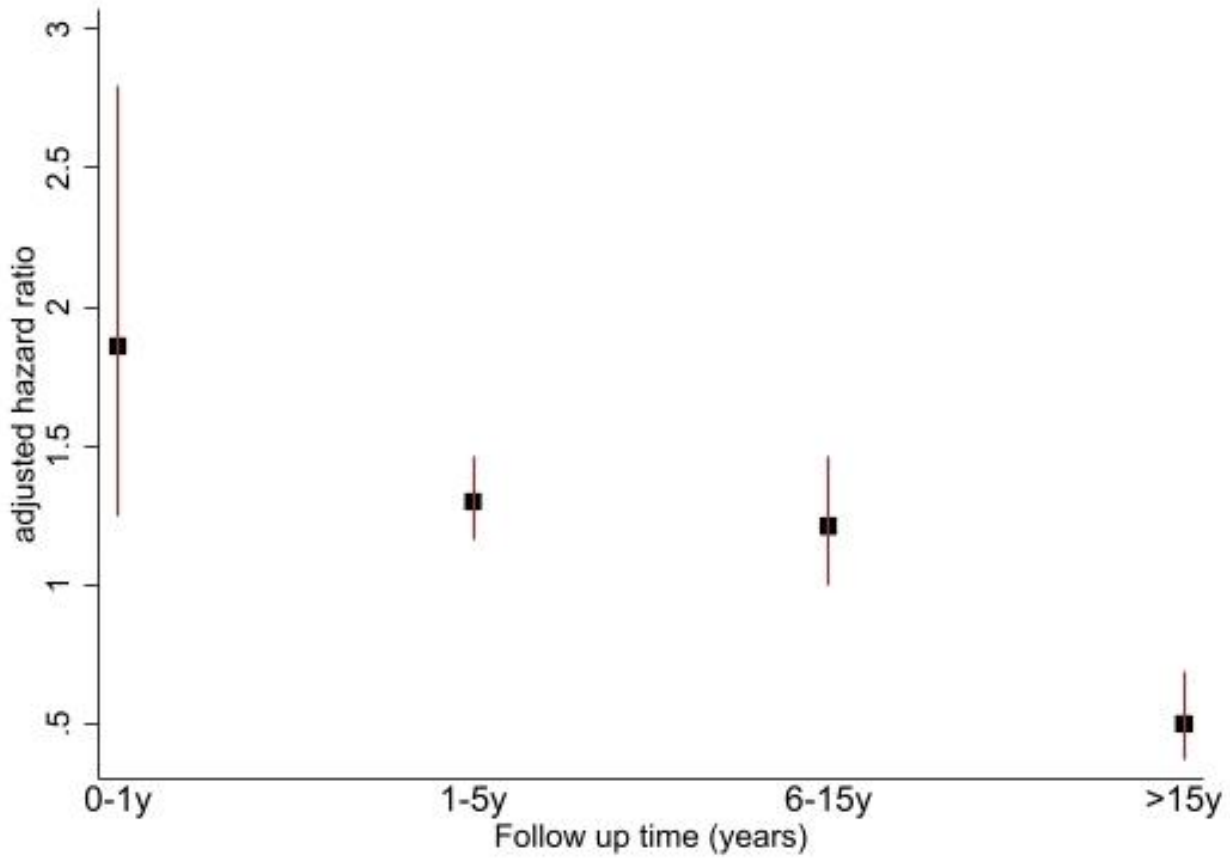


Figure 4.8 Adjusted hazard ratios for the association between severe PPH and CVD at different intervals after birth (model 3, n=44,726)

4.5.4.6 Potential effect modification by mode of birth and HDP

Potential effect modification of the association between PPH (and severe PPH) and the composite CVD outcome was explored for (a) HDP and (b) mode of birth. In the fully adjusted model, there was strong evidence of effect modification (p=0.003) by HDP (Table 4.14), with higher aHRs for the association between PPH (and severe PPH) and the CVD outcome among women who had at least one birth affected by a hypertensive disorder, compared with women who did not.

Table 4.14 Association between PPH and composite cardiovascular outcome in women with and without HDP (fully adjusted model 3)

Exposure	Time interval	Women without HDP n=53,451		Women with HDP n=17,453	
		HRs (95% CI)	p-value	HRs (95% CI)	p-value
PPH	0-1 year	1.85 (1.43-2.42)	<0.0001	2.14 (1.65-2.79)	<0.0001
	2-5 year	1.12 (1.03-1.21)	0.007	1.29 (1.18-1.41)	<0.0001
	6-15 year	1.06 (0.94-1.19)	0.354	1.22 (1.08-1.38)	0.001
	15+ year	0.57 (0.48-0.67)	<0.0001	0.66 (0.55-0.78)	<0.0001
Severe PPH	0-1 year	1.74 (1.15-2.63)	0.009	2.02 (1.34-3.05)	0.001
	2-5 year	1.20 (1.05-1.38)	0.01	1.39 (1.20-1.62)	<0.0001
	6-15 year	1.08 (0.88-1.32)	0.48	1.25 (1.01-1.54)	0.039
	15+ year	0.44 (0.32-0.61)	<0.0001	0.51 (0.37-0.71)	<0.0001

In contrast, there was only weak evidence of effect modification (p=0.09) by mode of birth (Table 4.15). In the fully adjusted model, the aHRs for the association between PPH and the CVD outcome were similar among women who had a caesarean birth or instrumental birth in any of their births, compared with women who had only spontaneous vaginal births.

Table 4.15 Association between PPH and composite cardiovascular outcome in women with instrumental/caesarean birth and women with spontaneous vaginal birth (fully adjusted model 3)

Exposure	Time interval	Women with spontaneous vaginal birth n=32,023		Women with caesarean or instrumental birth n=38,854	
		HRs (95% CI)	p-value	HRs (95% CI)	p-value
PPH	0-1 year	2.06 (1.60-2.64)	<0.0001	2.28 (1.80-2.88)	<0.0001
	2-5 year	1.10 (0.98-1.23)	0.107	1.21 (1.13-1.31)	<0.0001
	6-15 year	1.18 (1.03-1.35)	0.015	1.31 (1.18-1.45)	<0.0001
	15+ year	0.77 (0.65-0.91)	0.002	0.85 (0.73-0.98)	0.025
Severe PPH	0-1 year	2.23 (1.47-3.38)	<0.0001	2.29 (1.56-3.36)	<0.0001
	2-5 year	1.25 (1.02-1.53)	0.032	1.28 (1.13-1.45)	<0.0001
	6-15 year	1.23 (0.96-1.57)	0.097	1.26 (1.05-1.52)	0.013
	15+ year	0.63 (0.45-0.89)	0.009	0.65 (0.48-0.88)	0.006

4.5.4.7 Sensitivity analyses

A series of sensitivity analyses were carried out to explore the association between PPH and CVD, (a) after removing women who had a past medical history of CVD prior to their first birth, (b) after births with missing values of PPH were classified as having PPH, and (c) after restricting the outcome measure to CVD-related hospitalisation.

After (a) the exclusion of births to women who had a past medical history of CVD prior to their first birth, the association between PPH (and severe PPH) and the composite CVD outcome remained statistically significant in the fully adjusted model, with similar or higher adjusted hazard ratios, particularly within the first year after birth (Table 4.16).

Table 4.16 Association between PPH and composite cardiovascular outcome for different time intervals after birth, after exclusion of births to women with a self-reported past medical history of CVD prior to their first birth (fully adjusted model)

Exposure	Time interval	Model 3 (Original analysis)		Model 3 (Sensitivity analysis a)	
		aHRs (95% CI)	p-value	aHRs (95% CI)	p-value
PPH (n=62,404)	0-1 year	1.96 (1.51-2.53)	<0.0001	2.05 (1.56-2.70)	<0.0001
	2-5 year	1.19 (1.11-1.30)	<0.0001	1.18 (1.10-1.27)	<0.0001
	6-15 year	1.17 (1.05-1.30)	0.005	1.19 (1.07-1.33)	0.002
	15+ year	0.64 (0.55-0.75)	<0.0001	0.66 (0.56-0.78)	<0.0001
severe PPH (n=44,099)	0-1 year	1.86 (1.25-2.80)	0.002	2.03 (1.32-3.11)	0.001
	2-5 year	1.30 (1.16-1.46)	<0.0001	1.30 (1.15-1.46)	<0.0001
	6-15 year	1.21 (1.00-1.46)	0.047	1.24 (1.03-1.50)	0.026
	15+ year	0.50 (0.37-0.69)	<0.0001	0.53 (0.39-0.73)	<0.0001

After (b) re-classifying births with missing values of PPH as having PPH (n=851 births) and regenerating the 'Any PPH' exposure variable, the association between PPH (and severe PPH) and the composite CVD outcome remained statistically significant in the fully adjusted model, with very similar adjusted hazard ratios to the main analysis (fully adjusted model) (Table 4.17).

Table 4.17 Association between PPH and composite cardiovascular outcome for different time intervals after birth, after births with missing values of PPH were classified as having PPH (fully adjusted model)

Exposure	Time interval	Model 3 (Original analysis)		Model 3 (Sensitivity analysis b)	
		aHRs (95% CI)	p-value	aHRs (95% CI)	p-value
PPH (n=63,376)	0-1 year	1.96 (1.51-2.53)	<0.0001	1.96 (1.51-2.53)	<0.0001
	2-5 year	1.19 (1.11-1.30)	<0.0001	1.19 (1.11-1.28)	<0.0001
	6-15 year	1.17 (1.05-1.30)	0.005	1.17 (1.05-1.30)	0.006
	15+ year	0.64 (0.55-0.75)	<0.0001	0.64 (0.55-0.76)	<0.0001
severe PPH (n=44,726)	0-1 year	1.86 (1.25-2.80)	0.002	1.87 (1.25-2.80)	0.002
	2-5 year	1.30 (1.16-1.46)	<0.0001	1.30 (1.16-1.46)	<0.0001
	6-15 year	1.21 (1.00-1.46)	0.047	1.21 (1.00-1.46)	0.047
	15+ year	0.50 (0.37-0.69)	<0.0001	0.50 (0.37-0.69)	<0.0001

Finally, (c) the association between PPH (and severe PPH) and CVD-related hospitalisation was explored (Table 4.18). This showed a similar association between PPH (and severe PPH) and CVD-related hospitalisation in the fully adjusted model, particularly within the first year and up to five years after birth, diminishing and non-significant beyond five years after birth in both PPH groups (Table 4.18).

Table 4.18 Association between PPH and CVD-related hospitalisation for different time intervals after birth, after restricting the CVD outcome to hospitalisation

Exposure	Time interval	Model 3 (Original analysis)		Model 3 (Sensitivity analysis c)	
		aHRs (95% CI)	p-value	aHRs (95% CI)	p-value
PPH (n=64,124)	0-1 year	1.96 (1.51-2.53)	<0.0001	1.89 (0.90-3.98)	0.09
	2-5 year	1.19 (1.11-1.30)	<0.0001	1.37 (1.17-1.60)	<0.0001
	6-15 year	1.17 (1.05-1.30)	0.005	1.15 (0.89-1.49)	0.28
	15+ year	0.64 (0.55-0.75)	<0.0001	0.70 (0.53-0.92)	0.01
severe PPH (n=45,165)	0-1 year	1.86 (1.25-2.80)	0.002	2.86 (1.10-7.44)	0.031
	2-5 year	1.30 (1.16-1.46)	<0.0001	1.38 (1.06-1.80)	0.016
	6-15 year	1.21 (1.00-1.46)	0.047	1.05 (0.66-1.66)	0.839
	15+ year	0.50 (0.37-0.69)	<0.0001	0.52 (0.30-0.90)	0.02

4.6 Discussion

4.6.1 Summary of key findings

In this Scottish population-based cohort study, of 121,731 births to 70,904 women who gave birth between 1986-2016, 30,417 births to 25,177 women were complicated by PPH. The overall incidence of PPH increased over time from 10.5% in the late 1980s to 38% in the early 2010s. Having a PPH was found to be associated with an increased risk of CVD, but with a trend of diminishing risk over follow-up time, with an apparent reversal of the direction of association after 15 years. This association was independent of other obstetric complications, sociodemographic factors, and past medical history.

Women who had at least one episode of PPH in their birth history were up to twice as likely to experience the composite CVD outcome, including CVD-related hospitalisation, compared with women who had never experienced a PPH. This association was strongest in the first year after birth, continuing for up to 15 years, and was slightly stronger in women who had at

least one episode of hypertensive disorders in pregnancy. Similar associations were found between severe PPH and the same CVD outcome.

4.6.2 Interpretation

The incidence of PPH in this Scottish population after the year 2000 was significantly higher than in the rest of the UK. For example 14.5% of all births in NHS hospitals in England in 2014-2015 were affected by PPH, compared with 38% in this Scottish population. (147) Although incidence data for PPH were not available for the whole of Scotland, the overall incidence of severe PPH in Scotland was estimated to be 5.8 per 1000 births in 2012 according to the Scottish confidential audit of severe maternal morbidity, (36) compared with 5.1% in this study. This is comparable, and the slight difference is likely to be explained by the use of a stricter definition for severe PPH (more than 2500ml) in previously published data, compared with 1500ml used as the definition in the study reported here. (36, 38) Notwithstanding these differences, this study provides further evidence of the increasing incidence of PPH in high resource countries, including the UK. (3) One potential explanation for the overall increasing trends in PPH incidence could be due to improvement in quantification and recording of blood loss. Another potential explanation could be the increased prevalence of risk factors for PPH, including maternal obesity and older maternal age. For instance, the Health Survey in England reported that the prevalence of obesity among women of childbearing age increased from 12% in 1993 to 27% in 2016. (148)

In this study, women with at least one episode of PPH were at an increased risk of developing subsequent CVD up to 15 years following birth, after adjustment for year of birth, variation of HRs over time and confounding. PPH was found to be significantly associated with an increased risk of CVD, particularly in the first year following childbirth. Over time, the

relative increase in the risk of CVD associated with having a PPH declined, and beyond 15 years the risk of CVD was lower in the PPH group. This finding is very unlikely to have arisen because PPH is actually protective for CVD. Rather, while extended Cox regression models address the issues of HRs varying over time by reporting time-specific hazard ratios, it is likely that this approach introduces survival bias associated with time to CVD related prescriptions or hospitalisation. (149, 150) At the beginning of cohort, the proportion of women at risk was similar for both groups. As women in the PPH group developed CVD over time, particularly in the first year after birth, there was differential loss in the proportion of women at risk among the PPH group. This means that in the exposed group, many women may have had a CVD outcome event shortly after the beginning of follow up and in the subsequent years, whereas in the unexposed group, a greater proportion of women were at a relatively higher risk in the later time period as they had not developed CVD in the earlier follow-up years. This is the most likely explanation for the aHR beyond 15 years indicating an apparent inverse association between PPH and CVD rather than any real protective effect.

Three other population-based studies have investigated the potential association between PPH and CVD, in England, Korea, and Canada. (62, 63, 151) Two of these studies found that the risk of CVD was higher among women with PPH requiring blood transfusion (i.e. more severe PPH), compared with women who did not have PPH, after adjustment for potential confounders (aHR= 1.60, 95% CI= 1.25-2.06, aHR= 1.38, 95% CI= 1,13-1.68), (62, 63) but none found an association between less severe PPH (not requiring transfusion) and hypertension or CVD. (62, 63, 151) These studies were all conducted in high-resource settings, comparable to Scotland, using routine health care data, but some methodological differences with the study reported here may explain the difference in results. First, these

studies classified a woman as having had a PPH on the basis of events in the index or first birth only, while in the study reported here PPH was classified using all available birth records for the women in the cohort. Second, in these previous studies, records with PPH were identified using diagnostic or ICD-10 codes, compared with recorded estimated blood loss volume which was used in the present study. As acknowledged by the authors of one study investigating PPH and CVD using English routine data, using ICD-10 codes, in the absence of data about estimated blood loss, could lead to non-differential measurement errors of PPH and under-estimation of the association. (151)

Finally, outcome assessment for CVD in this study captured not only CVD-related hospitalisations but also CVD-related prescriptions, whereas previous studies have applied Read codes from English primary healthcare data (THIN), and ICD-10 diagnostic codes from Korean national health insurance claims. Using ICD-10 codes may lead to fewer outcomes identified, for example individuals with controlled hypertension could be managed with lifestyle modifications and CVD medication. This may explain different CVD risks and lead to an under-estimation of the true effect of PPH, particularly if the outcome events were more frequent among the exposed group. These differences may have contributed to an under-estimation of the true association between PPH and CVD in previous studies, and explain why the study reported here was able to identify an association between PPH and CVD that previous studies did not detect.

There are two possible explanations for the observed association between PPH and CVD. The first is that PPH may be an independent risk factor for developing CVD later in life. During pregnancy, total blood volume increases from between 20-100% above pre-pregnancy levels, to allow for adequate fetal growth and development. (152) The highest increase in volume

occurs before the onset of labour, associated with uterine contractions, resulting in a 300ml-500ml auto-transfusion of blood volume. (152) A postpartum blood loss of up to 500ml may be expected to be normal and well-tolerated by these haemodynamic changes during birth. (6) When women experience a PPH, haemorrhage causes a lowered blood volume reducing venous return to the heart, and a consequent reduced cardiac output and overall blood supply to organs. (153) This, in combination with hypoxaemia, can lead to ischaemic injuries of vital organs including the heart, brain and kidneys. If haemorrhage continues and is left untreated, this can lead to hypovolaemic shock, end organ failure and death. (153) With timely treatment, these more severe possible outcomes may be averted, but PPH may nevertheless put a strain on and cause irreversible damage to the cardiovascular system, which may in turn lead to a higher risk of developing CVD in later life.

Another possible explanation is that pre-existing 'occult' risk factors exist prior to pregnancy in some women and the experience of obstetric complications may 'unmask' this pre-existing susceptibility to CVD among such women. (130, 154-156) A growing body of research about pregnancy complications and CVD suggests that pregnancy complications may function as a 'stress test' to the cardiovascular system, exacerbating this latent cardiovascular risk by causing more vascular damage and metabolic stress on the body. (130, 156, 157) It has been established that haemodynamic changes in pregnancy and childbirth can worsen existing cardiac conditions such as coronary heart disease. (158) Adverse cardiovascular outcomes following pregnancy complications are thus seen as the individual's inability to cope with this metabolic stress on the body. Regardless, this creates an opportunity for the primary prevention or intervention of CVD as valuable information is revealed about women's underlying cardiovascular condition. (159)

Consideration should be given to these factors when exploring the potential mechanisms for a causal pathway between PPH and CVD. It remains unclear if PPH is an independent risk factor for CVD or an early indicator of pre-existing susceptibility to CVD. More information is needed about cardiovascular risk factors before pregnancy, such as assessing pre-pregnancy lipid profile, BMI, and blood pressure, and during pregnancy and after birth, to be able to distinguish between the two. Regardless, the first year after birth should be seen as a key opportunity for early prevention and lifestyle modification to prevent the subsequent development of CVD.

4.6.3 Strengths and limitations

4.6.3.1 Strengths

The main strength of this study is the large population-based cohort with a long duration of follow up that minimises selection bias. To date, this is the first population-based cohort study to establish a time-varying association between PPH and the later development of CVD. Stratification of cardiovascular risk by follow-up time allowed investigation of the way in which the risk of CVD associated with PPH changes over time. (154)

Classification of exposure to PPH was improved by using estimated blood loss volume from all available birth records. Looking beyond the first birth has been a well-recognised challenge for most registry-based studies investigating maternal cardiovascular risks. (160) This approach of classifying exposure to PPH based on whether or not PPH occurred in any available birth records for any individual woman, not only minimised misclassification of exposure to PPH, but also meant that analyses could be conducted at the level of the woman (rather than at the level of the birth). Studies that have used information only from the first

birth or first pregnancy exclude around 60% of births from the analysis. (160) For example, 55% of women in this cohort had more than one birth. This exclusion by other researchers may have distorted associations between obstetric risk factors and women's long-term health outcomes.

In terms of outcome assessment, using both prescription and hospital discharge data allowed a broader spectrum of CVDs to be captured, including individuals with less serious CVD who may not die or require hospitalisation for CVD.

In this retrospective cohort study, the recording of estimated blood loss, and other variables in AMND, preceded outcome assessment from SMR databases, reducing recall bias. Temporality for outcome events was also established by excluding women with pre-existing records of CVD-related prescriptions or hospitalisation before their first birth or first PPH, and further excluding women with a self-reported past medical history of CVD in a sensitivity analysis. The findings from sensitivity analyses reassuringly suggested that the association remained unchanged after further removing the self-reported CVD history in AMND data, after recoding missing values of PPH as having PPH, and after restricting the CVD outcome event to CVD-related hospitalisation only.

Several approaches were taken to minimise potential confounding and to explore effect modification. A stepwise approach was taken to adjust for a wide range of potential confounders, including smoking status and well-established risk factors for PPH, including HDP such as pre-eclampsia. (58, 115, 160) The higher proportion of non-smokers among women who had at least one PPH in this cohort suggests that this observed association could be an underestimate, since smoking is an overarching risk factor for CVD. Since 'smoking' variable was adjusted for in the final model with an overall 2% missing, this higher proportion

of non-smokers in the PPH group is unlikely to have an impact on the findings. The potential effect modification by HDP was further explored by including an interaction term between PPH and HDP in the final model, and reporting results separately for women who had a HDP and who did not have an HDP.

Although the follow up of the cohort was limited to CVD events within the Grampian region of Scotland only, Aberdeen and the Grampian region has a relatively stable population and only 3.8% of women who had a birth record in AMND migrated out of the region during the study period. (131) Differential loss to follow up of women is unlikely to have contributed to the observed associations as any migration is unlikely to have been influenced by CVD outcomes. Additionally, women who had births outside the Grampian region during the follow-up period were excluded to minimise potential measurement errors of PPH.

4.6.3.2 Limitations

As with all studies using routine healthcare data, there are some limitations related to data accuracy, and availability of certain variables. Although it was possible to adjust for a wide range of potential confounders, no information was available about factors linked to pre-pregnancy health risk for CVD, including blood pressure, lipid profile, genetic factors, and diet and lifestyle factors. It was not possible to identify the causes of PPH (e.g. uterine atony, placental abruption, etc.) from available data and therefore it was not possible to stratify aHRs by cause of PPH.

As a 'time to (first) event' analysis was conducted, 91% of the first events contributing to the composite CVD outcome were CVD-related prescriptions. Unlike CVD-related hospitalisation and death data, the prescription data did not permit identification of a specific CVD diagnosis

because similar medications could be prescribed for different types of CVD. For instance, calcium channel blockers such as Amlodipine are commonly prescribed to treat both stable angina and hypertension. (161) It was therefore not possible to report specific CVD diagnoses, and therefore infer severity, associated with the CVD outcome events. This limitation was partially addressed by conducting exploratory analyses describing the sequence of outcome events following the first outcome event. Sensitivity analysis was also used to explore whether the observed associations were the same for women with more severe outcomes, by restricting the composite outcome to CVD-related hospitalisations only. The latter analysis showed similar findings to the main analysis, supporting the evidence of increased aHRs between PPH and CVD up to five years, with diminishing and non-significant aHRs beyond five years after birth in both PPH groups.

Another potential weakness of this study is related to the choice to begin follow up at the woman's first birth, regardless of the timing of PPH. This decision meant that women who had more than one birth and had their first PPH in a second or subsequent birth had extra follow-up time. Since 66% of women had a PPH in their first birth, the potential effects of this might be to bias the aHRs towards the null with a slight underestimation of the association between PPH and CVD.

As this study was conducted in a Scottish population in which only 4% were from Black, Asian and other ethnic minority groups, it may not be generalisable to the other nations of the UK, or to other HICs with more diverse populations. It is also possible, given that exclusion criteria were applied for women who moved out of the Grampian region and gave birth elsewhere during the follow up period, that the results may not be applicable to these women, particularly if they have a different socio-demographic profile and risk factors.

4.6.3.3 Implications for clinical practice and research

To fully distinguish a pregnancy complication as an independent risk factor or a marker of pre-existing cardiovascular risk, it is important to collect pre-pregnancy health status of women, including potential genetic risk factors, physical activity, smoking and alcohol consumption. A comprehensive life-course study of women before, during and after pregnancy would be required to fully understand the complexities of the causal pathway between childbirth complications, including PPH, and CVD. Although effect modification for mode of birth and HDP were explored in this study, potential effect modification by timing and frequency of PPH was not explored because PPH was classified as 'Any PPH' to simplify the analysis. However, future studies should investigate this.

Women may experience other obstetric complications together with PPH, either at the same birth or in other subsequent births, rather than just an isolated episode of PPH. Therefore, future studies should be conducted to investigate the impact of such obstetric complications on women's health, to investigate possible heterogeneity in cardiovascular risk based on their lifetime parity and cumulative experience of obstetric complications beyond the first birth. This will help us to better understand the lifetime cardiovascular risk of women.

At the clinical level, the obstetric history of PPH, along with other important obstetric complications, should be integrated into risk prediction tools and heart risk assessment tools to structure efficient primary prevention and early intervention for CVDs. Women who have had a PPH, and other childbirth complications such as pre-eclampsia, preterm birth, and gestational diabetes, should be identified as high-risk groups regardless of whether these factors are considered as independent risk factors or early indicators of existing cardiovascular risk. The year after birth should be considered as an opportunity for such women to be offered

screening and early interventions for CVDs, including lifestyle modifications. The six-week postpartum check offers the opportunity for such screening to be introduced.

4.7 Conclusions

This study found that compared with women who have never had a PPH, women who have had at least one PPH are twice as likely to develop CVD in the first year after birth and some increased risk persists for up to 15 years, after adjustment for potential confounders. Severity of PPH does not seem to alter this association. The associated risk was slightly higher among women who had one episode of HDP, indicating some evidence of effect modification. Since women who had outcomes were identified using CVD-related prescriptions and hospitalisation, the findings may not be applicable to women who are not having medications or hospitalisation from CVD such as women with untreated or controlled hypertension managed with lifestyle modifications. PPH should be considered as an early indication for subsequent CVD, and women with such obstetric history should be followed up regularly in the first postnatal year for early identification and intervention.

Chapter 5. Primary PPH and mental health outcomes: A Scottish population-based record-linked cohort study

5.1 Introduction

Anxiety, depression, and PTSD have been observed to be more prevalent among women who have had a primary PPH than in the general perinatal population. Specifically higher prevalence has been found in those women who required intensive medical and surgical interventions such as blood transfusion, arterial embolization or EPH following PPH. (67, 70, 71) Such births are reported to be traumatic by women in qualitative studies. particularly when intensive surgical interventions were involved. (52, 103) Therefore, it was hypothesised that PPH might lead to longer-term mental health problems mediating through birth trauma, and the need for longer recovery from birth.

The systematic review reported in Chapter 3 found limited evidence for an association between PPH and longer-term mental illness. Studies reported inconsistent results and used symptom checklists or general health questionnaires as indicators of mental health, rather than diagnosis and/or treatment. Three recent studies, published after the systematic review, have reported the relative risk of postpartum depression and mental illness associated with PPH, and reported inconsistent results. (69, 162-164) Women's narratives from qualitative studies highlighted that they experienced psychological symptoms which for some lasted many years

after birth, particularly for women who had undergone intensive interventions. (52, 67, 100, 103, 104) Again it is unclear if these symptoms actually led to diagnosis and treatment.

An additional consideration informed by research in the general perinatal population is that the presence of mental illness in the immediate postnatal period can affect a woman's mental health over time. (165) Research indicates that women who experience perinatal depression and anxiety are more susceptible to long-term psychiatric disorders. (165) A cohort study in Denmark that followed up 132 women with a first psychiatric episode within 0-12 months postpartum suggested that having a first psychiatric contact within a month postpartum was associated with increased risk of conversion to bipolar disorder with a higher risk among postpartum inpatient admissions compared with outpatient contacts (RR=2.16, 95% CI=1.27-3.66). (166) Less is known about the trajectories of birth-related PTSD, with some evidence suggesting that 13% of women who had birth related PTSD at 4-6 weeks postpartum may progress to chronic PTSD at 12 months postpartum. (167) Therefore, it is important to consider the potential effect modification of perinatal mental illness when investigating the association between PPH and longer-term mental illness.

In summary, most quantitative studies to date have focused on the prevalence of perinatal mental illness following PPH in the first postnatal year and lacked appropriate comparison groups and objective clinical assessments. Very few quantitative studies that examined the association between PPH and longer-term mental illness had appropriate comparison groups and reported relative risks. (68, 71, 162-164) As there is limited and conflicting evidence, and given a potential link between PPH and a traumatic birth experience for women, (104) which may in turn increase the risk of longer-term mental illness, further investigation of an association between PPH and longer-term mental health outcomes, beyond the first postnatal

year, and while considering the potential impact of postnatal mental illness within the first postnatal year, was considered worthwhile.

5.2 Aim and objectives

The primary aim of this study was to investigate the association between primary postpartum haemorrhage and longer-term mental illness, beyond the first postnatal year. The specific objectives were:

1) To estimate the incidence of longer-term mental illness among women who have had at least one PPH, including severe PPH, compared with women who have never had a PPH.
2) To estimate the relative risk of longer-term mental illness among women who had at least one PPH, including severe PPH, compared with women who have never had a PPH.
3) To investigate whether any association between PPH and longer-term mental illness is modified by the presence of postnatal mental illness or mode of birth.

5.3 Methods

5.3.1 Study Design

A population-based retrospective cohort study design was used. Data about maternal and neonatal characteristics from the AMND were linked to the following Scottish routine data sources: SMR01, SMR04, PIS, NRS deaths, and Trakcare (as described in Chapter 4), pseudo-anonymised and accessed through the Grampian Data Safe Haven via secure VPN.

5.3.2 Exposures of interest

The main exposure of interest was primary PPH (blood loss of 500ml or more within 24 hours birth), as defined in Chapter 4, section 4.4.4. The presence of postnatal mental illness can affect a woman's mental health over time. (165) Research indicates that women who experience perinatal depression and anxiety are susceptible to long term psychiatric disorders. (168, 169) Therefore, within the study cohort, women were grouped into four exposure groups based on (i) whether they had a primary PPH in any of the birth records in AMND and (ii) whether they had 'postnatal mental illness'. For all analyses, postnatal mental illness was defined as having a record of (a) prescription of psychotropic medication and/or (b) a mental health related hospitalisation, within one year of any of their birth records in AMND.

Four exposure groups were defined:

1. Women who did not have a PPH and did not have 'postnatal mental illness' as defined above (No PPH and No MH1, 'unexposed' reference group)
2. Women who did not have a PPH, but had postnatal mental illness (No PPH and MH1)
3. Women who had at least one PPH, but had no postnatal mental illness. (Any PPH and No MH1)
4. Women who had at least one PPH, and had postnatal mental illness. (Any PPH and MH1)

The secondary exposure in this study was severe primary PPH, as defined in Chapter 4, section 4.4.4. For analyses relating to severe PPH, the following exposure groups were used.

1. Women who did not have a PPH and did not have postnatal mental illness (No PPH and No MH1, 'unexposed' reference group)

2. Women who did not have a PPH, but had postnatal mental illness. (No PPH and MH1)
3. Women who had at least one severe PPH, but had no postnatal mental illness (Any severe PPH and No MH1)
4. Women who had at least one severe PPH, and had postnatal mental illness (Any severe PPH and MH1)

By defining exposure groups based on a history of postnatal mental illness, it was possible to investigate the independent impact of having PPH on women's longer-term mental illness.

5.3.3 Identification of eligible cohort/records

This study used birth records from the same cohort of women described in Chapter 4. The inclusion and exclusion criteria were applied in two steps to identify eligible women. The following were applied as a first step:

5.3.3.1 Inclusion criteria

- Women who gave birth after 24 weeks of gestation between 1st January 1986 and 31st December 2016.
- Women for whom the first completed birth was recorded in AMND (i.e. parity at the first recorded antenatal visit in AMND was zero) and all of their subsequent births occurred in the Grampian region during the study period. The purpose was to minimise the misclassification of exposure to PPH by excluding women who may have had one of her births elsewhere. Births after the end of study period (i.e. 31st Dec 2016) were not taken into account as no relevant data were available.
- Singletons and multiple births

- Permanent registered patients with NHS Scotland (Patient category- NHS) to minimise loss to follow up of visitors.

5.3.3.2 Exclusion criteria

- Women whose first birth of more than 24 weeks of gestation was not recorded in AMND or was before 1st Jan 1986 (i.e. parity at the first recorded antenatal visit in AMND after 1st January 1986 was one or more).
- Women where parity information was conflicting (for example, where parity was recorded as the same number for two different birth records of the same woman with >24 weeks of gestation).
- All birth records for women who had at least one birth outside of the Grampian region (i.e, where parity recorded for two different birth records of the same woman with >24 weeks of gestation was not consecutive).
- Birth records occurring after the mental health outcome event.
- Birth records for which the inter-pregnancy interval was less than a year, or where the date of transfer out of the Grampian region was less than a year from the most recent previous birth (in order to appropriately derive exposure groups based on mental illness within one year of birth).

After application of these exclusions, it was found that there were very few records in the 'No PPH and MH1' and 'Any PPH and MH1' exposure groups for the years 1986-2007. This was because prescriptions data from PIS was only available from 2008 and most of the data to identify women with postnatal mental illness came from PIS (Appendix 13, Table A13.1). It was therefore decided to apply a further exclusion criterion as a second step. This excluded:

- Women whose first birth was before 1st January 2008.

The final cohort therefore comprised eligible women who gave birth between 1st January 2008 and 31st December 2016.

Women with a previous history of mental illness were not excluded from the final cohort due to the relapsing and recurrent nature of mental illness. (170, 171)

5.3.4 Outcomes and measurements

5.3.4.1 Rationale for a composite mental health outcome

The primary outcome for this study was 'longer-term mental illness', measured at up to 10 years after the first postnatal year. A composite outcome was used to capture a wide range of common mental illnesses. Existing evidence about PPH and postnatal mental illness was considered and a wide range of diagnoses were included to account for more common illnesses such as anxiety and depression and some relatively rare mental illnesses including psychotic disorder and dementia.

5.3.4.2 Operationalising the definition of longer term mental illness

After defining the composite longer term mental health outcome, individuals with outcome events were identified from four different data sources to assess the mental health related hospitalisation, prescription or death. This composite mental health outcome was defined as the time to first occurrence of one of the following after the first birth (excluding any occurrence in the first postnatal year after any birth):

- At least three prescriptions within any 365-day period of selected medications commonly used to treat mental illness such as depression, anxiety, and psychosis. This

was used to identify regular medication for mental illness and to exclude the prescription of such medication for other indications including, for example, a one-off prescription of a sleeping pill.

- Any mental health related hospitalisation with selected mental illness recorded as the main condition of diagnosis or in any other diagnostic fields
- Death in which the main or secondary cause was suicide, or intentional self-inflicted injury or poisoning.

Table 5.1 shows how these outcome events were operationalised within each of the data sources used.

Table 5.1 Summary of the composite mental health outcome with operationalised definitions and data sources

Mental health outcome event	Data Source	Definition(s)
First prescription date of selected psychotropic medications followed by two or more prescriptions of psychotropic medication within any 365-day period following the first PPH (exposed group) or following the first birth (unexposed groups), excluding the first postnatal year after any birth	PIS	Commonly prescribed psychotropic medications (172) in the following legacy British National Formulary (BNF) sub-sections: 4.1.1. Hypnotics; 4.1.2 Anxiolytics, used for relief of anxiety; 4.2. Antipsychotics and antimanic medications, used to treat psychosis and related disorders; 4.3 Antidepressants BNF item "Amitriptlyine Hcl Tab 10mg" was excluded as it has non-psychotropic (pain and migraine) use.
First date of mental health related hospitalisation following the first PPH (exposed group) or following the first birth (unexposed groups), excluding the first postnatal year after any birth	SMR01, SMR04	Hospital discharge with any of the following ICD-10 diagnostic codes recorded as main condition of diagnosis or in any diagnostic field: F40-49 Stress related disorder including anxiety; F30-39 Mood affective disorder including bipolar affective disorder and depressive disorder, F20-29 Schizophrenia and delusional disorder, F00-F09 Dementia, X60-84 Intentional self-inflicted injury and poisoning.
Date of death from suicide, or intentional self-inflicted injury or poisoning	NRS deaths	Deaths from any of the following ICD-10 codes recorded as the main or secondary cause: X60-84 Suicide, self-inflicted injury or poisoning.
Note: All the outcome data were identified from the PIS, SMR01,SMR04 and NRS deaths records from the Grampian region, including the Northern Isles.		

5.3.5 Potential confounders and effect modifiers

The same conceptual hierarchical framework described in section 4.4.6 of Chapter 4 was applied to explore potential confounders of the association between PPH and longer-term mental illness (Appendix 8).

5.3.6 Duration of follow up

The follow up for each woman began from one year following the date of their first birth recorded in the AMND between 2008 and 2016 for all exposure groups, regardless of whether the woman had a PPH in her first birth. As explained in Chapter 4, this decision was made a priori due to the lack of an 'index birth' for women who did not have a PPH, and the assumption that women were at some risk of mental illness even before they were under observation. This approach also ensured that follow-up duration was comparable across the four exposure groups.

The first postnatal year following any birth, including the first birth, did not contribute towards the total follow-up duration since exposure groups were defined based on whether the woman had postnatal mental illness, within the first year of any birth. Women could not therefore be at risk of developing the outcome during the first postnatal year after any birth.

Data linkage for outcomes was completed up to 31st December 2016. The duration of follow-up therefore ranged from a minimum of one year (excluding the first postnatal year) for a woman whose first birth was in 2016 to a maximum of 10 years for a woman whose first birth was in 2008 (Figure 5.1).

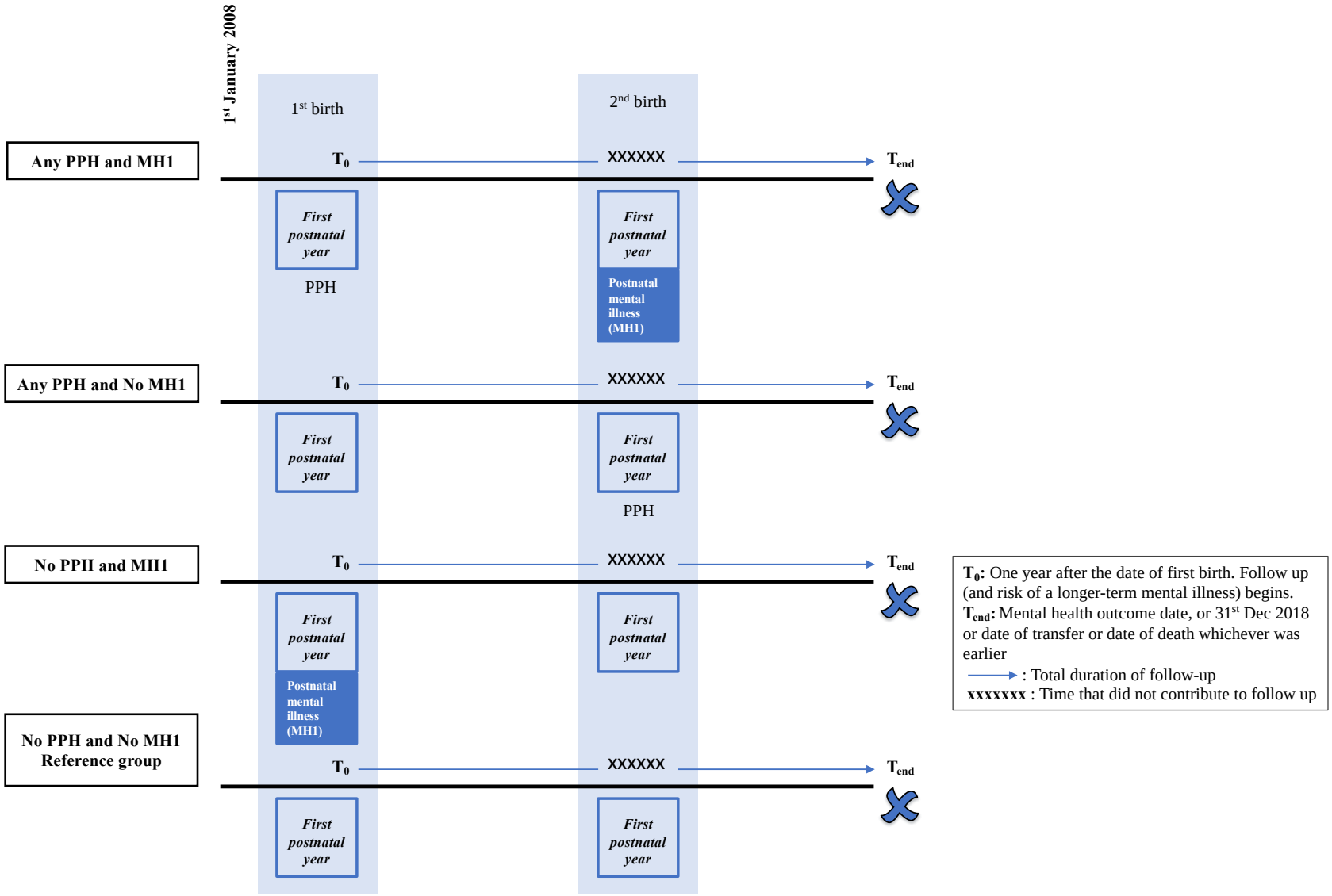


Figure 5.1 Follow-up duration for women in different exposure groups

The follow up period for all women ended on:

- 31st December 2018 (the end date of the period covered by the data linkage),

  or

- The date the woman experienced the outcome event (censored),

  or

- The date the woman became lost to follow up (e.g. date of migration outside the Grampian region, as recorded in Trakcare) (censored),

  or

- The date of death (recorded in NRS deaths) (censored),

whichever came earlier (Figure 5.1).

5.3.7 Ethical considerations and data access permissions

All the required data approvals were received, as described in Chapter 4, section 4.4.8.

5.3.8 Linking and merging data from different linked datasets

The AMND was the main dataset for this study. The information about the presence of postnatal mental illness within one year of birth was extracted from SMR01, SMR04 and PIS. The exposure platform file was generated by the author using the linkage and merge steps described in Box 5.1A and Figure 5.2.

Box 5.1A. Data linkage and merging steps for exposure platform file (See Figure 5.2)

Step 1: Using 'Preg_VS' data file (i.e. the AMND birth records merged with 'date of transfer' and 'date of death' information from Trakcare), the sequence variable 'birthseq' was generated using the value of 'parity' variable. Date of PPH was used to generate the variable 'PPH date' for women with a PPH, which was set to missing for women with no PPH or unknown PPH status. 'Study ID', 'birthseq', 'birth date', and 'PPH date' variables were kept.

Step 2: The data were reshaped from 'long' format (one row per birth) into 'wide' format (one row per woman) using study ID and birth sequence number. This file was saved as 'Preg_mhexp_dta'.

Step 3: In the SMR01 and SMR04 data files, all records mentioning mental health related ICD-10 codes (Table 4.1) were tagged. 'Admission date' variable was renamed 'date'. An indicator variable 'type' was created and set to 1 to indicate that these were hospitalisation records from SMR01 and SMR04. Three variables: 'Study ID', 'date' and 'type' variables were kept in each file and the data files were saved as 'SMR01_exp' and 'SMR04_exp' respectively.

Step 4: In the PIS data file, all records mentioning the relevant psychotropic medication codes (Table 5.1) were tagged. A mental health prescription variable 'Mhpresc' was generated, and set to 1 for a tagged record, and 0 for others. Prescription date variable 'presdate' was renamed 'date'. An indicator variable 'type' was created and set to 2 to indicate these were psychotropic medication records from PIS. Three variables: 'Study ID', 'date' and 'type' variables were kept and the file was saved as 'PIS_exp'.

Step 5: Files: 'SMR01_exp', 'SMR04_exp', 'PIS_exp' were appended to create 'mh_exp' file which contained the information to generate 'postnatal mental illness' for the exposure.

Step 6: The main birth data file 'Preg_mhexp' was merged with "mh_exp" file using a many-to-one match on 'Study ID'.

Step 7: An indicator variable 'PPH_mh' was generated and set to 1 if there was a mental health related prescription or hospitalisation within one year after PPH date, and 0 if not. Another indicator variable 'birth_mh' was generated and set to 1 if there was a mental health related prescription or hospitalisation within one year after birth date, and 0 if not.

Step 8: Women with more than one birth had multiple values for 'PPH_mh' and 'birth_mh' variables for each birth. These multiple values from different births for the same woman were collapsed using the 'collapse' function in Stata, and only the highest value was kept**.** The data were then reshaped from the wide format (one row per woman) into the long format (one row per birth) using Study ID and birth sequence. A categorical variable 'PPHmh_cat' was generated to indicate the exposure groups and set to 0 for births with no PPH and no postnatal mental illness (i.e. no prescription or hospitalisation within 1 year after birth date); 1 for births with PPH and no postnatal mental illness; 2 for births with no PPH and and postnatal mental illness; and 3 for births with both PPH and postnatal mental illness.

Step 9: Three variables: **'s**tudy ID', 'birth sequence' and 'PPHmh_cat' were kept. This data file was merged with the main birth datafile 'Preg-VS' and saved as the exposure platform file, 'Preg_VS_Mhexp'.

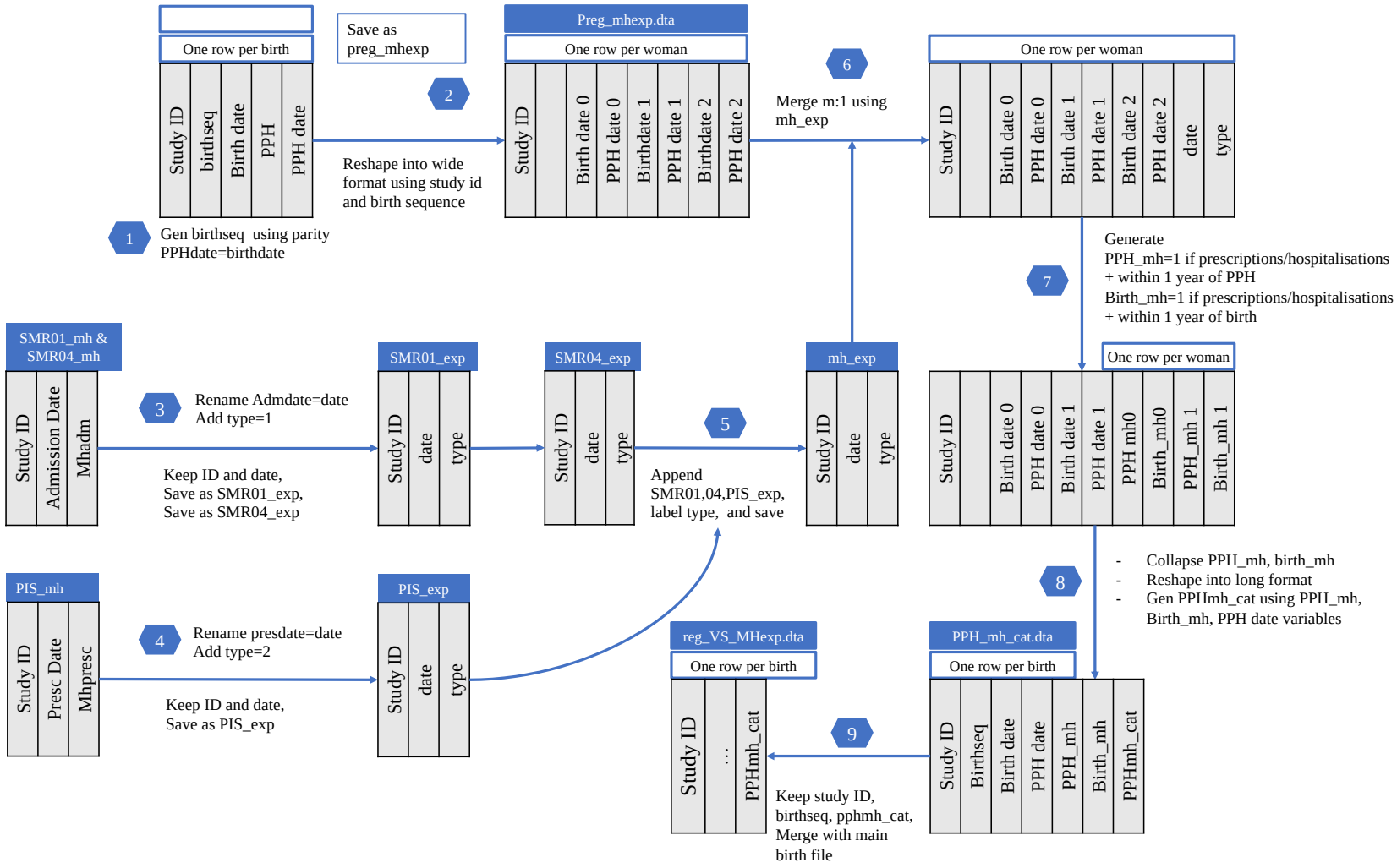


Figure 5.2 Data linkage flow diagram demonstrating the steps in generating the exposure platform file

After the exposure platform file was generated, the outcome platform files were merged by the author from five different data sources to this main dataset following the steps and specifications detailed in Box 5.1B and Figure 5.3**.**

Box 5.1B. Data linkage and merging steps for outcome platform file and final linked file (See Figure 5.3)

Creating mental health outcome platform file (Steps 1 to 9)

Step 1: In the SMR01 and SMR04 data files, all records mentioning the relevant mental health outcomes ICD-10 codes (Table 5.1) were tagged. A mental health admission variable "mhadm" was generated and set to 1 for a tagged record and 0 for others. An indicator variable 'type' was created and set to 1 to indicate these were hospitalisation records from SMR01 and SMR04.

Step 2: A sequence variable was created numbering tagged records within each unique ID in the ascending order of hospital admission date. Only mental health related hospitalisation records were retained and the files were saved as 'SMR01_mh' and 'SMR04_mh" data files. The hospital admission date variable 'admdate' was renamed as 'date'. Four variables: 'Study ID', 'date', 'sequence', and 'type' were then kept to create the cut down files 'SMR01_mhcutdown' and 'SMR04_mhcutdown'.

Step 3: In the PIS data file, all records mentioning the relevant psychotropic prescriptions (Table 5.1) were tagged. A mental health prescription variable 'mhpresc' was generated and set to 1 for a tagged record, and 0 for others. The prescriptions records with the BNF item name description 'Amitriptlyine Hcl' and the BNF item strength description '10mg" were dropped according to the specifications in the outcome assessment.

For outcome ascertainment for psychotrophic prescriptions, a 'year' variable was generated using the date of prescription. The time interval between subsequent prescriptions was calculated. An indicator variable 'mhpresc3' was generated and set to 1 for women who had three or more eligible prescriptions within any 365-day period and 0 for women with less

than three prescriptions, including no prescription. An indicator variable 'type' was created and set to 2 to indicate these were prescription records from PIS.

Step 4: A sequence variable was created numbering tagged prescription records (i.e. a minimum of three prescriptions in any 365-day period) within each unique ID in the ascending order of prescription date. The prescription date variable 'presdate' was renamed as 'date'. Four variables: 'Study ID', 'date', 'sequence', and 'type' were then kept, creating the cut down file 'PIS_mhcutdown'.

Step 5: In the NRS death data file, all death records mentioning relevant ICD codes for suicide and self-inflicted injuries (Table 5.1) as a primary or secondary cause of death were tagged. A mental health related death variable 'mhdeaths' was generated and set to 1 for a tagged record and 0 for others. An indicator variable 'type' was created and set to 3 to indicate these were death records.

Step 6: Tagged records were retained and the file was saved as 'NRS_mh'. The date of death variable 'DoD' was renamed as date. Four variables 'Study ID', 'date', sequence, and type was then kept to create the cut down file 'dth_mh cutdown'.

Step 7: Four outcome data files: 'SMR01_mhcutdown', SMR04_mhcutdown', 'PIS_mhcutdown' and 'dth_mhcutdown' were appended to create an antepenultimate mental health outcome platform file 'mhantepenult..dta'.

Step 8: The data file 'mhantepenult' was merged with the birth records data file in the wide format (one row per woman) 'Preg_mhexp' (Box 4.1A, Step 2) using a many-to-one match on 'Study ID'.

Step 9: Mental health outcome records where the 'date' fell within the first postnatal year were tagged. These records were dropped to avoid overlap between exposure and outcome measurement. This file contained the multiple records of prescriptions, hospitalisation, and death record (if any) for each individual ID. Therefore, any individual ID could have more than one outcome event.

A file sequence variable 'sequence' was generated numbering outcome events within each unique ID in the ascending order of the 'date' for these multiple records. The first record of a mental health outcome event (i.e. sequence=1) was kept as an index record. This contained the first record of either hospitalisation, or prescription or death, whichever was the earliest. Therefore, in this file any individual ID could only have one outcome record. The variables: 'date' and 'type' were renamed as 'mhdxdate' and 'mhdxtype'. This file was saved as an ultimate mental health outcome file 'mh_utlimate'.

Merging the main birth record file with the ultimate mental health outcome file

Step 10: The exposure platform file 'Preg_VS_MHexp' was merged with the outcome platform file 'mh_ultimate' using a many-to-one match on 'Study ID'. An indicator variable 'mhdx' was generated for the mental health composite outcome and set to 1 if there was a record of a mental health outcome event from the outcome platform file (i.e, if mhdxdate was not missing) and set to 0 if not. The linked datafile was saved as 'Preg_VS_MH1'.

Setting start and end date of follow up for each birth record

Step 11: Birth records were reshaped from long form (one row per birth) into wide format (one row per woman) by using Study ID and parity sequence number. A 'start' variable was generated by adding 365 days to the date of birth. An 'mhend' variable was generated and set to the date of subsequent birth or the date of the mental health outcome event if a mental health outcome event occurred between births, or the date of end of follow up (i.e. end of data linkage) for the final birth record (Figure 5.3). The data were then reshaped into long format (one row per birth) and saved as 'mh_followup_time'. The 'mh_followup_time' file was merged with the linked data file 'Preg_VS_MH1' and this file, including the start and end date of follow up for each birth record, was saved as 'Preg_VS_MH2'.

Generating key exposure variables

Step 12. A categorical variable 'any_pphmh' was generated using the "PPH_mhcat" variable **(Box 4.1A, Step 8)** and set to 0 for women who did not have a PPH and had no postnatal mental illness; 1 for women who did not have a PPH, but had at least one record of postnatal mental illness; 2 for women who had at least one PPH, but had no postnatal

mental illness; and 3 for women who had at least one PPH and at least one record of postnatal mental illness. Another categorical variable 'any_sevpphmh' was generated for severe PPH using the same approach. The data file was saved as 'Preg_VS_MH3'.

Final cohort restriction

Step 13: Exclusions were applied for the following: all birth records of women after occurrence of a mental health outcome event; all birth records of women with an interpregnancy interval of less than one year or a date of transfer within a year of childbirth; all birth records of women whose first birth was before 1st January 2008. The linked data file with the final eligible cohort was saved as 'PPH_VS_MHfinal'.

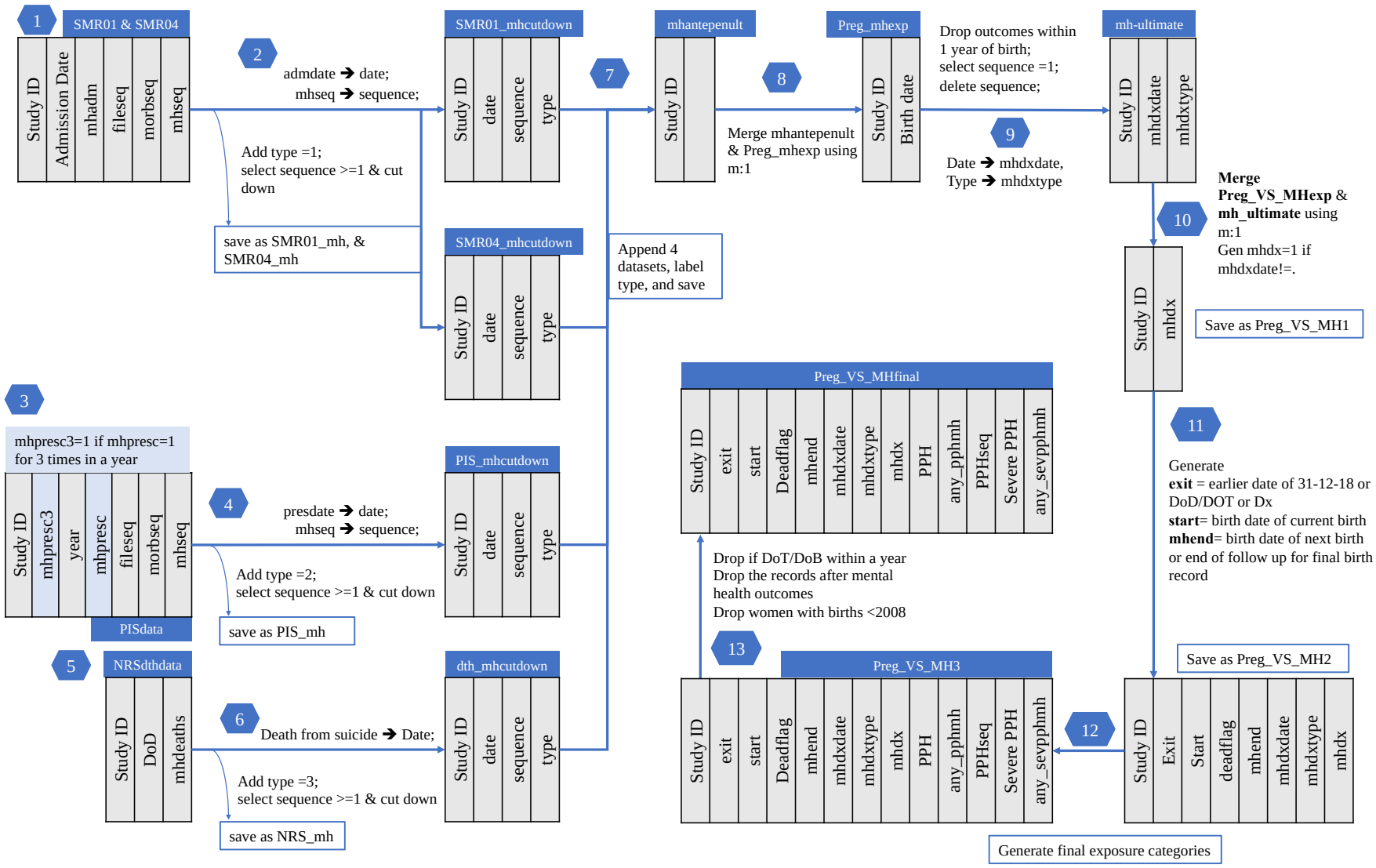


Figure 5.3 Data linkage flow diagram demonstrating the steps in generating the final linked dataset

5.3.8.1 Description of final linked dataset for mental health outcomes and derived variables

Table 5.2 summarises the key exposure and outcome variables, including 'time' variables generated for the time to event analysis and, where applicable, how derived variables were generated. Variables for the following co-variates: sociodemographic and clinical characteristics; maternal past medical history, except the variable 'previous psychiatric mental health disorder'; birth characteristics; and obstetric characteristics are all defined and described in Chapter 4 (Table 4.4).

Table 5.2 Data sources, codes, and data fields used to generate key exposure and outcome variables

Variable	Data Source	Type	Database field/codes	Categories or units of measurements
Key exposure variables				
Any PPH and/or MH1	AMND, PIS, SMR01, SMR04	Categorical	Derived variable, generated using a combination of whether or not a woman had at least one record of PPH and/or postnatal mental illness (psychotropic medication or mental health related hospitalisation within one year of birth in any eligible birth records).	0-No PPH and No MH1 1-No PPH and MH1 2-Any PPH and No MH1 3-Any PPH and MH1
Any severe PPH and/or MH1	AMND, PIS, SMR01, SMR04	Categorical	Derived variable, generated using whether or not a woman had at least one record of severe PPH and/or postnatal mental illness	0-No PPH and No MH1 1-No PPH and MH1 2-Any severe PPH and No MH1 3- Any severe PPH and MH1

Variable	Data Source	Type	Database field/codes	Categories or units of measurements
Past medical history				
Previous history of psychiatric and mental health disorder	AMND, PIS, SMR01, SMR04	Categorical	Derived variable, set to 'Yes' when past medical history codes from AMND matched ICD-10 descriptions for F01-F99, or when there was a record of psychotropic medication or hospitalisation from SMR 01,04, PIS before the date of first birth, and 'No' for others.	Yes; No
Key outcome variables				
Mental health outcome	PIS, SMR01, SMR04, NRS deaths	Categorical	First record of: at least three prescriptions within any 365-day period of selected psychotropic prescriptions or mental health related hospitalisation or death with suicide, self-inflicted injuries as underlying cause.	Yes; No
Mental health outcome date	PIS, SMR01, SMR04, NRS deaths	Date	Date of mental health outcome event	Date
Variables for time to event analysis				
Start	AMND	Date	Derived by adding 365.25 days to the 'date of delivery' variable	Date
MH End	AMND, SMR01, PIS, Trak care, NRS deaths	Date	Derived variable, generated using date of next birth record, or 'Mental health outcome date' if an outcome event occurs between two birth records, or end of follow-up if it was the final birth record during the follow up period. *Note: Follow-up ended on 31 Dec 2018 or date of death, date of transfer or date of first outcome event whichever was earlier.*	Date

5.3.9 Statistical analysis

5.3.9.1 Descriptive analysis

Maternal socio-demographic and clinical characteristics were summarised for women, and separately for births, by exposure group. Means and standard deviations were reported for continuous variables, and counts and percentages for categorical variables. The sequence of mental health outcome events was explored and summarised in a figure. This included: the number of each type (prescription, hospitalisation or death) of 'first occurrence' (i.e. primary outcome) of a mental health outcome event, followed by the number of 'second occurrence' mental health events i.e. the number of women who had a mental health related hospitalisation after having a mental health related prescription, and the number of women with a mental health related prescription after a mental health related hospitalisation.

5.3.9.2 Univariable analysis

Univariable survival analysis was performed using Cox proportional hazards regression models to assess the association between PPH and mental health outcome-free survival. Unadjusted incidence rates, the number of women with a mental health outcome event divided by follow-up time in person-years, were calculated separately for each of the four exposure groups for PPH: 'No PPH and No MH1', 'No PPH and MH1', 'Any PPH and No MH1', 'Any PPH and MH1' and for the corresponding exposure groups for severe PPH.

Univariable Cox proportional regression models were used to estimate hazard rate ratios (HRs) with 95% CIs for each of the three 'exposed' groups for PPH, and also for severe PPH, compared with women who did not have a PPH and had no postnatal mental illness, and using the same approach for the sub-group of women who had a severe PPH.

5.3.9.3 Investigating potential confounders

The same potential confounders as in Chapter 4, section 4.4.10.3 were investigated using the classical approach, fitting a logistic regression model between the potential confounder and PPH, and fitting a Cox regression model between the potential confounder and the mental health outcome event. The conceptual framework diagram was applied to ensure that the adjusted variables in the multivariable model were not on the causal pathway (Appendix 8). The potential confounding variables which were considered, and the variables included in the analysis are summarised in Table 5.3.

Table 5.3 Summary of potential confounding variables considered and then included in multivariable models

Characteristics	Potential confounding variables explored/considered in the analysis	Variables included in multivariable models[a]
Sociodemographic characteristics	• Ethnicity • Year of birth of baby • Residence status • Socioeconomic status (Social class, Deprivation category, Scottish index of multiple deprivation (SIMD)) • Blood group • Maternal age at birth • Body mass index (BMI) at first antenatal visit	• Ethnicity • Year of birth • SIMD • Maternal age at birth • BMI at first antenatal visit
Co-morbidity and past medical history	• Anaemia and bleeding disorders • Diabetes • Self-reported history of CVD • Congenital heart disease • Chronic renal disease • Hepatitis B and C • HIV • Chronic autoimmune disease • Psychiatric and mental disorder	• Anaemia and bleeding disorders • Diabetes • Self-reported history of CVD • Congenital heart disease • Psychiatric and mental disorder • Smoking status

Characteristics	Potential confounding variables explored/considered in the analysis	Variables included in multivariable models[a]
	• History of alcohol and substance abuse/self-inflicted injury • Uterine fibroids • Gynaecological cancers • Smoking status	
Obstetric characteristics	• Parity • Mode of birth • Multiple gestation	• Mode of birth
Obstetric complications	• Gestation diabetes • HDP • Antepartum haemorrhage • Antenatal Anaemia • Pre-labour rupture of membrane (PROM) or prolong pre-labour rupture of membrane (PPROM) • Postpartum complications including puerperium wounds and infections	• Gestational diabetes • HDP • PROM or PPROM
Baby's characteristics	• Gestational age at birth • APGAR score • Outcome of the baby • Weight of the baby • Admission to neonatal unit	• Gestational age at birth • Weight of the baby

[a]Variables were included in the multivariable models if they fully met all three criteria for the 'classical approach' to confounding and they were not strongly correlated with other covariates in the model. For these variables, information from each birth were used when adjusting for confounding.

5.3.9.4 Multivariable Cox proportional regression models

Multivariable Cox proportional hazards regression models, calculating aHRs with 95% CIs, were fitted by sequentially adjusting for each category of potential confounder starting with the baseline model adjusted for year of birth, followed by further adjustment for maternal age, ethnicity, BMI, and Scottish Index of Multiple Deprivation (Model 1). Model 2 built on Model 1 by further adjustment for past medical history (anaemia and bleeding disorders, diabetes, CVD, congenital heart disease, psychiatric and mental disorders) and smoking status.

Finally, the fully adjusted model (Model 3) further adjusted for mode of birth, obstetric complications (gestational diabetes, HDP, PROM or PPROM) and baby's characteristics (gestation at birth and birthweight). For these variables information from each birth of an individual woman were used to adjust for confounding in the multivariable model.

5.3.9.5 Investigating proportional hazard ratio assumptions

Log-log plots and the global proportional hazards test were applied to assess the proportional hazards assumptions using the same principles as described in Chapter 4, section 4.4.10.5.

5.3.9.6 Extended Cox regression models

Extended multivariable Cox regression models were used to explore if the association between PPH/severe PPH and longer-term mental illness changed over different follow-up time periods by using an interaction term between the exposure variables and time interval. The total follow-up time (t) of each woman was split into different time periods after birth: 'from 1-2 years' (excluding the first postnatal year), '3 to 5 years' and '6-10 years' after giving birth using the 'stsplit' command in Stata. Adjusted HRs were calculated for different follow-up time periods after birth to compare the hazard rates of longer-term mental illness among the three exposed groups with the unexposed group (No PPH and No MH1).

To explore whether having a PPH/severe PPH increased the risk of having a longer-term mental illness among women who had postnatal mental illness (i.e, the MH1 groups), a further exploratory analysis was carried out using the same extended Cox regression models, but changing the reference group from "No PPH and No MH1' to 'No PPH and MH1'. This approach provided further insight about the association between PPH and mental illness

among the MH1 group that might not have been evident when using "No PPH and No MH1' as the reference group.

5.3.9.7 Investigating potential effect modification

The main analysis, as described above, using four exposure groups, investigated whether the relationship between primary PPH/severe PPH and longer-term mental illness varied by whether the woman had a postnatal mental illness.

Potential effect modification of the association between PPH/severe PPH and longer-term mental illness was investigated for mode of birth by adding interaction terms to the final fully adjusted model and using likelihood ratio tests to check whether there was a statistically significant effect of these interaction terms.

5.3.9.8 Sensitivity analyses

Two sensitivity analyses were conducted using the final fully adjusted model (model 3) for the association between PPH/severe PPH and longer-term mental illness. The first of these was conducted to explore whether the association between PPH/severe PPH and longer-term mental illness was altered after removing births to women with a pre-existing history of psychiatric and mental health disorders. Births to women with a self-reported mental illness recorded in the 'past medical history' variable in AMND and births to women with a mental health outcome event before the date of their first birth were excluded.

A second sensitivity analysis was conducted to explore if there was any change in the association between PPH and longer-term mental illness if the outcome was restricted to the first occurrence of MH-related hospitalisation. Since the mental health outcome was restricted to hospitalisation only, four exposure groups for this analysis were re-generated based on PPH

status and postnatal mental illness, which was defined as having a record of a mental health related hospitalisation, within one year of any of their birth records in AMND (MHH1).In order to ensure that results were comparable with the main analysis, as well as making use of all available data, this sensitivity analysis was conducted in two separate cohorts: (i) a larger cohort, including all eligible women who gave birth between 1986-2016 which could be used since it did not rely on PIS data , and (ii) the same cohort as used in the main analysis, which included birth records of women who gave birth between 2008-2016.

5.3.9.9 Missing data

A 'missing' category was created for all other covariates with missing values to explore 'missingness'. The proportion and patterns of missingness for confounders were explored to determine the most suitable approach for handling missing data. The proportion of missing data was lower than 5% of the eligible births in this study. Since this is a cohort study using a routine administrative data, the missing values were less likely to be influenced by mental health outcome events. Therefore, a complete case analysis was performed using all the births data available for all co-variates in the multivariable model since it is a simple and efficient choice for this study because the amount of missing data is low with a large sample size. (145)

The other approaches to handle missing data such as multiple imputation was not applied as the risk of bias from making assumptions about the missingness patterns overweighs the benefits of imputation. (173, 174)

Data were analysed using Stata software version 16. (146)

5.4 Results

5.4.1 Cohort characteristics

The linked dataset contained information about 125,022 births from 72,593 women who gave birth between 1986 and 2016, 124,795 of which were births after at least 24 weeks of gestation (Figure 5.4). After all exclusion criteria were applied, the final cohort included data about 26,155 births to 18,798 women.

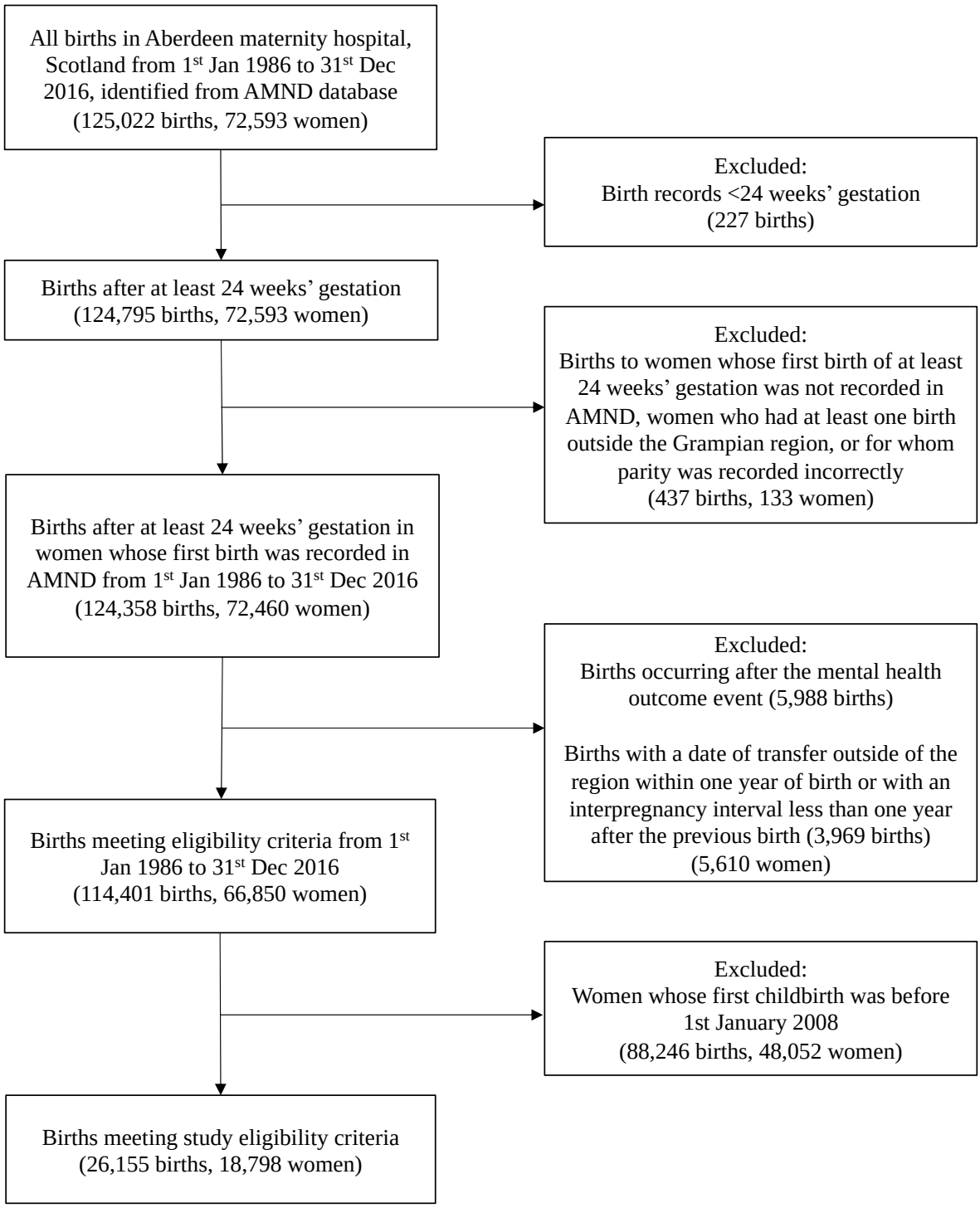


Figure 5.4 Cohort identification flow diagram

5.4.2 Characteristics of women

Of the eligible cohort of 18,798 women, 8,140 women (43%) had at least one primary PPH, including severe PPH, but did not have an indication of postnatal mental illness (i.e. mental health related prescriptions or hospitalisation in the year following any birth) (Any PPH and No MH1), and 1,027 women (5.5%) had at least one primary PPH and postnatal mental illness after at least one of their births (Any PPH and MH1) (Table 5.4). Overall, 2080 women (11%) had a mental health related prescription or hospitalisation in the first year after at least one of their births. Among the cohort, 61% of women (n=11,475) had one birth, nearly 35% (n=6,539) had two births, and the remaining 4% had three or more births. On average, women in the cohort were aged 28 at their first birth. Women who did not have a PPH, but had postnatal mental illness were on average younger than the other three groups, with a mean age of 25 years when they had their first birth.

Women who had a record of postnatal mental illness (No PPH and MH1, Any PPH and MH1) were more likely to be of White ethnicity, compared with the other two groups. Compared with women who did not have a PPH, women in both the 'PPH' groups were more likely to have a BMI of at least 30kg/m^2, with the highest proportion among women who had both a PPH and an indication of postnatal mental illness. At their first birth, women in both groups who had an indication of postnatal mental illness were more likely to have a previous history of psychiatric or mental health disorder. Women in both 'PPH' groups were more likely to be non-smokers, and were more likely to have a caesarean birth, compared with women who had not had a PPH.

Among the cohort, 9,631(51%) never had a PPH, whereas 7,795 (42%) had one PPH, and the remaining 1,372 women (7%) had a PPH on two or three occasions.

Table 5.4 Sociodemographic and clinical characteristics of the women included in the study

Characteristics	No PPH and No MH1[a] (Reference group)		No PPH and MH1[b]		Any PPH and No MH1[c]		Any PPH and MH1[d]		All women	
	n=8,578		n=1,053		n=8,140		n=1,027		n=18,798	
	n	%	n	%	n	%	n	%	n	%
Year of first childbirth										
2008-2012	4,879	56.9	718	68.2	4,634	56.9	706	68.7	10,937	58.2
2013-2016	3,699	43.1	335	31.8	3,506	43.1	321	31.3	7,861	41.8
Age at first childbirth (mean. SD)	28	5.5	25	6.1	29	5.3	28	6.0	28	5.6
<25	2,394	27.9	543	51.6	1,412	17.4	345	33.6	4,694	25.0
25-29	2,802	32.7	245	23.3	2,603	32.0	276	26.9	5,926	31.5
30-34	2,437	28.4	178	16.9	2,751	33.8	263	25.6	5,629	29.9
≥35	945	11.0	87	8.3	1,374	16.9	143	13.9	2,549	13.6
Ethnicity										
White	7,671	89.4	1,016	96.5	7,017	86.2	982	95.6	16,686	88.8
Black, Asian and Others	872	10.2	33	3.1	1,090	13.4	44	4.3	2,039	10.9
Missing	35	0.4	4	0.4	33	0.4	1	0.1	73	0.4
No. of births										
1	5,732	66.8	546	51.9	4,789	58.8	408	39.7	11,475	61.0
2	2,553	29.8	427	40.6	3,024	37.1	535	52.1	6,539	34.8
≥3	293	3.4	80	7.6	327	4.0	84	8.2	784	4.2
Scottish Index of Multiple Deprivation quintile at first birth										
1 (Most deprived)	1,152	13.4	179	17.0	971	11.9	177	17.2	2,479	13.2
2	1,360	15.9	196	18.6	1,197	14.7	182	17.7	2,935	15.6
3	2,014	23.5	188	17.9	2,011	24.7	221	21.5	4,434	23.6
4	2,794	32.6	311	29.5	2,898	35.6	331	32.2	6,334	33.7
5 (Least deprived)	370	4.3	14	1.3	425	5.2	11	1.1	820	4.4
Missing	1,152	13.4	179	17.0	971	11.9	177	17.2	2,479	13.2
BMI at first antenatal visit (kg/m^2) at first birth										
<18.5	308	3.6	49	4.7	175	2.2	30	2.9	562	3.0
18.5-24	4,841	56.4	562	53.4	3,906	48.0	447	43.5	9,756	51.9

Characteristics	No PPH and No MH1[a] (Reference group)		No PPH and MH1[b]		Any PPH and No MH1[c]		Any PPH and MH1[d]		All women	
	n=8,578		n=1,053		n=8,140		n=1,027		n=18,798	
	n	%	n	%	n	%	n	%	n	%
25-29	2,075	24.2	253	24.0	2,284	28.1	278	27.1	4,890	26.0
≥30	1,095	12.8	156	14.8	1,493	18.3	249	24.3	2,993	15.9
Missing	259	3.0	33	3.1	282	3.5	23	2.2	597	3.2
Past medical history before first birth										
Anaemia and coagulation disorders	78	0.9	12	1.1	111	1.4	11	1.1	212	1.1
Diabetes	31	0.4	<5	<0.5	71	0.9	10	1.0	112-116	<1
Psychiatric or mental health disorder	738	8.6	394	37.4	726	8.9	420	40.9	2,278	12.1
Cardiovascular disease	283	3.3	33	3.1	343	4.2	49	4.8	708	3.8
Congenital heart disease	27	0.3	7	0.7	39	0.5	11	1.1	84	0.5
Smoking status at first birth										
Non-smoker	6,691	78.0	607	57.6	6,839	84.0	737	71.8	14,874	79.1
Smoker	956	11.1	282	26.8	576	7.1	145	14.1	1,959	10.4
Ex-smoker	834	9.7	146	13.9	640	7.9	134	13.1	1,754	9.3
Missing	97	1.1	18	1.7	85	1.0	11	1.1	211	1.1
Mode of birth at first birth										
Spontaneous vaginal	5,482	63.9	678	64.4	1,795	22.1	250	24.3	8,205	43.7
Instrumental	2,152	25.1	270	25.6	2,522	31.0	314	30.6	5,258	28.0
Caesarean section	936	10.9	103	9.8	3,811	46.8	460	44.8	5,310	28.3
Missing	8	0.1	2	0.2	12	0.2	3	0.3	25	0.1
Number of PPH per woman										
Never had a PPH	8,578	100	1,053	100	NA		NA		9,631	51.2
1	NR		NR		6,905	85.0	890	87.0	7,795	41.5
2-3 times	NR		NR		1,235	15.0	137	13.0	1,372	7.3

[a] Women with no PPH and no postnatal mental illness
[b] Women with no PPH, but with postnatal mental illness after at least one birth
[c] Women with at least one PPH, but no postnatal mental illness
[d] Women with at least one PPH and with postnatal mental illness after at least one birth

5.4.3 Socio-demographic and clinical characteristics associated with births

Of all 26,155 births in the cohort, 9,698 (37%) were complicated by PPH, but the mother was not affected by postnatal mental illness in the year after birth, and 771 (3%) were complicated by both PPH and postnatal mental illness (Table 5.5). The 'row percentages' for the number and percentage of births with or without PPH and postnatal mental illness for each five-year interval highlight the increasing incidence of PPH over time from 36% to 38% between 2008-2012 and 2013-2016 among women who did not have postnatal mental illness, and the incidence of PPH varied little among women who had postnatal mental illness. The overall maternal age at birth in the cohort was 29 years, with a slighter younger maternal age (26 years) in births that were not complicated by PPH, but where the woman had postnatal mental illness in the year after birth. Compared with births not affected by PPH, a higher percentage of births affected by PPH, regardless of their postnatal mental illness status, were to women having a first baby.

The overall distribution of BMI, smoking and past medical problems among births in the cohort was similar to the distribution of these variables at first birth among women in the cohort (Table 5.4). A higher proportion of births affected by PPH, regardless of postnatal mental illness, were to women living in more deprived areas.

Compared with births unaffected by PPH, a higher percentage of births affected by PPH were instrumental births or caesarean births, regardless of postnatal mental illness status. Compared with births unaffected by PPH or postnatal mental illness, a higher percentage of births affected by either PPH or postnatal mental illness were multiple births. Births affected by PPH or where the mother had postnatal mental illness were also more likely to be affected by other

obstetric complications, with the highest percentage of these complications observed among births complicated by both PPH and postnatal mental illness. Babies born in births affected by PPH were more likely to be post term and were more likely to weigh more than 4000 grams, compared with babies born in births unaffected by PPH. Babies born in births where the woman had postnatal mental illness were more likely to be preterm and were more likely to weigh less than 2500 grams, compared with babies born in births unaffected by postnatal mental illness.

Table 5.5 Maternal sociodemographic and clinical characteristics of births

Characteristics	Births with no PPH and no MH1[a] n=14,442		Births with no PPH and MH1 n=1,244		Births with PPH and no MH1 n=9,698		Births with both PPH and MH1 n=771		All births n=26155	
	n	%	n	%	n	%	n	%	n	%
Year of childbirth (row %)										
2008-2012	7,402	55.6	702	5.3	4,810	36.1	396	3.0	13,310	100
2013-2016	7,040	54.8	542	4.2	4,888	38.1	375	2.9	12,845	100
Age at childbirth (mean, SD)	**29**	**5.4**	**26**	**6.2**	**30**	**5.3**	**29**	**6.3**	**29**	**5.5**
<25	3,268	22.6	558	44.9	1,466	15.1	223	28.9	5,515	21.1
25-29	4,405	30.5	293	23.6	2,833	29.2	179	23.2	7,710	29.5
30-34	4,686	32.5	253	20.3	3,436	35.4	221	28.7	8,596	32.9
≥35	2,083	14.4	140	11.3	1,963	20.2	148	19.2	4,334	16.6
Parity										
Primiparous	9,726	67.4	861	69.2	7,614	78.5	597	77.4	18,798	71.9
Parity 1	4,149	28.7	341	27.4	1,911	19.7	157	20.4	6,558	25.1
Parity ≥2	567	3.9	42	3.4	173	1.8	17	2.2	799	3.1
Scottish Index of Multiple Deprivation quintile										
1 (most deprived)	1,422	9.9	194	15.6	743	7.7	79	10.3	2,438	9.3
2	1,806	12.5	201	16.2	1,115	11.5	131	17.0	3,253	12.4
3	2,195	15.2	209	16.8	1,431	14.8	142	18.4	3,977	15.2
4	3,591	24.9	256	20.6	2,450	25.3	172	22.3	6,469	24.7
5 (least deprived)	4,929	34.1	366	29.4	3,470	35.8	238	30.9	9,003	34.4
Missing	499	3.5	18	1.5	489	5.0	9	1.2	1,015	3.9
BMI at first antenatal visit (kg/m^2)										
<18.5	463	3.2	50	4.0	182	1.9	18	2.3	713	2.7
18.5-24	7,817	54.1	636	51.1	4,542	46.8	315	40.9	13,310	50.9
25-29	3,714	25.7	307	24.7	2,723	28.1	204	26.5	6,948	26.6
≥30	2,085	14.4	215	17.3	1,955	20.2	214	27.8	4,469	17.1
Missing	363	2.5	36	2.9	296	3.1	20	2.6	715	2.7
Past medical history										
Anaemia and coagulation disorders	117	0.8	13	1.1	118	1.2	8	1.0	256	1.0
Diabetes	45	0.3	<5	<0.5	76	0.8	6	0.8	127-131	<1

Characteristics	Births with no PPH and no MH1[a] n=14,442		Births with no PPH and MH1 n=1,244		Births with PPH and no MH1 n=9,698		Births with both PPH and MH1 n=771		All births n=26155	
	n	%	n	%	n	%	n	%	n	%
Psychiatric or mental health disorder	1,521	10.5	466	37.5	984	10.2	288	37.4	3,259	12.5
Cardiovascular disease	367	2.5	33	2.7	370	3.8	31	4.0	801	3.1
Congenital heart disease	35	0.2	7	0.6	44	0.5	6	0.8	92	0.4
Smoking during pregnancy										
Non-smoker	11,690	80.9	770	61.9	8,270	85.3	581	75.4	21,311	81.5
Smoker	1,461	10.1	305	24.5	645	6.7	96	12.5	2,507	9.6
Ex-smoker	1,138	7.9	150	12.1	677	7.0	87	11.3	2,052	7.9
Missing	153	1.1	19	1.5	106	1.1	7	0.9	285	1.1
Mode of birth										
Spontaneous vaginal	10,037	69.5	836	67.2	2,050	21.1	151	19.6	13,074	50.0
Instrumental	2,651	18.4	247	19.9	2,580	26.6	190	24.6	5,668	21.7
Caesarean section	1,732	12.0	159	12.8	5,050	52.1	427	55.4	7,368	28.2
Missing	22	0.2	2	0.2	18	0.2	3	0.4	45	0.2
Multiple pregnancies	196	1.4	26	2.1	345	3.6	53	6.9	620	2.4
Obstetric complications										
Gestational diabetes	213	1.5	19	1.5	262	2.7	19	2.5	513	2.0
Hypertensive disorder of pregnancy	1,744	12.1	133	10.7	1,819	18.8	164	21.3	3,860	14.8
Antenatal anaemia	779	5.4	88	7.1	627	6.5	56	7.3	1,550	5.9
PROM or PPROM[b]	995	6.9	80	6.4	846	8.7	78	10.1	1,999	7.6
Gestational age at birth (weeks)										
<28	36	0.3	6	0.5	21	0.2	5	0.7	68	0.3
28-31	105	0.7	15	1.2	90	0.9	16	2.1	226	0.9
32-36	838	5.8	101	8.1	595	6.1	62	8.0	1,596	6.1
37-38	2,197	15.2	211	17.0	1,272	13.1	113	14.7	3,793	14.5
39-40	7,815	54.1	657	52.8	4,601	47.4	361	46.8	13,434	51.4
≥41	3,451	23.9	254	20.4	3,119	32.2	214	27.8	7,038	26.9

Characteristics	Births with no PPH and no MH1[a] n=14,442		Births with no PPH and MH1 n=1,244		Births with PPH and no MH1 n=9,698		Births with both PPH and MH1 n=771		All births n=26155	
	n	%	n	%	n	%	n	%	n	%
Birthweight (grams)										
<2500	847	5.9	124	10.0	572	5.9	65	8.4	1,608	6.2
2500-3499	7,666	53.1	671	53.9	3,956	40.8	321	41.6	12,614	48.2
3500-3999	4,412	30.6	341	27.4	3,332	34.4	241	31.3	8,326	31.8
>4000	1,517	10.5	108	8.7	1,838	19.0	144	18.7	3,607	13.8

[a] Postnatal mental illness, indicated by having a record of mental health related prescription or hospitalisation within one year after childbirth.
[b] Prelabour rupture of membranes (PROM) or preterm pre-labour rupture of membranes (PPROM)

5.4.4 Association between primary PPH and longer-term mental illness

5.4.4.1 Components of composite mental health outcome and event-free survival

Among women who never had a PPH ('No PPH' groups), 974 (11%) of the 8,578 women who did not have a postnatal mental illness had a longer-term mental illness, compared with 736 (69%) of the 1,053 women who had a postnatal mental illness (Table 5.6). Among women who had at least one PPH (Any PPH groups) 860 (8.8%) of the 8,140 women who did not have a postnatal mental illness had a longer-term mental illness, compared with 69.8% among women who had a postnatal mental illness. The distribution of the outcome events contributing to the composite mental health outcome is shown in Table 5.6. For all groups, prescription records accounted for the overwhelming majority (≥98%) of first mental health events contributing to the composite outcome, with mental health related hospitalisation accounting for the remaining 2%. There were no deaths related to suicide or self-inflicted injury observed among the women in the cohort.

Table 5.6 Percentage contribution of individual outcome events to the composite mental health outcome, 'longer-term mental illness', in each group

Outcome	No PPH and No MH1[a] n=8,578		No PPH and MH1[b] n=1,053		Any PPH and No MH1[c] n=8,140		Any PPH and MH1[d] n=1,027		All women n=18,798	
First record of prescription	954	98%	729	99%	840	98%	711	99%	3,234	98%
First record of hospitalisation	20	2%	7	1%	20	2%	6	1%	53	2%
Number of women with first MH outcome	974	100%	736	100%	860	100%	717	100%	3,287	100%

[a] Women with no PPH and no postnatal mental illness
[b] Women with no PPH, but with postnatal mental illness after at least one birth
[c] Women with at least one PPH, but no postnatal mental illness
[d] Women with at least one PPH and with postnatal mental illness after at least one birth

Across all four exposure groups, between 1% to 4% of women who had a prescription as the first event contributing to the composite mental health outcome had a subsequent mental health related hospitalisation (Figure 5.5). Most women who had a mental health related hospitalisation as the first event contributing to the composite mental health outcome had a subsequent mental health related prescription, with slightly lower proportions among women who did not have a postnatal mental illness.

The overall mental health event-free survival for women in each exposure group in the cohort is summarised in Figure 5.6.

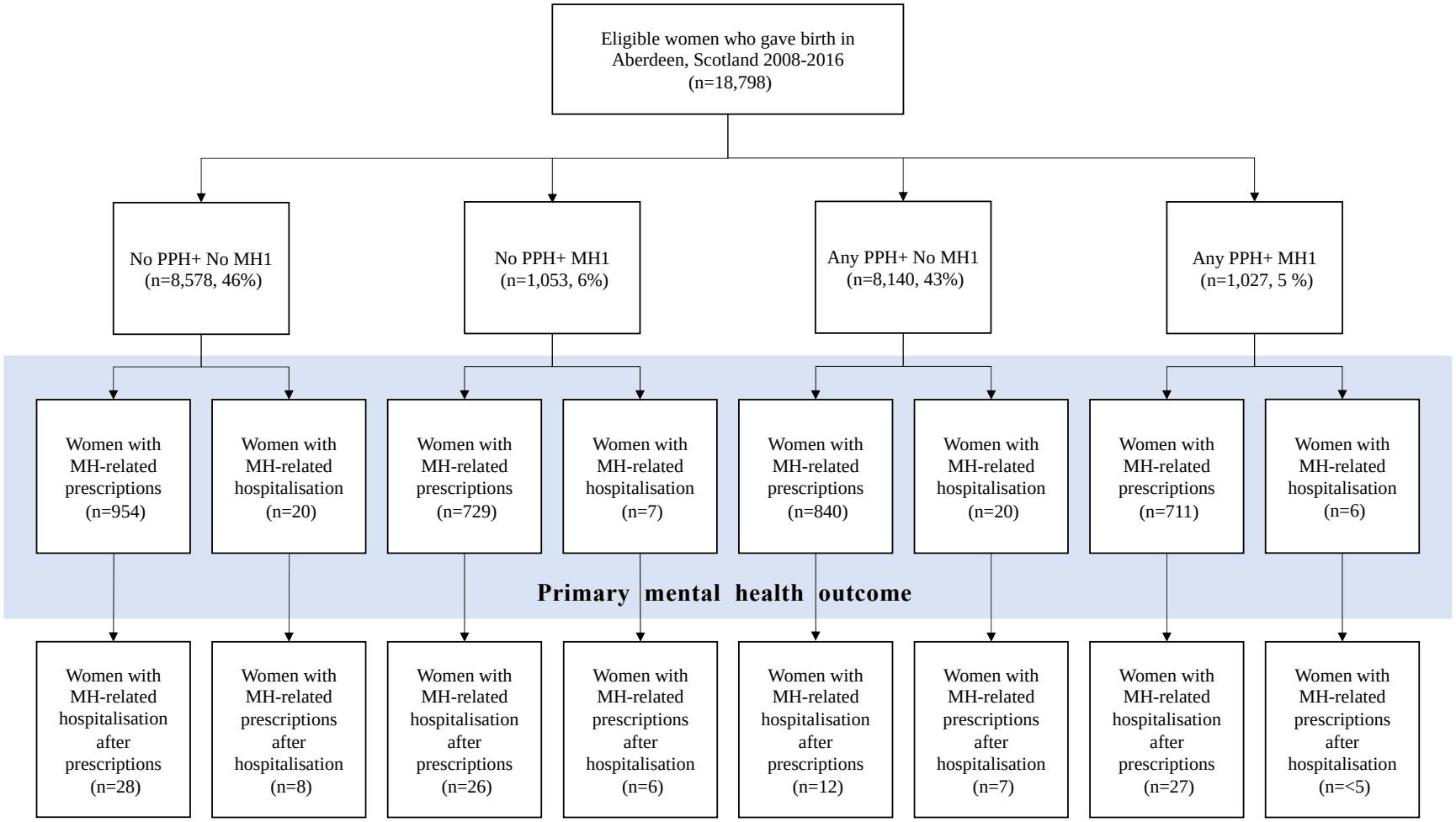


Figure 5.5 Events contributing to the composite mental health outcome, and subsequent mental health events in each exposure group

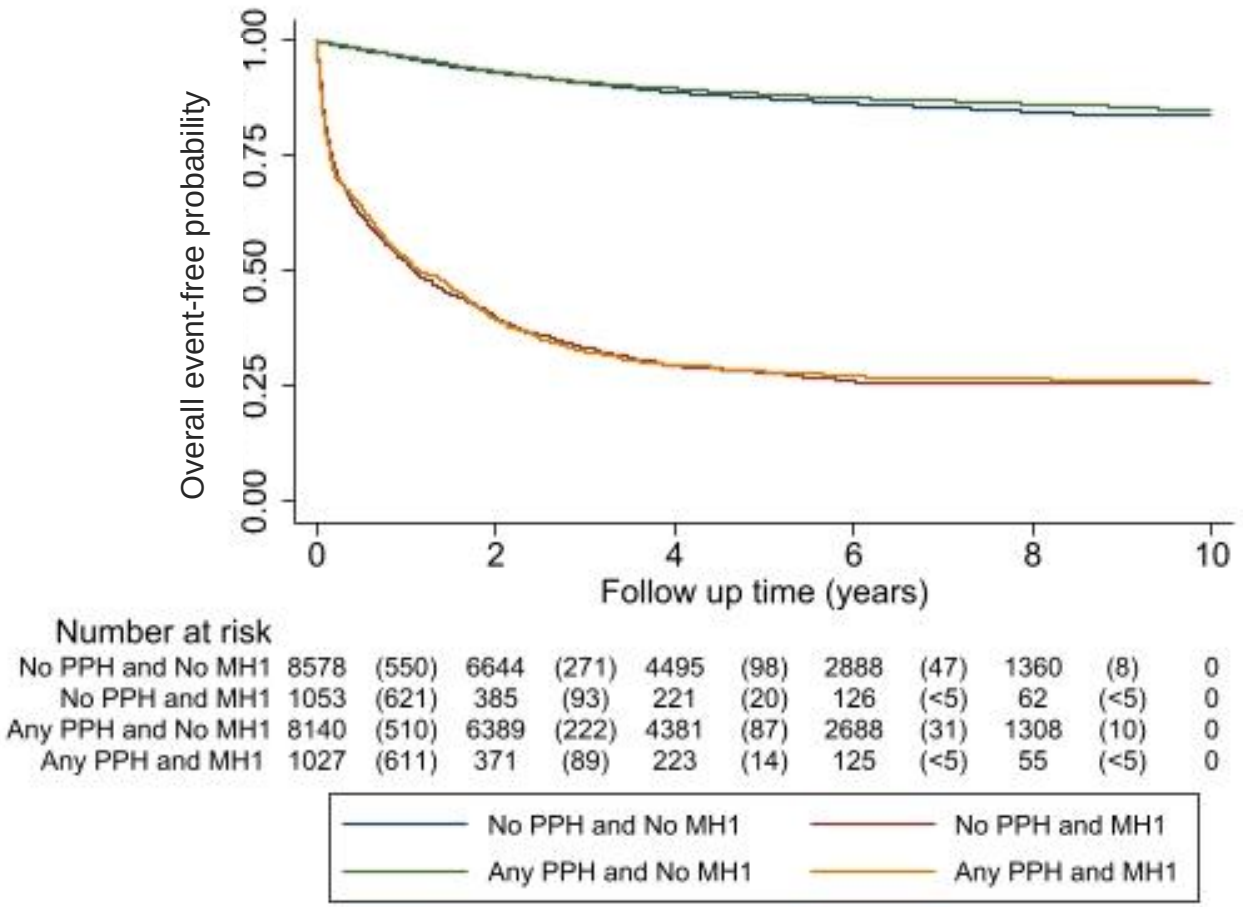


Figure 5.6 Mental health event-free probability over time across all exposure groups

Mental health outcome events occurred at a faster rate in the first two years of follow up after the first postnatal year among women who had postnatal mental illness (MH1 groups) and then continued to occur at a slightly slower rate over the next 8 years. Event-free survival probabilities were similar for women who had at least one PPH and women who did not have a PPH if they had the same postnatal mental illness 'status'. A similar pattern was observed in the subgroup analysis focusing on women who had at least one severe PPH (Appendix 13, Figure A13.3).

5.4.4.2 Univariable analysis

As observed in the Kaplan-Meier curves (Figure 5.6), among women with the same postnatal mental illness 'status', there was no significant difference in the risk of having a longer-term mental illness during the follow-up period among women who at least one PPH compared with women who did not have a PPH (Table 5.6). However, compared with women without postnatal mental illness (No MH1 groups), women with postnatal mental illness (MH1 groups), were approximately ten times more likely to develop a longer-term mental illness during the follow up period, regardless of their PPH status (HR=10.82 in No PPH and MH1; HR=10.71 in PPH and MH1). Models with severe PPH showed similar results (Appendix 13, Table A9.2).

Table 5.7 Association between PPH and postnatal mental illness and risk of longer-term mental illness

Exposure	Women with MH event	Total person-years (PY)	Incidence rate per 10,000 PY	Univariable model n=18,798		
				HR	95% CI	p-value
No PPH and No MH1[a]	974	39,402	247	Reference		
No PPH and MH1[b]	736	2,301	3,199	10.82	9.83-11.91	<0.001
Any PPH and No MH1[c]	860	37,777	228	0.92	0.84-1.01	0.08
Any PPH and MH1[d]	717	2,252	3,184	10.71	9.72-11.80	<0.001

[a] Women with no PPH and no postnatal mental illness
[b] Women with no PPH, but with postnatal mental illness after at least one birth
[c] Women with at least one PPH, but no postnatal mental illness
[d] Women with at least one PPH and with postnatal mental illness after at least one birth

5.4.4.3 Multivariable Cox proportional hazards regression models

The overall pattern of associations seen in the univariable analysis remained after adjustment for year of birth, and further sequential adjustment for sociodemographic factors (model 1), pre-existing medical history (model 2) and birth-related factors (model 3) (Table 5.8). The association between postnatal mental illness (MH1 groups) and longer-term mental illness, regardless of PPH 'status' was slightly attenuated after adjustment for year of childbirth and further attenuated by subsequent adjustment for socio-demographic factors and medical history. Further adjustment for birth-related factors did not materially alter the hazard ratios and in the final model, postnatal mental illness was associated with an almost seven-fold increase in the risk of having a longer-term mental illness, irrespective of PPH status (aHRs: 6.86, 6.82).

Table 5.8 Association between PPH and longer-term mental illness, with sequential adjustment for potential confounders

Exposed groups	Base Model[a] n=18,798			Model 1[b] n=17,588			Model 2[c] n=17,490			Model 3[d] n=17,471		
	aHR	95% CI	p-value	aHR	95% CI	p-value	aHR	95% CI	p-value	aHR	95% CI	p-value
No PPH and No MH1		Reference			Reference			Reference			Reference	
No PPH and MH1	10.22	9.28-11.26	<0.001	8.93	8.08-9.88	<0.001	6.95	6.26-7.72	<0.001	6.86	6.17-7.62	<0.001
Any PPH and No MH1	0.93	0.85-1.02	0.13	0.99	0.90-1.09	0.81	0.99	0.90-1.09	0.78	0.93	0.84-1.03	0.16
Any PPH and MH1	10.19	9.24-11.23	<0.001	9.17	8.29-10.13	<0.001	7.27	6.55-8.07	<0.001	6.82	6.11-7.61	<0.001

[a] Base model adjusted for year of birth only

[b] Model 1 adjusted for year of birth and sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation)

[c] Model 2 adjusted for variables in model 1, and additionally adjusted for pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric or mental disorder, cardiovascular disease) and smoking status

[d] Model 3 adjusted for variables in model 2, and additionally adjusted for pregnancy-related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at birth, baby's birthweight

5.4.4.4 Testing the proportional hazards assumption

The proportional hazard plots of hazard function against analysis time were convergent (Appendix 13, Figure A13.1, Figure A13.2). The p-value from the global test for the proportional hazards assumption was <0.001, indicating that the association between PPH and the composite mental health outcome, and also the association between several confounding variables (year of birth, maternal age at childbirth, mode of birth, PROM or PPROM) and the composite mental health outcome were not constant over time. Therefore, extended Cox regression models were conducted, with stratification by the variables that violated the proportional hazards assumption.

5.4.4.5 Extended Cox regression models for different time periods

Table 5.9 and Figure 5.7 summarise the results of extended multivariable Cox regression models reporting aHRs for the association between PPH and longer-term mental illness in the different exposure groups and for different follow-up periods starting from one year after the first postnatal year.

In the fully adjusted model (model 3) for different follow-up periods, the association between primary PPH and longer-term mental illness followed the same pattern as previously described, with no evidence of variation over time (Table 5.9 and Figure 5.7). In all models, time-varying aHRs were observed for the association between postnatal mental illness and longer-term mental illness, irrespective of PPH status. Within the first two years following the first postnatal year, in the fully adjusted model (model 3), women with an indication of postnatal mental illness were approximately twelve times more likely to develop a longer-term mental illness than women who had no PPH and no postnatal mental illness, irrespective of

their PPH status. Beyond these first two years of follow-up, this association remained, but was attenuated over time. A sub-group analysis for women with at least one severe PPH showed similar hazard ratios (Appendix 13, Table A13.3).

Table 5.9 Association between PPH and longer-term mental illness for different time intervals following the first postnatal year, stratified by the presence of postnatal mental illness and with sequential adjustment for potential confounders

Follow up	Exposure groups	Base Model[a] n=18,798			Model 1[b] n=17,588			Model 2[c] n=17,490			Model 3[d] n=17,471		
		aHR	95% CI	p	aHR	95% CI	p	aHR	95% CI	p	aHR	95% CI	p
1-2 years	No PPH and No MH1		Reference			Reference			Reference			Reference	
	No PPH and MH1	17.88	15.51-20.62	<0.001	16.86	14.52-19.57	<0.001	13.07	11.22-15.22	<0.001	12.77	10.94-14.91	<0.001
	Any PPH and No MH1	0.93	0.79-1.10	0.40	0.97	0.82-1.15	0.72	0.98	0.83-1.16	0.83	0.97	0.81-1.16	0.75
	Any PPH and MH1	17.50	15.15-20.20	<0.001	16.34	14.09-18.96	<0.001	12.79	10.98-14.89	<0.001	12.59	10.70-14.82	<0.001
3-5 years	No PPH and No MH1		Reference			Reference			Reference			Reference	
	No PPH and MH1	6.37	5.46-7.44	<0.001	5.30	4.51-6.23	<0.001	4.14	3.51-4.88	<0.001	4.03	3.41-4.76	<0.001
	Any PPH and No MH1	0.96	0.85-1.08	0.49	1.04	0.92-1.17	0.55	1.03	0.91-1.17	0.63	0.96	0.84-1.10	0.55
	Any PPH and MH1	6.87	5.89-8.01	<0.001	5.88	5.01-6.89	<0.001	4.76	4.05-5.60	<0.001	4.50	3.80-5.34	<0.001
6-10 years	No PPH and No MH1		Reference			Reference			Reference			Reference	
	No PPH and MH1	3.19	1.75-5.81	<0.001	2.46	1.31-4.63	0.01	1.94	1.03-3.65	0.04	1.84	0.97-3.48	0.06
	Any PPH and No MH1	0.90	0.66-1.22	0.50	1.07	0.78-1.47	0.68	1.04	0.76-1.43	0.81	0.87	0.61-1.24	0.43
	Any PPH and MH1	2.49	1.21-5.14	0.01	2.38	1.15-4.92	0.02	2.08	1.01-4.30	0.05	1.76	0.84-3.70	0.14

[a] Base model adjusted for year of birth only.
[b] Model 1 adjusted for year of birth and sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation)
[c] Model 2 adjusted for variables in model 1, and additionally adjusted for pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric or mental disorder, cardiovascular disease) and smoking status
[d] Model 3 adjusted for variables in model 2, and additionally adjusted for pregnancy-related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at birth, baby's birthweight
Follow up began after the first postnatal year.

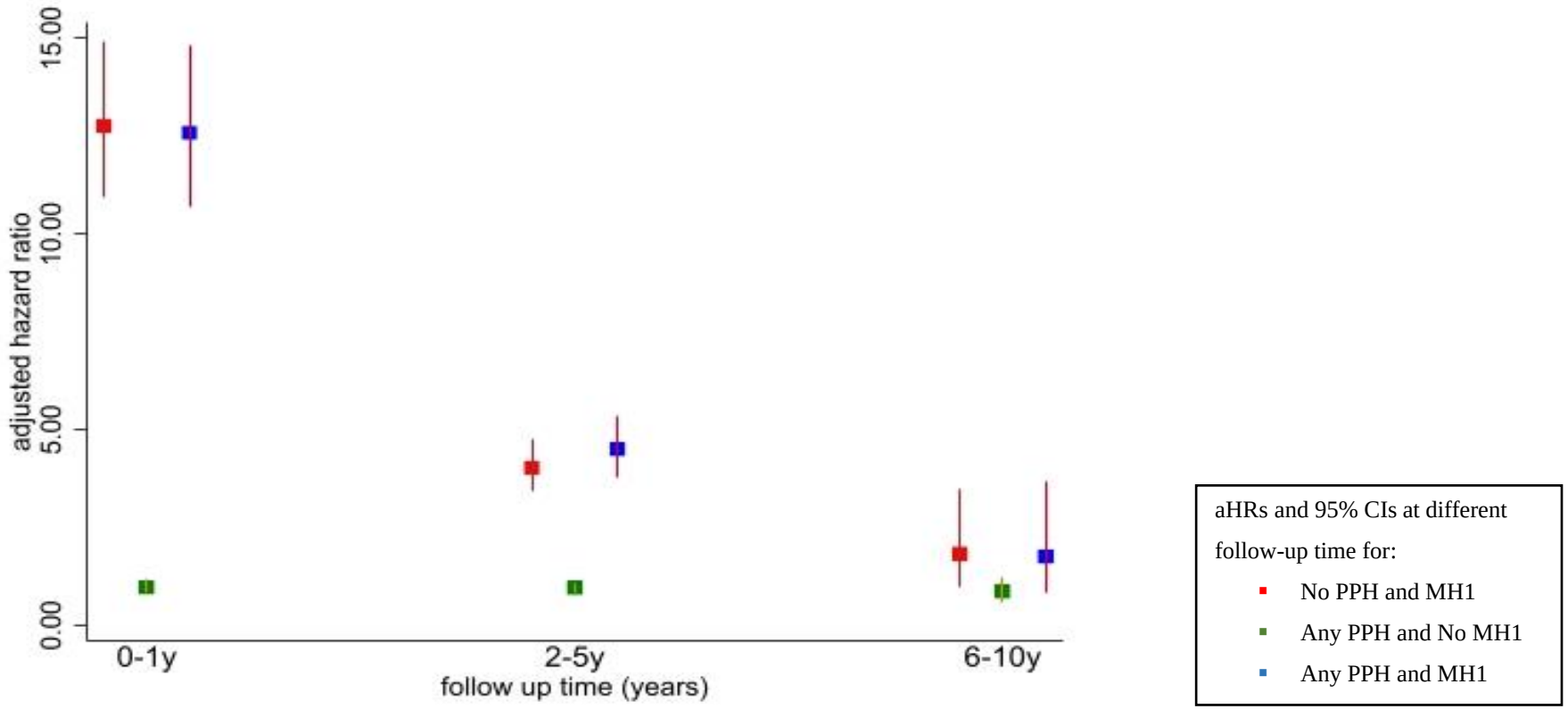


Figure 5.7 Adjusted HRs (aHRs) for the association between PPH and longer-term mental illness in different follow up periods, stratified by postnatal mental illness status (Model 3, n=17,471)

To explore whether having a PPH increased the risk of a longer-term mental illness among women who had postnatal mental illness, a further exploratory analysis was carried out changing the reference group from 'No PPH and No MH1' to 'No PPH and MH1' in the final model (Table 5.10). Among women with postnatal mental illness, there was no difference in the risk of developing a longer-term mental illness for women who had a PPH (Any PPH and MH1) compared with those who did not have a PPH (aHR=0.99, 95% CI=0.86-1.14). The findings were the same for severe PPH (Appendix 13, Table A13.4).

Table 5.10 Association between PPH and longer-term mental illness for different time intervals following the first postnatal year, stratified by the presence of postnatal mental illness (reference group 'No PPH and MH1') fully adjusted for potential confounders

Follow-up time	Exposure groups	Model 3[a] n=17,471		
		aHR	95% CI	p-value
1-2 year	No PPH and MH1		Reference	
	No PPH and No MH1	0.08	0.07-0.09	<0.0001
	Any PPH and No MH1	0.08	0.06-0.09	<0.0001
	Any PPH and MH1	0.99	0.86-1.14	0.847
3-5 year	No PPH and MH1		Reference	
	No PPH and No MH1	0.25	0.21-0.29	<0.001
	Any PPH and No MH1	0.24	0.20-0.29	<0.001
	Any PPH and MH1	1.12	0.91-1.37	0.279
6-10 year	No PPH and MH1		Reference	
	No PPH and No MH1	0.54	0.29-1.03	0.063
	Any PPH and No MH1	0.47	0.24-0.93	0.030
	Any PPH and MH1	0.96	0.37-2.45	0.929

Model 3 adjusted for year of birth, sociodemographic and clinical factors, past medical history of women, and pregnancy related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at delivery, baby's birthweight

5.4.4.6 Potential effect modification by mode of birth

Potential effect modification of the association between PPH (and severe PPH) and longer-term mental illness was explored for mode of birth. In the fully adjusted model, there was no evidence of effect modification by mode of birth (p=0.89).

5.4.4.7 Sensitivity analyses

A series of sensitivity analyses were carried out to explore the association between PPH and longer-term mental illness, (a) after removing women who had a previous history of psychiatric or mental health disorder before their first birth, and (b) after restricting the outcome measure to mental health related hospitalisation.

After the exclusion of births to women with a previous history of mental health disorder, the results for the association between PPH and longer-term mental illness were consistent with those reported in the main analysis (Table 5.11). The analysis for severe PPH also showed similar results (Appendix 13, Table A13.5).

Table 5.11 Association between PPH and longer-term mental illness for different time intervals following the first postnatal year, after exclusion of births to women with pre-existing mental illness (fully adjusted model 3)

Follow-up time	Exposure groups	Model 3[a] (original analysis) n=17,471			Model 3[a] (Sensitivity analysis a) n=15,369		
		aHR	95% CI	p-value	aHR	95% CI	p-value
1-2 year	No PPH and No MH1	Reference			Reference		
	No PPH and MH1	12.77	10.94-14.91	<0.001	17.70	14.61-21.43	<0.001
	Any PPH and No MH1	0.97	0.81-1.16	0.75	1.08	0.87-1.33	0.50
	Any PPH and MH1	12.59	10.70-14.82	<0.001	16.08	13.06-19.79	<0.001
3-5 year	No PPH and No MH1	Reference			Reference		
	No PPH and MH1	4.03	3.41-4.76	<0.001	4.73	3.83-5.83	<0.001
	Any PPH and No MH1	0.96	0.84-1.10	0.55	0.98	0.84-1.14	0.75
	Any PPH and MH1	4.50	3.80-5.34	<0.001	4.88	3.92-6.07	<0.001
6-10 year	No PPH and No MH1	Reference			Reference		
	No PPH and MH1	1.84	0.97-3.48	0.06	3.51	1.73-7.15	<0.001
	Any PPH and No MH1	0.87	0.61-1.24	0.43	0.93	0.62-1.39	0.72
	Any PPH and MH1	1.76	0.84-3.70	0.14	1.75	0.69-4.46	0.24

[a]Model 3 adjusted for year of birth, sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation), pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric or mental disorder, cardiovascular disease), smoking status, pregnancy related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at delivery, baby's birthweight

In the second sensitivity analysis, the association between PPH and longer-term mental health related hospitalisation was explored by restricting the outcome measure to hospitalisation only. This analysis was conducted in two separate cohorts: (i) eligible women who gave birth between 1986-2016, and (ii) eligible women who gave birth between 2008-2016.

These analyses showed similar findings to the main analysis, with no evidence of an association between PPH and longer-term mental health related hospitalisation in either cohort (Table 5.12). The association between postnatal mental illness (MHH1 groups) and mental health related hospitalisation remained statistically significant, but the strength of the association was reduced in both cohorts, in all time periods, compared with the main analysis. Beyond five years after the first postnatal year, in the smaller 2008-2016 cohort, although the direction of the association remained the same, this was no longer statistically significant and confidence intervals were wide and consistent with a range of effects.

The second sensitivity analysis was also repeated for severe PPH. However, the analysis was only conducted for women who gave birth between 1986-2016 because there were few women with MH events for births between 2008-2016 (Appendix 13, Table A13.6). The results showed similar patterns for severe PPH and there was no evidence of association between severe PPH and mental health related hospitalisation (Appendix 13, Table A13.7).

Table 5.12 Association between PPH and longer-term mental health related hospitalisation for different time intervals following the first postnatal year, after restricting the MH outcome to hospitalisation

Follow-up time	Exposure groups	Original analysis			Sensitivity analysis b					
		All births (Model 3)[a] n=17,471			Births after 2008 (Model 3)[a] n=18,936			All births (Model 3)[a] n=61,663		
		aHR	95% CI	p-value	aHR	95% CI	p-value	aHR	95% CI	p-value
1-2 year	No PPH and No MHH1		Reference			Reference			Reference	
	No PPH and MHH1	12.77	10.94-14.91	<0.001	3.02	1.40-6.50	0.005	1.40	0.99-1.96	0.053
	Any PPH and No MHH1	0.97	0.81-1.16	0.75	0.92	0.36-2.35	0.863	1.05	0.83-1.33	0.702
	Any PPH and MHH1	12.59	10.70-14.82	<0.001	5.51	2.50-12.10	<0.0001	1.74	1.23-2.47	0.002
3-5 year	No PPH and No MHH1		Reference			Reference			Reference	
	No PPH and MHH1	4.03	3.41-4.76	<0.001	2.58	1.36-4.87	0.004	1.22	0.95-1.56	0.115
	Any PPH and No MHH1	0.96	0.84-1.10	0.55	1.22	0.64-2.34	0.549	1.05	0.90-1.23	0.539
	Any PPH and MHH1	4.50	3.80-5.34	<0.001	3.90	2.04-7.47	<0.0001	1.73	1.37-2.18	<0.0001
6-10 year	No PPH and No MHH1		Reference			Reference			Reference	
	No PPH and MHH1	1.84	0.97-3.48	0.06	2.05	0.68-6.23	0.21	1.44	1.01-2.05	0.041
	Any PPH and No MHH1	0.87	0.61-1.24	0.43	0.75	0.20-2.86	0.68	0.71	0.58-0.87	0.001
	Any PPH and MHH1	1.76	0.84-3.70	0.14	1.94	0.48-7.89	0.35	1.42	0.98-2.04	0.062

Postnatal mental illness, indicated by having a record of mental health related hospitalisation within one year after any births (MHH1) in this sensitivity analysis.

[a]Model 3 adjusted for year of birth, sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation), pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric and mental disorder, cardiovascular disease), smoking status, pregnancy related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at delivery, baby's birthweight

5.5 Discussion

5.5.1 Summary of key findings

In this Scottish population-based cohort study of 18,798 women who gave birth between 2008 and 2016, 46% of women did not have either a PPH or postnatal mental illness; 43% of women had at least one primary PPH but no indication of postnatal mental illness in any of their births; 5.6% had no PPH but had a postnatal mental illness; and the remaining 5.5% had both a PPH and postnatal mental illness.

There was no major difference between the incidence rate of longer-term mental illness among women who had at least one PPH compared with women who did not have a PPH, if they had the same postnatal mental health 'status'. The incidence rate of longer-term mental illness among women who had postnatal mental illness was significantly higher compared with those without postnatal mental illness.

There was no evidence of an association between PPH and longer-term mental illness, from one to ten years after the first postnatal year, among women who had the same postnatal mental health illness 'status' in the first postnatal year. Furthermore, among women who had a postnatal mental illness, there was no evidence that having a PPH increased the risk of having longer-term mental illness.

The findings indicate that the association between PPH and longer-term mental illness was not modified by mode of birth. However, the adjusted HRs for PPH and longer-term mental illness were different for the exposure groups stratified by the presence of postnatal mental illness in all models. The different aHRs in each stratum showed significant effect modification of the association by the presence of postnatal mental illness.

Women who had an indication of postnatal mental illness, indicated by the prescription of psychotropic medication or mental health related hospitalisation in the first postnatal year, were as much as ten times more likely to develop a longer-term mental illness in their second and third postnatal year. This association continued for up to ten years after the first postnatal year, irrespective of whether they had a PPH. This association remained after adjustment for the presence of mental illness before the first birth, and in a sub-group analysis restricted to birth episodes in women without pre-existing mental illness.

5.5.2 Interpretation

The main focus of this study was the association between PPH and longer-term mental illness, beyond the first postnatal year. By investigating three different exposure groups, defined by the presence or absence of PPH and mental illness within the first postnatal year, it was possible to explore the association between PPH and longer-term mental illness, stratified by postnatal mental illness.

The incidence of postnatal mental illness in this cohort, indicated by the prescription of psychotropic medication or mental health related hospitalisation in the first postnatal year, was around 5-6%. This is lower than the pooled prevalence of 10–15% for depression, and 10% for anxiety disorders in the postpartum period found by Dennis et al. in their 2018 systematic review. (175) However, there is significant overlap between common mental health conditions, with Falah-Hassani et al. in 2017 suggesting an estimated prevalence of 8% for clinically diagnosed co-morbid anxiety and depression. (176) Less is known about PTSD, but around 4% of women may be affected by PTSD after birth. (110, 177) This lower estimate reflects more severe mental illness that has been diagnosed and treated, with medications and hospitalization, in contrast with much prevalence data for common mental disorders which are

based on self-report data, including women with symptoms that may not be diagnosed and treated.

Previous studies investigating the potential impact of PPH on postnatal mental illness, focused on the first postnatal year, (51, 69-71, 162) with some investigating outcomes within five years, (66-68, 163, 164) and only three studies investigating longer-term outcomes beyond five years after birth. (67, 163, 164) These studies have reported conflicting findings, with differing directions of association between PPH and postnatal mental illness, some of which may be explained by differences in sample selection, follow-up time and the tools used to measure PPD or PTSD. Many of these studies did not adjust for potential confounders, including previous mental health history, or did not have comparison groups. Two studies with comparison groups found no association between PPH and PPD and PTSD at 1.5 months and 12 months after birth respectively. (69, 162) However, these findings cannot be compared directly to the findings of the research presented here, as the follow-up period in this study only commenced after the first postnatal year. This was because the purpose here was not to replicate earlier findings but to investigate longer-term outcomes.

Two English studies investigated longer-term mental illness up to eight years after birth, including one in a large population-based cohort of over 40,000 women, and reported no increase in the overall risk of anxiety, depression and severe mental illness following PPH beyond the first postnatal year. (67, 164) The findings of the research presented here are consistent with these results. In contrast, a small single-centre study of 142 women in Switzerland, which was published after the systematic review reported in Chapter 3, reported an increased risk of depression and PTSD (aOR=5.1, 95% CI= 1.5-17.5, $p<0.005$) among women who underwent arterial embolisation for PPH compared with matched controls with

uneventful births, at an average of eight years after birth. (163) Although women who had embolisation had a higher average score for the Trauma Screening Questionnaire (TSQ), the average TSQ scores for both cases and controls were below the ≥7 threshold score of PTSD.

While it seems apparent that PPH itself is not directly associated with longer-term mental illness in this study, it is possible that traumatic birth events potentially associated with PPH, including for example negative experiences of care, or emergency management, and lack of support may mediate trajectories of longer-term mental health. Therefore, the extent to which any PTSD symptoms identified could be linked to PPH itself or to trauma associated with birth experiences, for example due to the interventions required or negative experiences of care, remains unclear. This kind of investigation was beyond the scope of the study reported here, but is worthy of further exploration.

The study reported here also found that having a mental illness in the first postnatal year, irrespective of PPH, increased the risk of having a longer-term mental illness in subsequent postnatal years. This finding is consistent with previous research, which has demonstrated a strong association between perinatal depression or anxiety and long-term mood disorders, specifically unipolar and bipolar depression. (165) It is also estimated that 14% of women who experience a psychiatric episode during the first month after birth will develop a bipolar disorder within the first 15 years after their initial postpartum episode. (166) In the study reported here, women who had an indication of postnatal mental illness were more likely to have had pre-existing mental health problems before their first birth, confirming the well-established link between pre-existing mental health problems, perinatal mental illness and its progression to longer-term mental illness. For example, one study found that over half of women with a history of psychosis had a psychiatric episode in the first year after childbirth.

(178) Past history of psychiatric illness is one of the strongest predictors of PPD, along with anxiety and depression during pregnancy, stressful life events, and low levels of social support. (179-181) In a recent study that used electronic health records from a large London mental health provider, women who had severe mental illness in the two years before pregnancy had an increased risk of relapse during pregnancy and postpartum. (182) In summary, the epidemiology of mental illness is complex and may be caused by a combination of various exposures through the life course including genetics, stressful life events, socioeconomic and environmental conditions such as living in poverty, (183) but this study provides no evidence of an association between PPH and longer-term mental illness.

5.5.3 Strengths and limitations

This Scottish population-based cohort study investigating the impact of PPH on longer-term mental illness had several strengths, including a large sample size and up to ten years of follow up for longer-term mental illness that provided population coverage and minimised selection bias. The large sample size meant that stratification by the presence of postnatal mental illness and by follow-up time was possible. This allowed for a more nuanced investigation of the independent effects of PPH and postnatal mental illness on longer-term mental illness, and how this may change over time. As discussed in Chapter 4, the classification of PPH was also improved by using estimated blood loss volume from all available birth records and conducting analyses at the level of the woman, rather than birth.

This study retrospectively linked prescriptions for psychotropic medications and mental health related hospitalisation to identify women with a longer-term mental illness starting from after the first postnatal year and for up to ten years after that. Mental health outcomes were captured from three different data sources to form the longer-term mental illness composite outcome. This increased the statistical power to identify an association between PPH and longer-term mental illness, if in reality such an association exists, by increasing the observed rates of mental illness outcomes in the cohort. This was particularly helpful for an outcome that may have a relatively low prevalence in the study population.

For these analyses it was decided to include women with pre-existing mental health problems before their first birth. Women with pre-existing mental health problems were identified using self-reported past medical history of mental health disorders in AMND and by linking prescriptions and hospitalisation occurring before the first birth. Including these women in the cohort was considered to be more appropriate because it is well-established that the use of

psychotropic medication before and during pregnancy, and after birth have an impact on the subsequent onset of severe mental illness. (171, 178, 184) Also women with pre-existing mental illness have an increased risk of relapse in the perinatal period. (182, 184, 185) Including such women in this cohort improved the generalisability of the study. Furthermore, the additional sensitivity analysis confirmed that the lack of association between PPH and longer-term mental illness remained after exclusion of women with pre-existing mental health problems.

This study also addressed potential confounding by taking a systematic sequential approach to adjustment of potential confounders. A wide range of potential confounders including well-established risk factors for PPH, and other obstetric complications were adjusted to minimise the potential confounder. However, given the retrospective cohort study design, there may be some residual confounding. For example, there was a lack of information about genetic risks, childhood abuse, addiction problems or abuse during pregnancy.

There were two main limitations to this study. First, it was not possible to distinguish between specific mental illnesses or diagnoses due to the nature of the composite mental health outcome used. Furthermore, approximately 98% of the composite mental health outcome data was identified from prescriptions for psychotropic medications. Due to the complex nature of prescriptions for a range of mental illness diagnoses, it was not possible to draw inferences about risks for specific mental illnesses. Diagnostic codes for hospital admission or death by self-inflicted injury or poisoning of unknown intent were not included. While this would have strengthened the outcome ascertainment, including these codes is unlikely to have changed the results as most outcomes were contributed by prescriptions, and no deaths were identified for self-inflicted injury or poisoning.

The second limitation was that a large proportion of mild to moderate mental illness is not generally managed with the prescription of psychotropic medication or hospitalisation. For example, the first line treatment for a mental illness typically includes psychological interventions such as individual facilitated self-help, cognitive behavioral therapy and other managed by general practitioners. Psychotropic medications are only typically recommended for more severe mental health conditions such as severe depression, psychosis and schizophrenia. (186) With the available data, it was not possible to include women who had mental health symptoms or diagnoses, but were not prescribed medication or admitted to hospital. This will have underestimated the population of women with subsequent mental health outcomes, and this may have resulted in the overall underestimation of the aHRs between PPH and longer-term mental illness. As a result, it is not possible to draw conclusions about any associations between PPH and relatively milder longer-term mental illness.

5.6 Conclusions

This study found no association between primary PPH and longer-term mental illness, as indicated by the prescription of psychotropic medication or a mental health related hospitalisation beyond the first postnatal year. This finding was unchanged after adjusting for potential confounders and irrespective of the presence of postnatal mental illness in the first postnatal year. In line with well-established evidence, the relationship between pre-existing mental illness, postnatal mental illness and a longer-term mental illness was confirmed. Women with pre-existing mental illness and perinatal mental illness should be adequately identified and supported during pregnancy and after birth. An efficient follow up system should be in place for early identification, monitoring and care for such women beyond the perinatal period because of the increased risk of longer-term mental illness in this group.

Chapter 6. Discussion and conclusion

6.1 Introduction

The overall aim of the research presented in this thesis was to provide high quality evidence about the longer-term physical and psychological consequences of primary PPH in a high-income setting. To achieve this aim, three studies were conducted between 2019 and 2022, each with distinct research objectives contributing towards this overarching aim. First, a mixed-methods systematic review (Chapter 3) was conducted with the objective of synthesising existing qualitative and quantitative evidence about longer-term consequences of PPH for women and their partners, and about experiences of PPH and their care. The results of this review provided the guidance to further refine the scope of two population-based cohort studies that focused on two composite outcomes: a CVD outcome event (Chapter 4) and a mental health outcome event (Chapter 5). These studies were conducted using a bespoke record-linkage between routine Scottish health care datasets, designed specifically for these studies. This final chapter summarises the main findings from these three studies, placing them in the context of other relevant research, considering overarching strengths and limitations, summarising implications for policy and practice, and making recommendations for further research.

6.2 Background

The incidence of PPH has increased in HICs including Ireland, Canada, Australia, France, Switzerland, UK, and the United States over the past two decades. (3, 26-29) NHS maternity statistics for England indicate that in 2018-2019 20% of all women giving birth in NHS

hospitals experienced PPH, (31) compared with 13% in 2011-2012. (32) The incidence of PPH increased by three-fold from 1999 to 2009 in Ireland and doubled in Switzerland from 1993 to 2014. (26, 29) According to confidential enquiries into maternal deaths in the UK, obstetric haemorrhage accounted for 16 maternal deaths between 2018 and 2020, with a mortality rate of 0.76 per 100,000 maternities. (34) While most women who experience PPH in HICs do not die, PPH can result in severe morbidity, (4) and the impact of this is a population health concern considering the increasing incidence of PPH. (3, 26, 29, 35) This remains a significant concern not only for near-miss maternal morbidity, but also in relation to the potential longer-term physical and psychological consequences.

Existing research has established that the immediate consequences of PPH can be severe resulting in sepsis, hypovolemic shock, and DIC, which in turn can lead to acute organ damage including myocardial ischaemia and renal failure. (42) Beyond these near-miss complications, evidence has suggested a high prevalence of low general health, breastfeeding problems, and mental health problems including anxiety, PPD, and PTSD following PPH, particularly in the first year after birth. (51, 69, 93, 96)

PPH may also be associated with other negative consequences, including a recurrence of PPH in subsequent pregnancies, longer length of hospital stays, and maternal readmission. (47, 187). However, there was a comparative knowledge gap about the longer-term health impact of primary PPH with most studies lacking appropriate comparison groups and adequate follow-up time to infer meaningful associations between PPH and longer-term health outcomes.

6.3 Longer-term consequences of primary PPH

6.3.1 Summary of main findings

The mixed-methods systematic review (Chapter 3) included 21 studies from nine different countries and demonstrated that there was limited research about the longer-term health consequences of PPH. Only seven studies in the review investigated the consequences of PPH beyond five years after the birth and just one study had a follow-up period of more than ten years. There was some evidence that women who had experienced PPH might be more likely to have persistent physical health problems, including being less likely to breastfeed in the postpartum period, compared with women who had not had a PPH. These negative health consequences were more pronounced among women who had a severe PPH and included long recovery time, low general health, symptoms of tiredness, and general fatigue. Two large population-based cohort studies included in the review suggested that severe PPH or PPH requiring blood transfusion was a major risk factor for VTE at six weeks postpartum (aRR=5.3, 95% CI= 1.6-17, p=0.005; aOR= 1.4, 95% CI= 0.5-3.5). (45, 92) There was consistent evidence from two cohort studies suggesting that PPH requiring blood transfusion was associated with an increased risk of CVD. (62, 63)

The studies included in the review provided conflicting evidence about the association between PPH and psychological disorders, including depression and PTSD, despite some prevalence studies indicating a higher prevalence of anxiety and PTSD symptoms among women who had a PPH. There was no strong evidence from the review for a causal association between PPH and longer-term psychological wellbeing, but there were indications that some women experienced the symptoms of post-traumatic stress following PPH for many

years after childbirth and suggestions that these may be mediated by women's experiences of support and care during and after childbirth.

The retrospective cohort study of 70,904 women who gave birth in Aberdeen between 1986 and 2016 (Chapter 4) showed that women who had at least one PPH in this period were at a higher risk of developing CVD in later life, compared with women who had not had a PPH. Within the first postnatal year the risk of CVD was almost doubled for women who had experienced a PPH, with the excess risk continuing but diminishing over time, with no evidence of an excess risk associated with PPH beyond 15 years after birth. This association between PPH and longer-term CVD was slightly stronger among women who also had at least one episode of HDP.

Finally, analysis of a cohort of 18,798 women who gave birth between 2008 and 2016 in the same geographical area (Chapter 5) showed that there was no association between PPH and longer-term mental illness beyond the first postnatal year, irrespective of severity of PPH or mode of birth. However, women who were prescribed medication, or admitted to hospital, for postnatal mental illness in the first year after giving birth were around twelve times more likely to experience mental illness in the second and third postnatal year, with a continuing association for up to ten years after the first postnatal year. This association was independent of PPH and, among women who had postnatal mental illness, having a PPH did not further increase this risk.

6.3.2 PPH and cardiovascular disease

The potential association between PPH and the development of CVD was not well understood at the beginning of this research. There was limited evidence that women with severe PPH

were at a higher risk of acute myocardial ischaemia, which may result from PPH-induced haemorrhagic shock. (46, 113) It was hypothesised that haemorrhagic instability resulting from PPH might expose women to a higher risk of developing CVD, particularly ischaemic heart disease (IHD), compared with women who have not had a PPH. (128, 129) There was some evidence of an association between severe PPH requiring blood transfusion and CVD, but not between more moderate PPH, not requiring blood transfusion, and CVD. Two studies in Canada and South Korea, both included in the review reported in Chapter 3, found that PPH requiring blood transfusion increased the risk of hospitalisation for CVD by 38% and 60% respectively after adjusting for potential confounders (aHR= 1.38, 95% CI= 1,13-1.68, aHR= 1.60, 95% CI= 1.25-2.06). (62, 63) One additional English cohort study published since the systematic review did not find an association between PPH and CVD (aHR= 1.03, 95% CI= 0.87-1.22). (151) The study reported here was therefore the first population-based study to find that having at least one PPH increases the risk of subsequent longer-term CVD up to 15 years after childbirth.

All these studies, including the study carried out for this thesis, were conducted in high resource settings, and all adjusted for potential confounders. However, there were some key methodological differences between the study reported here and previous studies (discussed in full in Chapter 4) that might explain the different results. The main methodological difference was that for the study reported here, exposure to PPH was classified on the basis of whether a woman had a PPH throughout her birth history whereas earlier studies classified women as 'exposed' to PPH based on the index birth or first birth only. The approach used here enabled the use of all available birth records for the women in the cohort, and minimised the non-differential misclassification of exposure to PPH that might have occurred in other studies,

with the potential effect in those studies of biasing the results towards the null association between PPH and CVD. In the study reported here, outcome assessment was based on CVD-related prescriptions using BNF codes and hospitalisation data, whereas two of the earlier studies used ICD diagnostic codes for outcome classification. Using the latter approach, women with CVD managed by medication only would not have been identified as having the outcome, another possible cause of an underestimation of the risk of CVD in the earlier studies.

The study reported here investigated the relative risk of CVD among women who had at least one PPH compared with women who never had a PPH, over different time periods following birth. In addition to the establishment of the association between PPH and CVD, another important contribution by the research reported here was the investigation of the proportional hazards assumption and further application of extended Cox regression models to calculate time varying hazards. This demonstrated that the adjusted hazard ratio was underestimated as a pooled result, whereas the adjusted hazard ratio was much higher for the first year after birth and decreased thereafter.

While this research has provided evidence of association between PPH and subsequent CVD, the mechanism for a potential causal pathway remains unclear. Two possible explanations for the observed association between PPH and CVD were discussed in Chapter 4. The first of these is that PPH may be an independent risk factor for developing CVD later in life. The Bradford Hill criteria for causation, where applicable, were considered as a framework to assess whether it is justifiable to consider the observed association as a causal relationship. (188) The first criterion, ‘strength of association’ is typically considered to be indicated by a relative risk of two or more, (189) and is considered relevant to causality on the basis that the

observed effect is less likely to be due to confounding or other bias. The highest adjusted hazard ratio for the association between PPH and CVD observed in the study reported in Chapter 4 was 1.96, at the lower end of this range. Two other studies reported an association between PPH requiring blood transfusion and CVD, with aHRs that were lower than two, (aHR=1.38 and 1.60). (62, 63) The strength of association criterion was therefore met by the current study, while the two previous studies potentially reported underestimated aHRs as discussed earlier.

The 'consistency' criterion requires that an association is demonstrated across multiple studies as it reduces the likelihood of bias or chance, whereas 'coherence' is assessed by how the relationship fits into existing evidence. Although there were some differences in effect size, there is a consistent finding across all studies that severe PPH increases the risk of CVD, and the differences in effect size across the studies are able to be explained by methodological differences in how exposure to PPH was classified and how time varying hazards were analysed. On the basis of the evidence so far, more studies will be required before the 'consistency' and 'coherence' criteria can be fully assessed.

'Specificity' was not assessed as CVD is multicausal and could be affected by many exposures throughout the life course, and this criterion has limited applicability to many epidemiological studies. The criterion of 'temporality' was established since the measurement of PPH preceded the CVD diagnosis in the cardiovascular study reported in Chapter 4, as well as in three other comparable studies. (62, 63, 151) Furthermore, women with pre-existing CVD were identified and excluded from the eligible cohort in the study reported in Chapter 4 and in two earlier studies. (62, 63)

The evidence for a dose-response relationship, a 'biological gradient' is also limited. (190, 191) There were no significant differences in the observed effect sizes by severity of PPH in the study reported in Chapter 4. There is some evidence to support biological 'plausibility' for the association. The increase in total blood volume during pregnancy prepares women to be able to well-tolerate postpartum blood loss of up to 500ml without reducing overall blood flow to major organs. (6, 152) PPH can cause a reduction in cardiac output and overall blood supply to vital organs including the heart, brain and kidneys resulting in hypovolaemic shock and acute heart failure. (153) Although these severe outcomes may be averted by timely treatment, it is plausible that PPH may lead to acute myocardial infarct or heart failure and cause irreversible damage to the cardiovascular system, which may in turn lead to a higher risk of developing CVD in later life. For example, a recent study which explored the long-term risk for recurrent cardiovascular events for both acute and chronic myocardial infarction found that acute myocardial infarct increased the risk of deaths and other ischaemic events, with a higher recurrent cardiovascular events rate compared to patients with chronic myocardial infarct (Incidence rate 35.6 per 1000 person-years). (65) It is concluded that the 'biological plausibility' criterion is satisfied and there are plausible causal pathways between PPH and CVD mediating through acute myocardial ischaemia or heart failure. Using the Bradford Hill criteria is helpful to assess a potential causal relationship between PPH and CVD. Overall, it is highly possible that PPH can be an independent risk factor for the development of CVD.

A second possible explanation for the association is that pre-existing 'occult' risk factors for CVD exist prior to pregnancy in some women and the experience of obstetric complications may 'unmask' this pre-existing susceptibility to CVD among such women. (130, 154-156) A

growing body of research about pregnancy complications and CVD suggests that some pregnancy complications may function as a 'stress test' to the cardiovascular system, exacerbating this latent cardiovascular risk by causing more vascular damage and metabolic stress on the body. (130, 156, 157) It has been established that haemodynamic changes in pregnancy and childbirth can worsen existing, potentially unidentified, cardiac conditions such as coronary heart disease. (158) Furthermore, the findings from a recent study in the United States suggests that women with cardiometabolic conditions of pregnancy such as HDP and diabetes had a three-fold increased risk of developing severe cardiovascular outcomes. (192) It seems possible that women may have different cardiometabolic risk profiles prior to and during pregnancy, and adverse cardiovascular outcomes following PPH could therefore be interpreted as a consequence of inability to cope with metabolic stress on the body exacerbating pre-existing CVD risks. More prospective cohort studies assessing the cardiometabolic risk profile/factors of women, including both traditional and newer cardiometabolic risk factors such as family history of CVD, dyslipidaemia, dysglycaemia, abdominal obesity, high-sensitivity C-reactive protein level, and daily consumption of fruits and vegetables before and during pregnancy, and after birth, would be required before concluding whether PPH might function as a metabolic stress test. (193-195)

Finally, it is important to note that the relationship between PPH and CVD, and between PPH and mental illness were explored as two separate sets of outcomes in this research. However, in reality a woman might develop both CVD and mental illness in later life, which may interact or influence the trajectory of each other. For example, having a chronic physical health problem may result in emotional distress and poor mental health, particularly depression and anxiety-related disorders, and vice versa. (196) There is also consistent

evidence that anxiety is more common in people with heart disease, and depression is a risk factor for heart disease. (197) The potential inter-relationship between mental health and CVD was not investigated in the research presented in this thesis, but they should be considered as potential effect modifiers for future research as the risk of CVD might be different from women who developed mental illness after birth.

Regardless of the mechanisms behind the association identified here, it is important to recognise that having primary PPH following childbirth may be an important marker for an increased risk of subsequent CVD. Pregnancy and childbirth should be considered as a 'critical period' for women in the development of CVD and an opportunity for primary prevention or intervention. (159)

6.3.3 PPH and mental illness

The systematic review reported in Chapter 3 suggested that women who had severe PPH reported persistent mental health problems including anxiety, and PTSD symptoms that lasted for years after birth. While prevalence studies have indicated a higher prevalence of mental illness, including anxiety, depression, and PTSD, following PPH, (51, 66) studies with appropriate comparison groups exploring the association between PPH and perinatal mental illness have reported conflicting findings. (66, 68, 69, 71) From existing evidence, it was not possible to conclude whether PPH was directly associated with longer-term mental illness or whether any longer-term psychological impact was mediated through traumatic childbirth due to events surrounding the childbirth and PPH. Therefore, robust evidence was required to investigate whether there is an independent association between PPH and longer-term mental illness.

The research reported here (Chapter 5) found no association between PPH and longer-term mental illness requiring hospitalisation or prescriptions up to nine years following the first postnatal year. By stratifying the PPH 'exposed' group according to the presence of postnatal mental illness it was possible to explore the independent association between PPH and longer-term mental illness. In addition to demonstrating the lack of association between PPH and mental illness, this study also clearly showed the well-established relationship between postnatal illness and longer-term mental illness.

Previous studies indicated a higher prevalence of symptoms of anxiety and PTSD in the first postnatal year among women who had a PPH or EPH. (51, 67, 68, 70, 71) Three studies investigating the psychological impact of PPH have been published since the systematic review reported in Chapter 3, with two exploring the longer term impact. (162-164) One Swedish record-linked study which explored the association between PPH and PPD at 12 months did not find an association. (aHR=1.08, 95% CI 0.99-1.17) In keeping with the findings of the study reported here, one English population-based study of over 40,000 women investigated the association between PPH and mental illness up to 8 years after birth, and reported no evidence that PPH increased the overall risk of anxiety (aHR=0.99), depression (aHR=0.94) or severe mental illness (aHR=0.65, p =0.24) beyond the first postnatal year. (164) As reported earlier, a small Swiss study of 142 women, also published since the systematic review, suggested an increased risk of depression and PTSD among women who underwent arterial embolisation for PPH compared with matched controls with uneventful births (aOR=5.1, 95% CI= 1.5-17.5, $p<0.005$), but with wide CIs due to the small sample size, and with average TSQ scores for both PPH cases and controls that were below the ≥7 threshold score for PTSD. (163) The heterogeneity of findings for the association between

PPH and longer-term mental illness in different studies may be explained by differences in both the measurement of PPH and the definition of the outcome of ‘mental illness’. Most earlier studies had small samples, and also lacked appropriate comparison groups and adjustment for potential confounding.

Births affected by PPH are reported to be traumatic by women in qualitative studies included in the systematic review reported here, particularly when intensive surgical interventions were involved. (52, 67) Therefore, it was hypothesized that PPH may lead to longer-term mental health problems mediating through birth trauma, and longer-term mental illness was explored as a potential longer term health outcome. As discussed in Chapter 5, it seems likely that the presence of longer-term mental health problems may not be associated directly with PPH itself, but rather may arise because of other traumatic birth experiences around birth and PPH, or because of negative experiences of care. While some births may be physically traumatic (for example emergency caesarean, EPH, PPH) they may not be perceived as traumatic by the woman, and other births may be experienced or perceived as traumatic, perhaps because of experiences of care or (lack of) support, even when the birth itself may be objectively straightforward. (186) The subjective nature of birth trauma highlights that whether a woman experiences a birth as ‘traumatic’ can vary depending on her life perspectives and experiences. (198) This is supported by the findings of a Brazilian study that found no association between severe maternal morbidity, including severe bleeding, and PTSD from one to five years after the birth. (199) The authors of that study also argued that the perception of birth trauma by women may be more important than the nature of the birth event itself. A systematic review and meta-analysis that investigated the risk factors for PTSD following childbirth found that perception of a negative subjective experience during childbirth and obstetric emergencies,

including lack of support from staff during birth, were the most important risk factors for PTSD. (200, 201)

While there is some quantitative evidence suggesting a higher prevalence of PTSD following PPH, the outcome assessments used to identify the symptoms of PTSD are unable to distinguish the source of the trauma causing PTSD (202) Therefore, it is difficult to conclude whether PTSD following PPH is directly associated with PPH or if it is caused by other stressful events centering around childbirth that may trigger PTSD, for example domestic violence or lack of support from family.

Furthermore, the progression from first symptoms of postnatal mental illness to a longer-term mental illness may be driven by other factors such as quality of follow-up care, and other physical, environmental, and socioeconomic determinants. (171, 203) In most retrospective studies using routine administrative data, including the study reported in this thesis, there was no information available about the quality of the maternity care women received. The complexity of the various determinants which affect an individual's mental health might explain the heterogeneity in the quantitative population study findings in perinatal mental health, that cannot simply be explained by methodological differences.

In summary, the causes of mental illness are multi-dimensional, affected by a combination of exposures through the life course, including genetics, stressful life events, socioeconomic and environmental conditions, including living in poverty. (183) At a population level PPH is unlikely to be directly associated with longer-term severe mental illness. At an individual level PPH, in combination with other events (e.g., emergency caesarean, peripartum hysterectomy, ICU admission) around the same time, may contribute to an overall negative experience of childbirth (i.e., traumatic birth), which in turn may contribute to the

development of mental illness. It is challenging to separate the underlying causal pathways for mental illness, particularly when the sequence of events is closely linked together in a short timeframe (e.g., going through childbirth, obstetric complications, negative care experiences, or lack of family support at the same time). With the routine administrative data available for this research, it was not possible to explore this level of complexity.

6.4 Contribution to methodology

Studies using linkage of routine data sources are not new, but there are few research papers that report the detailed steps involved in the preparation of linked datasets. (204, 205) The research reported here took a structured, systematic approach that may be useful for others conducting similar studies.

6.4.1 Conceptual diagrams for data preparation

Most of the datasets used in this research were data files containing more than one record relating to each individual woman. (e.g., AMND, PIS, SMR01, and SMR04) Preparing the linked data files was complex, requiring detailed planning. File flow diagrams or syntax flow diagrams are commonly used to assist with data preparation for the final linked dataset. (204) In this research, file flow diagrams (Figure 4.3, Figure 5.2, Figure 5.3) were used to plan the data preparation steps. The advantage of file flow diagrams over syntax flow diagrams is that the concepts used can be applied regardless of the statistical programming language used. Different versions of these diagrams were formulated and tested until the development of the outcome platform file was satisfactory. Finally, to complement these flow diagrams, the detailed replicable steps to prepare the final linked data file were fully described (Box 4.1, Box 5.1A, Box 5.1B).

6.4.2 Outcome algorithms

Outcome algorithms are commonly used to combine available information and records from different health care data sources at different timepoints, including prescriptions, laboratory tests, health survey responses, hospitalisations and/or operation procedures to establish the full health profile of the same individual. (206, 207) In the research reported here, outcome

algorithms were applied to identify women with CVD or mental illness from the linked datasets using a pre-defined set of BNF codes, and ICD codes for each composite outcome based on clinical guidance about the management of CVD and mental illness and previous research using these outcomes (e.g., ICD-10, BNF and OPCS codes in Table 4.2 and Table 5.1). The earliest prescribed date or hospital admission dates were identified from each data source for each individual woman. A definition of a minimum of three consecutive prescriptions within any 365-day period was used in this research to address the fact that medications used to treat the outcomes of interest could also be used in the short-term for other indications unrelated to the outcomes of interest.

6.4.3 Application of sequencing variables

Sequencing variables are commonly used in health data linkage studies to establish temporal health profiles of individuals, as multiple data sources contain information pertaining to exposures and outcomes occurring at different times. (205, 208) The analysis of a linked data file and indexing outcomes from multiple data sources (e.g., four data sources in this study) can be simplified by generating sequence variables that represent the sequences of records in different ways. In the studies reported here sequencing variables (morbseq, fileseq, cvsseq, mhseq, etc, Figure 4.3, Figure 5.3) were used to identify the order in which cardiovascular or mental health outcome events occurred. For example, if a woman was prescribed antihypertensive medications, was later admitted to the hospital for a heart attack, and died from CVD, sequencing variables were generated to ensure the identification of the correct chronological order of these events, pertaining to the individual woman.

6.5 Strengths and limitations

6.5.1 Mixed-methods systematic review

This research used a mixed-methods systematic review approach to synthesize the literature about the physical and psychological consequences of PPH. A total of 14,036 references identified from five different databases were screened to yield 28 articles reporting a total of 21 included studies. This was the first review integrating quantitative and qualitative evidence investigating the longer-term physical and psychological consequences of PPH. The inclusion of qualitative evidence about women's and partner's experiences in this review helped illuminate the potential role of other important factors such as care experiences that might influence the development of perinatal mental illness, for example. The main limitations of the review were related to the lack of appropriate comparison groups, and insufficient follow-up time for longer-term outcomes in individual studies, leading to a small number of studies investigating longer-term health outcomes. Due to resource limitations, five potentially eligible papers not written in English were not considered for inclusion and grey literature were not searched as originally planned in the protocol. The high degree of heterogeneity of the included studies, including different definitions of PPH, and widely varying outcome measurements using different clinical and self-reported tools, meant that it was not appropriate to perform meta-analysis. Although the conclusions that could be drawn were limited by the availability of high-quality evidence about the longer-term consequences of PPH, the review provided information to guide the selection of outcomes for investigation in the other studies conducted for this thesis.

6.5.2 Population-based studies with large samples

The main strengths of the record linkage studies presented here were the size of the cohorts and the capacity for long-term follow-up. The retrospective cohort design and the routinely available data enabled time and resources to be used efficiently to investigate longer-term health outcomes after PPH. This was possible due to the application of an extensive record linkage of Aberdeen birth records (AMND database) to a range of Scottish of routine health administrative data. Scotland has a long-standing history of extensive high-quality administration data linkage. (209) The AMND holds all the birth-related records of women residing in the Grampian region of Scotland since the 1950s, stored in an electronic database since 1986. By 2016, AMND held the information about roughly 181,145 women with 274,323 births. (131) Although a small proportion of home births and deliveries in peripheral hospitals were not captured in AMND, it covered 99% of all births in Aberdeen and 97% of all births in the overall Grampian region, providing a good population coverage. Currently Public Health Scotland, previously known as ISD Scotland, holds health-related data for over five million people in Scotland across the individual's whole life, from mothers' antenatal records to that individual's death registration record, which can be linked to support research studies. (210) The combination of this large representative sample, a relatively stable population in the Grampian region of Scotland, (131) and limiting the sample to NHS registered patients meeting the inclusion criteria, minimised loss to follow up and selection bias and enabled generalization of findings to the Scottish population.

6.5.3 Generalisability

Previous comparable studies investigating the longer-term consequences of PPH classified PPH based on whether a woman had the PPH in her first birth or the index birth to classify the

PPH exposure groups. (62, 63, 151, 164) The consequence of this approach not only imposes the risk of measurement errors for PPH if women have PPH in their second or third births, but also limits the generalisability of such studies to women with one birth. In contrast, in the studies reported in Chapters 4 and 5 PPH was classified using data from all available births for each individual woman. This approach maximised the generalisability to women with more than one birth.

These studies were carried out using data from one region of Scotland, where approximately 90% of the childbearing population are of White ethnicity according to Scotland's 2011 census data. (211) While the findings are applicable to other parts of Scotland and the UK with similar demographics, they may not be generalizable to areas of the UK with a higher percentage of childbearing women from ethnic minority backgrounds. Beyond the UK, the findings may be applicable to other HICs with comparable health care systems and settings, and populations with similar demographic characteristics.

6.5.4 Exposure measurements

The studies reported here used the Scottish data linkage system to combine data about maternal sociodemographic characteristics, past medical history, and obstetric characteristics from the AMND with outcome data from other administrative datasets. The creation of PPH exposure groups based on estimated blood loss data from AMND minimised the chance of measurement error for PPH in contrast with other studies that have used ICD codes for the definitions of PPH. (151, 164) While there may be some inaccuracies in the estimation and recording of the amount of blood loss, any residual measurement errors for PPH are only likely to have underestimated the effect size. As with other retrospective cohort studies, the measurement of PPH preceded the outcome measurements of CVD and mental illness,

minimising differential measurement errors and reducing the potential for recall bias. Although there was a small number of missing values for the blood loss variable used to define PPH, potentially affecting PPH measurement in the CVD study, this was addressed by the sensitivity analysis presented in section 4.4.10.8 by initially considering these as births with no PPH, and then re-coding them as having PPH. This made no material difference to the findings. However, there was no specific information available about how blood loss variable was measured and recorded in AMND.

6.5.5 Confounding

The AMND includes a wide range of data collected during pregnancy and at birth allowing adjustment for many potential confounders. An extensive range of potential confounders such as maternal sociodemographic, and obstetric variables were adjusted for in this research to minimise the risk of confounding. As with other observational studies however, there is a chance of residual confounding as the routinely collected data did not provide information about some potentially important risk factors. This included, for example, lifestyle factors such as lack of physical activity and unhealthy diet for CVD, and experience of childhood trauma or abuse during pregnancy for mental illness. Quality of care information such as timely treatment of PPH, informed decision making, and negative care experiences were also not available, and it was not possible to explore potential effect modification by care received during pregnancy, during or after birth, because of the limitations of routine health data.

6.5.6 Outcome measurement

Since 2009 it has been possible to link AMND with Scottish data (PIS) about prescriptions dispensed in the community. For the studies reported here this meant that it was possible to

derive outcome measures using prescription data as well as data about hospitalisation and death, capturing a broader range of less severe health outcomes. This capacity for linkage was a strength, as compared to a single linkage to hospitalisation data for example, but outcome measurement was still limited to those women who were prescribed medication or were hospitalised for the selected outcomes. As discussed earlier, the inferences from the studies reported here can be applied to women who required medication or hospitalisation for the selected outcomes, but not to women with CVD or mental illness managed without medication or hospitalisation, or who did not have access to health services.

6.5.7 Follow-up timing, duration, and availability of data

The data linkage used for the studies reported here enabled the identification of women with selected health outcome data with a minimum duration of follow up of two years, for women who gave birth in 2016 and a maximum of 32 years of follow up for women who gave birth in 1986 in the CVD study. Follow up for the mental health study was slightly shorter using birth data from 2008 to 2016, because of the availability of linkage with PIS only since 2008, with a maximum of 10 years follow up for women who gave birth in 2008.

Follow up was determined to begin at the woman's first birth in the CVD study and at one year following the date of first birth in the mental health study, regardless of the timing of PPH. As described in the earlier chapters, this was decided on as the best possible methodological approach because of the lack of an 'index birth' for women who did not have a PPH, and based on the assumption that women were at some risk of CVD and mental illness even before they were under observation. This approach also ensured that follow-up duration was comparable across the different exposure groups. This decision meant that women who had more than one birth and had their first PPH in a second or subsequent birth had extra

follow-up time that contributed to the time to event analysis that was not related to PPH (i.e., time between their first birth and their PPH). The potential consequence of this is that aHRs would be biased towards the null, that is that any observed association may be an underestimation of the association between PPH and selected outcomes. This would not have materially altered the result for the CVD outcome, but a large underestimation of the association between PPH and mental illness could potentially have had an impact on the results.

6.6 Implications for clinical practice and policy

The current model for maternity care in Scotland includes a six-week postnatal check with the GPs for new mothers. (212) Since 2020, a six-week postnatal check for new mothers has been part of the contract for routine care provided by GPs in England as an opportunity to review the woman's physical and mental health. (213) Current national guidance about postnatal care in England emphasises that women who had hypertension in pregnancy or pre-eclampsia should be provided with postnatal investigation and monitoring for their blood pressure and a follow up care plan. (214) There is limited information about follow up care provided after PPH and any long-term implications. There could be additional benefit of expanding this cardiovascular monitoring and follow up care to women who had postpartum bleeding, potentially helping with early identification and prevention of CVD. Women who had a PPH and other childbirth complications such as pre-eclampsia, preterm birth, and gestation diabetes should be identified as high-risk groups regardless of whether these factors are considered as independent risk factors for CVD or early indicators of existing cardiovascular risk. The first postnatal year after birth should be considered as an opportunity for such women for early identification and interventions for CVDs including lifestyle modifications.

The maternal six-week postnatal check also provides primary health care providers with an opportunity for the early identification of postnatal mental health problems. (215, 216) It is important to identify and adequately support women with perinatal mental illness, particularly those with a previous history of mental illness and who are on medication, throughout the pregnancy and postpartum. This may lead to improved identification of women at risk since they may have a higher susceptibility to long term psychiatric outcomes. (165) Clinicians should provide timely psychological interventions if women with such a history experience distress either during pregnancy or after birth. The current NICE guidance on antenatal and postnatal mental health includes asking symptom identification questions for depression and anxiety during the first contact with primary care or her booking visit and during early postnatal period. If their responses fit the risk profile, it is recommended that they have a full assessment or refer to GP for severe mental health problem. (217)

6.7 Recommendations for future research

6.7.1 Research recommendations for PPH and CVD

In addition to the increased risk of CVD associated with PPH, the present study reported here has found that there is some evidence of effect modification by hypertensive disorders in pregnancy, suggesting that the increased risk of CVD associated with PPH was slightly higher among women who also had at least one episode of HDP. There is substantial research that pre-eclampsia, gestational diabetes and preterm birth increase the lifelong risk of CVD, with the relationship for pre-eclampsia being better established than others. (58, 116, 117, 218, 219) Systematic reviews and meta-analyses have shown that women with a history of pre-eclampsia have around a four-fold increased risk of hypertension and over a two-fold

increased risk of ischaemic heart disease or CVD in later life. (58, 218, 220) Since there is some evidence of effect modification by HDP, there is a potential that the presence of gestational diabetes, pre-term birth or antenatal anaemia might interact with each other additively, as "risk clusters" (221) contributing towards the overall lifetime risk of developing CVD.

A population-based cohort study is recommended to investigate the impact of these obstetric complications on women's lifetime cardiovascular risks based on their lifetime parity and cumulative experience of PPH, pre-eclampsia, gestational diabetes and antenatal anaemia beyond their first birth. This could be conducted using the hospital administrative dataset 'SMR02' for maternal inpatient and day care data, linked with the same data sources as used in the CVD study reported in Chapter 4. Exposure groups could be classified based on the combination of the range of obstetric complications, accounting for the timing and frequency of these complications. For example, a variable to indicate total frequency of each complication might be generated to be included in the model. Finally, prediction models could be used to estimate the risk of CVD by PPH, pre-eclampsia, gestational diabetes and antenatal anemia throughout the study period including all available births.

Once there are more research papers available, a systematic review and meta-analysis should be conducted to synthesize the evidence about PPH and CVD. The Bradford Hill criteria should then be re-applied to assess causality. If there is convincing evidence that PPH can increase the risk of CVD based on meta-analysis results, future research should focus on establishing the integration of PPH into clinical predictive models for CVD based on the strength of association.

6.7.2 Research recommendations for PPH and mental illness

This study did not find an association between primary PPH and longer-term mental illness, but the classification of postnatal mental illness and outcome assessment was limited to women who received a prescription for psychotropic medication or hospitalisation. Many women with mild to moderate mental illness are likely to be treated with non-pharmaceutical therapies during pregnancy and in the postpartum period, in part because of a lack of information about the safety of psychotropic medications during pregnancy and while breastfeeding. (222) Future research should consider how to identify and include data about women with mild to moderate mental illness and to include women who are not receiving services and women who have a mental health problem but may not have been diagnosed. For example, data about GP appointments with mental health related complaints, referrals and waiting time to access psychological therapies might be helpful to identify such women. At the time of data linkage for the research reported here, linkage to primary health care/GP data was not available in Scotland. Currently, there is a limited use of data about access to mental health services via primary health care such as therapies, counselling, or GP consultations for the medical complaints of mental health problems. Data custodians and researchers should also explore potential options for a more advanced data linkage to identify and link women receiving other psychological interventions such as cognitive behavioral therapy or talking therapies to capture women with mild to moderate symptoms who are not prescribed psychotropic medications. A further elaborated data linkage such as linkage to the Scottish Primary Health Care data may be beneficial. For example, information about the use of NHS talking therapies for anxiety and depression may complement the outcome assessment and

therefore could be beneficial to follow up women who would not have been identified otherwise. (223)

6.7.3 Research recommendations for PPH and other chronic diseases

Cardiovascular disease and longer-term mental illness were explored as longer-term physical and psychological consequences of PPH in this thesis. There is scope to explore associations between PPH and other longer-term physical health outcomes, for example chronic kidney disease. Postpartum ARF is a rare but serious immediate postpartum complication. PPH is one of the most common causes of postpartum ARF among patients admitted to ICU. (224, 225) One case study, excluded at the screening stage of the review due to ineligibility, suggested a rapid onset of acute kidney injury resulting in renal cortical necrosis may follow PPH. (224) These patients, identified from French nephrology departments, remained dialysis dependent at six months postpartum, and none recovered normal kidney function. (127) Therefore, it is possible that PPH may have a longer-term negative impact on renal function leading to chronic renal disease.

A record-linked retrospective cohort study, using an approach similar to that used in this thesis, would be beneficial to investigate whether having a PPH increases the risk of prescription, hospitalisation and death from renal disease in the subsequent postnatal years. The same birth data from AMND could be linked with ICD codes, OPCS codes and prescriptions related to chronic renal disease using outcome algorithms. For example, the extension of the existing linkage to identify the additional outcome codes from the same data sources such as SMR01 was previously conducted for two studies from the University of Aberdeen investigating the association between pre-eclampsia and its longer-term outcomes. (115, 226)

6.8 Summary and conclusions

PPH is the leading direct cause of maternal morbidity and maternal mortality worldwide, accounting for up to 140,000 maternal deaths each year. In the developed world few women die due to PPH, but the incidence of PPH is increasing. In England in 2021-2022, 25% of all births in NHS hospitals (n=570,000) were affected by PPH. Few studies have investigated longer-term physical and psychological problems after PPH, but at the start of this research there was some evidence that PPH may have long-lasting negative impacts many years after birth.

The research presented in this thesis provides a comprehensive synthesis of evidence about the longer-term physical, psychological, and psychosocial consequences of primary PPH for women. It contributes towards a more comprehensive understanding of the impact of PPH on the risk of longer-term mental illness, and CVD. No evidence was found for an association between PPH and longer-term mental illness after taking account of the presence of mental illness in the first postnatal year. PPH is unlikely to be directly associated with longer-term mental illness. For CVD, women who had a PPH were at a higher risk of longer-term CVD, compared with women who had not had a PPH, particularly in the first postnatal year when the risk of CVD was almost doubled for women who had a PPH. This association was slightly stronger among women who also had a hypertensive disorder of pregnancy. Further population-based prospective cohort studies are required to assess causality and to understand the causal pathways behind the observed association. The increased risk of CVD associated with primary PPH should be considered alongside existing evidence about the increased risk of CVD associated with pre-eclampsia, gestational diabetes, pre-term birth and antenatal anaemia in considering women's overall lifetime risk of developing CVD. The six-week

check and regular follow up within the first postnatal year should be considered as an opportunity window for women who have had a PPH and other complications, for routine follow up, primary prevention, and early intervention for CVD in affected women.

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Appendix 1. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 28
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	NA
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 28
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 29
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 31-34
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 35
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 35, Appendix 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 35,36, Appendix 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 36, Appendices 5,6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 30,32,34, Appendices 5,6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 33-34 ,Appendices 5,6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 36,37
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Table 3.6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 37-40
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable (NA)

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 38
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 38
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 36,37
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 42-43
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 43 Figure 3.1
Study characteristics	17	Cite each included study and present its characteristics.	Pages 44,45 Table 3.2,3.3,3.4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 74
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 3.6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 58-59
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Table 3.6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 58-59, Table 3.5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 99-101
	23b	Discuss any limitations of the evidence included in the review.	Page 104

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Page 105
	23d	Discuss implications of the results for practice, policy, and future research.	Page 105-107
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 31
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 31
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 9
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendices 3-7

Appendix 2. ENTREQ checklist

Item No.	Guide and Description	Report Location
1. Aim	State the research question the synthesis addresses	Page 29
2. Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis)	Pages 38-40
3. Approach to searching	Indicate whether the search was pre-planned (comprehensive search strategies to seek all available studies) or iterative (to seek all available concepts until they theoretical saturation is achieved)	Page 35
4. Inclusion criteria	Specify the inclusion/exclusion criteria (e.g. in terms of population, language, year limits, type of publication, study type)	Page 32
5. Data sources	Describe the information sources used (e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists) and when the searches conducted; provide the rationale for using the data sources	Page 35
6. Electronic Search strategy	Describe the literature search (e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits)	Page 35
7. Study screening methods	Describe the process of study screening and sifting (e.g. title, abstract and full text review, number of independent reviewers who screened studies)	Page 35-36
8. Study characteristics	Present the characteristics of the included studies (e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions)	Page 52, Table 3.4

Item No.	Guide and Description	Report Location
9. Study selection results	Identify the number of studies screened and provide reasons for study exclusion (e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development)	Page 43, Figure 3.1
10. Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings (e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings)	Page 37
11. Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings (e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and interpretations, reporting)	Page 37
12. Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required	Page 37
13. Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale	Page 74, Table 3.8
14. Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? (e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software)	Page 36
15. Software	State the computer software used, if any	Page 36
16. Number of reviewers	Identify who was involved in coding and analysis	Pages 36, 38
17. Coding	Describe the process for coding of data (e.g. line by line coding to search for concepts)	Pages 38,39

Item No.	Guide and Description	Report Location
18. Study comparison	Describe how were comparisons made within and across studies (e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary)	Pages 38,39
19. Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive	Pages 38,39
20. Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation	Pages 78-98
21. Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct)	Figure 3.2, Pages 78-98

Appendix 3. Search strategy for Medline (Ovid)

#	Searches
1	exp Postpartum Hemorrhage/
2	((postnatal or post-natal) adj2 h?emorrhag*).mp.
3	((peripart* or peri-part*) adj2 h?emorrhag*).mp.
4	((postpart* or post-part*) adj2 h?emorrhag*).mp.
5	((postnatal or post-natal) adj2 (bleeding or blood loss)).mp.
6	((peripart* or peri-part*) adj2 (bleeding or blood loss)).mp.
7	((postpart* or post-part*) adj2 (bleeding or blood loss)).mp.
8	(obstetric adj2 h?emorrhag*).mp.
9	(obstetric adj2 (bleeding or blood loss)).mp.
10	((postnatal or post-natal) adj5 transfus*).mp.
11	((peripart* or peri-part*) adj5 transfus*).mp.
12	((postpart* or post-part*) adj5 transfus*).mp.
13	((postnatal or post-natal) adj10 hysterectom*).mp.
14	((peripart* or peri-part*) adj10 hysterectom*).mp.
15	((postpart* or post-part*) adj10 hysterectom*).mp.
16	((postnatal or post-natal) adj10 morbidit*).mp.
17	((peripart* or peri-part*) adj10 morbidit*).mp.
18	((postpart* or post-part*) adj10 morbidit*).mp.
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	(("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj2 (interview* or discussion* or questionnaire*)).tw,kw.
21	(focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant").tw,kw.
22	interviews as topic/ or focus groups/ or narration/ or qualitative research/
23	20 or 21 or 22
24	epidemiologic studies/
25	(observational adj (study or studies)).tw.
26	exp case control studies/
27	exp cohort studies/
28	Case control.tw.
29	(cohort adj (study or studies)).tw.
30	Cohort analy$.tw.
31	(Follow up adj (study or studies)).tw.
32	Longitudinal.tw.
33	Retrospective.tw.
34	Cross sectional.tw.
35	Cross-sectional studies/
36	(case$ and series).tw.
37	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38	23 or 37
39	19 and 38

Appendix 4. Eligibility criteria checklist

1. General Information

Study ID:		Date form completed:
First author:	Year of study:	Data extractor:
Citation:		
Publication type: Journal Article ☐ Abstract ☐ Other (specify e.g. book chapter)_____		
Country of study:		

2. Study Eligibility

Study Characteristics	**Eligibility criteria**	**Eligibility criteria met?** **Yes** **No** **Unclear**	**Location in text or source *(pg & ¶/fig/table/other)***
Type of study	Qualitative study (Interpretative) , Qualitative part of mixed-method study	☐ ☐ ☐	
	Quantitative Study or quantitative part of mixed-method study ☐ Intervention study (RCTs) ☐ Prospective cohort studies ☐ Retrospective cohort studies ☐ Case-control studies ☐ Cross-sectional studies	☐ ☐ ☐	
	If RCT, Data Extraction for control group can be done.	☐ ☐ ☐	
	Other design (specify):	☐ ☐ ☐	
Participants		☐ ☐ ☐	
Exposure		☐ ☐ ☐	
Phenomenon of interests	Interpretative studies on women and their partners experience of PPH which explore	☐ ☐ ☐	

(Only Qualitative)			
Types of outcome measures	Physical ---------- ---------- Psychological and Emotional ---------- ---------- ----------	☐ ☐ ☐	
INCLUDE ☐		EXCLUDE ☐	
Reason for exclusion			
Notes:			

If Included, Proceed as follow:

Quantitative study

☐ Data extraction form for qualitative study

Qualitative study

☐ Data extraction form for qualitative study

Mixed-methods study

☐ Integrated data extraction form for mixed-methods study

Appendix 5. Quantitative data collection form

Adapted from Cochrane data extraction form (needs a reference ideally)

General Information

Article Endnote ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Article title	
Year of publication	
Year of study	
Study location (Country)	
Study Author Contact Details	

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	
Aim of study		
Study Design		
Ethical approval obtained for study	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	

Participants

	Description *Include comparative information for each exposure or comparison group if available*
Population description *(from which study participants are drawn)*	
Site and Setting *(including location(s) and type of setting) e.g. multicentre cohort study at the tertiary hospitals in Victoria State*	

Eligibility criteria for participants (Inclusion and exclusion criteria)		
Method of recruitment of participants, if applicable *(e.g. phone, mail, clinic patients)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	
Sample size (*e.g.N=30, F=20, M10)*		
Response/participation Rate (e.g. 80% responded) if applicable		
Age range or mean age if applicable		
Other relevant sociodemographic (if applicable)		
Subgroups (if applicable)		

Exposed groups (*copy and paste table for each exposure group)*

Exposed group (Had PPH) 1

	Description as stated in report/paper
Group Name (if more than one exposed group)	
Definition of exposure and Data source	
Definition of comparison group (if any)	
Interventions received for PPH (if applicable as exposed group criteria)	
Other Co-morbidities or pregnancy complications (if applicable)	

Outcomes (*Copy and paste table for each outcome)*

Outcome 1

	Description as stated in report/paper	
Outcome name		
Outcome definition and categories		
Outcome measurement (e.g. self-report, clinical diagnosis, records)		
Is outcome/tool validated?	☐ ☐ ☐ ☐ Yes No Unclear Not applicable	
Frequency and time of measurement (*in relation to birth, e.g. 1 month postpartum and 3 month Post-partum)*		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Authour's Conclusions or Recommendations as reported in the paper		
Notes:		

Data and analysis

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Description as stated in report/paper
Outcome	

Subgroup				
Time point(s)				
Results (Cohort study)	Exposed group (e.g. PPH)		Unexposed group (e.g. No PPH)	
	No. with event (n/ %)	Total in group	No. with event (n/%)	Total in group
Results (case control study)	Cases		Control	
	No. with PPH (n/%)	Total in group	No. without PPH (n/%)	Total in groups
Any other results reported *(e.g. odds ratio, risk difference, CI or P value)*				
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*				

Continuous outcome

	Description as stated in report/paper					
Outcome						
Subgroup						
Time point(s)						
Results	Exposed			Non-exposed		
	Mean	SD *(or other variance, specify)*	No. participants	Mean	SD *(or other variance, specify)*	No. participants
Any other results reported *(e.g. mean difference, CI, P value)*						
Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*						

Other outcome

	Description as stated in report/paper

Comparison				
Outcome				
Subgroup				
Time point (s)				
No. participants	Exposed (e.g. PPH) (n/%)		Unexposed (e.g. No PPH) (n/%)	
Results	Exposed result	SE (or other variance)	Control result	SE (or other variance)
	Overall results		SE (or other variance)	
Any other results reported				
Statistical methods used and adjusted confounders				

Appendix 6. Qualitative data collection form

General Information

Article Endnote ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Article title	
Year of publication	
Year of study	
Study location (Country)	
Study Author Contact Details	

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	
Aim of study		
Study Design		
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear ☐ Not applicable	

Participants

	Description
Population description *(from which study participants are drawn)*	
Site and Setting *(including location and social context)*	
Eligibility criteria for participants (Inclusion and exclusion criteria)	

Sampling Method or Strategy for qualitative study (e.g. Snowball sampling, purposive sampling, convenience sampling, etc)	
Method of recruitment of participants, if applicable *(e.g. phone, mail, clinic patients)*	
Informed consent obtained	☐ Yes ☐ No ☐ Unclear/unreported
Sample size (*e.g.N=30, F=20, M10)*	
Participants Response/participation Rate (if applicable)	
Age range or mean age if applicable	
Other relevant sociodemographic characteristics of participants (if applicable)	

Data collection and analysis

	Description as stated in report/paper
Data Collection	Summarise the data collection approach. Include: type of data collection/source (e.g. semi-structured interviews/FGDs), total number of interviews/Focused Group Discussions (FGDs)/ open-ended survey; how the data were collected (e.g. face to face/telephone/email) ; location (s) (e.g. home, clinics); number of participants in FGDs if applicable; Duration of interviews/FGDs (e.g. 60 to 90 mins); information for interviewers/facilitators (e.g. by an experienced midwives) ; timing of interviews (e.g. 3- 6 months postpartum); whether they are interviewed separately if the partners were included.
Questions or topics covered for interviews/ FGDs/Survey(s)	Describe topics covered by interviews/ FGD(s) and/or open-ended survey questions asked.

Data Analysis (Summarise approach to data analysis and synthesis) (e.g. content analysis, thematic analysis, etc) Describe the theoretical approach if reported (e.g. naturalistic inquiry, grounded theory)	
Results (copy/paste the themes reported)	

Other

Study funding sources *(including role of funders)*	
Possible conflicts of interest *(for study authors)*	
Authors' Conclusion and Recommendation (if applicable)	
Notes:	

Appendix 7. Modified risk of bias assessment tool for non-randomized studies (ROBANS)

	Domain	Adapted criteria	
		Low risk of bias[1]	High risk of bias[1]
1	Participant selection	The following criteria should be considered for participant's selection **Cohort studies** • Women with and without PPH were selected from the same population group(s) and time period(s) (appropriate comparison group) • Cohort studies: The cohort started with healthy (i.e. outcome free) participants and assure that people with the outcomes occurring before pregnancy/ at the time of birth were excluded. **Case-control studies** • Only incident cases were included (e.g. newly diagnosed/treated cases) • The selection of cases and controls was independent of the exposure status (i.e. PPH) , and cases and controls were derived from the similar source population , and the source of controls was population-based. • Observational study designs with a proper comparison group (e.g. women with or without PPH were followed up over time; exposures were assessed for cases and comparable controls) **Cross-sectional studies** • Selection/participation was independent of the exposure (i.e. PPH) and outcome status	**Cohort studies** • Women with or without PPH were selected from different population groups and/or time periods (e.g. historical unexposed cohort) • Participants had the outcomes at baseline or they were likely to have undiagnosed outcomes. **Case-control studies** • Both the incident and prevalent (pre-existing) cases were included. • The selection of cases and control was dependent of the exposure status, or the cases and controls were not selected from the similar source population, or the source of controls was not population-based. • Observational study designs without a proper control group (e.g. case series or exposed only cohorts) **Cross-sectional studies** • A clear case of Selection bias. Selection/Participations varies by combination of exposure and outcomes (e.g. Women with PPH who were mentally unfit did not participate in the survey)

2	Confounding variables	The major confounding variables were adequately considered and adjusted in the study design (through participant restriction/exclusion or matching) and/or in the analysis. Such confounders might include, for example 1. Maternal age at the time of birth 2. Maternal education or socioeconomic status (or family socioeconomic status) 3. Maternal BMI (at first antenatal visit) or gestational weight gain 4. Parity 5. Maternal smoking habit Other major confounders include: 6. Presence of other obstetric complications (e.g. pre-eclampsia, gestational hypertension/diabetes, prolonged third stage of labour) 7. Neonatal condition (e.g. admission to neonatal unit, baby weight or outcomes of pregnancy)	The major confounding variables were not considered in the study design or analysis (i.e. the study did not confirm or adjust for the potential confounders such as maternal age, maternal education or socioeconomic status, BMI, Parity etc.)
3	Exposure measurement	The following criteria should be considered for exposure measurement • PPH was defined using standardised diagnostic criteria, for example using definitions of WHO, RCOG, ACOG, or ICD-10 codes. • The amount of blood loss was assessed prospectively and in a standardised manner by a qualified/trained health care professional.	Any of the following • PPH was defined using non-standard or unclear criteria. • The measurement of PPH was not comparable among all study participants. • The data on PPH was self-reported. For case-control/cross-sectional studies, please consider • A clear case of interviewer bias (e.g. The interviewer knew the case status and the exposure of interest (PPH), so they asked questions differently to women with outcomes) • A clear case of recall bias (e.g. Participants were asked the history of PPH 10 years after birth and cases (women who are unwell) recalled PPH more frequently than controls.)

4	Blinding and outcome measurement	The following criteria should be considered • The outcome was evaluated using established diagnostic/classification criteria or validated tool (e.g. Postnatal depression scale) or laboratory tests • Outcome evaluation was performed in a standardised fashion by qualified assessors (e.g. midwives, doctors, psychologists) • The duration of the follow-up is reasonably long enough for the outcomes assessed to occur. • The timing of outcome assessment was comparable for all participants • Outcome assessors were blinded to women's medical history/record for PPH or were blinded to the research question. If blinding is absent, it is less likely to be the source of differential measurement error (e.g. the outcome measurement was based on the laboratory test, or existing records)	• The outcome was defined using non-established (e.g. ad hoc) diagnostic criteria/tools with uncertain validity/reliability (including self-reporting using such tools) or diagnostic criteria were not clear • In cohort studies, the outcome was evaluated retrospectively from medical records that were not validated or did not have quality checks. • The outcome was assessed using procedures or diagnostic criteria, which were not comparable for all the study participants • The duration of outcome assessment was not long enough for outcomes to occur. • The timing for outcome measurement was not comparable for all participants • Evaluation of the outcome was unblinded to the women's medical history when the absence of blinding can be the source of potential measurement errors
5	Incomplete data	The following criteria should be considered • The proportion and causes of missing data were similar between exposed and unexposed groups (women with or without PPH), or between cases and controls • In cohort studies, women lost to follow-up were comparable to women that were not lost to follow-up regarding characteristics relevant to the study outcome (i.e. non-differential LTFU) • The potential impact of missing data was corrected in the analysis • The study results were demonstrated to be robust to the presence of missing data (e.g. via sensitivity analyses)	• Women lost to follow-up and those who were not lost to follow-up differed in characteristics deemed relevant to the study outcome (differential LTFU) (e.g. LTFU was more common in women with PPH because they were emotionally unfit) , and these differences were not addressed in the analysis. • The proportion and causes of missing data differed between participants with or without PPH (or cases and controls) , and these differences were not addressed in the analysis • The study results were influenced by the missing data

6	Selective reporting (within study)	The following criteria should be considered • If a study protocol is available, the pre-defined primary/secondary analyses were described as planned or justified in the study report if there were any legitimate changes from the protocol. • Analyses of all of the outcomes/exposures that are relevant to the study objectives were reported (e.g. check the outcomes mentioned in the methods section and the reported results, or consider missing report of the measures which are usually collected together e.g. SBP and DBP) • The effect estimates reported do not seem to have been selected from (i) alternative outcome/exposure measurements, (ii) multiple analytic approaches, or (iii) multiple subgroups	• The pre-defined primary analyses were not fully reported or reported as planned in a protocol or not justified for the differences. • Additional analyses that were not pre-specified or directly relevant to the study objectives were included (e.g. subgroup analyses, secondary variables), except for those with a clear justification • Some analyses of exposures/outcomes that are relevant to the study objectives were not reported • The effect estimates reported seem to have been selected from (i) alternative outcome/exposure measurements, (ii) multiple analytic approaches, or (iii) multiple subgroups

[1] If there is insufficient information to determine whether the risk of bias is low or high, it should be classified as "unclear".

Form for risk of bias assessment (RoBANs tool)

Domain	**Risk of bias**			**Support for judgement** *(Include direct quotes where available with explanatory comments)*	**Location in text or source** *(pg & ¶/fig/table/other)*
	Low	**High**	**Unclear**		
1. Participant selection	☐	☐	☐		
2. Confounding variables	☐	☐	☐		
3. Exposure measurement	☐	☐	☐		
4. Blinding and outcome measurement *(detection bias)*	☐	☐	☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐	☐	☐	Outcome group:	
5. Incomplete data	☐	☐	☐		
6. Selective reporting	☐	☐	☐		
Notes:					

Appendix 8. Conceptual framework diagram

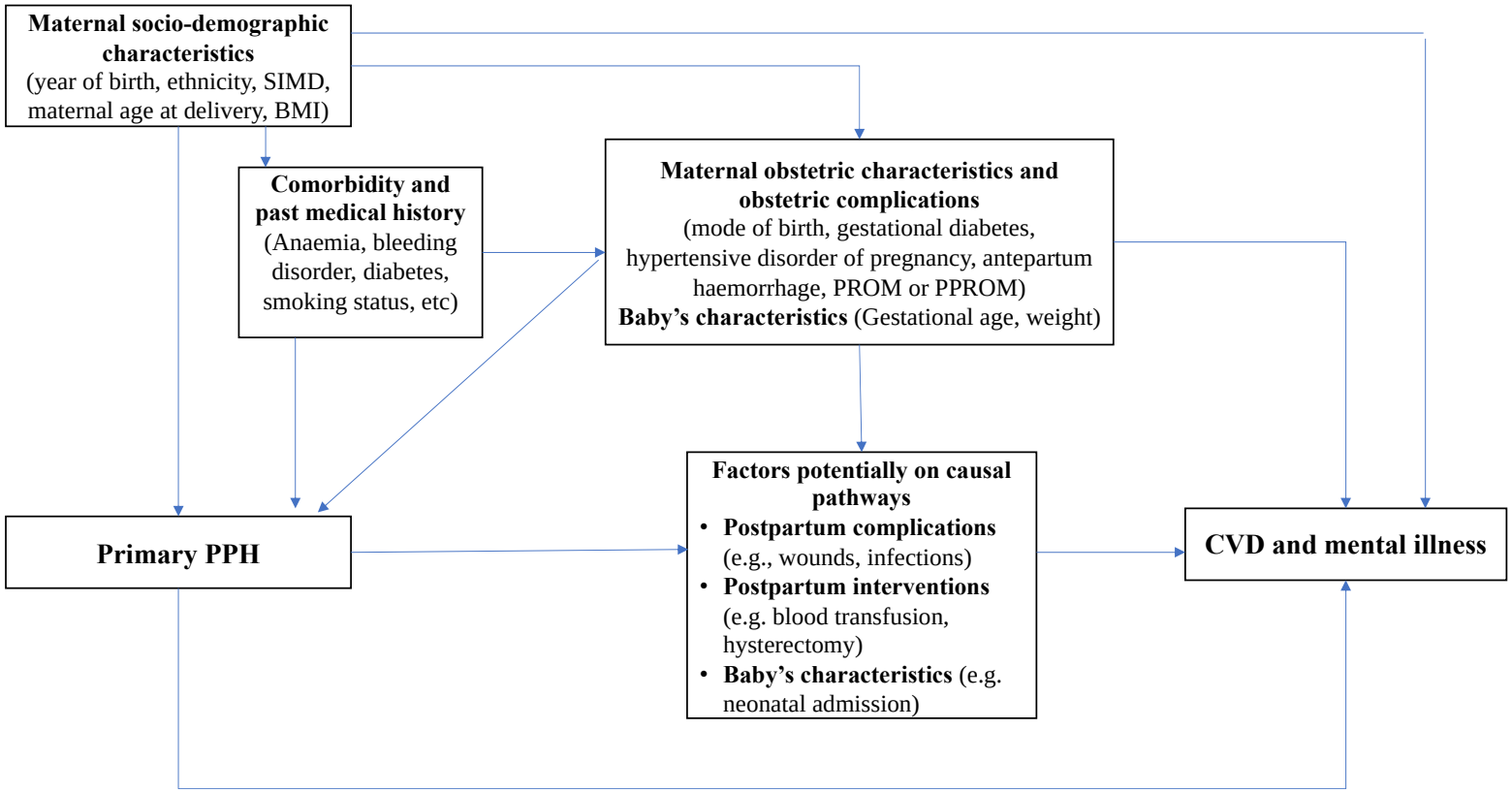
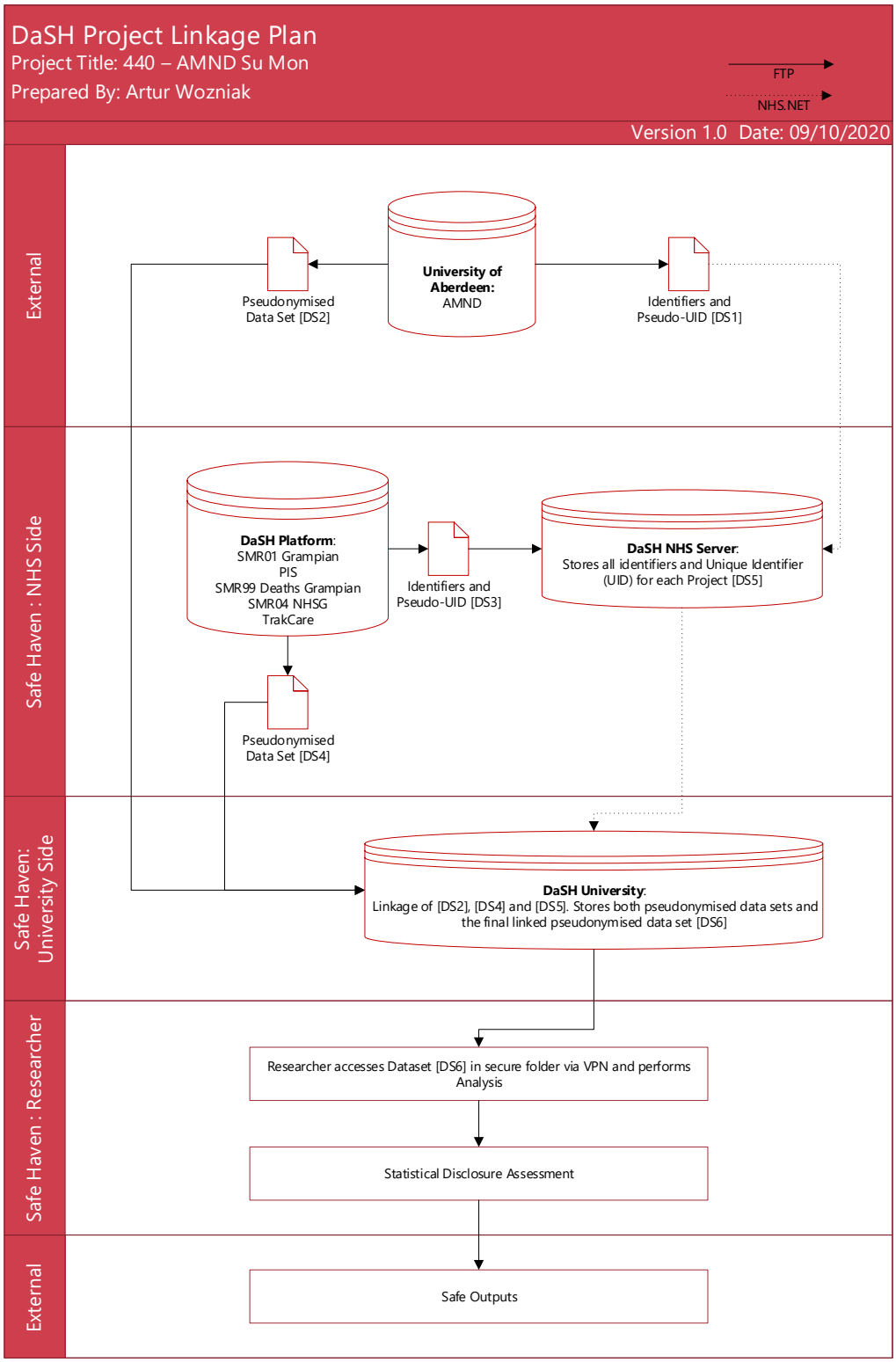


Figure A8.1. Conceptual framework diagram illustrating how maternal socio-demographic characteristics, past medical history, obstetric characteristics, obstetric complications might confound the association between PPH and development of CVD and mental illness in later life.

Appendix 9. DaSH project linkage plan



Appendix 10. Coding guidance to generate 'ethnicity' variable

Ethnicity	coding	Intermediate code	Ru Code
North Africa	1	African	Other
Sub-Sahra	2	African	Black
Africa Other	3	African	Black
India	4	S.E Asia	Asian
Pakistan	5	S.E Asia	Asian
Bangladesh	6	S.E Asia	Asian
China	7	Asia	Asian
East Asia - Other	8	Asia	Asian
South East Asia	9	S.E Asia	Asian
Asia Other	10	Asia	Asian
Caribbean	11	Caribbean	Black
North America	12	American	White
South America	13	American	Other
Britain	14	European	White
Ireland	15	European	White
Northern Europe	16	European	White
Western Europe	17	European	White
Eastern Europe	18	European	White
Southern Europe	19	European	White
Europe Other	20	European	White
Middle East	21	Middle Eastern	Other
Middle East Other	22	Middle Eastern	Other
Declined	23		Missing
Australasia	24	Australian	White
Missing	25		Missing
Historic white	26	European	White
Historic asian	27	Asian	Asian
Historic Indian	28	SE Asian	Asian
Historic Negro	29	African	Black
Historic Arabic	30	Middle Eastern	Other
Historic African	31	African	Black
.			Missing
Total			

Appendix 11. Statistical analysis plan

Statistical analysis section of protocol prepared for research governance approvals (IRAS 290656)

The pseudo-anonymised linked dataset will be stored in the Grampian Data Safe Haven (DaSH) and the dataset will be available as a Stata data file. Access to the pseudo-anonymised data will be via Virtual Private Network, as per DaSH processes and within a secure analytics platform. Descriptive analysis will be conducted to explore baseline characteristics for women with PPH (PPH group) compared with women who did not have a PPH in any of their pregnancies (non-PPH group), summarising using frequencies and percentages or means and standard deviation as appropriate. The incidence risk of emergency peripartum hysterectomy by year of birth will be estimated to investigate how the trend of EPH following PPH changes over time.

Survival analysis will be performed using Poisson regression and cox proportional hazard models. We will first calculate the unadjusted incidence rates (i.e., number of first hospital admissions/prescriptions divided by accumulated person-years) for PPH and non-PPH groups separately for each composite outcome (i.e. 1. cardiovascular outcomes, 2. mental illness). For instance, first time hospitalizations or prescriptions from any cardiovascular conditions listed in Table 1 will be analysed as a composite cardiovascular outcome, and from any mental illness listed in Table 2 will be analysed as a composite mental illness.

Unadjusted log-linear Poisson regression models will be fitted to estimate the incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of the selected outcomes in the PPH group compared with the non-PPH group. Potential confounders will be explored and adjusted IRRs will be calculated, together with 95% CIs. A threshold value of $p<0.05$ will not be used to declare statistical significance as this can lead to a misinterpretation, but the actual p-values will

be reported, and the interpretations will be made along the continuum of differing level of evidence against null hypothesis.

The results will be stratified according to the sub-groups of PPH to see if any associations differ by timing and frequency of PPH. Potential effect modification according to severity of PPH, mode of birth, presence of other obstetric complication at the time of PPH will be investigated using likelihood ratio (LR) tests. Similar Poisson regression models will be fitted to calculate the incidence rate ratios (IRRs) between severe PPH and non-PPH groups.

Cox proportional hazard models will be used to calculate hazard ratios for all-cause mortality, cause-specific mortality due to selected cardiovascular outcomes, and mental health related mortality between PPH and non-PPH groups. Potential confounders such as maternal age, relevant pre-existing diseases and presence of other obstetric complications will be explored and included as appropriate. The proportional hazard assumption will be tested both visually and statistically by adding an interaction term between PPH and time period. If there is an interaction between time and PPH, the extended cox regression models will be performed by including time varying covariant (tvc) option in the model to allow non-proportional hazards.
Data will be analysed using Stata software version 14.

Appendix 12. Supplementary figures for PPH and cardiovascular disease

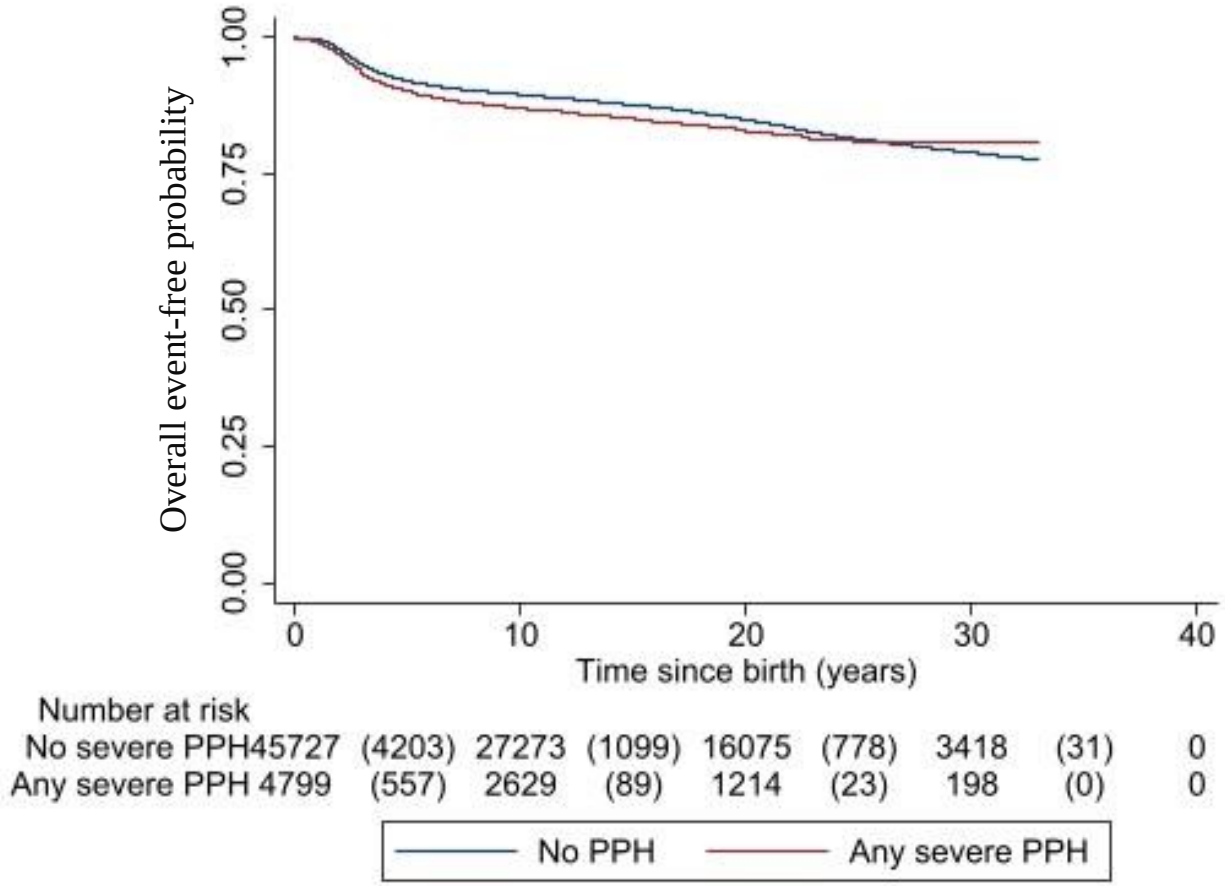


Figure A12.1. CVD event-free survival probability over time among women with at least one severe PPH and women with no PPH

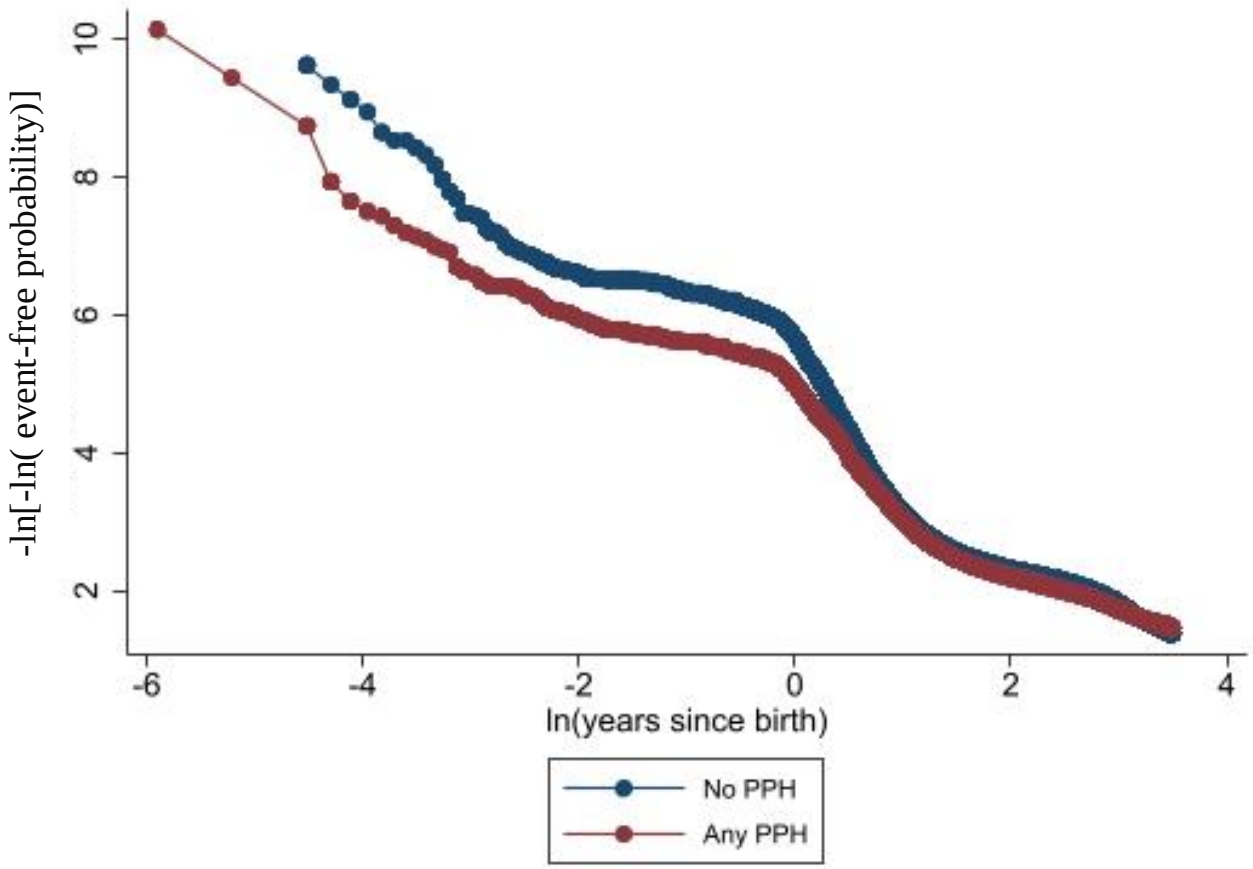


Figure A12.2. Log (-log plot) for survival probability over time for 'Any PPH' vs 'No PPH'

Figure A12.2 illustrates violation of the proportional hazards assumption for the association between PPH and CVD, since the lines are not parallel (Reference: Table 4.11, Model 3 (n= 63,376))

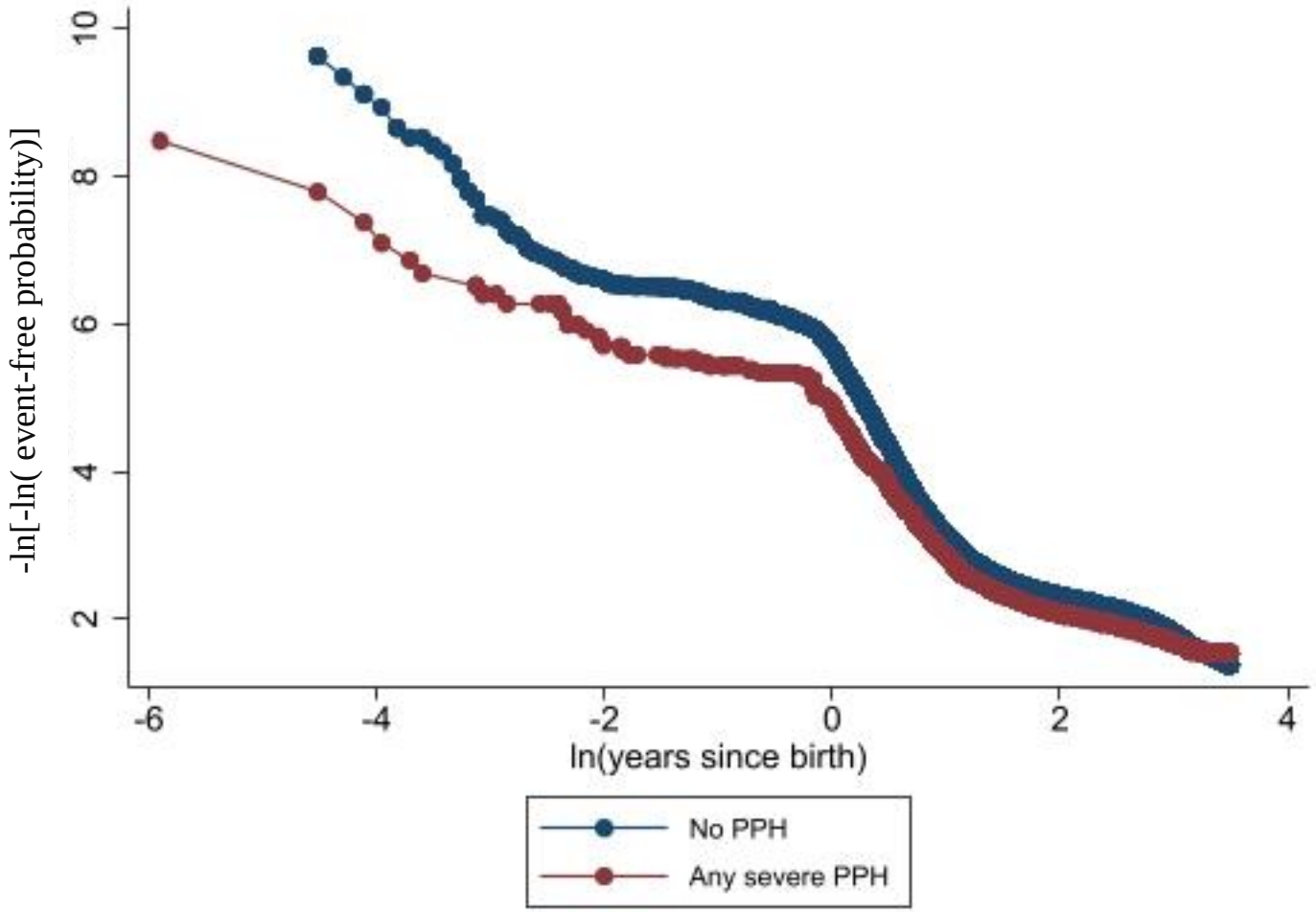


Figure A12.3 Log (-log plot) for survival probability over time for 'Any severe PPH' vs 'No PPH'

Figure A12.3 illustrates violation of the proportional hazards assumption for the association between severe PPH and CVD, since the lines are not parallel (Reference: Table 4.11, Model 3 (n= 44,726))

Appendix 13. Supplementary figures for PPH and longer-term mental illness

Table A13.1. Number of births in AMND between 1986-2016, stratified by presence of PPH and postnatal mental illness (before the final exclusion of births before the year 2009)

Characteristics	Births with no PPH and no MH1[a] n=85,807		Births with no PPH and MH1 n=1,900		Births with PPH and no MH1 n=27,831		Births with both PPH and MH1 n= 1,055		All births n=116,594	
	n	%	n	%	n	%	n	%	n	%
Year of childbirth (row %)[b]										
1986-1990	14,052	89.5	<5	<0.3	1,643	10.5	<5	<0.3	15,695-15,703	100
1991-1995	18,975	87.0	<5	<0.3	2,832	13.0	<5	<0.3	21,807-21,815	100
1996-2000	15,356	78.4	26-34	<0.3	4,176	21.3	8-16	<0.3	19,566-19,582	100
2001-2005	12,832	72.4	46	0.3	4,821	27.2	14	0.1	17,713	100
2006-2010	12,136	61.5	780	4.0	6,476	32.8	363	1.8	19,755	100
2011-2016	12,456	56.5	1,040	4.7	7,892	35.8	662	3.0	22,050	100

[a] Postnatal mental illness, indicated by having a record of mental health related prescription or hospitalisation within one year after childbirth.
[b] Approximate numbers are presented due to the data privacy and confidentiality.

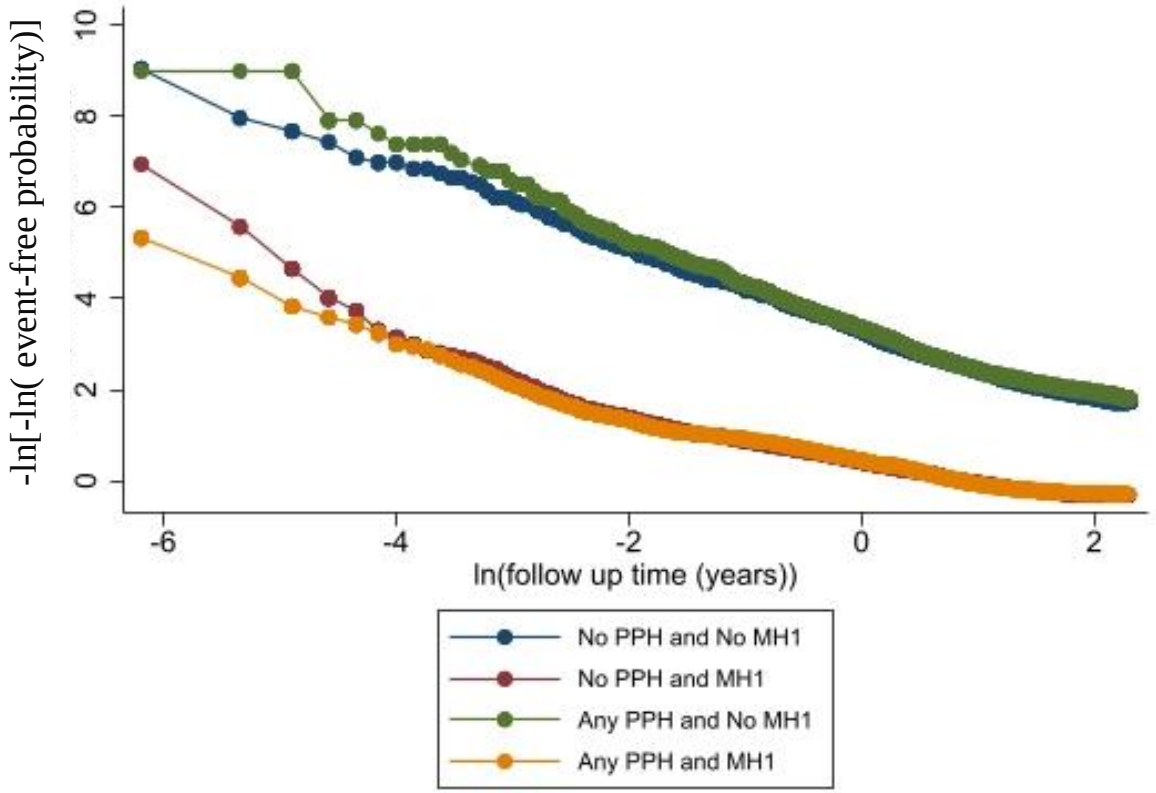


Figure A13.1. Log(-log plot) for survival probability over for PPH exposure groups

Figure A13.1 illustrates violation of the proportional hazards assumption for the association between PPH and longer term mental illness, since the lines are not parallel (Reference: Table 5.8, Model 3 (n=17,471))

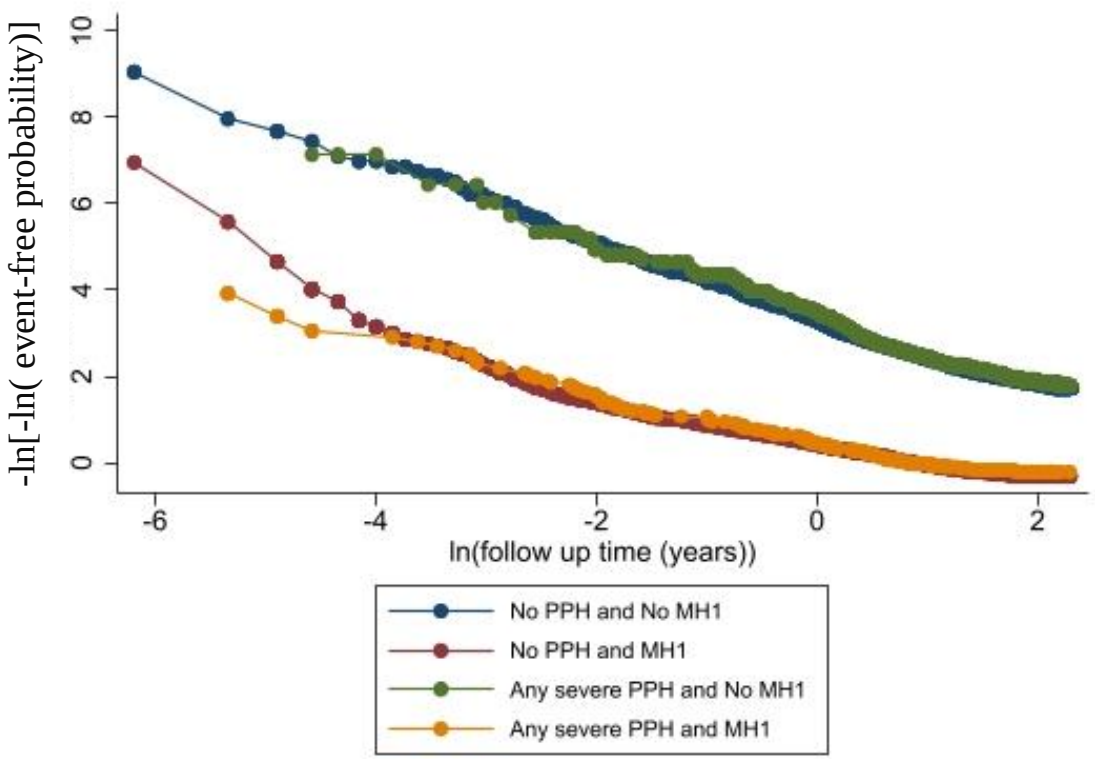


Figure A13.2. Log (-log plot) for survival probability over time for severe PPH exposure groups

Figure A13.2 illustrates violation of the proportional hazards assumption for the association between severe PPH and longer term mental illness, since the lines are not parallel (Reference: Table A9.3, Model 3 (n=10,280))

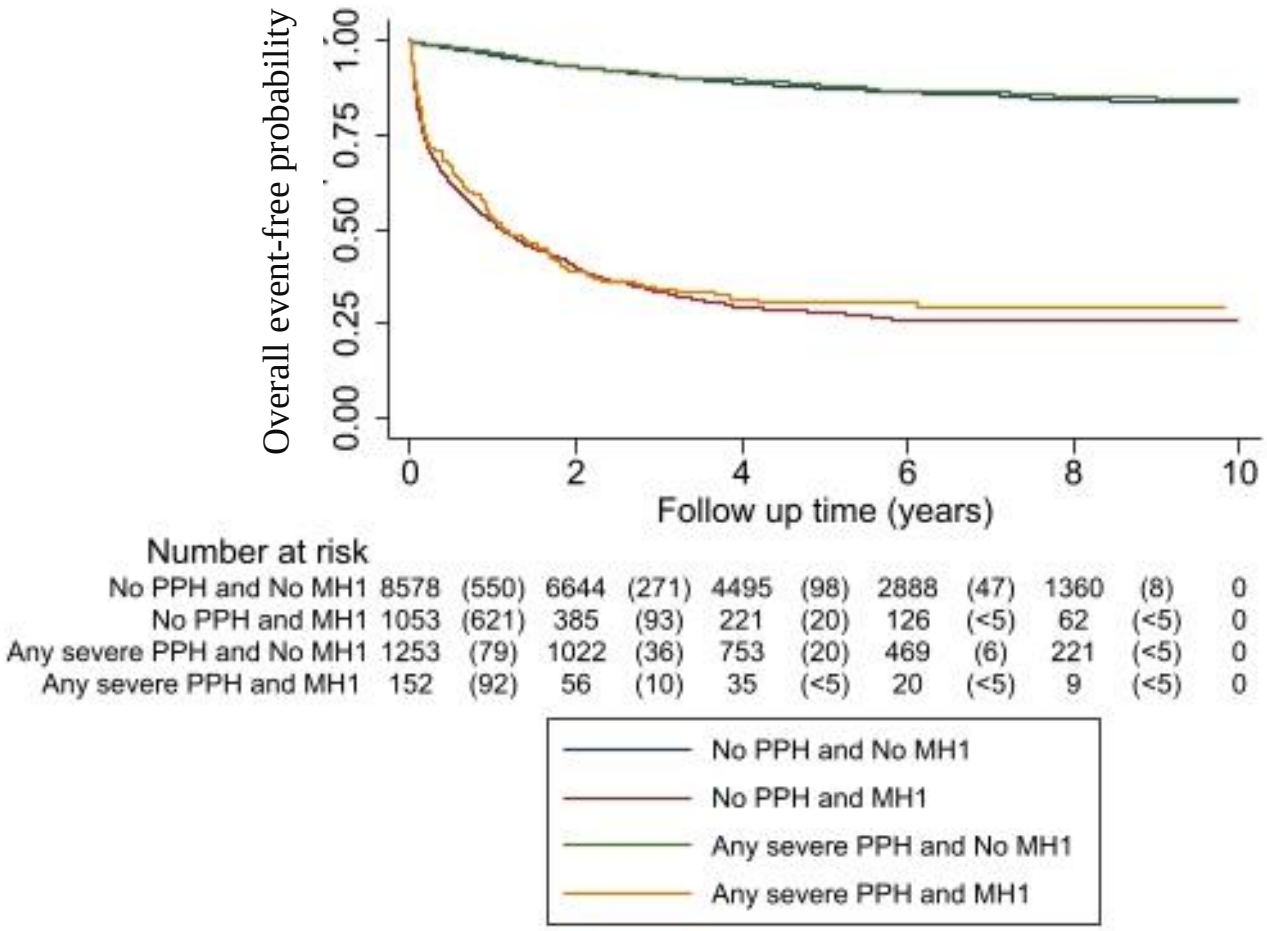


Figure A13.3. Mental health event-free survival probability over time across all exposure groups for severe PPH

Table A13.2 Association between severe PPH and risk of longer-term mental illness

Exposure groups				Univariate Analysis n=11,036		
	Women with MH event	Total person-years (PY)	Incidence rate per 10,000 PY	HR	95% CI	p-value
No PPH and No MH1[a]	974	39,402	247	Reference	Reference	Reference
No PPH and MH1[b]	736	2,301	3,199	10.88	9.88-11.98	<0.001
Any Severe PPH and No MH1[c]	142	6,190	229	0.95	0.80-1.14	0.60
Any Severe PPH and MH1[d]	104	350	2,968	10.12	8.27-12.40	<0.001

[a] Women with no PPH and no postnatal mental illness
[b] Women with no PPH, but with postnatal mental illness after at least one birth
[c] Women with at least one severe PPH, but no postnatal mental illness
[d] Women with at least one severe PPH and with postnatal mental illness after at least one birth

Table A13.3. Association between severe PPH and longer-term mental illness for different time intervals following the first postnatal year, stratified by the presence of postnatal mental illness and with sequential adjustment for potential confounders

Follow-up time	Exposure groups	Base Model[a] n=11,036			Model 1[b] n=10,354			Model 2[c] n=10,290			Model 3[d] n=10,280		
		aHR	95% CI	p	aHR	95% CI	p	aHR	95% CI	p	aHR	95% CI	p
1-2 year	No PPH and No MH1		Reference			Reference			Reference			Reference	
	No PPH and MH1	17.82	15.45-20.56	<0.001	16.22	13.95-18.87	<0.001	12.63	10.80-14.78	<0.001	12.57	10.73-14.74	<0.001
	Any severe PPH and No MH1	0.80	0.57-1.13	0.21	0.87	0.62-1.23	0.44	0.89	0.63-1.26	0.53	0.91	0.64-1.30	0.61
	Any severe PPH and MH1	16.77	12.95-21.75	<0.001	15.45	11.88-20.09	<0.001	11.58	8.86-15.13	<0.001	11.42	8.55-15.25	<0.001
3-5 year	No PPH and No MH1		Reference			Reference			Reference			Reference	
	No PPH and MH1	6.38	5.46-7.45	<0.001	5.23	4.44-6.15	<0.001	4.11	3.48-4.86	<0.001	3.96	3.34-4.70	<0.001
	Any severe PPH and No MH1	1.03	0.82-1.29	0.80	1.10	0.87-1.38	0.42	1.08	0.86-1.36	0.51	1.03	0.80-1.31	0.84
	Any severe PPH and MH1	6.29	4.41-8.98	<0.001	5.55	3.85-7.99	<0.001	4.25	2.93-6.17	<0.001	4.25	2.88-6.25	<0.001
6-10 year	No PPH and No MH1		Reference			Reference			Reference			Reference	
	No PPH and MH1	3.18	1.74-5.80	<0.001	2.42	1.28-4.56	0.01	1.91	1.01-3.61	0.05	1.83	0.96-3.49	0.07
	Any severe PPH and No MH1	1.19	0.69-2.05	0.53	1.50	0.86-2.60	0.15	1.46	0.84-2.53	0.18	1.24	0.68-2.27	0.48
	Any severe PPH and MH1	2.06	0.29-14.75	0.47	1.98	0.27-14.23	0.50	1.48	0.21-10.68	0.70	1.56	0.21-11.39	0.66

[a] Base model adjusted for year of birth only

[b] Model 1 adjusted for year of birth and sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation)

[c] Model 2 adjusted for variables in model 1, and additionally adjusted for pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric or mental disorder, cardiovascular disease) and smoking status

[d] Model 3 adjusted for variables in model 2, and additionally adjusted for pregnancy-related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at birth, baby's birthweight

Follow up began after the first postnatal year.

Table A13.4. Association between severe PPH and longer-term mental illness for different time intervals following the first postnatal year, stratified by the presence of postnatal mental illness (reference group "No PPH and MH1") fully adjusted for potential confounders

Follow-up time	Exposure groups	Model 3[a] n=10,280		
		aHR	95% CI	p-value
1-2 year	No PPH and MH1	Reference		
	No PPH and No MH1	0.08	0.07-0.09	<0.001
	Any severe PPH and No MH1	0.07	0.05-0.10	<0.001
	Any severe PPH and MH1	0.91	0.69-1.20	0.494
3-5 year	No PPH and MH1	Reference		
	No PPH and No MH1	0.25	0.21-0.30	<0.001
	Any severe PPH and No MH1	0.26	0.20-0.34	<0.001
	Any severe PPH and MH1	1.07	0.72-1.60	0.736
6-10 year	No PPH and MH1	Reference		
	No PPH and No MH1	0.55	0.29-1.04	0.066
	Any severe PPH and No MH1	0.68	0.29-1.57	0.366
	Any severe PPH and MH1	0.86	0.11-7.65	0.882

Model 3 adjusted for year of birth, sociodemographic and clinical factors, past medical history of women, and pregnancy related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at delivery, baby's birthweight

Table A13.5. Association between severe PPH and longer-term mental illness for different time intervals following the first postnatal year, after exclusion of births to women with pre-existing mental illness (fully adjusted model 3)

Follow-up time	Exposure groups	Model 3[a] n=9,057		
		aHR	95% CI	p-value
1-2 year	No PPH and No MH1		Reference	
	No PPH and MH1	17.02	14.00-20.69	<0.001
	Any severe PPH and No MH1	1.07	0.71-1.60	0.74
	Any severe PPH and MH1	13.96	9.15-21.32	<0.001
3-5 year	No PPH and No MH1		Reference	
	No PPH and MH1	4.64	3.75-5.74	<0.001
	Any severe PPH and No MH1	1.03	0.78-1.37	0.83
	Any severe PPH and MH1	3.64	1.97-6.72	<0.001
6-10 year	No PPH and No MH1		Reference	
	No PPH and MH1	3.60	1.75-7.39	<0.001
	Any severe PPH and No MH1	1.43	0.75-2.72	0.28
	Any severe PPH and MH1	2.56	0.35-19.04	0.36

[a]Model 3 adjusted for year of birth, sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation), pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric or mental disorder, cardiovascular disease), smoking status, pregnancy related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at delivery, baby's birthweight

Table A13.6 Number of women with mental health related hospitalisation among severe PPH groups and incidence rate for all births and births after 2008

Exposure groups	All births n=48,583			Births after 2008 n=11,888		
	Total number of women	No. of women with event	Incidence rate per 10,000 PY	Total number of women	No. of women with event	Incidence rate per 10,000 PY
No PPH and No MH1	41,685	1,622	25	8,914	50	11
No PPH and MH1	2,209	159	92	1,475	46	59
Any severe PPH and No MH1	4,368	144	24	1,296	8	11
Any severe PPH and MH1	321	38	154	203	10	50

Table A13.7. Association between severe PPH and longer-term mental health related hospitalisation for different time intervals following the first postnatal year, after restricting the mental health outcome to hospitalisation

Follow-up time	Exposure groups	All Births (Model 3) n=43,431		
		aHR	95% CI	p-value
1-2 year	No PPH and No MHH1		Reference	
	No PPH and MHH1	1.41	1.00-1.98	0.050
	Any severe PPH and No MHH1	1.31	0.90-1.91	0.163
	Any severe PPH and MHH1	2.30	1.17-4.51	0.016
3-5 year	No PPH and No MHH1		Reference	
	No PPH and MHH1	1.21	0.94-1.55	0.134
	Any severe PPH and No MHH1	1.10	0.84-1.44	0.483
	Any severe PPH and MHH1	2.97	1.95-4.51	<0.0001
6-10 year	No PPH and No MHH1		Reference	
	No PPH and MHH1	1.45	1.02-2.06	0.040
	Any severe PPH and No MHH1	0.81	0.57-1.14	0.228
	Any severe PPH and MHH1	0.94	0.35-2.56	0.908

Postnatal mental illness, indicated by having a record of mental health related hospitalisation within one year after any births (MHH1) in this sensitivity analysis.

[a]Model 3 adjusted for year of birth, sociodemographic factors (age at delivery, BMI, Ethnicity, Scottish index of multiple deprivation), pre-existing medical history of women (anaemia and coagulation disorders, diabetes, existing psychiatric and mental disorder, cardiovascular disease), smoking status, pregnancy related factors: mode of birth, obstetric complications (HDP, pre-labour rupture of membrane, preterm pre-labour rupture of membrane, gestational diabetes), gestation age at delivery, baby's birthweight