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# The epidemiology of peripartum cardiomyopathy in Scotland from 1998-2017

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# Abstract


## Background

Peripartum cardiomyopathy (PPCM) is a type of heart failure, secondary to left ventricular systolic dysfunction, that develops around the time of pregnancy. The incidence of PPCM and its outcomes vary markedly between countries. There are few reports of the epidemiology of PPCM in Europe and none from the United Kingdom (UK). Extrapolation of existing data to the UK is limited by geographical and racial variation. It is likely that true regional variation does exist, but it is equally as likely that some of the differences in incidence and outcomes seen are explained by inconsistencies in the data sources, definition of PPCM, inclusion criteria, and applied methodology across studies. There are also large gaps in our understanding of long-term outcomes for women with the condition and for their babies.

## Aim

To describe the epidemiology of PPCM in Scotland, with a focus on incidence, factors associated with the development of the condition, long term outcomes, subsequent pregnancies and outcomes for children.

## Methods

I performed a retrospective, observational, population-level study of consecutive women hospitalised with incident PPCM using linked, national, administrative data, supplemented by data I collected directly from patients records throughout Scotland. Possible cases of PPCM were defined as woman with a discharge diagnosis of PPCM, heart failure or cardiomyopathy up to 6 months prior to or 2 years following a pregnancy outcome from 1998-2017 in Scotland. I reviewed case records to validate (or refute) the diagnosis of PPCM using the following criteria: impaired LV systolic function (left ventricular ejection fraction on transthoracic echocardiography of ≤50% or a qualitative assessment reporting left ventricular systolic dysfunction if no ejection fraction available), no clear alternative cause for left ventricular systolic dysfunction, no pre-

existing diagnosis of left ventricular systolic dysfunction or cardiomyopathy, and diagnosis during pregnancy (excluding the first trimester) or up to 2 years postpartum. Each case was matched to 10 controls.

Data on demographics, comorbidities, socioeconomic status, clinical data (including laboratory tests, electrocardiographic and echocardiographic data), obstetric data and neonatal data were merged. I examined the following outcomes: death (all-cause, CV); rehospitalisation (all-cause, CV); a composite of death or rehospitalisation (all-cause, CV); total (recurrent) hospitalisations; a composite of CV death, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation or cardiac transplantation; stroke or thromboembolism; implantation of a cardiac device; LV recovery; and LV decline after recovery. Outcomes relating to a subsequent pregnancy were also examined. Neonatal outcomes, disease incidence, hospitalisation (any cause), total (recurrent) hospitalisations and death (any cause) were analysed in children born to women with PPCM.

**Results**

The incidence of PPCM in Scotland over a 20-year period was 1 in 4950 deliveries and was similar in England at 1 in 4717. In Scotland, the incidence of PPCM was greater in women over the age of 32 years than in those aged 32 years or less. Among 225 women with PPCM (and 2240 matched controls), obesity, gestational hypertensive disorders, multiparity and multiple gestation were independently associated with the development of PPCM. Socioeconomic deprivation was also relevant, although this appeared to be explained by other baseline factors studied.

Over a median follow-up of 8.3 years/1,911 person-years for 221 women with PPCM (9.7 years/2024 person-years for echocardiographic outcomes), 8% of women died, 40% were rehospitalised at least once for a CV cause and 23% had at least two further CV hospitalisations (i.e. recurrent hospitalisations). The rates of death from any cause and of CV death or CV rehospitalisation in women with PPCM were approximately 12 – and 14-times that of controls, respectively. Complete LV recovery occurred in 76% of women throughout the whole study

period (47% within 1 year), and, of those who recovered, 13% had sustained decline of LV systolic function despite initial recovery, at a median of 2.9 years after recovery.

A total of 36/225 (16%) women with PPCM had a subsequent pregnancy; these women were younger and more socioeconomically deprived than those without a subsequent pregnancy. The rate of all-cause death or all-cause rehospitalisation was similar in women with PPCM irrespective of whether or not they went on to have a subsequent pregnancy. Although 15% of women had a CV hospitalisation in the 1st year after the subsequent pregnancy, no women had a CV death or required mechanical circulatory support or cardiac transplantation up to 5 years after a subsequent pregnancy.

Over a median follow-up 8.8 years/1946 person-years for children born to women with PPCM, approximately 1 in 3 had an adverse neonatal outcome, with 4% case-fatality (including stillbirths) and a mortality rate approximately 5-times that of children born to controls. Children born to women with PPCM also had an approximately 3-times greater incidence of CV disease than children born to controls.

**Conclusion**

PPCM affects 1 in 4950 women around the time of pregnancy. A number of factors were associated with the development of the condition in this population, including obesity, pregnancy-induced hypertension, pre-eclampsia and multiple gestation. Overall, 8% of women with PPCM died and 76% had recovery of cardiac function, but 13% of those who recovered had a sustained decline in LVEF after initial recovery. Outcomes were worse for women with PPCM than for controls. Adverse neonatal outcomes were more frequent, rates of all-cause mortality greater, and incident CV disease more common in children born to women with PPCM than in those born to controls. These findings suggest that PPCM is associated with considerable morbidity and mortality, both for the mother and the child.

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# Publications relating to this work

**Jackson AM,** Petrie MC, Frogoudaki A, Laroche C, Gustafsson F, Ibrahim B, Mebazaa A, et al. Hypertensive disorders in women with peripartum cardiomyopathy: insights from the ESC Peripartum Cardiomyopathy Registry. Eur J Heart Fail. 2021 Jun 11. doi: 10.1002/ejhf.2264.

Sliwa K, van der Meer P, Petrie MC, Frogoudaki A, Johnson MR, Hilfiker-Kleiner D, Hamdan R, **Jackson AM,** et al. Risk stratification and management of women with cardiomyopathy/heart failure planning pregnancy or presenting during/after pregnancy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail. 2021 Feb 20. doi: 10.1002/ejhf.2133.

Sliwa K, Petrie MC, van der Meer P, Mebazaa A, Hilfiker-Kleiner D, **Jackson AM**, Maggioni AP, et al. Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry. Eur Heart J. 2020;41(39):3787-3797.

Bauersachs J,, Tobias K, van der Meer P, Petrie MC[3], Hilfiker-Kleiner D[1], **Jackson AM**, Mbakwem A, Hamdan R, de Boer RA, Mueller C, Lyon AR, Lund LH, Piepoli MF, Heymans S, Chioncel O, Anker SD, Ponikowski P, Seferovic PM, Johnson MR, Mebazaa A, Forsyth P, and Sliwa K. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail. 2019 Jul;21(7):827-843.

Sliwa K, Hilfiker-Kleiner D, Petrie M, Mebazaa A, **Jackson A**, Bauersachs J. Long-term prognosis and management in peripartum cardiomyopathy: contraception, subsequent pregnancy and drug treatment. A position paper by the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail. 2018. doi: 10.1002/ejhf.1178.

**Jackson AM,** Dalzell J, Walker N, Coats C, Jhund PS, Petrie MC. Peripartum cardiomyopathy: diagnosis and management. Heart. 2017. doi: 10.1136/heartjnl-2016-310599.

## Presentations relating to this work

Hypertensive disorders in women with peripartum cardiomyopathy: insights from the ESC EORP PPCM Registry
*European Society of Cardiology Congress 'Latest Science' platform, August 2021*

Diagnostic work-up of PPCM
*European Society of Cardiology HFA Congress, July 2021*

Peripartum Cardiomyopathy: results from the ESC Registry and Future Directions
*British Society of Heart Failure Annual Training Day, March 2018*

Peripartum Cardiomyopathy: the ESC Registry and Current Best Practice
*Royal Society of Medicine, September 2018*

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# Author's declaration

The work presented in this thesis was performed during my employment as a Clinical Research Fellow (BHF Clinical Research Training Fellowship [FS/18/14/33330]) in the Institute of Cardiovascular and Medical Sciences at the BHF Glasgow Cardiovascular Research Centre, University of Glasgow. I was supervised by Professor Mark Petrie and Professor Pardeep Jhund.

I designed and wrote the study protocol and obtained ethical approval for the study. I coordinated a focus group of women with PPCM to guide the aims of the study. I designed the data specification for data extraction from Scottish administrative datasets. I performed additional data collection across Scottish health boards myself. I cleaned and merged all datasets myself. All statistical analyses were performed by me.

I confirm that this thesis has been composed by me solely and that it has not been submitted for any other degree at the University of Glasgow or any other institution. The writing of this thesis is entirely my own work. All sources of information within this thesis are specifically acknowledged.

Alice M Jackson

October 2022

# Abbreviations

| | |
|---|---|
| APH | Antepartum haemorrhage |
| BMI | Body mass index |
| BHF | British Heart Failure |
| CI | Confidence interval |
| CM | Cardiomyopathy |
| CRT | Cardiac resynchronisation therapy |
| CV | Cardiovascular |
| DCM | Dilated cardiomyopathy |
| DQA | Data Quality Assurance |
| ECMO | Extracorporeal membrane oxygenation |
| ESC | European Society of Cardiology |
| HES | Hospital Episode Statistics |
| HF | Heart failure |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| ICD-9 | International Classification of Diseases-9 |
| ICD-10 | International Classification of Diseases-10 |
| ICD | Implantable cardioverter defibrillator |
| IGARD | Independent Group Advising on the Release of Data |
| IRR | Incidence rate ratio |
| ONS | Office for National Statistics |

| | |
|---|---|
| LV | Left ventricular |
| LVEDD | Left ventricular end diastolic diameter |
| LVEF | Left ventricular ejection fraction |
| MRR | Mortality rate ratio |
| NHS | National Health Service |
| NRS | National Records Scotland |
| NSS | National Services Scotland |
| PBPP | Public Benefit and Privacy Panel |
| PIH | Pregnancy-induced hypertension |
| PIS | Prescribing Informations System |
| PPCM | Peripartum cardiomyopathy |
| PPH | Postpartum haemorrhage |
| sFLT-1 | Soluble fms-like tyrosine kinase 1 |
| SMR | Scottish Morbidity Record |
| SSP | Subsequent pregnancy |
| TRED-HF | Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy |
| UK | United Kingdom |
| USA | United States of America |
| VAD | Ventricular assist device |
| VEGF | Vascular endothelial growth factor |
| WHO | World Health Organisation |

# Chapter 1 Introduction and review of the literature

## 1.1 Overview of PPCM

### *1.1.1 Definition*

Peripartum cardiomyopathy (PPCM), as its own entity, was first defined by Demakis and Rahimtoola in 1971 as the 'development of cardiac failure in the last month of pregnancy or within 5 months of delivery, the absence of a determinable aetiology for the cardiac failure, and the absence of demonstrable disease prior to the last month of pregnancy'[1]. The authors concluded that, in order to assign the diagnosis, there should be no evidence of congenital or acquired heart disease, or myocardial disease due to determinable causes. In 1997, The National Heart, Lung, and Blood Institute and Office of Rare Diseases convened a workshop resulting in an additional stipulation — the presence of left ventricular (LV) systolic dysfunction[2]. Later, the diagnostic criteria were revisited by the European Society of Cardiology (ESC) Heart Failure Association (HFA) PPCM Study Group. In their 2010 position statement, the Study Group proposed the following updated definition: 'an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%'[3]. The main definitions are summarised in Table 1-1.

All three definitions, although eventually adopting the requirement for LV systolic dysfunction and relaxing the arbitrary time frame within which the diagnosis must be made, are underpinned by the premise that PPCM is a diagnosis of exclusion. Importantly, alternative CV conditions can manifest for the first time, or worsen, in the peripartum period: for example, pre-existing cardiomyopathies, congenital heart disease and valvular heart disease. Acute coronary events can also lead to LV dysfunction, with or without heart failure. In reality, without a programme of echocardiographic screening of pregnant women, it remains challenging to determine which women might have a cardiomyopathy that predates conception and which women develop new

cardiac dysfunction related to pregnancy (or indeed other factors, such as pregnancy-induced hypertension). The overlap between PPCM and inherited dilated cardiomyopathy (DCM) will be discussed later in this chapter.

**Table 1-1 Major definitions of PPCM**

| Author/group, year | Diagnostic criteria |
|---|---|
| Demakis and Rahimtoola, 1971 | '(1) Development of heart failure in the last month of pregnancy or within the first 5 postpartum months,<br>(2) Absence of a determinable aetiology for the cardiac failure, and<br>(3) Absence of demonstrable heart disease prior to the last month of pregnancy. Thus, congenital, or acquired heart disease or myocardial disease due to determinable causes are presumed to be absent.' |
| National Heart, Lung, and Blood Institute and Office of Rare Diseases, 1997 | 'Development of cardiac failure in the last month of pregnancy or within 5 months of delivery, absence of an identifiable cause for the cardiac failure, absence of recognizable heart disease prior to the last month of pregnancy.<br>LV systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed shortening fraction or ejection fraction.' |
| European Society of Cardiology PPCM Study Group, 2010 | 'PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.' |

### *1.1.2 Incidence*

The incidence of PPCM varies markedly between countries. Studies reporting incidence are shown in Table 1-2. In Africa, amongst predominantly Black populations, the incidence is around 1 in 1000 live births[4]. There are a few countries where PPCM appears to be much more common. For example, in Nigeria and Haiti incidences of 1 in 100 and 1 in 300 pregnancies, respectively, have been reported[5,6]. In the United States, the incidence in predominantly White populations is between 1 in 1000-4000, but in African-American populations it is more common, at between 1 in 1000-2000[7, 8, 9]. There are far fewer reports of the incidence of PPCM in Europe and Australasia. There appears to be a trend towards increasing incidence in the USA, possibly due to increased awareness and diagnosis[10].

Anecdotally, delay in the recognition and diagnosis of PPCM occurs. It is possible that less severe heart failure goes undiagnosed, with symptoms being attributed to 'normal pregnancy' or alternative diagnoses, such as respiratory tract infection. In the ESC EORP PPCM Registry, the mean time between symptom-onset and diagnosis was 10 days (IQR 3-34)[11]. To establish the true incidence of PPCM, a prospective initiative monitoring healthy women throughout pregnancy and postpartum is required. This might be achievable if cardiac biomarkers are identified as a gateway to further investigation.

Extrapolation of existing data to the UK population is hindered by geographical and racial variation. A few factors have been shown to be associated with developing PPCM in non-European cohorts. The incidence of PPCM increases with age[12–14] and is as much as 16-times more likely in women of African descent than women of non-African descent[7, 8, 12, 15]. Multiparous women may be at higher risk, but multiparity in Europe is less common than in some other parts of the world, again limiting the generalisability of existing data[16, 17].

**Table 1-2 Studies reporting the incidence of PPCM after 1998, by region/country**

| Author | Year | Region/country | Study design | Study period | Data source | ICD codes used | PPCM definition supplied | No. women | Mean/median age (years) | Incidence |
|---|---|---|---|---|---|---|---|---|---|---|
| **Europe** | | | | | | | | | | |
| Ersboll[18] | 2017 | Denmark | Cohort, retrospective | 2005-2014 | Danish National Patient Register | O903 I50 O754 I42 I43 | Yes | 61 | 31.7 ± 6.3 | 1 in 10,149 |
| Barasa[19] (includes all cardiomyopathies) | 2017 | Sweden | Case-control, retrospective | 1997-2010 | Linked administrative datasets | O903 I50 I42 I43 | No | 241 | 33.1(32.3–33.9) | 1 in 5719 |
| **North America and Canada** | | | | | | | | | | |
| Douglass[20] | 2021 | Olmsted County | Case-control | 1970-2014 | Rochester Epidemiology Project (linked medical records) | 674.5, 428 | Yes | 48 | 28 ± 7 | 1 in 4926 |
| Phan[21] | 2020 | Kaiser Permanente, South California, USA | Case-control, retrospective | 2003-2014 | Linked administrative datasets | 425, 428 | No | 333 | 33.2 (29.4-36.9) | 1 in 1159 |
| Masoomi[22] | 2018 | USA | Case-control | 2013 | Nationwide Readmissions Database | 674.50- 674.54 | No | 568 | 30.0 (29.3–30.6) | 1 in 2187 |
| Dhesi[23] | 2017 | Alberta, Canada | Case-control, retrospective | 2005-2014 | Linked administrative datasets | I50 J81 O903 | Yes | 194 | 30.4 ± 6.6 | 1 in 2418 |
| Krishnamoorthy[24] | 2016 | USA | Cohort, retrospective | 2009-2010 | Nationwide Inpatient Sample | 67451–67454 | No | 4859 | 30.3 ± 0.2 | 1 in 2367 (prevalence) |
| Afana[25] | 2016 | USA | Case-control | 2004-2011 | Nationwide Inpatient Sample | 674.50–674.54 | No | 1337 | NA | 1 in 5352 |
| Kolte[12] | 2014 | USA | Cohort, retrospective | 2004-2011 | Nationwide Inpatient Sample | 674.50-674.55 | No | 34,219 | 30.3 ± 7.0 | 1 in 968 |
| Kao[14] | 2013 | USA | Case-control, retrospective | 2003-2007 | Inpatient administrative datasets | 6745 | No | 535 | NA | 1 in 7500 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Harper[26] | 2012 | North Carolina, USA | Cohort, retrospective | 2002-2003 | Hospital Discharge Database | 674.5 674.8 648.6 425.4 428 | Yes | 85 | NA | 1 in 2772 (prevalence) |
| Gunderson[13] | 2011 | Kaiser Permanente, North California, USA | Case-control | 1995-2004 | Hospitalisation database | 39891 40201 40211 40291 4254 4257 4258 4259 4280 4281 4289 | Yes | 110 | NA | 1 in 2066 |
| Kuklina[27] | 2010 | USA | Cohort, retrospective | 2004-2006 | Nationwide Inpatient Sample | 6745 | No | 2332 | NA | 1 in 5556 |
| Brar[7] | 2007 | Kaiser Permanente, Southern California | Cohort, retrospective | 1996-2005 | Hospitalisation database | 4280 4281 4284 4289 4254 4259 | Yes | 60 | 33 ±7 | 1 in 4025 |
| Mielniczuk[8] | 2006 | USA | Case-control, retrospective | 1990-2002 | National Hospital Discharge Survey | 674.8 + 514 or 428 or 4254 or 64864 | No | 16,269 | 29.7 (14-49) | 1 in 3189 |
| Chapa[9] | 2005 | Chicago, USA | Cohort, retrospective | 1988-2001 | Hospital records | Not stated | Yes | 35 | 27 ± 6 | 1 in 1149 |
| **Central and South America** | | | | | | | | | | |
| Sebillotte[28] | 2010 | Martinique | Cohort, retrospective | 1997-2007 | Survey and medical database | - | Yes | 13 | 30.0 (17-44) | 1 in 5500 |
| Fett[6] | 2005 | Deschapelles, Haiti | Cohort, prospective | 2000-2005 | Registry | - | Yes | 98 | 32.2 (16-50) | 1 in 300 |
| Fett[29] | 2002 | Deschapelles, Haiti | Cohort, retrospective + prospective | 1994-2001 | Hospital records + registry | 4254 6748 | Yes | 47 | 31.8 (17-49) | 1 in 400 |
| **Africa** | | | | | | | | | | |
| Karaye[30] | 2020 | Nigeria | Case-control, prospective | 2017-2018 | NA | - | Yes | 403 | 28.6 ± 7.2 | 1 in 96-1350 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Isezuo[5] | 2007 | Sokoto, Nigeria | Cohort, prospective | 2003-2005 | NA | - | Yes | 65 | 28.2 ± 8.1 | 1 in 102 |
| **Asia-Pacific** | | | | | | | | | | |
| Boyle[31] | 2019 | Brisbane, Australia | Cohort, retrospective | 2006-2015 | Medical records | - | No | 12 | 29 | 1 in 3448 (prevalence) |
| Lee[32] | 2018 | South Korea | Case-control, retrospective | 2010-2012 | Korea National Health Insurance Claims Database (mandatory enrolment) | O9093 I428 I429 I501 I502 I504 I509 | No | 795 | 32.1±4.3 | 1 in 1741 |
| Wu[33] | 2017 | Taiwan | Cohort, retrospective | 1997-2011 | National Health Insurance Research Database | 428 4254 4259 6745 4290 | | 925 | 30.4 ± 5.7 | 1 in 3790 |
| Lim[34] | 2013 | Singapore | Cohort, retrospective | 2009-2010 | Hospital records | - | Yes | 11 | 32.3 ± 5.7 | 1 in 1124 |
| Samonte[35] | 2013 | Single centre, Philippines | Cohort, retrospective | 2009-2010 | Medical records | - | Yes | 9 | 27 | 1 in 1270 |
| Kamiya[36] | 2011 | Japan | Cohort, retrospective | 2007-2008 | Questionnaire/survey | - | Yes | 102 | 32.7 (22-43) | 1 in 20,000 |
| Chee[37] | 2009 | Kuala Lumpur, Malaysia | Cohort, retrospective | 2001-2004 | Hospital records | O903 O994 | Yes | 8 | 31.2 ± 7.1 | 1 in 2900 |
| **Middle East and East Asia** | | | | | | | | | | |
| Binu[38] | 2020 | Tamil Nadu, India | Cohort, retrospective | 2008-2014 | Hospital records | - | Yes | 54 | 25.5 | 1 in 1541 |
| Kezerle[39] | 2018 | Southern Israel | Cohort, retrospective | 2004-2014 | Hospital electronic database | 6745 6786 | Yes | 46 | 31 | 1 in 3239 |
| Perveen[40] | 2016 | Karachi, Pakistan | Cohort, prospective | 2012-2013 | NA | - | No | 22 | NA | 1 in 263 (prevalence) |
| Hasan[41] | 2010 | Karachi, Pakistan | Cohort, prospective | 2003-2008 | Hospital records | - | Yes | 32 | 32 ± 3 | 1 in 837 |
| Pandit[42] | 2009 | Manipal, India | Cohort, retrospective | 1997-2007 | Hospital records | - | Yes | 9 | 28.5 ± 2.5 | 1 in 1374 |

### *1.1.3 Aetiology and risk factors*

The aetiology of PPCM is unclear. A number of factors have been shown to be associated with its development and suggest that it is likely to be a highly heterogenous condition. Hormones, such as prolactin and relaxin-2, tyrosine kinase proteins and genetics have been implicated. Hypertensive disorders of pregnancy, multiparity and Black race have also been shown to be more common in women with PPCM than in controls. A degree of interplay between all these factors may exist. The most important hypotheses are discussed in this section.

**Prolactin**

Animal models have demonstrated that excessive oxidative stress during pregnancy can lead to the cleavage of 23kDa prolactin, produced in the anterior pituitary, into an abnormal N-terminal 16kDa prolactin fragment[43, 44]. This is thought to be mediated by enhanced expression and activity of the lysosomal endoprotease, cathepsin D. In one very small study (n=10), increased cathepsin D activity in women with PPCM was identified, as compared to healthy matched pregnant controls[43]. In the same study, immunoprecipitation identified the presence of 16kDa prolactin in the serum of breastfeeding women with PPCM, while it was barely detectable in healthy breastfeeding women. Larger studies are required to explore this theory further. The pathogenic effects of 16kDa prolactin have been shown to be initiated by a downstream mediator, microRNA-146a[44]. Ultimately, the pathway ends in the induction of apoptosis, anti-angiogenesis and endothelial dysfunction with additional adverse effects on cardiomyocytes[45].

**Relaxin-2**

Relaxin-2 is produced in the ovaries, breast and placenta, with receptors in the heart, smooth muscle and connective tissue. It has a variety of protective haemodynamic effects, including augmenting cardiac output and decreasing systemic vascular resistance, as well as anti-inflammatory and antifibrotic properties[46]. Levels of relaxin-2 are elevated in pregnancy and start to fall soon after delivery[47]. In a study of 55 women with PPCM and 47 age- and pregnancy stage-matched controls, serum relaxin-2 levels were lower in women with PPCM

than in controls in the first week postpartum[47]. No difference was observed beyond this time. Relaxin-2 has also been identified as a potential prognostic marker; higher levels early postpartum have been found to be associated with a smaller LV size and higher LV ejection fraction (LVEF) at 2 months[48].

**Gestational hypertensive disorders**

Hypertensive disorders complicate as many as 5-10% of pregnancies worldwide, with pre-eclampsia in approximately 3%[49-52]. The prevalence of hypertensive disorders in women with PPCM is disproportionately higher; globally, 20-25% of women with PPCM develop pre-eclampsia during the index pregnancy and 40% develop hypertension (with or without pre-eclampsia) [11, 17]. The relationship between hypertensive disorders of pregnancy and PPCM is not fully understood. Mutual pathophysiological pathways resulting in angiogenic imbalance and endothelial dysfunction have been identified, suggesting that overlap between the conditions may exist[53]. Pre-eclampsia is a disorder of placental function, the development of which may be mediated by an ischaemic cascade, initiated by impaired remodelling of the spiral artery and resulting in an excess of circulating antiangiogenic factors[54]. In healthy women, levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor (VEGF) released from the placenta, peak at delivery and return to normal within 48-72 hours postpartum[55]. In pre-eclampsia, upregulation of sFlt-1 has been shown to induce endothelial dysfunction, reduce capillary density, and oppose VEGF-induced vasodilatation, resulting in hypertension, proteinuria and oedema[53, 55, 56]. This upregulation precedes the onset of pre-eclampsia by several weeks[55, 56]. Elevated levels of sFlt-1 have also been identified in a small number of women with PPCM, and, not only do they remain higher after delivery than in women with pre-eclampsia alone, but the degree of elevation is greater in women with worse symptoms of heart failure[48, 53, 57]. In addition to endothelial dysfunction, there appears to be a degree of myocyte cardiotoxicity associated with abnormal levels of sFlt-1[53, 58]. In contrast to relaxin-2, higher levels of sFlt-1 have been shown to be a marker of poor prognosis in PPCM[48]. Although existing data suggest that pre-eclampsia and PPCM share a common pathway, larger, confirmatory studies are required.

**Genetics**

The potential genetic basis of PPCM has gained recognition in recent years. A 'two-hit' pathophysiological process has been hypothesised; the first hit is a vascular insult, precipitated by factors previously discussed, and the second hit arises due a susceptibility to develop heart failure in this context, such as in women with a genetic predisposition for cardiomyopathy[59, 60]. Familial clustering of PPCM has been reported. In a study from the Netherlands, clinical screening of first-degree relatives of three women with PPCM identified an 'idiopathic' DCM in a first degree relative of all women[61]. Amongst 19 North American women with PPCM, two were sisters both with the condition[62]. Other isolated case reports of familial PPCM exist[63–65]. In a German PPCM registry (n=115) and in the prospective IPAC (Investigations of Pregnancy-Associated Cardiomyopathy) study (n=100), the proportions of women who reported a family history of cardiomyopathy were 17% and 10%, respectively[66, 67]. In a gene sequencing study of 172 patients, the prevalence of truncating variants in women with PPCM was 15% and was similar to that in a comparison cohort of patients with DCM[68]. Approximately two-thirds of these affected the *TTN* gene, which encodes titin, an important sarcomeric protein found in cardiac and skeletal muscle. In a subset of women in this study, although the presence of a *TTN* variant was not associated with more severe cardiac dysfunction at the time of diagnosis, it was associated with a lower chance of recovery of LVEF at one year[68]. In that study, hypertension was less common in women with a gene variant than in those without (hypertension in 51% with no variant, 27% with any variant and 9% with *TTN* variant). In a more contemporary and larger genetic study of 469 women with PPCM, the prevalence of a gene variant was similar, but its association with baseline LVEF and outcomes differed; women with a *TTN* variant had a lower LVEF on presentation than did women without, but rates of clinical recovery and the prevalence of pre-eclampsia were similar[69].

**Race**

African-American women have been found to have a greater risk of developing PPCM than non-African-Americans. In three studies from North America, the odds of developing PPCM ranged from 3.6 to 15.7 for African-American women (vs non-African American women)[7, 8, 15]. Indeed, the highest prevalence of PPCM

ever reported is in Black women in Nigeria at around 1 in 100 live births [5, 30]. The reasons for this are not entirely clear, but may relate to genetic factors, as well as a greater prevalence of other risk factors for PPCM seen in Black women, such as multiparity and hypertension[70, 71].

**Placental factors**

PPCM tends to develop more frequently in multiparous women and in women with a multigestational pregnancy (i.e. twins or triplets)[14, 17, 22, 72]. In a systematic review of 30 studies, predominantly from North America, multiple gestation occurred in 9% (95% CI 7-11) of women and multiparity in 67% (95% CI 60-74). In the United Kingdom (UK), a twin or triplet pregnancy occurs in around 1.5% of pregnancies. Towards the end of pregnancy, antiangiogenic factors secreted by the placenta (such as sFLT-1), bind and neutralises VEGF. As in pre-eclampsia, higher circulating levels of sFLT-1 may explain the link between multiple gestation (during which placental mass is increased) and multiparity (which may cause a cumulative insult)[17, 73]. Greater haemodynamic change and CV demand in a multigestational pregnancy may also be relevant[74, 75]. Furthermore, multiparity has been shown to be associated with adverse cardiac remodelling in women without PPCM[76, 77].

### *1.1.4 Maternal outcomes*

**Mortality**

Reported case-fatality varies widely. Differences are largely geographical but may also be explained by inconsistencies in the inclusion criteria and definitions of PPCM used across studies. Table 1-3 summarises studies reporting case-fatality for women with PPCM which include at least 40 women from 1998 onwards, shown by region and duration of median/mean follow-up. Interpretation and generalisability of existing data is challenging due small cohort sizes and regional differences in population demographics.

A small number of studies, predominantly from the USA, have examined very early outcomes for women with PPCM (either in-hospital or 30-day mortality). Death occurred in fewer than 2% of women in all except two studies — one

including 41 women in Togo (5% case-fatality)[78] and the other including 391 women in Taiwan (3% case-fatality)[79].

The majority of studies reporting outcomes at 6 months are from Africa, with death occurring in 21-46% of women[80-85]. Reported 6-month case-fatality is lowest in Europe, at approximately 2%[8, 12, 66]. In the ESC PPCM Registry, a total of 6% of women from 49 countries died by 6 months; case-fatality in this global registry ranged from 4% in Europe to 10% in the Middle East[11].

Population-based studies describing longer-term (12 months and beyond) mortality are predominantly from the USA[7, 13, 21, 23]. There are further case series from Africa[30, 84], Haiti[6], Turkey[86-88] and China[89, 90]. Reported 1-year case-fatality ranges from <1% in the USA to 19% in Nigeria. Only one, small population-based study from Europe (Denmark) reporting longer-term (12 months and beyond) for women with PPCM has been published. There are no data from the United Kingdom.

Sudden death and progressive heart failure have been identified as the main modes of death[11]. Descriptions of the timing of death suggest that it tends to occur in the first 6-12 months postpartum[6, 26, 85, 91]. Case reports of later deaths do exist[26, 84, 92]. Deaths have been reported in women with recovered LV function, although the causes of death are not well-characterised[84]. It remains unclear whether or not a risk of CV death persists despite apparent recovery of LV function. There are gene variants known to cause both a DCM and channelopathies, such as SCN5A, which could increase the risk of ventricular arrhythmias even in the absence of LV systolic dysfunction. This may be relevant, but our understanding of the genetic basis of PPCM is in its early stages.

**Morbidity**

PPCM is also associated with a risk of major adverse events, such as thromboembolism, cardiac device implantation (i.e. implantable cardioverter defibrillator or cardiac resynchronisation therapy) and cardiac transplantation[12]. Thromboembolic complications developed in as many as 7% of women across two studies[11, 12]. In postpartum women without heart failure, the risk of

thromboembolism persists to at least 12 weeks after delivery, although from 6 weeks the absolute risk is low[93]. In women with PPCM, thromboembolic events tend to occur at the time of presentation. It is not known whether the risk of thromboembolic complications persists beyond the early postpartum period in women with PPCM specifically.

The use of advanced heart failure interventions (e.g. mechanical circulatory support or cardiac transplantation) have been described in up to 1 in 10 women with PPCM, although these data come from small studies[92, 94].

In the largest study of mechanical circulatory support, comprising women enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), 8% of the cohort had PPCM (n=99)[95]. In this registry, women with PPCM who received durable mechanical circulatory support had better crude survival than women with other causes of heart failure, although adjustment for differences in baseline factors suggested this may be driven by younger age and less comorbidity.

Reports on long-term outcomes of patients with PPCM undergoing cardiac transplantation are sparse. Data suggest survival is similar in women with PPCM and young patients with other causes of DCM[96, 97]. However, rates of rejection and re-transplantation appear to be higher in women with PPCM[96-98].

**Recovery of cardiac function**

In unselected cohorts of patients with 'idiopathic' DCM, improvements in LV function and size are seen in approximately 40% of individuals[99]. LV recovery in PPCM occurs more frequently, with the frequency of recovery ranging from around 50-70%, although there is major regional variation[67, 100]. Studies reporting recovery are shown in Table 1-3. There are limited prospective data on cardiac recovery in the era of contemporary heart failure therapies. In the Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, a prospective multicentre American study of 100 women with PPCM, recovery (LVEF >50%) occurred in 72% of women at 12 months[101]. In the ESC PPCM Registry, recovery (LVEF ≥50%) occurred in 46% of women by 6 months and was different in each region (25% in the Middle East vs 62% in Asia-Pacific)[11]. Recovery in patients in Europe has been reported in the ESC PPCM Registry (57% at 6 months[11]) and in German (47% at 6

months[66], 72% at 5 years[102]) and Danish (52% at 1 year) groups of women. Recovery appears to occur less frequently in African women[83, 103]. The reasons for such differences are likely to be multifactorial; genetics, aetiology of LV dysfunction, disparities in access to healthcare and treatment, inconsistencies in diagnostic/inclusion criteria and in a universal definition of LV recovery may all be relevant. It does seem likely that "PPCM" has been a term historically used to describe a range of "pregnancy-associated heart failure" and that variation in the epidemiology of the condition reflects heterogeneity of what has been categorised as PPCM.

Although much of the focus in the literature is on recovery at 6 or 12 months, delayed myocardial recovery is a recognised concept and improvement in LVEF has been shown to extend beyond 12 months in some cases[104–106].

Deterioration in cardiac function after normalisation of LVEF has been described in case reports of women with PPCM, but there are no published cohort studies systematically examining this[92, 94, 105]. Whether or not cessation of heart failure treatments preceded decline in cardiac function is not consistently reported, though there are case reports of women who deteriorate after medical therapy is stopped[105]. The long-term CV risk, or risk of recurrent heart failure, in women with recovered PPCM has not been determined. Historically, there has been no consensus on whether or not heart failure treatments should be continued after apparent normalisation of LV systolic function, and published data on deterioration with cessation of drug therapy in PPCM are conflicting[107]. More recently, the prospective TRED-HF (Withdrawal of pharmacological treatment for heart failure in patients with recovered DCM) study showed that, in 51 patients with recovered DCM, almost 1 in 2 patients in whom treatment was withdrawn relapsed, compared to none in whom treatment was continued[108]. Although only 2 women in this study presented in the peripartum period, it is likely that these findings will underpin future recommendations for the longer-term management of women with PPCM.

**Table 1-3 Studies reporting case-fatality ± myocardial recovery after 1998, stratified by duration of follow-up (only those including n≥40 participants)**

*This table is an extension of a smaller table put together by me and published*[107].

| Author | Year | Study period | Region/country | Design | No. women | Age (years) | Case-fatality | Follow-up (mean/median) | Recovery of LVEF |
|---|---|---|---|---|---|---|---|---|---|
| **In-hospital/early** | | | | | | | | | |
| **USA** | | | | | | | | | |
| Shah[109] | 2018 | 2013-2014 | USA | Retrospective, population | 6880 | 31 | 1.4%<br>2% if readmit | In-hospital<br>13% readmit 30d<br>20% survivors readmit 6m | |
| Chhabra[110] | 2017 | 2013 | USA | Retrospective, population | 3800 | 32 | 1.6% | In-hospital<br>15% readmission 30d | |
| Mallikethi-Reddy[111] | 2017 | 2007-2012 | USA | Retrospective, population | 9841 | 30 | 1.4%<br>(2.1% arrhythmia) | In-hospital | |
| Dhesi[23] | 2017 | 2005-2014 | Alberta, Canada | Retrospective, population | 194 | 30 | 1.03% | 6w | |
| Afana[25] | 2016 | 2004-2011 | USA | Retrospective, national registry | 1337 | NA | 0.5% | In-hospital | |
| Krishnamoorthy[24] | 2016 | 2009-2010 | USA | Retrospective, national registry | 4859 | 30 | 1.8% (n=4817) | In-hospital | |
| Lima[112] | 2015 | 2006-2010 | USA | Retrospective, national registry | 1039 | 29 | 0.7% | In-hospital | |
| Kolte[10] | 2014 | 2004-2011 | USA | Retrospective, population | 34 219 | 30 | 1.3% | In-hospital | |
| Kao[14] | 2013 | 2003-2007 | USA | Retrospective, multicentre | 535 | NA | 1.3% | In-hospital | |
| Mielniczuk[8] | 2006 | 1990-2002 | USA | Retrospective, population | 171 | 30 | 1.4% | In-hospital | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Africa** | | | | | | | | | |
| Pio[78] | 2014 | 2010-2012 | Lome, Togo | Prospective, single centre | 41 | 31 | 4.9% | In-hospital (mean 16d) | 78% |
| **Asia** | | | | | | | | | |
| Lee[32] | 2018 | 2010-2012 | South Korea | Retrospective, population | 795 | 32 | 1%<br>1% | In-hospital<br>30d | |
| Lu[79] | 2017 | 1997-2011 | Taiwan | Retrospective, population | 391 | 32 | 3.3% | In-hospital | |
| Isogai[113] | 2017 | 2007-2014 | Japan | Retrospective, population | 283 | 32 | 1.4% | In-hospital | |
| Huang[114] | 2012 | 2007-2009 | Shandong Province | Prospective, single centre | 52 | 29 | 0%<br>1.9% | In-hospital (mean 21.6d) | |
| **6 months** | | | | | | | | | |
| **Africa** | | | | | | | | | |
| Nabbaale[80] | 2020 | 2018-2019 | Uganda | Prospective, single centre | 41 | 32 | 0% | 6m | 46% |
| Gambahaya[81] | 2017 | 2012-2013 | Harare, Zimbabwe | Prospective, single centre | 43 | 27 | 11.6% | 6m | 43% (n=35) |
| Libhaber[82] | 2015 | NA | South Africa | Prospective, 2 centre | 206 | 30 | 12.6% | 6m | |
| Blauwet[83] | 2013 | NA | Soweto, South Africa | Prospective, single centre | 176 | 30 | 13% (n=162) | 6m | 21% |
| Sliwa[84] | 2011 | NA | Soweto, South Africa | Prospective, single centre | 80 | 29 | 10% | 6m | |
| Isezuo[5] | 2007 | 2003-2005 | Nigeria | Prospective, single centre | 65 | 28 | 12.3% | 9.7m | |
| Sliwa[85] | 2006 | NA | Johannesburg, South Africa | Prospective, single centre | 100 | 31 | 15% | 6m | 23% |
| **Asia** | | | | | | | | | |
| Ravi Kiran[115] | 2021 | 2016-2020 | Kurnool, India | Prospective, singe centre | 43 | 25 | 4.7% | 6m | 63% |
| Sarojini[116] | 2013 | NA | Nellore, India | Prospective, single centre | 46 | 21 | 15% | 6m | 35% |
| Kamiya[36] | 2011 | 2007-2008 | Japan | Survey (73% response) | 102 | 32 | 4% | 9.6m (mean) | 63% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hu[117] | 2007 | NA | China | Prospective, 3 centre | 106 | 28 | Only survivors included | 6m | 52% |
| **Europe** | | | | | | | | | |
| Haghikia[118] | 2013 | 2004-2012 | Germany | Prospective, multicentre registry | 115 | 34 | 2% (n=96) | 6m (mean) | 47% (n=96) |
| **USA** | | | | | | | | | |
| Dhesi[23] | 2017 | 2005-2014 | Alberta, Canada | Retrospective, population | 194 | 30 | 1.55% | 6m | |
| Irizarry[119] | 2017 | 1986-2016 | Pennsylvania, USA | Retrospective, single centre | 220 | 29 | 5.5% | 5.5m | 66% (n=123) |
| **Global** | | | | | | | | | |
| Sliwa[11] | 2020 | 2012-2018 | Global | Prospective, multicentre | 739 | 31 | 6% | 6m | 46% |
| **1-2 years** | | | | | | | | | |
| **USA** | | | | | | | | | |
| Phan[21] | 2020 | 2003-2014 | Kaiser Permanente, South California | Retrospective, population | 333 | 33 | 0.6% | 1y | |
| Tremblay-Gravel[120] | 2019 | 1994-2015 | Canada | Retrospective, multicentre | 76 | NA | 3.9% | 25m | |
| Briasoulis[121] | 2016 | 2009-2014 | Detroit, USA | Retrospective, single centre | 47 | 29 | 10.6% | 12.5m (median) | 57% |
| McNamara[101] | 2015 | 2009-2012 | USA | Prospective, multicentre (30) | 100 | 30 | 4% (n=91) | 1y | 72% |
| Goland[70] | 2013 | 1993-2007 | USA | Retrospective, 2 centre | 187 | 29 | 7% (n=156) | 19m (mean) | 55% (n=136) |
| Goland[92] | 2009 | NA | USA | Retrospective, NA | 182 | 29 | 7.1% | 19m (mean) | 49% (n=145) |
| Modi[104] | 2009 | 1992-2003 | Louisiana, USA | Retrospective, single centre | 44 | 25 | 15.9 % | 2y (mean) | 35% |
| Elkayam[122] | 2005 | 1997-1998 | USA | Survey (2% response) | 100 | 30 | 9% | 23m | 54% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Central and South America** | | | | | | | | | |
| Fett[6] | 2005 | 2000-2005 | Haiti | Prospective, single centre | 98 | 32 | 15% | 2.2y | 28% (n=92) |
| **Asia** | | | | | | | | | |
| Binu[38] | 2020 | 2008-2014 | Tamil Nadu, India | Retrospective, single centre | 54 | 25 | 9.3% | 24.2m (median) | |
| Salam[123] | 2020 | 2012 | Middle East (Oman, Saudi, UAE, Qatar, Bahrain, Yemen, Kuwait) | Prospective, multicentre registry | 64 | 32 | 3.2% | 1y | |
| Wu[33] | 2017 | 1997-2011 | Taiwan | Retrospective, population | 925 | 30 | 7.8% | 1y | |
| Lu[79] | 2017 | 1997-2011 | Taiwan | Retrospective, population | 391 | 32 | 8.4% | 1y | |
| **Europe** | | | | | | | | | |
| Ersboll[18] | 2017 | 2005-2014 | Denmark | Retrospective, population | 61 | 31 | 3.3% | 1y | 52% |
| **Africa** | | | | | | | | | |
| Karaye[103] | 2020 | 2017-2018 | Nigeria | Prospective, multicentre | 244 | 28 | 18.7% | 17m (median) | 23% |
| Sliwa[84] | 2011 | NA | Soweto, South Africa | Prospective, single centre | 80 | 29 | 28% | 2y | |
| **3-5 years** | | | | | | | | | |
| **USA** | | | | | | | | | |
| Peters[124] | 2018 | 1992-2016 | Philadelphia, USA | Retrospective, single centre | 53 | 31 | 1.9% | 3.6y (median) | 36% at median 2.9y |
| Dhesi[23] | 2017 | 2005-2014 | Alberta, Canada | Retrospective, population | 194 | 30 | 1790/100,000 person-years | 3.9y (mean) | |
| Gunderson[13] | 2011 | 1995-2004 | North California, USA | Retrospective, population | 110 | NA | 1.8% | 3y | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Habli[125] | 2008 | 2000-2006 | Ohio + Kentucky, USA | Retrospective, 2 centre | 70 | NA | 0% | 3.4y (mean) | |
| Brar[7] | 2007 | 1996-2005 | South California, USA | Retrospective, population | 60 | 33 | 3.3% | 4.7y (mean) | |
| Amos[94] | 2006 | 1990-2003 | North Carolina, USA | Retrospective, single centre | 55 | 29 | 0% | 43m (mean) | 45% (n=49) |
| Felker[126] | 2000 | 1982-1997 | Baltimore, USA | Retrospective, single centre | 51 | 29 | 6% | 5y | |
| **Asia** | | | | | | | | | |
| Ma[90] | 2019 | 1998-2017 | Beijing | Prospective, single centre | 76 | 29 | 5.3% | 5y | 90% |
| Biteker[127] | 2018 | 2005-2016 | Turkey | Prospective, single centre | 52 | 28 | 19.2% | 40m | 58% |
| Lu[79] | 2017 | 1997-2011 | Taiwan | Retrospective, population | 391 | 32 | 10.7% | 3y | |
| Li[89] | 2016 | 2004-2011 | Beijing, China | Retrospective, single centre | 71 | 28 | 0% | 43m | 56% |
| Akil[88] | 2016 | 2002-2012 | Turkey | Retrospective, 3 centre | 58 | 31 | 15% | 32m (mean) | 29% |
| Biteker[105] | 2012 | 2005-2009 | Turkey | Prospective, 2 centre | 42 | 27 | 23.8% | 39m (mean) | 48% |
| **Europe** | | | | | | | | | |
| Moulig[102] | 2019 | 2006-2013 | Germany | Retrospective, 2 centre | 66 | 34 | 2% | 5y | 72% |

### *1.1.5 Subsequent pregnancies*

**Maternal risk**

Women diagnosed with PPCM often ask about the risk associated with a subsequent pregnancy. Tailored counselling regarding the risks for both the mother and the baby is important. Our understanding of maternal risk during a subsequent pregnancy has developed over the last 10-20 years. Outcomes appear to differ according to cardiac function prior to the subsequent pregnancy, i.e. whether or not cardiac function has recovered. As discussed earlier in this chapter, myocardial recovery is usually defined as LVEF of greater than or equal to 50% or 55% and occurs in approximately 40-70% of patients with PPCM by 6-12 months[18, 66, 67].

Table 1-4 summarises the studies reporting maternal and foetal outcomes for women with PPCM during a subsequent pregnancy. Combining data from the three largest American studies, relapse occurred in around 30% of pregnancies (approximately 1 in 5 with recovered cardiac function and just under half of those without recovered cardiac function)[128-130]. These 3 trials included 148 well-characterised subsequent pregnancies and defined relapse as a significant decline in LVEF and/or the development of heart failure symptoms. Only 4 women died, all of whom had not recovered (equivalent to 1 in 7 women without recovery). Although LVEF thresholds of 50% and 55% were used to define recovery in these studies, there is no single, standardised definition of recovery. In the only international study of subsequent pregnancies (34 women from South Africa, Germany and Scotland, recovery defined as ≥50%), case-fatality was 12% and occurred exclusively in women without recovery[131]. Outcomes appear to be worse in Black women in Africa; combining two studies, case-fatality was 46%, including deaths in approximately a third of women with recovered cardiac function and half of those without[132, 133]. The frequency of persistent LV dysfunction after a subsequent pregnancy is highly variable, ranging from 0-53% in contemporary studies[130, 131].

In women with a history of PPCM, a further pregnancy may be associated with a deleterious maternal outcome. Although normalisation of LV function does not completely negate risk in future pregnancies, outcomes appear to be worse for

those with persisting LV dysfunction. Current recommendations from the ESC are that women should be counselled against future pregnancies if cardiac function has failed to recover[49, 107]. The use of stress echocardiography has been investigated in two studies of women with a history of PPCM and recovered LV function[129, 134]. In the first, among 35 subsequent pregnancies in which the pre-pregnancy LVEF was ≥55%, relapse occurred in 17%, but in no women who demonstrated adequate contractile reserve on exercise stress echocardiography (n=9)[129]. In the second, in 7 women with recovered PPCM and normal resting echocardiographic parameters, contractile reserve was significantly lower than in matched non-pregnant controls[134]. There may be a role for stress testing in providing a means of more sophisticated risk stratification for women with recovery of LVEF prior to a subsequent pregnancy, but this remains a largely evidence-free area. As yet, no studies have investigated whether there is a role for biomarkers in prognostication of a subsequent pregnancy.

The modified World Health Organisation classification stratifies women with prior PPCM into the two highest risk pregnancy categories depending on whether or not there is recovery of LV function[49]. For women without full recovery, a 40-100% maternal cardiac event rate is quoted, and for those with full recovery, a 19-27% event rate. However, the definition of residual LV dysfunction is not provided and variation in outcomes according to region, race and genetics are not incorporated. Other risk stratification tools exist, including the CARPREG II score, which provides an estimate of risk associated with pregnancy based on a number of predictor variables such as New York Heart Association functional class, systemic ventricular dysfunction and late pregnancy assessment[135]. This has similar limitations when it comes to generalisability and applicability specifically to women with PPCM.

**Foetal risk**

Foetal and neonatal outcomes associated with a subsequent pregnancy are not well-described. Studies which have reported foetal outcomes are described in Table 1-4. The overall frequency of miscarriage ranges from 0-40%[128, 130, 133]. Termination occurs in as many as half of pregnancies[136]. Premature delivery has been reported in 0-26% of women, and, in one American study which described this in more detail, it was less common in women with recovered cardiac

function than in those without (13% in recovered women, 50% in unrecovered women)[128, 130, 137]. It is not known which characteristics are associated with a greater likelihood of an adverse foetal outcome.

**Table 1-4 Studies reporting maternal and foetal outcomes following a subsequent pregnancy**

*This table is an extension of a smaller table put together by me and published*[107].

| Author | Year | Country | Study design | No. women | No. pregnancies* | Maternal death | | Miscarriage/ foetal death N (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | In all women N (%) | In unrecovered women N (% of total deaths) | |
| Sutton[138] | 1991 | USA | Prospective, single centre | 4 | 4 | 0 | - | 0 |
| Witlin[139] | 1997 | USA | Prospective, single centre | 6 | 7 | 1 (17) | 1 (100) | 0 |
| Albanesi Filho[137] | 1999 | Brazil | Prospective, NA | 12 | 16 | 1 (8) | 1 (100) | 0 |
| de Souza[140] | 2001 | Brazil | Retrospective, single centre | 7 | 7 | 0 | - | 0 |
| Elkayam[128] | 2001 | USA | Retrospective, select population | 44 | 35 | 3 (7) | 3 (100) | 0 |
| Avila[141] | 2002 | Brazil | Prospective, single centre | 18 | 19 | 1 (6) | 1 (100) | 0 |
| Sharieff[142] | 2003 | Pakistan | Prospective, single centre | 9 | NA | 2 (22) | NA | NA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sliwa[133] | 2004 | South Africa | Prospective, single centre | 6 | 6 | 2 (33) | 2 (100) | 0 |
| Chapa[9] | 2005 | USA | Retrospective, single centre | 6 | 8 | 0 | - | NA |
| Fett[143] | 2006 | Haiti | Prospective, single centre | 15 | 16 | 1(7) | NA | NA |
| Mishra[144] | 2006 | India | Prospective, NA | 9 | NA | 5 (56) | NA | NA |
| Hilfiker-Kleiner[43] | 2007 | Germany | Prospective, NA | 12 | 12 | 3 (25) | 0 | NA |
| Habli[125] | 2008 | USA | Retrospective, 2 centre | 37 | 21 | 0 | - | 0 |
| Modi[104] | 2009 | USA | Retrospective, single centre | NA | 15 | 0 | - | 6 (40) |
| Chee[37] | 2009 | Malaysia | Retrospective, single centre | 2 | 1 | 0 | - | 0 |
| Fett[129] | 2010 | Haiti | Prospective, single centre + support group | 56 | 61 | 1 (2) | 1 (100) | NA |
| Mandal[145] | 2011 | India | Prospective, single centre | 6 | 6 | 1 (17) | 1 (100) | 1 (17) |
| Hilfiker-Kleiner[131] | 2017 | Germany Scotland | Prospective, multicentre | 34 | 31 | 4 (12) | 4 (100) | 1 (3) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | South Africa | | | | | | |
| Codsi[146] | 2017 | USA | Retrospective, single centre | 25 | 39 | 0 | - | 6 (15) |
| Hauge[136] | 2018 | Denmark | Retrospective, population | 13 | 9 | 0 | - | 2 (22) |
| Yameogo[132] | 2018 | Burkina Faso | Prospective, 2 centre | 29 | 29 | 14 (48) | NA | 10 (34) |
| Moulig[102] | 2019 | Germany | Prospective, multicentre | 16 | 15 | 0 (0) | - | 1 (6.3) |
| Douglass[20] | 2021 | USA | Retrospective, multicentre | 23 | 30 | 0 (0) | - | 5 (13.5) |

**Number without therapeutic termination (i.e. only pregnancies ending in a delivery or a spontaneous termination)*

# 1.2 Gaps in the knowledge

## *1.2.1 Epidemiology and incidence of PPCM in the UK*

There are no population-level data describing the epidemiology of PPCM in the UK. Much of what we understand about the epidemiology of PPCM is extrapolated from geographical pockets, with large variation in study methodology and duration of follow-up. The incidence of PPCM, factors associated with the development of the condition and outcomes for women and their children in the UK is unknown. There is a need for evidence to underpin information-giving and informed decision-making in the UK, and to improve the understanding of all health care workers involved in the care of these women, not solely in the peripartum period, but also later in life.

The epidemiology of PPCM in European cohorts has been reported in 8 studies, 5 of which were small, single-centre case series including 10-24 women and 2 of which report on the same cohort of patients in a German registry[18, 66, 102, 147-151]. In the largest European study, 6-month mortality was 2% in a cohort of 115 German women[66]. In a Danish study, the only published population-level account of PPCM in Europe, case-fatality was similar at 3%[18]. There is one further study from Sweden which includes women with any type of cardiomyopathy, not just PPCM[19].

## *1.2.2 Long-term outcomes*

There are a lack of data on outcomes beyond 5 years in women with PPCM. The only studies to have examined this are shown in Table 1-5. In 4 studies from the USA, mortality ranged from 7% to 16% between 7 and 8.6 years[26, 71, 126]. A further 4 studies (one from India[144], one from Nigeria[152] and small case series from Malaysia[153] and Germany[150]) reported rates of 0-26%. The longer term data from Europe are generally small case series not including the whole population, or do not exclusively comprise women with PPCM (i.e. other cardiomyopathies were also included)[19, 150, 151, 154].

**Table 1-5 Studies reporting long term (beyond 5 years) outcomes in PPCM**

*This table is an extension of a smaller table put together by me and published*[107].

| Author | Year | Study period | Region | Design | No. women | Age (years) | Case-fatality | Follow-up (mean/median) | Recovery of LVEF |
|---|---|---|---|---|---|---|---|---|---|
| **USA** | | | | | | | | | |
| Douglass[20] | 2021 | 1970-2014 | Olmsted Country | Retrospective, population | 48 | 28 | 2.1% | 7.3y | 90% |
| Pillarisetti[71] | 2014 | 1999-2012 | Kansas + Michigan, USA | Retrospective, 2 centre | 100 | 30 | 11% | 8.2y | 23% (mean 35m) |
| Harper[26] | 2012 | 2002-2004 | North Carolina, USA | Retrospective, population | 85 | NA | 16.5% | 7y | |
| Felker | 2000 | 1982-1997 | Baltimore, USA | Retrospective, single centre | 42 | 29 | 7% | 8.6y | 43% (n=36) (median 137d) |
| **Africa** | | | | | | | | | |
| Adesanya[152] | 1989 | 1969-1972 | Zaria, Nigeria | Prospective, single centre | 181 | NA | 26% | 10y | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Asia** | | | | | | | | | |
| Tak[155] | 2019 | 2009-2018 | Ankara, Turkey | Retrospective, single centre | 90 | 34 | 6.7% | 67m | 40% (LVEF>45%) |
| Chee[153] | 2013 | 2000-2009 | Kuala Lumpur, Malaysia | Retrospective, single centre | 12 | 32 | 8.3% | 77m | 66.7% (n=9) (at 12m) |
| Mishra[144] | 2006 | 1995-2005 | Cuttack Orissa, India | Prospective, NA | 56 | 31 | 23.2% | 6.1y | |
| **Europe** | | | | | | | | | |
| Ersboll[154] | 2018 | 2005-2015 | Denmark | Retrospective, select population | 24 | 30 | 3% (original cohort of n=61) | 7.6y | 93% |
| Lamparter[150] | 2007 | 1989-2003 | Marberg, Germany | Prospective, registry | 10 | 30 | 0% | 69m | 80% |
| Barasa[19] (includes all cardiomyopathies) | 2017 | 2010-2017 | Sweden | Retrospective, population | 241 | 33 | 4% | 5.7y | |
| Barasa[151] | 2018 | ’10 years’ | West Sweden | Retrospective, multicentre | 24 | 34 | 4% | 7.9y | 82% (n=17) (median 2.1y) |

### *1.2.3 Outcomes for women with a subsequent pregnancy*

Our understanding of outcomes for women with PPCM and a subsequent pregnancy is limited. Published data are discussed earlier in this chapter. There are no population-based studies of subsequent pregnancies in women with PPCM. The risk of future pregnancies is a concern for patients, and determination of this risk has clear implications. Despite this, there are few data available to support decision-making[3, 49]. The ESC PPCM Study Group currently recommends that women with a LVEF <25% at diagnosis, and those in whom LVEF has not normalised, should be advised against a subsequent pregnancy[3]. Few studies have examined whether non-echocardiographic variables can predict future outcomes in a subsequent pregnancy[129]. Informed counselling on family planning is paramount, but there is a lack of real-world evidence to underpin recommendations.

### *1.2.4 Child morbidity and mortality*

To date, research into outcomes following a pregnancy complicated by PPCM has largely focussed on maternal outcomes, rather than infant outcomes. The studies which have reported outcomes for children born to women with PPCM are summarised in Table 1-6. In one study from Northern California, compared to neonates born to women without PPCM, neonates born to women with PPCM were more likely to be premature, low or very low birth weight, small for gestational age, and have lower 5-minute Apgar scores, although infant mortality did not differ[13]. Conversely, another North American study reported a higher risk of stillbirth in women with PPCM[14]. Data on longer-term outcomes following a subsequent pregnancy are spare, with only one study reporting outcomes at 1 year in infants born to women with PPCM in Haiti[156].

**Table 1-6 Studies reporting outcomes for children born to women with PPCM**

| Author | Year | Study period | Region | Design | No. infants | Outcomes |
|---|---|---|---|---|---|---|
| Douglass[20] | 2021 | 1970-2014 | Olmsted County, USA | Retrospective, population | 57 (48 mothers) | Lower birth weight, more frequent prematurity (vs controls) |
| Phan[21] | 2020 | 2003-2014 | Kaiser Permanente, South California | Retrospective, population | 333 | Lower APGAR scores, less SGA, similar neonatal death (vs non PPCM cardiomyopathy) |
| Sliwa[11] | 2020 | 2012-2018 | Global | Prospective, multicentre | 580 | Low birth weight in 28%, neonatal death in 5% |
| Ersboll[18] | 2017 | 2005-2014 | Denmark | Retrospective, population | 66 | APGAR score <7 in 4.5%, SGA in 27.3%, neonatal death in 1.5% |
| Barasa[19] (includes all cardiomyopathies) | 2017 | 1997-2010 | Sweden | Retrospective, population | 241 | Lower birth weight, more SGA, lower gestational age (vs controls) |
| Dhesi[23] | 2017 | 2005-2014 | Alberta, Canada | Retrospective, population | 209 | Lower birth weight, more frequent prematurity and neonatal death (vs controls) |
| Kao[14] | 2013 | 2003-2007 | USA | Retrospective, multicentre | 535 | More frequent stillbirth (vs controls) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Chee[153] | 2013 | 2000-2009 | Kuala Lumpur, Malaysia | Retrospective, single centre | 11 | All live births, low APGAR scores in 1.8%, prolonged NNU stay in 0.9%, no congenital anomalies |
| Gunderson[13] | 2011 | 1995-2004 | North California, USA | Retrospective, population | 122 | More frequent prematurity, lower birth weight, more SGA, lower APGAR scores, similar neonatal death (vs controls) |
| Fett[156] | 2006 | NA | Haiti | Prospective, single centre | 25 | 12.0% neonatal death, 63.6% dead at 1 year |

# Chapter 2 Methods

## 2.1 Aims and objectives

The aim of this population-level study was to describe the epidemiology of PPCM in Scotland from 1986-2017. Later, this was modified to 1998-2017.

This aim was expanded into the following objectives:

1) Descriptive objectives:

- To define the incidence of PPCM
- To describe patient characteristics for women with PPCM
- To determine morbidity and mortality in women with PPCM (including death, rehospitalisation, cardiac transplantation, mechanical circulatory support, stroke, thromboembolism, implanted cardiac device therapy, recovery of LV function)
- To describe patient characteristics and outcomes for women with a subsequent pregnancy
- To determine infant morbidity and mortality

2) Analytical objectives:

- To identify factors associated with the development of PPCM (including patient demographics, comorbidities, obstetric factors)
- To compare mortality and morbidity of women with PPCM and controls
- Identify factors associated with a greater risk or likelihood of mortality and morbidity, and recovery of cardiac function, in women with PPCM
- To compare mortality and morbidity of women with PPCM and controls relating to a subsequent pregnancy
- To compare mortality and morbidity of children born to women with PPCM and controls
- To identify factors associated with a greater likelihood of adverse outcomes in children born to women with PPCM

## 2.2 Study design

The study is a retrospective, observational, population-based cohort study with a nested case-control study. The design of the project was guided by a focus group. In order to explore patients' views on the study design, and to ensure research questions important to women who have had the condition were addressed, I held a focus group attended by women with prior PPCM. The information collected at the focus group was used solely to inform study design, and not for research purposes. Six women with a history of PPCM were invited to participate in a discussion about the study. Themes arising from the focus group included a feeling that there was a lack of awareness about the condition and a lack of recognition of heart disease in pregnant woman altogether, with a perceived delay to diagnosis. The study design was discussed, including the unconsented nature of data collection from patient records. Participants were reassured that no woman in the study would be identifiable and that data would be collected by a cardiologist involved in caring for women with PPCM. No objections were raised and the group were supportive of anonymised research which might help women with the condition. We discussed whether or not it would be feasible to obtain consent from some women, but not others. It was felt that this was likely to be prohibitive to conducting the study, given that identification of cases would be via national datasets, over a period of decades, details such as address would not be accessible, and that highly selective inclusion would not allow for incidence estimation or a meaningful description of the condition at population-level. The discussion also explored which research questions were important to women with the condition and a number of areas were identified, with a particular focus on outcomes for children.

The study has three arms:

1) Cohort study of women with PPCM in Scotland, with a nested case-control study:

The epidemiology of PPCM was examined in a population cohort of women with the condition in Scotland. A control group (matched for age at delivery, year of delivery, and health board) of women without heart failure (i.e. without PPCM, any other kind of cardiomyopathy or heart failure), was also examined.

2) Cohort study of children born to women with PPCM in Scotland, with a nested case-control study:

Outcomes for all children born to women with PPCM (during the index pregnancy) in Scotland were examined. Children born to the maternal control cohort were used as the child control cohort.

3) Cohort study of women with PPCM in England:

As a sensitivity analysis, the incidence of PPCM was determined in the English population.

## 2.3 Data sources

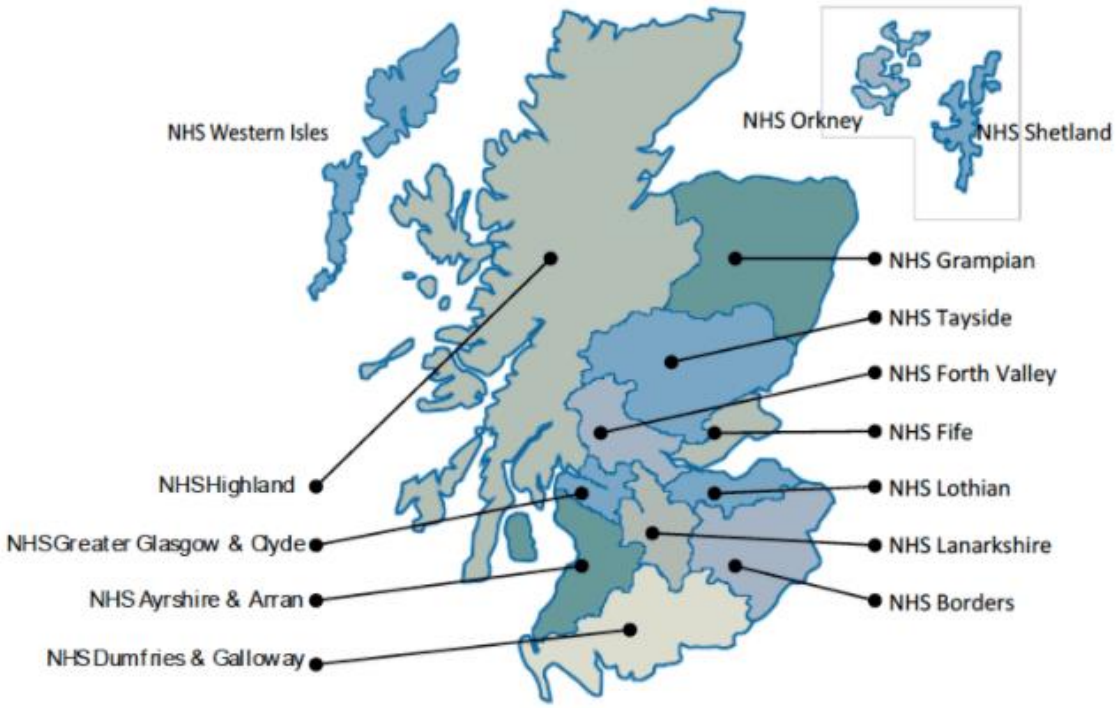
1) Administrative data from NHS National Services Scotland
2) Data collected directly from patient records (women with PPCM in Scotland only)
3) Administrative data from NHS Digital (England)

### *2.3.1 Data sources in Scotland*

**Scottish Morbidity Record**

The NHS National Services Scotland (NSS) collects data on all hospital admissions across all Scottish NHS health boards, by use of the Scottish Morbidity Record (SMR) scheme[157]. Figure 2-1 shows the distribution of health boards within Scotland. The population of Scotland in the 2011 census was 5.3 million.

**Figure 2-1 National Health Service health boards in Scotland**



The SMR record type denotes the general type of healthcare received during an episode. A series of SMR schemes exist, which include outpatient attendances (SMR00), general/acute inpatient and day cases (SMR01), maternity inpatient and day cases (SMR02), mental health inpatients and day cases (SMR04), the cancer registry (SMR06) and the Scottish Drugs Misuse Database (SMR25). Both elective and emergency admissions are captured through these. SMR01 (general admissions) and SMR02 (maternity) were used for this study.

A record is generated at the time of a hospital discharge, transfer to a different healthcare facility, transfer to another speciality, care of a new clinician within the same healthcare facility, or upon death in hospital. Each of these is called an 'episode' and a complete collection of episodes for the whole attendance or admission (from admission, through any inter- or intrahospital transfers, to either discharge or death) is termed the 'continuous index stay'. In every case, data collected include patient demographics, such as age, sex and up to six diagnostic and four operative codes. They also include data pertaining to the management of the patient, such as type of admission, length of stay, location and transfer details. In addition, SMR02 captures additional obstetric, delivery and neonatal data, such as parity, mode of delivery, APGAR scores and birth weight.

**Discharge diagnostic codes**

In the SMR scheme, each patient receives up to six diagnostic codes, with the main reason for admission being recorded as the principal diagnosis. Diagnoses are coded using the World Health Organisation International Classification of Diseases (ICD) system. In the United Kingdom, the 10th revision of ICD was adopted on 1st April 1996. Operation codes are recorded according to the OPCS Classification of Interventions and Procedures. Diagnostic position is discussed in more detail in the next chapter.

**Quality and accuracy**

The quality and accuracy of SMR01 data is periodically audited by a Data Quality Assurance (DQA) team using a Scotland-wide random sample. The three-digit accuracy for the principal diagnosis and main operation, respectively, was 87.8%

and 92.2% in 2004-2006, 88.3% and 94.3% in 2010-2011 and 89.0% and 92.8% in 2014-2015[158]. The Data Quality Assurance team have been assessing the quality of SMR01 data for over 25 years; the accuracy rates for recording of the principal condition and the main operation have remained stable at around 89% and 94%, respectively, throughout this time. The accuracy of coding of CV conditions is higher than average (heart failure 91%, ischaemic heart disease 97% and myocardial infarction 99%)[158]. Auditing of accuracy is conducted by assessing patient records in NHS boards and cross check these with randomly sampled SMR01 episodes. The DQA team compare the quality of submitted information against all patient records available to determine the accuracy of coding and the quality of information available to coders.

The accuracy of SMR02 data varies depending on the variable, although the majority are of high accuracy (>90%). Figure 2-2 shows the accuracy of assessed data items taken from the DQA Assessment of Maternal Data (SMR02) 2010 Scotland Report[159]. No SMR02 data items with accuracy <80% were used in this study, except for height and weight; audit of the former shows that part of the inaccuracy identified came from incorrect rounding (e.g. 65.6kg documented as 65Kg is considered an inaccuracy). Accuracy of maternity discharge ICD conditions varies according to health board and according to the condition. Taking all conditions, in the whole of Scotland, the three-digit accuracy for the principal diagnosis is 72%, ranging from 95% in NHS Fife to 22% in NHS Borders[160]. In this study, SMR02 data accuracy of the principal diagnostic condition, calculated according to the health board distribution of women included in the final cohort, averaged 81%.

**Figure 2-2 Accuracy of SMR02 data items (directly from 2010 Scotland Report)**

| Priority | Data Item | Matched (%) |
|---|---|---|
| **90-100%** | | |
| C | Number of Births this Pregnancy | 100 |
| C | Outcome of Pregnancy | 100 |
| C | Sex (gender) | 100 |
| C | Date of Delivery | 100 |
| C | Birthweight | 99 |
| M | Previous Caesarean Sections | 98 |
| M | Admission Date | 98 |
| M | Discharge Date | 98 |
| M | Previous Therapeutic Abortions | 97 |
| C | Neonatal Indicator | 96 |
| M | Previous Spontaneous Abortions | 96 |
| M | Previous Pregnancies | 94 |
| C | Apgar Score | 93 |
| C | Induction of Labour | 93 |
| C | Estimated Gestation | 92 |
| C | Episiotomy | 92 |
| C | Antenatal Steroids | 92 |
| M | Smoker During Pregnancy | 90 |
| **80-89%** | | |
| C | Resuscitation | 88 |
| C | Mode of Delivery | 87 |
| C | Tear | 87 |
| C | Diabetes | 85 |
| M | Smoking History at Booking | 81 |
| **70-79%** | | |
| C | Analgesia During Labour and/or Delivery | 79 |
| C | Weight of Mother at Booking | 77 |
| C | Duration of Labour | 74 |
| O | Height | 72 |
| **40-69%** | | |
| C | Presentation at Delivery | 69 |
| O | Booking Date | 67 |
| **Less than 40%** | | |
| O | Typical Weekly Alcohol Consumption | 39 |
| O | Drug Misuse During this Pregnancy | 33 |
| O | Ever Injected Illicit Drugs | 29 |
| O | Drugs Used | 25 |
| O | Ethnic Group | 11 |

**Key:** M – Mandatory, C – Conditional, O - Optional
**Source:** DQA, ISD Scotland, April 2010

## Record linkage

In Scotland, there is a unique opportunity to link routine datasets and use these for research purposes. This is done through a combination of deterministic matching, which involves matching the unique patient identifier, the Community Health Index (CHI) number, and probabilistic matching, which involves the use of other variables, such as name, date of birth or postcode, to determine whether

the records belong to the same individual[161]. Table 2-1 lists and describes the Scottish administrative datasets linked for the purposes of this study. Together, these linked datasets allow tracking of an individual from birth, through subsequent hospital admissions or attendances, including all pregnancies, to the end of life. There is also the ability to identify and link equivalent data for children born to female patients (retaining linkage with the mother).

**Table 2-1 Complete list of administrative datasets in Scotland linked for this study**

| Dataset | Description |
|---|---|
| SMR01 | General/acute and inpatient day cases from acute specialities |
| SMR02 | Maternity inpatient and day cases from any obstetric event (this can be an antenatal, delivery or postnatal episode) |
| NRS Deaths | Deaths occurring in Scotland, including registered cause of death |
| NRS Stillbirths and Infant Deaths | Births, stillbirths and death in the first year of life |
| Scottish Index of Multiple Deprivation | Socioeconomic deprivation index for 7000 data zones throughout Scotland, based on the combination of a large number of domain-specific indicators |
| Prescribing Information System | All medications that are prescribed and dispensed in the community in Scotland (with the ability to link with other datasets from 2009 onwards) |

**Patient health records in Scotland**

In Scotland, there was also review of paper and electronic patient records and additional data collection directly from these records (by me). R&D approval was obtained for 13/15 health boards in Scotland, excluding NHS Orkney and NHS Shetland. A total of 9/15 health boards across the country were physically visited, all paper and electronic records available at each site were reviewed, and relevant clinical data were collected. Electronic and paper records were accessed remotely (i.e. paper records were scanned) for the remaining health boards. All available echocardiogram reports were reviewed.

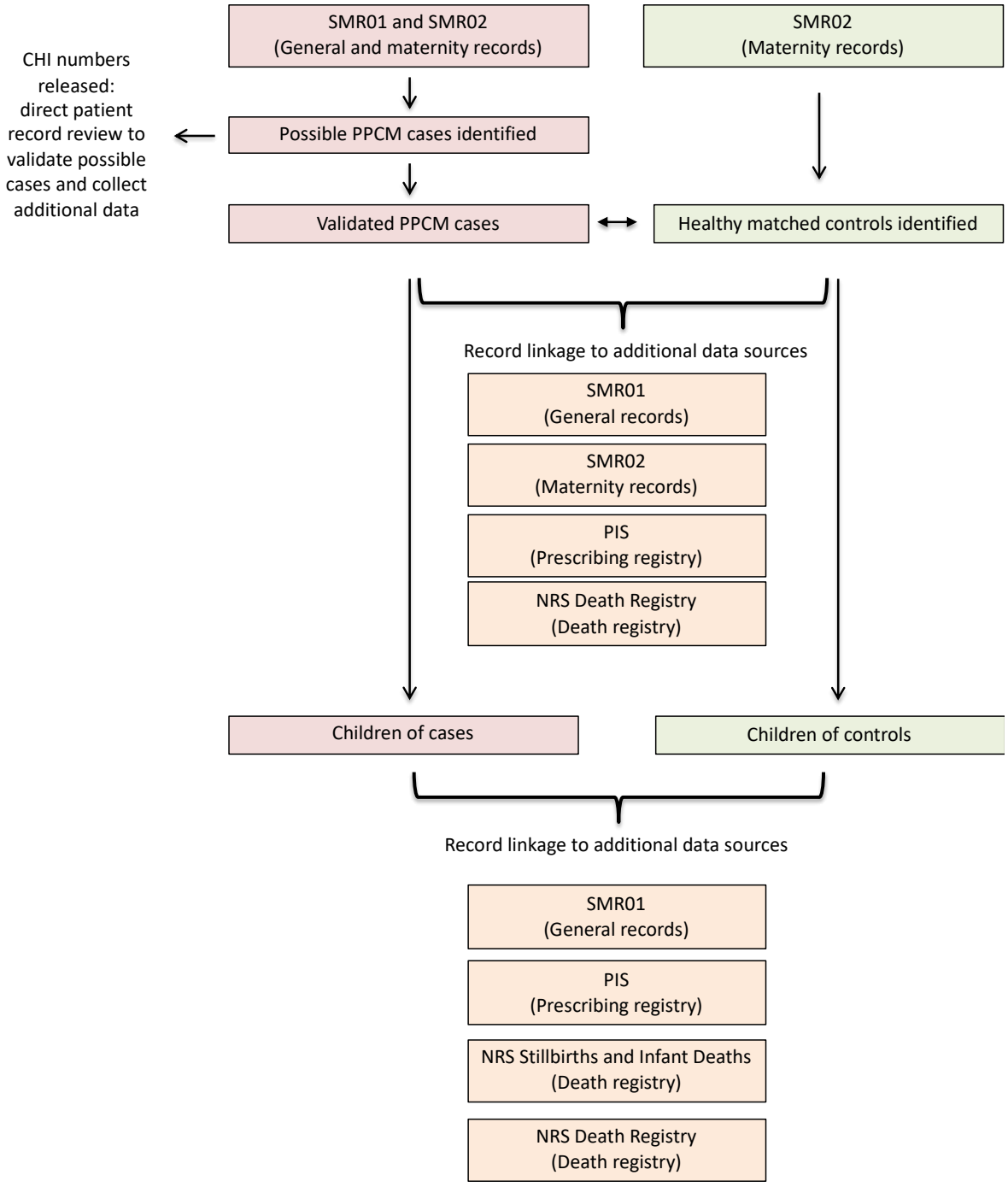
The additional data collection allowed:

— Validation of the diagnosis of PPCM in possible cases identified through SMR datasets
— Collection of additional, granular, clinical data not available in SMR datasets, such information from diagnostic cardiac investigations
— Completion of missing data fields in SMR datasets

Figure 2-3 illustrates the steps involved in the development of the final dataset in Scotland and how different datasets were linked.

Possible cases of PPCM were first identified through the relevant diagnostic codes from both SMR01 (general admissions) and SMR02 (maternity admissions) datasets. Outpatient records were not screened due to limitations with the outpatient dataset, although it seems likely that most incident diagnoses are made at the time of a hospital admission. The codes used to identify possible cases are described later in this chapter. The unique identifier (CHI number) for each patient was subsequently provided. Next, data were collected from patient records at each health board in Scotland, including Golden Jubilee National Hospital, but not including NHS Shetland and NHS Orkney.

**Figure 2-3 Data flow and linkage of Scottish administrative datasets**



### *2.3.2 Data sources in England*

**Hospital Episode Statistics**

Hospital Episode Statistics (HES) is a separate database housing details of all admissions, Accident and Emergency attendances and outpatient appointments at NHS hospitals in England[162]. Similar to the SMR scheme, each HES record contains a range of information about an individual with an NHS encounter, including demographics such as age group, sex and ethnicity, clinical information about diagnoses and operations, administrative and geographical information such as date and method of admission and where the patient is treated[163]. This can be linked with mortality data in England collated by the Office for National Statistics (ONS). The population of England in the 2011 census was 53.0 million.

# 2.4 Definitions

## *2.4.1 Possible cases of PPCM*

Possible cases of PPCM were defined as consecutive women with a discharge diagnosis of PPCM, heart failure or cardiomyopathy up to 6 months prior to or 2 years following a pregnancy outcome (delivery or termination), as defined by ICD codes listed in Table 2-2. In order to increase the number of records reviewed, and to ensure as complete a capture of cases as possible, women were initially identified irrespective of prior history (i.e. not solely incident diagnostic codes). Initially, the time frame used was 1986-2017. This later changed to 1998-2017; the reasons for this are discussed in the next chapter.

**Table 2-2 ICD diagnostic codes used to identify possible cases of PPCM**

| | **ICD-9 codes** | **ICD-10 codes** |
|---|---|---|
| PPCM | 674.5 | O90.3 |
| Heart failure | 428, 402, 404 | I50, I11, I13 |
| Cardiomyopathy | 425, 414.8 | I42, I43, I25.5 |

## *2.4.2 Pregnancies*

Pregnancies were identified using the following methods:

- A delivery outcome in SMR02
- An abortive outcome (termination) in SMR02
- An ICD discharge code or OPCS procedural code relating to either a delivery or termination in SMR01 or SMR02, not already identified, defined by the ICD codes listed in Table 2-3.

**Table 2-3 ICD diagnostic codes and OPCS procedural codes used to identify additional pregnancies**

| | **ICD-9 codes** | **ICD-10 codes** | **OPCS codes** |
|---|---|---|---|
| Termination | 63 | O0 | Q091, Q10, Q11 |
| Delivery | 650-652 | O80-O84 | R17-R25 |

In addition, in the event there was SMR02 record without a clear pregnancy (i.e. no delivery or termination and no ICD or OPCS code relating to a delivery or termination) up to 6 months after or 2 years prior to a heart failure admission, it was considered to be a *possible* pregnancy (since a woman is assumed to be pregnant in order to have a maternity admission).

### *2.4.3 Case validation*

In the Scottish arm of the study, the diagnosis of PPCM was validated by reviewing patient records for possible cases identified through methods described above. The diagnostic criteria were adapted from the ESC PPCM Study Group 2010 criteria[3]. For patients without a quantitative assessment of LVEF, a qualitative assessment documenting LV systolic impairment was used.

Criteria for case validation and inclusion were:

1. Impaired LV systolic function:
LVEF on transthoracic echocardiography of ≤50% or qualitative assessment reporting the presence of LV systolic dysfunction if LVEF was not available (this is detailed further in Table 2-5).

2. No clear alternative cause for LV dysfunction.

3. No pre-existing diagnosis of LV dysfunction or cardiomyopathy.

4. Diagnosis during pregnancy (excluding the first trimester), up to 2 years postpartum.

The following conditions were felt to be consistent with alternative causes and were thus excluded:

*Primary cardiac*
Hypertrophic cardiomyopathy, Fabry's disease, arrhythmogenic cardiomyopathy, adult congenital heart disease, proven or suspected coronary artery disease, myocarditis, moderate or severe valvular heart disease, suspected takotsubo cardiomyopathy

*Others*

Vasculitis, sarcoidosis, phaeochromocytoma, active systemic autoimmune disease, significant renal disease (haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura, nephritic/nephrotic syndrome, end-stage renal failure, dialysis), major systemic upset (subarachnoid hemorrhage, severe sepsis, major hemorrhage, evidence of significant drug or alcohol misuse), diabetes with multiple documented micro- and/or macrovascular complications.

Borderline cases were adjudicated with a second investigator, Professor Mark C Petrie, consultant cardiologist, who has extensive experience in managing women with PPCM over 20 years.

### *2.4.4 Matched controls*

Matching is used in case-control studies in an attempt to adjust for confounding and to enhance study efficacy by improving precision. Matching should be performed on variables which are confounders and can be carried out in two ways: a) frequency matching, in which selection of controls is done in such a way that the distributions of matching variables are similar between the cases and controls, or b) individual matching, in which individual cases are matched to[164]. There are several considerations when conducting and analysing a matched case-control study[165]. One is that matching can introduce confounding by the matching factors. This can occur if the matching factor renders the controls more similar to the cases with respect to not only the matching factor, but also the exposure itself[166]. There are different approaches to addressing this, all of which, in some way, allow controlling of the matched factors in the analyses. These include a standard method of adjusting, such as analysing the cohort stratified by the matching factor (for example, age), or adjusting for the matching factor in a multivariable model, using unconditional logistic regression. Another option is to perform a matched analysis, in which conditional logistic regression is used to retain the matched case-control strata. Both methods have strengths and weaknesses; which is chosen tends to be related to strata size[166, 167]. Unconditional methods are generally recommended when strata sizes are larger, with adjustment for the matching factors, and conditional methods when the converse is true. Furthermore, a standard, or unconditional analysis can improve precision when matched factors are identical between cases and

controls, since variance is lower in this situation, or when matching is 'loose', or matching is only on a limited set of factors (e.g. age alone)[164, 166]. Another important consideration is sparse data. Sparse data bias occurs when there is an inadequate number of cases with respect to a particular exposure and outcome and can be exacerbated by multivariable adjustment in a regression analyses; in this setting estimates may be inflated and the corresponding 95% confidence intervals wide[168]. Conditional logistic regression was originally designed to counteract the problem of sparse data, although other methods such as shrinkage methods, which are not discussed in this thesis, can be considered[168].

In this study, 10 matched controls were identified for each case. Controls were women without PPCM, heart failure or a cardiomyopathy (i.e. women without a hospital admission with any of the diagnostic codes used to identify cases and listed in Table 2-2) and were matched for: 1) age at delivery, 2) year of delivery $\pm$ 1 year, and 3) health board of delivery. Health board was chosen as a matching criterion in order to attempt to reduce biases that could arise due to regional differences in access to, or provision of, health care. Due to smaller health boards and extremes of age potentially limiting the ability to find a match using the above criteria, if required, the health board criterion was dropped.

### *2.4.5 Children*

Only children whose data could be linked to their mother were included in the study. For children, two different sources of data were used; neonatal and delivery data, which is included in the mother's SMR02 (delivery) record and the child's own records going forward (SMR01 for the purposes of this study). Because of this, in some cases, children were included at the neonatal stage, but not beyond this (i.e. in the event that linkage with their mother beyond birth was not possible).

## 2.5 Data capture

The following variables were included across the linked administrative datasets:

*Mothers (cases and controls)*

— Demographics (e.g. age, ethnicity, smoking status, socioeconomic deprivation category, timing of diagnosis)
— Comorbidities
— Subsequent hospitalisations
— Obstetric data (e.g. parity, duration of pregnancy, previous terminations, multiple gestation, factors relating to labour, mode of delivery)
— CV medical therapy (from April 2009)
— Timing and cause of death

*Children (cases and controls)*

— Neonatal data (e.g. stillbirth, sex, birth weight, APGAR score)
— Comorbidities
— Subsequent hospitalisations
— Medical therapy (from April 2009)
— Timing and cause of death

The following additional data were collected during review of patient records, for PPCM cases (mothers only):

- Investigations (e.g. laboratory blood tests, electrocardiography, echocardiography)
- Clinical assessment
- Specific treatments (e.g. intravenous diuretic therapy, haemodynamic support, mechanical ventilation, renal replacement therapy, mechanical circulatory support)

**Medication**

**Table 2-4 Formulary codes used to identify community dispensed medications**

| Drug | Formulary Code |
|---|---|
| Bromocriptine | 0607010B0 |
| Digoxin | 0201010F0 |
| Beta blocker | 020400 |
| Alpha blocker | 020504 |
| Diuretic | 020200 |
| Thiazide /thiazide-like diuretic | 020201 |
| Loop diuretic | 020202 |
| Potassium-sparing diuretic | 020203 |
| Combination diuretics | 020204 |
| Renin-angiotensin modulator* | 020505 |
| Sacubitril-valsartan | 0205052AE |
| Nitrate | 020601 |
| Calcium-channel blocker | 020602 |
| Ivabradine | 0206030Y0 |
| Nicorandil | 0206030N0 |
| Ranolazine | 0206030Z0 |
| Anti-platelet | 020900 |
| Anticoagulant | 020800 |
| Parenteral anticoagulant | 020801 |
| Oral anticoagulant | 020802 |
| Lipid lowering drug | 021200 |

**ACE inhibitor, ARB, renin inhibitor or sacubitril-valsartan*

**Reporting of LV function**

Table 2-5 shows how echocardiographic parameters relating to LV systolic function were defined and classified.

**Table 2-5 Classification of LV systolic function**

| | |
|---|---|
| Qualitative assessment of LV function | Where only qualitative assessment was performed, the degree of dysfunction was categorised into mild, moderate or severe. In some instances, an equivalent description of LV function was provided and, where possible, this was categorised as normal, mild, moderate or severe (e.g. 'very poor' categorised as severe). Qualitative assessment of mild-moderate was categorised as mild and moderate-severe as moderate. |
| Quantitative assessment of LV function | Simpson's biplane measurement; if absent, modified apical 4 chamber measurement; if absent, Teichholz measurement; if absent, estimated measurement; if absent, assignment of LVEF based on qualitative assessment (as per rules set out below).<br><br>Mild or equivalent = LVEF 50%<br><br>Moderate or equivalent = LVEF 40%<br><br>Severe or equivalent = LVEF 25%<br><br>Mid-point values were adapted from the British Society of Echocardiography LVEF ranges for mildly, moderately and severely impaired systolic function[169]. |

## 2.6 Outcomes

Definitions of outcomes are provided in the relevant chapters. The following outcomes were examined:

For women with PPCM and controls

1. All-cause death
2. CV death
3. All-cause rehospitalisation
4. CV rehospitalisation
5. All-cause death or all-cause rehospitalisation
6. CV death or CV rehospitalisation
7. Recurrent hospitalisation

For women with PPCM

1. CV death, intra-aortic balloon pump, ventricular assist device (VAD), or extracorporeal membrane oxygenation (ECMO), or cardiac transplantation
2. Stroke or thromboembolism
3. Implantable cardiac devices (implantable cardioverter defibrillator or cardiac resynchronization therapy)
4. LV recovery
5. LV decline after recovery

For women with PPCM and controls relating to a subsequent pregnancy

1. All-cause death or all-cause rehospitalisation
2. CV death or CV rehospitalisation
3. Composite CV endpoint: CV death, any mechanical circulatory support or cardiac transplantation
4. Neonatal outcomes

For children of women with PPCM and controls:

1. Neonatal outcomes
2. All-cause death
3. All-cause hospitalisation
4. Incidence of CV disease, non-CV congenital anomalies, respiratory disease, gastrointestinal disease and infection

## 2.7 Statistical analysis

The statistical methods which relate to the specific objectives within each chapter of this thesis are detailed at the start of each chapter, but the following section provides an overview of and theoretical background to the methods applied throughout the thesis.

### *2.7.1 Tests of significance*

All analyses were performed using Stata version 16 (StataCorp LLC, College Station, TX). Tests for statistical significance were all two-tailed, and a conventional two-sided p value of <0.05 was considered statistically significant.

There are limitations of using a dichotomised p value to determine the significance of a result; in particular, a p value may indicate that no statistically significant difference exists, but does not differentiate between a true absence of difference and a sample size that is too small to detect a true difference (i.e. one that is underpowered)[170, 171]. Indeed, a number of medical journals, including the British Medical Journal, Lancet and New England Journal of Medicine, have moved away from presenting p values and place much greater importance on the presentation of confidence intervals[172]. Confidence intervals become more relevant when an inference drawn from the study is to be applied to a wider population. The width of the confidence interval, and thus the degree of imprecision, is dependent on three factors: 1) sample size (the larger the sample size, the narrower the confidence interval); 2) variability of the parameter being analysed (the less variability, the narrower the confidence interval); 3) degree of confidence required (the lower the degree of confidence, the narrower the confidence interval)[170]. In this thesis, 95% confidence intervals are presented throughout. This provides a more accurate reflection of the imprecision of the findings and better places them into the wider population context than a p value alone.

### *2.7.2 Incidence and event rates*

In epidemiology, a rate represents the frequency at which an event of interest occurs, within a defined population and within a specified period of time. It is

an estimate of risk. Rates can be used to express a number of epidemiological measures, including disease incidence, prevalence, morbidity and mortality[173, 174].

When the period of time is specified and equal in the population, the rate can be defined as:

*Annual rate = number of events in a given year / number of individuals at risk in that year*

When the specified period of time differs between individuals, such as the total duration of follow-up, rates can be expressed in terms of person-time at risk: for example, the rate of an event of interest, per 1000 patient years. In this setting, a rate can be defined as:

*Rate =number of events / person-time at risk*

An incidence rate of a condition is defined as the number of *new* cases of the condition that occur during a specified period of time, in a population at risk for developing the condition, who did not have it previously[174]. In this study, the incidence rate of PPCM was calculated as follows:

*Incidence rate of PPCM per 10,000 deliveries = (number of new cases of PPCM occurring in the population during the study period / number of women at risk of developing PPCM during the study period [i.e.women with a delivery]) x 10,000*

When examining incidence, in order for the measure to be meaningful, an individual who is included in the denominator (i.e. is one of the 'at risk' population), must have the potential to become part of the numerator (i.e. can develop the condition). In this study, the 'at risk' population must only include women with a pregnancy.

An incidence rate ratio is defined as the ratio of two incidence rates and is a relative difference measure that can be used to compare the incidence rates of a particular event of interest in two different groups (e.g. exposed patients and

unexposed patients) at any given point in time, or to compare the incidence rates of a particular event of interest at two different time points[175].

Rate ratios and 95% confidence intervals were calculated using the method proposed by Rothman et al[176]. First, an incidence rate ratio was derived by dividing the incidence at a specific time point (incidence rate 1) by the incidence of the referent group (in this case, the earliest year – incidence rate 0):

*Rate ratio = incidence rate 1 / incidence rate 0*

Next, 95% confidence intervals were generated by calculating the standard deviation of the log rate ratio using the following equation, where A1 is the number of women with PPCM in the year group of interest and A0 is the number of women with PPCM in the referent year group:

*SD[ln(rate ratio)] = (1/A1 + 1/A0)^1/2*

Finally, the upper and lower confidence intervals were calculated using the following equation, where Z is equal to the standard deviation of the log rate ratio determined in the previous equation:

*exp[ln(rate ratio) ± 1.96(Z)]*

### *2.7.3 Comparison of patient characteristics*

Descriptive analyses were carried out by comparing characteristics and outcomes between women with PPCM and controls. Comparisons were performed using t-tests, Wilcoxon rank-sum test, and chi-squared tests, where appropriate.

### *2.7.4 Factors associated with the development of PPCM*

Associations between baseline characteristics, such as patient demographics, characteristics, comorbidities and obstetric factors, and the development of PPCM were examined using unconditional logistic regression, adjusted for age at delivery, year of delivery (1998-2007 vs 2008-2017) and health board of delivery,

to account for matching factors. This method was chosen given the strata size. Both univariable and multivariable analyses were conducted.

### *2.7.5 Outcomes*

**Event rates**

Rates of events of outcomes were calculated using the date of diagnosis (defined as the start date of the episode of care during which the diagnosis was made) for women with PPCM, and the date of delivery for controls, to the date of the event (defined as the start date of the episode of care during which the event occurred, or the date of operation, or the date of death) or, if no event occurred, to the censor date (31st December 2017).

**Mortality rate vs case-fatality rate**

The mortality rate of a population, or group of individuals, is defined as the total number of deaths (either from any cause, or from a particular cause) as a proportion of the total number of individuals in the population, within a specified period of time. Taking 30-day mortality rate as an example, this is defined as:

*30-day mortality rate, per 1000 population = (total number of deaths within 30 days / number of individuals in the population*) x 1000*
** where all individuals have 30-day follow-up*

In contrast, case-fatality expresses the percentage of individuals with a certain disease who die within a certain time. Therefore, 30-day case-fatality is defined as:

*30-day case-fatality rate, per 1000 population = (total number of deaths within 30 days / number of individuals in the population with the disease of interest*) x 1000*
** where all individuals have 30-day follow-up*

The difference between these two measures is the population included in the denominator; when calculating mortality rate, this can be the whole population of individuals at risk of dying (both those with and without the disease of interest), and when calculating case-fatality rate, this is usually the population of individuals with the disease of interest.

**Survival analysis**

Survival data is constructed around two main concepts: survival and hazard[177]. The former is the probability that a participant survives to a time of interest. The latter is the probability that a participant under observation has an event by a time of interest. Survival data encompasses the time to an event of interest occurring[178]. Survival models consist of two parts: the underlying baseline hazard function, which describes how the risk of the event changes over time at baseline levels of covariates, and the effect parameters, which describe how the hazard changes for different covariates.

In survival analysis, the probability of being alive at a time of interest (S[tj]) is calculated from the probability of being alive just before the time of interest (S[tj-1]), the number of patients alive and at risk just before the time of interest (nj) and the number of events by the time of interest (dj)[177]:

$$S(tj) = S(tj-1)(1-dj/nj)$$

Patients are only at risk if they remain event-free and have not been censored; i.e. are event-free with ongoing follow-up.

The Kaplan-Meier survival curve is an illustration of the probability of survival over time[178]. Between-group differences can be assessed using the log rank test.

**Regression analysis**

Regression analysis estimates the relationship between two variables – a dependent variable (the outcome) and at least one independent variable (the predictor[s]). In this study, the following types of regression modelling were used to examine outcomes[179, 180]:

- Logistic regression
- Cox proportional hazards regression
- Negative binomial regression

Table 2-6 summarises the main features of these methods and their assumptions.

**Table 2-6 Different regression models used**

| **Regression model** | **Outcome/ dependent variable** | **Main assumptions** | **Measure** |
|---|---|---|---|
| Binary logistic | Binary<br>e.g. Recovery of cardiac function (yes/no) | - No strongly influential outliers<br>- Absence of multicollinearity<br>- Independence of observations<br>- Linear relationship between continuous independent variables and the logit transformation of the dependent variable | Odds ratio: a measure of association between an exposure and an outcome |
| Cox proportional hazards | Time-to-first-event<br>e.g. Death or first hospitalisation | - Random censoring: data censoring should be noninformative, which means that the censoring time for an individual should be independent of their event (or failure) time.<br>- Proportional hazards: the hazard function (hazard ratio) for the two groups should remain proportional, which means that the hazard ratio is constant over time. | Hazard ratio: the extent to which an outcome of interest is affected by a covariate |
| Negative binomial | Count data, where overdispersion exists | - Linear relationship between the independent variable(s) and the natural logarithm (ln) of | Incidence rate ratio:<br>ratio of the expected number of |

| | | | |
|---|---|---|---|
| | e.g. Recurrent rehospitalisations | the expected value of the outcome<br>- Independence of observations | events for a unit increase in the explanatory variable to the expected number of events |

**Missing data**

Missing data were excluded and imputation was not performed. Table 2-7 shows the comparison of important baseline characteristics, according to whether or not data were missing for the following frequently used variables: a) parity, multiple gestation, estimated gestation, socioeconomic deprivation quintile, body mass index and smoking in cases and controls and b) any assessment of LV function, heart rate, and systolic blood pressure in cases only. Only p values, and not numbers and proportions, are shown due to frequent small numbers, the presentation of which would violate NHS NSS reporting standards.

## Table 2-7 Missing data according to important baseline characteristics

| | P value for missing vs non-missing | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Parity** | **Multiple gestation** | **Estimated gestation** | **Deprivation quintile** | **BMI** | **Smoking** | **Any assessment LV function** |
| Year of delivery* | 0.001 | 0.88 | 0.95 | 0.29 | <0.001 | <0.001 | <0.001 |
| Health board | <0.001 | 0.94 | 0.41 | <0.001 | <0.001 | <0.001 | 0.78 |
| Age (years) | 0.52 | 0.11 | 0.20 | 0.81 | 0.20 | 0.006 | 0.16 |
| Deprivation quintile | 0.62 | 0.34 | 0.91 | - | 0.24 | 0.72 | 0.25 |
| BMI ($kg/m^2$) | 0.91 | 0.68 | 0.87 | 0.39 | - | 0.28 | 0.68 |
| Smoking | 0.19 | 0.029 | 0.33 | 0.77 | 0.064 | - | 0.49 |
| Any hypertension | 0.38 | 0.38 | 0.15 | 0.49 | 0.18 | 0.18 | 0.067 |
| Any diabetes | 0.51 | 0.13 | 0.41 | 0.60 | <0.001 | 0.73 | 0.46 |
| Gestational diabetes | 0.68 | 0.74 | 0.66 | 0.74 | <0.001 | 0.11 | 0.36 |
| PIH | <0.001 | 0.44 | 0.30 | 0.44 | 0.84 | 0.37 | 0.017 |
| Pre-eclampsia | 0.57 | 0.66 | 0.55 | 0.66 | 0.74 | 0.51 | 0.052 |
| Parity | - | 0.22 | 0.42 | 0.41 | 0.062 | <0.001 | 0.053 |
| Multiple gestation | 0.66 | - | | 0.73 | 0.51 | 0.28 | 0.33 |
| Estimated gestation (weeks) | 0.66 | | - | 0.96 | 0.26 | 0.73 | 0.005 |
| Induction of labour | 0.94 | | | 0.76 | 0.72 | 0.91 | 0.40 |
| Mode of delivery | 0.26 | | | 0.56 | <0.001 | 0.17 | 0.17 |

*BMI = body mass index; PIH = pregnancy-induced hypertension*
**(2008-2017 vs 1998-2007)*
*Comparisons denoted by the grey boxes were not performed as missing data for multiple gestation and estimated gestation were due to terminations occurring, so data on other delivery-specific factors such as induction of labour and mode of delivery were therefore not available in the missing group.*

## 2.8 Data handling

Linked administrative data were managed and analysed on the secure National Safe Haven platform. Once data from patient records were collected, this additional dataset was uploaded to the secure National Safe Haven platform for analysis in conjunction with the linked administrative datasets.

## 2.9 Ethical approval

Approval was given by the Public Benefit and Privacy Panel (PBPP) of NHS National Services Scotland ISD for use of linked data from Scotland (Ref:1617-0359) and by the Independent Group Advising on the Release of Data (IGARD) of NHS Digital for use of linked data from England (Ref:DARS-NIC-262206-F1P5Z). The West of Scotland Regional Ethics Committee (WoS REC) granted approval for data collection from patient records in Scotland (Ref:GN18CA603). A patient focus group was conducted to explore patient views on the study design and was supportive.

**Ethical considerations**

Ethical considerations were identified and discussed with the WoS REC. The first main consideration was regarding the unconsented review of patient records to facilitate case validation and inclusion of important clinical data, without which reporting of the condition at population-level, including an estimate of incidence, would not have been possible. It was guaranteed that data collection would be done by a cardiologist already involved in the clinical care of women included in the study, and that all data would be held anonymously. A focus group was conducted to explore patient views on this approach and no objections were raised (the focus group is described in more detail in section the Methods chapter, section 2.2). The second main consideration was regarding the potential for unexpected findings during data collection, such as incorrect management of a patient or loss to follow-up. It was guaranteed that any such issues would be highlighted to the clinical team responsible for the care of the patient.

## 2.10 Funding

The project was funded through a British Heart Foundation Clinical Research Training Fellowship (Fellowship no. FS/18/14/33330).

## 2.11 Reporting epidemiological data

Guidelines to improve the reporting of epidemiological research exist. The STROBE (STrengthening the reporting of OBservational studies in Epidemiology) checklist highlights the important considerations when designing and reporting an observational study[181]. These ensure the background and rationale to the study are clear, the methods and statistical analyses are relevant, the results are reported thoroughly, including reasons for non-participation, amount of missing data, and precision estimates, and that the discussion summarises and interprets the findings appropriately with acknowledgement of study limitations. The STROBE guidelines are included in Appendix 1.

# Chapter 3 Case validation and incidence of PPCM

## 3.1 Introduction and aims

This chapter focusses on the validation of the diagnosis of incident PPCM in women with discharge diagnosis of PPCM, heart failure or cardiomyopathy around the time of pregnancy in Scottish hospitals between 1986 and 2017 and incidence of the condition. Later, this time frame for inclusion changed to 1998-2017 and reasons for this will be discussed. Excluded conditions will also be described. Incidence will be reported over time, both in a crude fashion and using age-standardisation, and compared across three different groups with respect to the timing of diagnosis: a) within 6 months postpartum, b) within 12 months postpartum, and c) within 2 years postpartum. Incidence rates per 10,000 deliveries (including both live deliveries and stillbirths) will be calculated using population-level national records for all births in Scotland. Incidence rate ratios will be calculated to demonstrate trends in incidence rates over time, referent to the earliest year grouping. Crude incidence rates and incidence rate ratios for unvalidated cases of PPCM in England will be calculated in the same way, and these women will be identified by applying the combination of ICD-10 discharge codes resulting in the highest sensitivity for PPCM in the Scottish cohort.

## 3.2 Methods

### *3.2.1 Study population*

The initial, unfiltered dataset comprised all women with an ICD-9 (coding used prior to 1997) or ICD-10 discharge (coding used from 1997 onwards) diagnosis of PPCM, heart failure or cardiomyopathy in any diagnostic position from January 1st 1986 to 31st December 2017 in either the SMR01 (general adult hospital day case or admission) or SMR02 (maternity hospital day case or admission) datasets. All SMR02 (maternity) records for these women were linked. Any diagnostic position was chosen in order to 'cast the net wide' given that the possible cases would subsequently be validated.

In order to capture all possible cases of PPCM, women with at least one of the relevant discharge codes up to 6 months prior to, or up to 24 months after the end of a pregnancy, irrespective of pregnancy outcome, were identified to begin with. These were deemed to be 'possible' cases of PPCM. In the dataset, all dates were provided in the format MMYYYY and so time periods were measured in 'N' months, and not in 'N' days.

All accessible medical and maternity paper and electronic patient records for each possible case of PPCM were reviewed across Scotland. Of the 15 health boards in Scotland, including NHS National Waiting Times Centre (an additional special NHS board in Scotland which is home to the Scottish National Advanced Heart Failure Service in the Golden Jubilee National Hospital). Records were physically accessed on site in 9/15 health boards, and either on site or remotely in 13/15 health boards. Patient records from NHS Orkney and NHS Shetland were not accessed, although these health boards account for <1% of the Scottish population and for <1% of women identified as possible PPCM cases. Based on the totality of data from all available medical and maternity patient records, possible PPCM cases were then validated against the inclusion and exclusion criteria detailed in the Methods chapter.

In the subset of women for whom records were insufficient, the sensitivity and specificity of different combinations of discharge codes in those with sufficient information to confirm or refute a PPCM diagnosis were applied, and the

combination of codes with the optimal sensitivity for PPCM were applied to patients with insufficient records. This is described in more detail later in this chapter. In this way, likely cases of PPCM were identified despite insufficient records. Different combinations of ICD-10 codes shown in Table 3-1 were used for this.

**Table 3-1 ICD-10 discharges codes used to calculate sensitivity and specificity of the PPCM diagnosis**

| ICD-10 code | Disease |
|---|---|
| **Inclusions** | |
| O903 | PPCM |
| I420 | DCM |
| I428 | Other cardiomyopathies |
| I429 | Unspecified cardiomyopathy |
| I50 | Heart failure |
| **Exclusions** | |
| I21 I22 | Acute myocardial infarction, subsequent myocardial infarction |
| I421 I422 I423 I424 I425 I426 I427 I43 | Alternative cardiomyopathies, in order: obstructive hypertrophic, other hypertrophic, eosinophilic, endocardial fibroelastosis, restrictive, alcoholic, due to drugs and other external agents, secondary to other diseases |
| I255 | Ischaemic cardiomyopathy |
| I05 I06 I07 | Rheumatic mitral, aortic, tricuspid valve disease |
| Q2 | Congenital malformations of the circulatory system |
| I270 | Primary pulmonary hypertension |

### *3.2.2 Statistical analyses*

Crude population-level incidence rates were calculated per 10,000 deliveries, including both live deliveries and stillbirths. In Scotland, total deliveries per year, stratified by age, were obtained from National Records of Scotland (NRS) Births Time Series Data[182]. In England, total deliveries per year were obtained from the Office for National Statistics[183]. Both data sources are publicly available online. In Scotland, crude incidence rates were also calculated by maternal age, using a categorisation of ≤32 years and >32 years, as well as overall age-standardised rates, standardised to total deliveries in each respective age group in the year 2007.

The traditional threshold of 5-6 months postpartum previously used as an inclusion criterion for the diagnosis of PPCM was arbitrary. In clinical practice, a delay between symptoms onset and diagnosis can occur. More recently, some studies have extended the inclusion of women to up to 1 year postpartum[18, 32, 33] and the previous stringent time thresholds included in diagnostic criteria were relaxed by the European Society of Cardiology PPCM Study Group in their 2010 definition. Therefore, incidence rates for PPCM diagnosed up to 6 months, 1 year and 2 years postpartum were also reportedly separately.

Rate ratios and 95% confidence intervals were calculated using the method proposed by Rothman et al[176], which is described in detail in the Methods chapter.

The presence and absence of different combinations of ICD discharge codes, in different diagnostic positions (first or second, versus any), were tabulated for women with sufficient records to confirm or refute a diagnosis of PPCM in order to assess the sensitivity and specificity of coding combinations. The Youden's J statistic, a measure of the performance of a dichotomous diagnostic test, was calculated using the following formula:

J = sensitivity + specificity -1

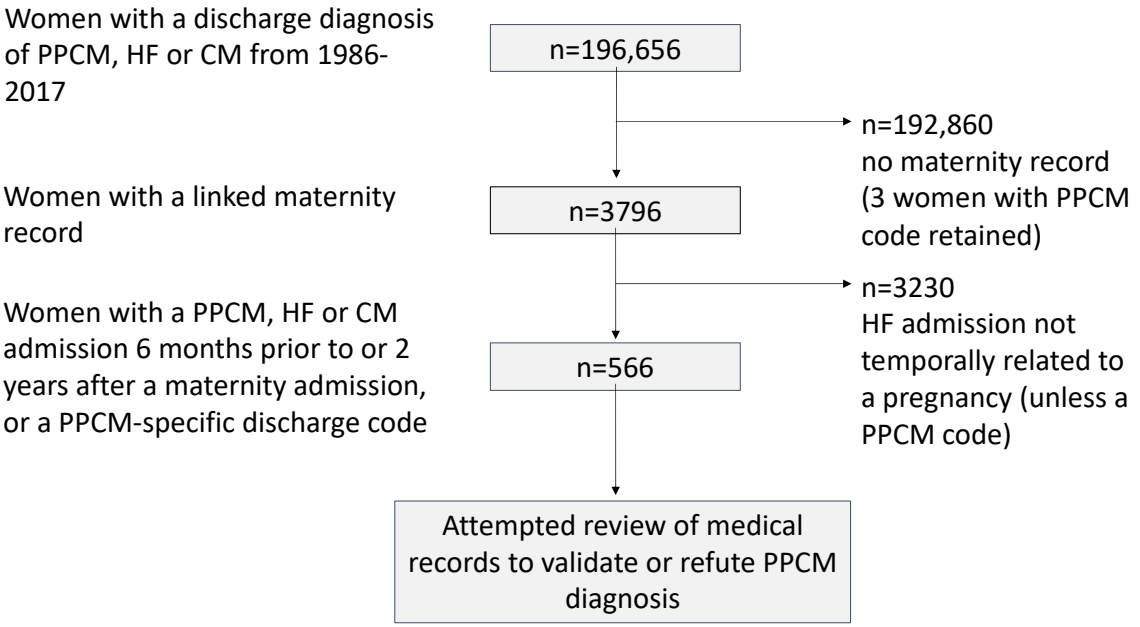
All graphs were generated in Windows Excel 2016.

# 3.3 Results

## *3.3.1 Case validation and inclusion*

**Scotland**

**Figure 3-1 CONSORT diagram for identification of women with PPCM, heart failure or cardiomyopathy around the time of pregnancy in Scotland from 1986-2017**




*PPCM = peripartum cardiomyopathy; HF = heart failure; CM = cardiomyopathy*

Figure 3-1 depicts the study CONSORT diagram for the identification of women with heart failure around the time of a pregnancy. In total, 196,656 women had a discharge diagnosis consistent with PPCM, heart failure or cardiomyopathy between 1986 and 2017 in Scotland, as defined by the ICD diagnostic codes specified in the Methods chapter. Overall, 192,860 women without a linked SMR02 (maternity) record at any time were excluded, except for three women with a discharge code specific to PPCM (despite not having a maternity record).

Of the remaining 3796 women, 533 (14%) women had an admission with PPCM, heart failure or cardiomyopathy with an appropriate temporal relationship to a

maternity admission resulting in either a delivery or termination, as defined in the Methods chapter.

In addition to this, a further 33 women were included for the case validation stage. These comprised:

- 23 women (0.6%) who had an admission with PPCM, heart failure or cardiomyopathy with an appropriate temporal relationship to a maternity admission, without a clear pregnancy outcome. The rationale for this was that, since a woman should only generate an SMR02 record in the event of pregnancy, it was likely a pregnancy had occurred and could be clarified during the case validation process.

- 10 women (0.3%) with a code specific to PPCM, but without a temporal relationship to a maternity admission.

The final cohort taken forward for review of patient records and case validation consisted of 566 (15%) women with a discharge diagnosis consistent with PPCM, heart failure or cardiomyopathy which was temporally related to a maternity admission (i.e. from 6 months prior up to 2 years following), or with a code specific to PPCM (ICD-9 6745; ICD-10 O903) at any time.

**Figure 3-2 CONSORT diagram for the validation of cases of PPCM in Scotland**

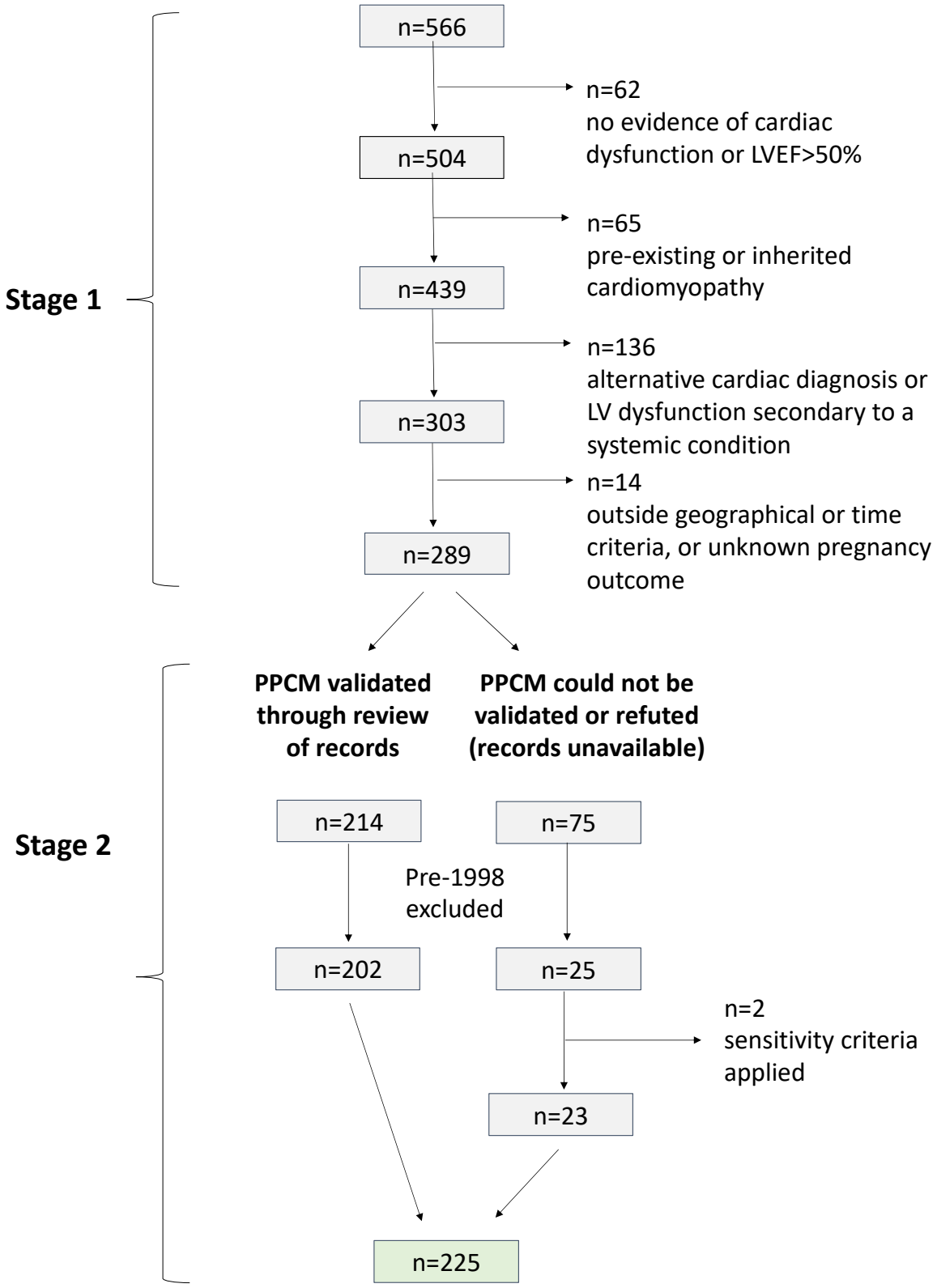


Figure 3-2 illustrates the case validation process and exclusions. Stage 1 represents the record review process and stage 2 represents the refining of the study cohort and application of optimal sensitivity/specificity criteria to identify women likely to have PPCM among those with insufficient records.

Of 566 women, a total of 277 (49%) were excluded in the first stage of the validation process. These comprised:

- 62 (11%) women in whom there was no evidence of cardiac dysfunction (including those with an LVEF above the threshold of 50%);

- 201 (36%) who had either a known, pre-existing cardiomyopathy or a de novo inherited cardiomyopathy other than a DCM (e.g. hypertrophic cardiomyopathy), an alternative cardiac diagnosis, or in whom LV dysfunction was deemed most likely to be secondary to a systemic condition (Table 3-2);

- 14 (5%) who did not meet the inclusion criteria for other reasons (delivery not in Scotland, visiting Scotland at the time of delivery, pregnancy terminated in first trimester, or no record of a clear pregnancy outcome).

Overall, 214 (38%) women met the criteria for inclusion/validation as described in the Methods chapter in section 2.4.3 (i.e. impaired LV systolic function, no clear alternative cause, no pre-existing diagnosis of LV dysfunction or cardiomyopathy and a diagnosis during pregnancy or up to 2 years postpartum). Records were insufficient in 75 (13%) of women (in these, PPCM could neither be validated nor refuted).

Overall, 67% of unvalidated cases but only 6% of validated cases were from prior to 1998. Therefore, the decision was made to exclude all women with a delivery prior to 1998 from the final study; this resulted in the exclusion of 12 validated PPCM cases and 50 unvalidated cases.

**Table 3-2 Classification of women excluded due to an alternative cause for LV dysfunction**

| **N=201** | **N (%)** | **Examples** |
|---|---|---|
| Any pre-existing cardiomyopathy (e.g. HCM, DCM, restrictive CM) or de novo inherited cardiomyopathy (as for pre-existing, except for DCM) | 65 (32.3) | Hypertrophic cardiomyopathy, Fabry disease |
| Coronary artery disease | 37 (18.4) | Ischaemic heart disease, spontaneous coronary artery dissection |
| Congenital or valvular heart disease | 47 (23.4) | Transposition of the great arteries, septal defects, rheumatic valvular disease, heart valve replacement |
| LV dysfunction secondary to a systemic condition | 52 (25.9) | Major haemorrhage, vasculitis, severe sepsis with confirmed bacteraemia, end stage advanced renal disease, phaeochromocytoma, proven myocarditis |

Next, women with validated PPCM, in combination with those excluded, were examined to determine the sensitivity and specificity of different combinations of ICD discharge codes; these different combinations (A to L) are shown in Table 3-3. In the sensitivity and specific calculations, only incident cases were included (the original cohort comprised all women with a code for PPCM, heart failure or cardiomyopathy around the time of a pregnancy, irrespective of previous history). As many discharge diagnoses include symptoms (e.g. first in the list of diagnoses is 'chest pain' or 'breathlessness'), first diagnostic position alone was not examined. Similarly, as complications such as thromboembolism are common in women with PPCM, it is plausible that a complication could be listed in the first diagnostic position.

In each case, the codes which were not present (in either the first and second diagnostic position, or in any diagnostic position) were the same in each combination:

- I21 & I22 (myocardial infarction)
- I421 & I422 (hypertrophic CM)
- I423 (eosinophilic myocarditis)
- I424 (endocardial fibroelastosis)
- I425 (restrictive CM)
- I426 (alcoholic CM)
- I427 (CM due to exogenous agents)
- I43 (CM secondary to systemic disease)
- I255 (ischaemic CM)
- I270 (primary pulmonary hypertension)
- I05 & I06 & I07 (rheumatic valvular disease)
- Q2 (CV congenital heart disease)

**Table 3-3 Sensitivity and specificity of different combinations of ICD-10 discharges codes**

| Combination | ICD 10 code(s) PRERSENT | | ICD 10 code(s) NOT PRESENT | | Specificity (%) | Sensitivity (%) | Youden's J statistic |
|---|---|---|---|---|---|---|---|
| | First or second position | Any position | First or second position | Any position | | | |
| **A – D codes present:** O903 (PPCM) | | | | | | | |
| A | | | | | 93.1 | 41.8 | 0.35 |
| B | | | | | 94.1 | 33.8 | 0.28 |
| C | | | | | 94.1 | 33.3 | 0.27 |
| D | | | | | 93.1 | 42.3 | 0.35 |
| **E – H codes present:** O903 (PPCM), I420 (dilated CM), I428 (other CM), I429 (unspecified CM) | | | | | | | |
| E | | | | | 77.7 | 72.6 | 0.50 |
| F | | | | | 84.2 | 60.7 | 0.45 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| G | | | | | 84.2 | 59.7 | 0.44 |
| H | | | | | 77.7 | 74.1 | 0.52 |
| I – L codes present: O903 (PPCM), I420 (dilated CM), I428 (other CM), I429 (unspecified CM), I50 (heart failure) | | | | | | | |
| I | | | | | 34.7 | 92.0 | 0.27 |
| J | | | | | 56.4 | 76.6 | 0.33 |
| K | | | | | 58.4 | 74.6 | 0.33 |
| L | | | | | 30.2 | 94.5 | 0.25 |

In order to maximise identification of women with PPCM in the unvalidated group (i.e. concentrating on sensitivity), the combination of diagnostic codes represented by 'Combination I' was applied (sensitivity 92%, specificity 35%), resulting in the exclusion of a further 2 unvalidated cases. 'Combination I' was chosen over 'Combination L' due to a greater increase in specificity at the expense of a smaller reduction in sensitivity. The combination which resulted in the highest Youden's J statistic yielded a sensitivity of 74% and specificity of 78%.

The final cohort included in the study comprised 225 women with PPCM, with 90% validation. Of the 225, 113 (50%) women had a code for PPCM (O903) at any time.

**Differences in women with and without case validation**

Compared to women with case validation, those without validation were more often from the first half of the study (1998-2007), more often had pregnancy-induced hypertension and pre-eclampsia, and had a shorter duration of pregnancy. There were no differences in age, health board, socioeconomic deprivation quintile, multiple gestation, or mode of delivery.

**England**

In England, application of the combination diagnostic codes in 'Combination I', resulted in the identification of 2091 women with a first admission between 2003 and 2017 with unvalidated PPCM (only women aged 50 or younger). In the English cohort, because of the inability to perform validation, cases from 2003 onwards only were identified to allow a minimum 5-year 'lookback' period and the exclusion codes displayed in Table 3-3 were applied back to 1998.

## *3.3.2 Incidence of PPCM in Scotland*

**Crude incidence**

From 1998 to 2017, the total number of women with incident PPCM in Scotland was 225 from 1,113,266 deliveries with a crude incidence of 2.02 (95% CI 1.76-2.29) per 10,000 deliveries (Table 3-4). The incidence was similar irrespective of whether an inclusion threshold of 6 months (n=197), 1 year (n=209) or 2 years (n=225) after delivery was applied; in total, 88% of women included were hospitalised with PPCM within 6 months after delivery and 93% within 1 year (Figure 3-3 and Table 3-4). The mean age at the time of diagnosis in all women was 31.9 years (95% CI 31.6-32.1) and increased from 30.7 years (95% CI 28.7-32.6) to 32.1 years (95% CI 30.5-33.8) between 1998 and 2017.

The crude incidence increased over time from 1.60 (95% CI 1.12-2.07) per 10,000 deliveries in 1998-2002 to 2.22 (95% CI 1.66-2.77) per 10,000 deliveries in 2013-2017, with an incidence rate in 2013-2017 1.39 (95% CI 0.94-2.05) times that of 1998-2002 (Figure 3-3 and Table 3-4).

**Figure 3-3 Crude incidence of PPCM per 10,000 deliveries and age at delivery in Scotland from 1998 to 2017**

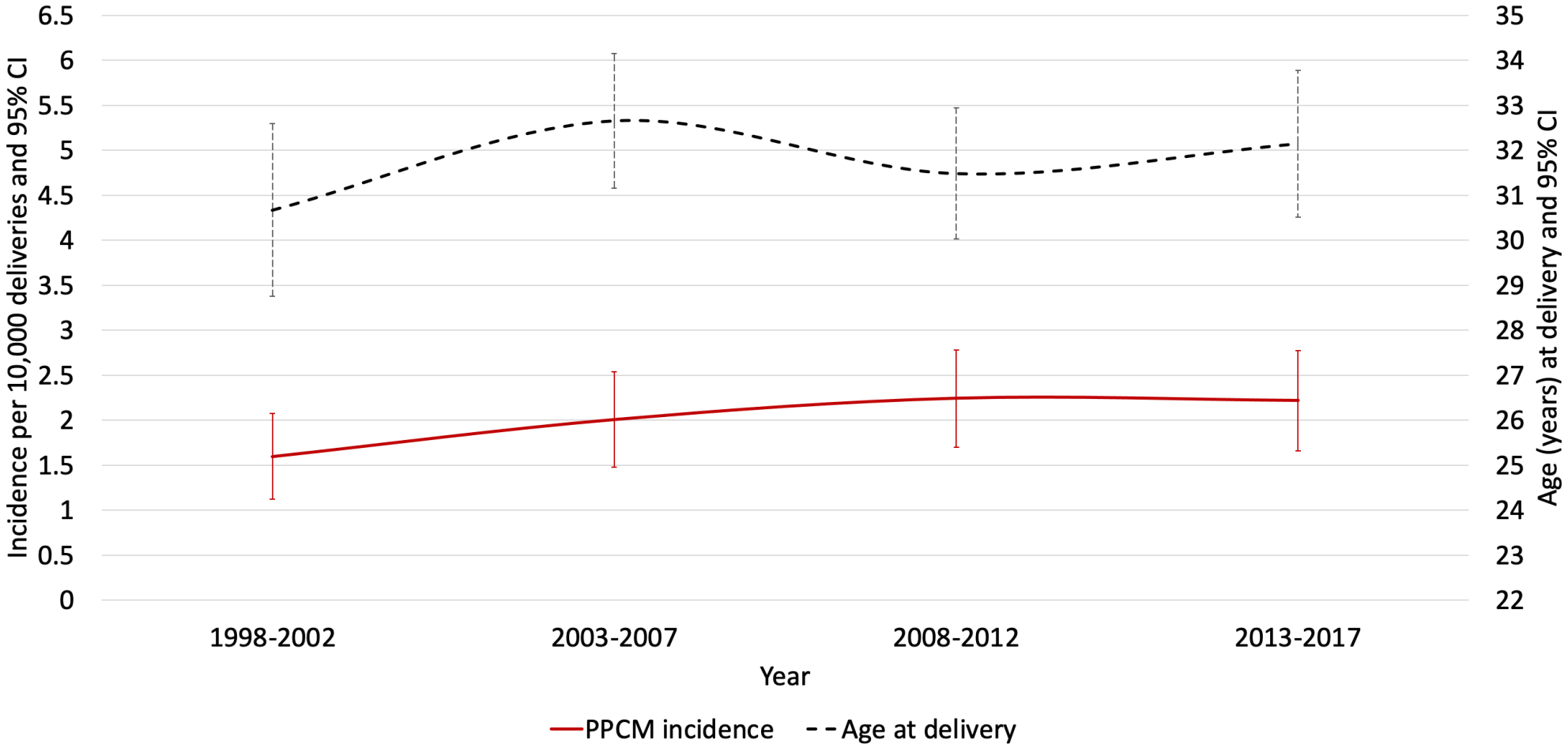
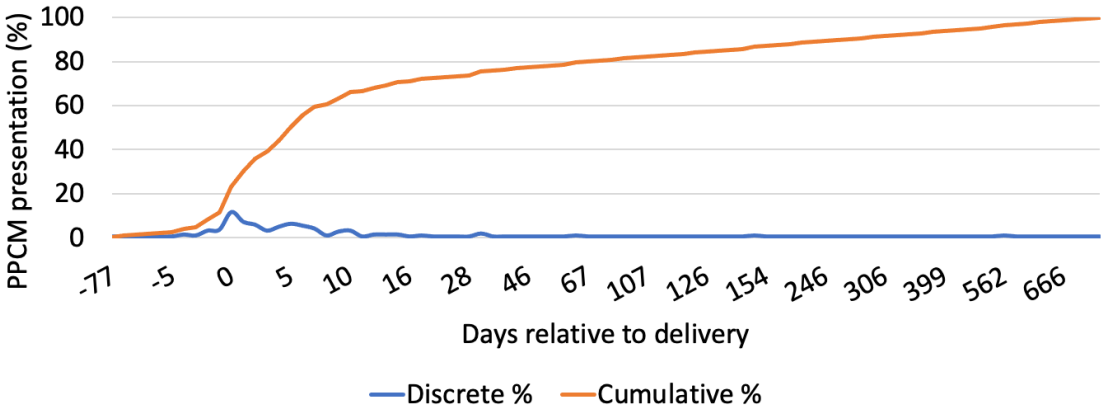


**Table 3-4 Incidence rates and incidence rate ratios of PPCM per 10,000 deliveries in Scotland from 1998 to 2017**

| | Crude incidence | | | | | | | | | Age-standardised incidence | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Up to 6 months postpartum N=197 | | | Up to 1 year postpartum N=209 | | | Up to 2 years postpartum N=225 | | | All N=225 | |
| Year | No. (%) | Rate (95% CI) | IRR (95% CI) | No. (%) | Rate (95% CI) | IRR (95% CI) | No. (%) | Rate (95% CI) | IRR (95% CI) | Rate (95% CI) | IRR (95% CI) |
| 1998-2002 | 37 (18.8) | 1.37 (0.93-1.82) | 1 | 40 (19.1) | 1.49 (1.02-1.95) | 1 | 43 (19.1) | 1.60 (1.12-2.07) | 1 | 1.68 (1.18-2.18) | 1 |
| 2003-2007 | 50 (25.4) | 1.82 (1.32-2.33) | 1.33 (0.87-2.03) | 50 (23.9) | 1.82 (1.32-2.33) | 1.23 (0.81-1.86) | 55 (24.4) | 2.01 (1.48-2.54) | 1.26 (0.84-1.87) | 1.99 (1.47-2.52) | 1.18 (0.80-1.77) |
| 2008-2012 | 54 (27.4) | 1.83 (1.34-2.32) | 1.33 (0.88-2.03) | 58 (27.8) | 1.97 (1.46-2.48) | 1.33 (0.89-1.98) | 66 (29.3) | 2.24 (1.70-2.78) | 1.40 (0.96-2.06) | 2.25 (1.71-2.80) | 1.34 (0.91-1.97) |
| 2013-2017 | 56 (28.4) | 2.03 (1.50-2.57) | 1.48 (0.98-2.24) | 61 (29.2) | 2.22 (1.66-2.77) | 1.49 (1.00-2.22) | 61 (27.1) | 2.22 (1.66-2.77) | 1.39 (0.94-2.05) | 2.20 (1.65-2.76) | 1.31 (0.89-1.94) |
| **Overall** | 197 | 1.77 (1.52-2.02) | | 209 | 1.88 (1.62-2.13) | | 225 | 2.02 (1.76-2.29) | | 2.04 (1.77-2.31) | |

In the majority of women, the hospitalisation with PPCM had occurred by the early postpartum period (70% by day 14 postpartum and 75% by 1 month postpartum) (Figure 3-4).

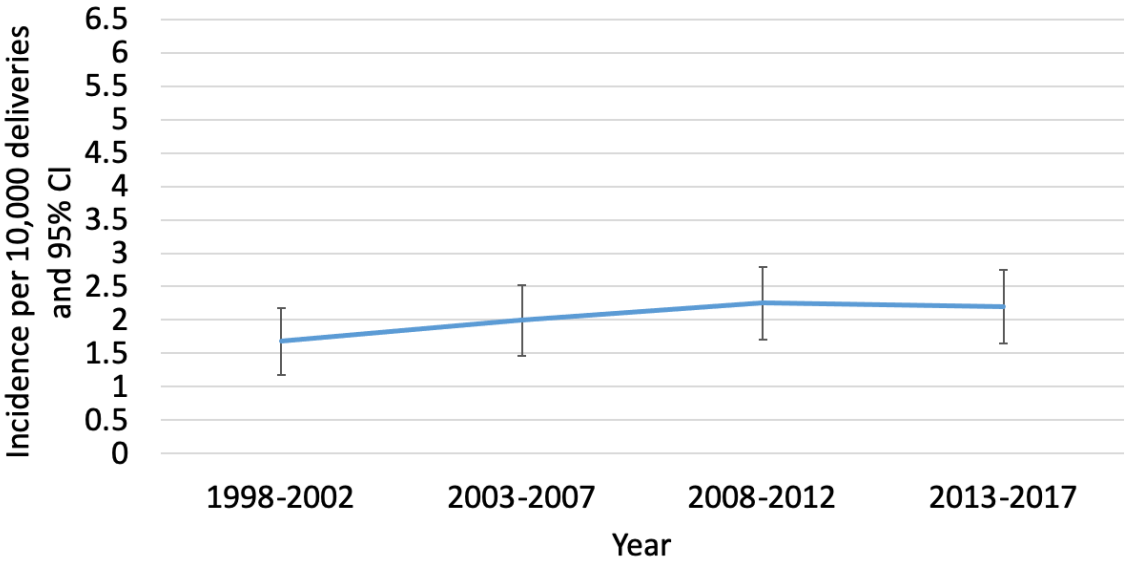
**Figure 3-4 The timing of the PPCM presentation relative to the end of pregnancy**




**Age-standardised incidence**

The age-standardised incidence of PPCM during the 20-year study was 2.04 (95% CI 1.77-2.31) per 10,000 deliveries. The incidence rate per 10,000 deliveries in 1998-2002 was 1.68, (95% CI 1.18-2.18) and in 2013-2017 was 2.20 (95% 1.65-2.76), with IRR 1.31 (95% CI 0.89-1.94) (Figure 3-5 and Table 3-4).

**Figure 3-5 Age-standardised incidence of PPCM per 10,000 deliveries in Scotland from 1998 to 2017**



### Incidence stratified by age

When stratified by age group, the overall incidence of PPCM per 10,000 deliveries during the study was higher in women aged above 32 years (3.34, 95% CI 2.90-3.78) than in women aged 32 years or less (1.45, 95% CI 1.26-1.64) (Figure 3-6 and Table 3-5). In women in the older age group, the incidence per 10,000 deliveries increased from 2.53 (95% CI 1.77-3.29) in 1998-2002 to 3.66 (95% CI 2.74-4.57) in 2013-2107 (IRR 1.44, 95% CI 0.81-2.56). In younger women, the incidence per 10,000 deliveries increased from 1.26 (95% CI 0.89-1.64) in 1998-2002 to 1.52 (95% CI 1.13-1.90) in 2013-2017 (IRR 1.20, 95% CI 0.70-2.06).

**Figure 3-6 Incidence of PPCM per 10,000 deliveries in Scotland from 1998 to 2017 according to age**

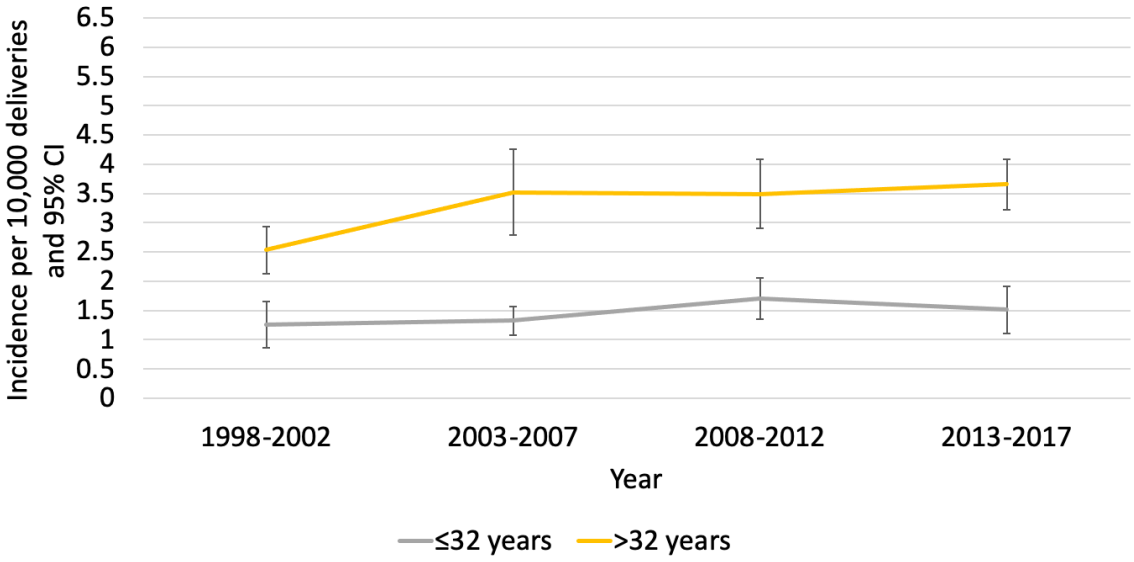


**Table 3-5 Incidence rates and incidence rate ratios of PPCM per 10,000 deliveries in Scotland from 1998 to 2017 according to age**

| | Age ≤32 years N=113 | | | Age >32 years N=112 | | |
|---|---|---|---|---|---|---|
| Year | No. (%) | Rate (95% CI) | IRR (95% CI) | No. (%) | Rate (95% CI) | IRR (95% CI) |
| 1998-2002 | 25 (22.1) | 1.26 (0.89-1.64) | 1 | 18 (16.1) | 2.53 (1.77-3.29) | 1 |
| 2003-2007 | 25 (22.1) | 1.32 (0.97-1.67) | 1.05 (0.60-1.83) | 30 (26.8) | 3.52 (2.59-4.45) | 1.39 (0.78-2.50) |
| 2008-2012 | 35 (31.0) | 1.70 (1.29-2.11) | 1.35 (0.81-2.25) | 31 (27.7) | 3.49 (2.65-4.33) | 1.38 (0.77-2.47) |
| 2013-2017 | 28 (24.8) | 1.52 (1.13-1.90) | 1.20 (0.70-2.06) | 33 (29.5) | 3.66 (2.74-4.57) | 1.44 (0.81-2.56) |
| **Overall** | 113 | 1.45 (1.26-1.64) | | 112 | 3.34 (2.90-3.78) | |

*IRR = incidence rate ratio*

**Sensitivity analyses**

In order to assess the change in incidence rates and to allow comparison with other reported incidences globally (accounting for potential differences in inclusion criteria), two sensitivity analyses were conducted. First, unvalidated cases of PPCM were excluded and, second, women with an LVEF above 45% (or a qualitative assessment of mild LV dysfunction) were excluded. Over 20 years, the age-standardised incidence of PPCM per 10,000 deliveries in only validated cases (n=202) was 1.83 (95% CI 1.58-2.08) and in only women with a baseline LVEF below or equal to 45% (n=155) was 1.40 (95% CI 1.18-1.62) (Table 3-6). The corresponding incidence rates for the most recent year group (2013-2017) were 2.20 (95% CI 1.65-2.76) for women with validated PPCM and 1.66 (95% CI 1.18-2.13) for women with an LVEF equal to or below 45%.

**Table 3-6 Age standardised incidence rates of PPCM per 10,000 deliveries in Scotland from 1998 to 2017 in a) validated cases of PPCM and b) women with at least moderate LV dysfunction**

| | Validated cases of PPCM N=202 | | | Baseline LVEF ≤45% N=155 | | |
|---|---|---|---|---|---|---|
| **Year** | **No. (%)** | **Rate (95% CI)** | **IRR (95% CI)** | **No. (%)** | **Rate (95% CI)** | **IRR (95% CI)** |
| 1998-2002 | 30 (14.9) | 1.16 (0.75-1.58) | 1 | 24 (15.5) | 0.90 (0.54-1.25) | 1 |
| 2003-2007 | 46 (22.8) | 1.66 (1.18-2.14) | 1.43 (0.90-2.26) | 39 (25.2) | 1.41 (0.97-1.85) | 1.57 (0.94-2.61) |
| 2008-2012 | 65 (32.2) | 2.22 (1.68-2.76) | 1.91 (1.24-2.94) | 46 (29.7) | 1.57 (1.12-2.02) | 1.75 (1.07-2.87) |
| 2013-2017 | 61 (30.2) | 2.20 (1.65-2.76) | 1.90 (1.22-2.94) | 46 (29.7) | 1.66 (1.18-2.13) | 1.85 (1.13-3.03) |
| **Overall** | 202 | 1.83 (1.58-2.08) | | 155 | 1.40 (1.18-1.62) | |

*IRR = incidence rate ratio*

### *3.3.3 Incidence of PPCM in England*

**Crude incidence**

In England, a total of 2091 women were hospitalised with incident PPCM from 2003 to 2017, with 9,863,883 deliveries in this time. The crude incidence was 2.12 (95% CI 2.03-2.21) per 10,000 deliveries (Figure 3-7 and Table 3-7). Similar to the findings in Scotland, the incidence did not differ much according to the time at which inclusion was capped (i.e. 6 months, 1 year or 2 years postpartum), with 1929 (92%) of all women included in the study hospitalised up to 6 months after delivery and 2033 (97%) up to 1 year (Table 3-7). The mean age at the time of diagnosis in all women was 31.2 years (95% CI 30.9-31.5) and was similar at the start and end of the study.

Data on age-stratified total numbers of deliveries were unavailable in England prior to 2013, thus age-standardisation was not performed. However, age-standardisation had little effect on the overall incidence rate for the 20-year study period in the Scottish cohort.

There was an increase in incidence per 10,000 deliveries over time from 1.26 (95% CI 0.98-1.55) in 2003 to 3.13 (95% CI 2.70-3.56) in 2017 with an incidence rate in 2017 2.47 (95% CI 1.90-3.22) times that of 2003 (Figure 3-7 and Table 3-7).

In order to examine the incidence in England in parallel with that of Scotland, equivalent year groups were generated. The incidence per 10,000 deliveries in the final year group, 2013-2017, was 2.94 (95% CI 2.76-3.13), as compared with 1.37 (95% CI 1.24-1.50) in the earliest year group, 2003-2007, with an incidence rate ratio of 2.15 (95% CI 1.92-2.41) (Table 3-7).

**Figure 3-7 Crude incidence of PPCM per 10,000 deliveries and age at hospitalisation in England from 2003 to 2017 according to timing of diagnosis**

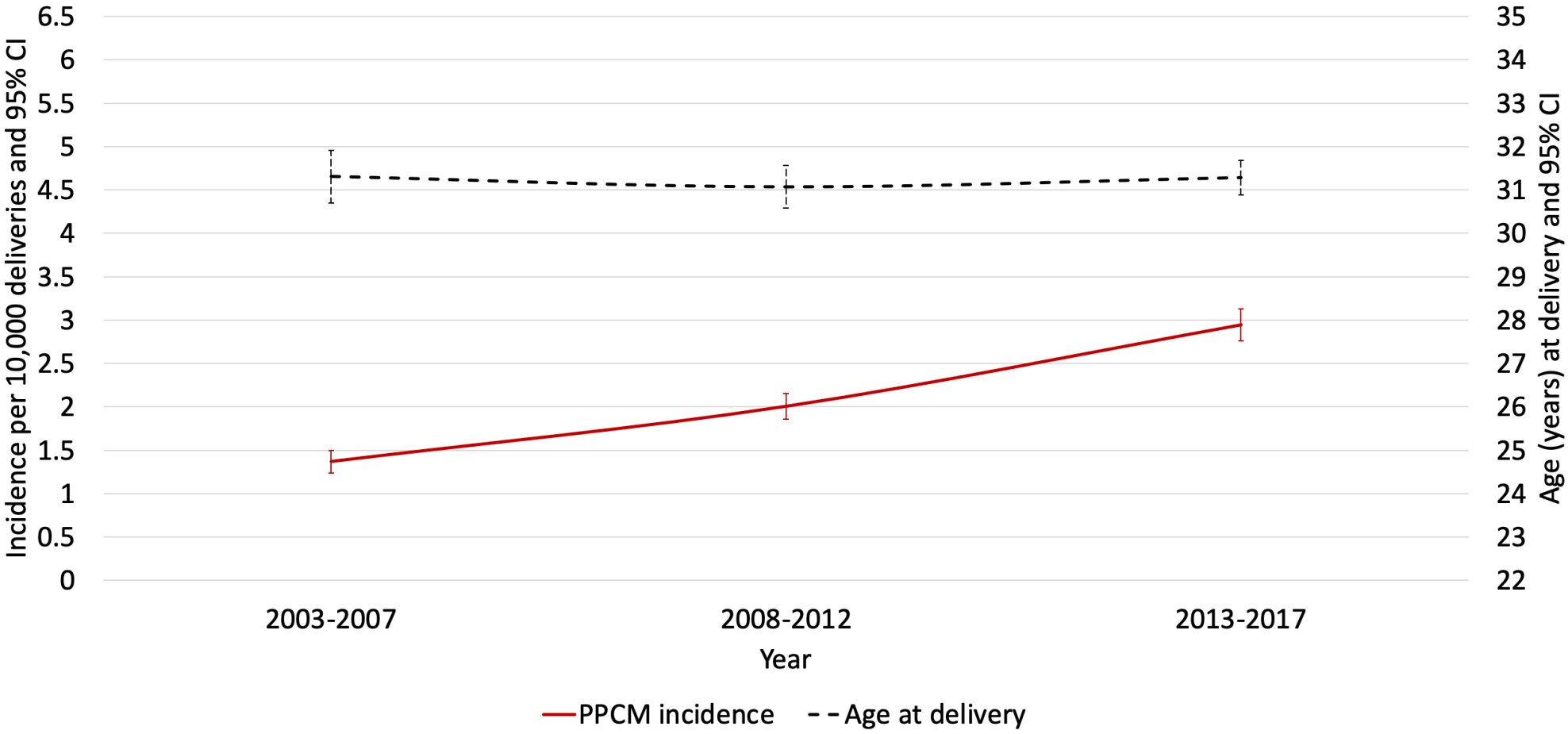


**Table 3-7 Incidence rates and incidence rate ratios of PPCM per 10,000 deliveries in England from 2003 to 2017**

| | Up to 6 months postpartum | | | Up to 1 year postpartum | | | Up to 2 years postpartum | | |
|---|---|---|---|---|---|---|---|---|---|
| | N=1929 | | | N=2033 | | | N=2091 | | |
| | No. (%) | Rate (95% CI) | IRR (95% CI) | No. (%) | Rate (95% CI) | IRR (95% CI) | No. (%) | Rate (95% CI) | IRR (95% CI) |
| **Year** | | | | | | | | | |
| 2003 | 69 (3.6) | 1.16 (0.89-1.44) | 1 | 73 (3.6) | 1.23 (0.95-1.51) | 1 | 75 (3.6) | 1.26 (0.98-1.55) | 1 |
| 2004 | 72 (3.7) | 1.18 (0.91-1.45) | 1.01 (0.73-1.41) | 79 (3.9) | 1.29 (1.01-1.58) | 1.05 (0.76-1.45) | 81 (3.9) | 1.33 (1.04-1.62) | 1.05 (0.77-1.44) |
| 2005 | 75 (3.9) | 1.22 (0.94-1.49) | 1.05 (0.75-1.45) | 78 (3.8) | 1.27 (0.98-1.55) | 1.03 (0.75-1.42) | 81 (3.9) | 1.31 (1.03-1.60) | 1.04 (0.76-1.42) |
| 2006 | 85 (4.4) | 1.33 (1.05-1.61) | 1.14 (0.83-1.57) | 92 (4.5) | 1.44 (1.15-1.73) | 1.17 (0.86-1.59) | 97 (4.6) | 1.52 (1.22-1.82) | 1.20 (0.89-1.62) |
| 2007 | 85 (4.4) | 1.29 (1.02-1.56) | 1.11 (0.81-1.52) | 88 (4.3) | 1.34 (1.06-1.61) | 1.09 (0.80-1.48) | 93 (4.4) | 1.41 (1.12-1.70) | 1.12 (0.82-1.51) |
| 2008 | 92 (4.8) | 1.36 (1.08-1.64) | 1.17 (0.86-1.60) | 99 (4.9) | 1.46 (1.18-1.75) | 1.19 (0.88-1.61) | 101 (4.8) | 1.49 (1.20-1.78) | 1.18 (0.88-1.59) |
| 2009 | 119 (6.2) | 1.76 (1.45-2.08) | 1.52 (1.13-2.04) | 125 (6.1) | 1.85 (1.53-2.18) | 1.51 (1.13-2.01) | 126 (6.0) | 1.87 (1.54-2.19) | 1.48 (1.11-1.97) |
| 2010 | 133 (6.9) | 1.93 (1.60-2.25) | 1.66 (1.24-2.22) | 140 (6.9) | 2.03 (1.69-2.36) | 1.65 (1.24-2.19) | 144 (6.9) | 2.09 (1.74-2.43) | 1.65 (1.25-2.18) |
| 2011 | 141 (7.3) | 2.04 (1.70-2.37) | 1.75 (1.31-2.34) | 146 (7.2) | 2.11 (1.77-2.45) | 1.72 (1.30-2.27) | 151 (7.2) | 2.18 (1.83-2.53) | 1.73 (1.31-2.28) |
| 2012 | 151 (7.8) | 2.16 (1.82-2.51) | 1.86 (1.40-2.47) | 159 (7.8) | 2.28 (1.92-2.63) | 1.85 (1.40-2.44) | 166 (7.9) | 2.38 (2.02-2.74) | 1.88 (1.43-2.47) |
| 2013 | 164 (8.5) | 2.46 (2.08-2.83) | 2.11 (1.59-2.80) | 176 (8.7) | 2.64 (2.25-3.03) | 2.14 (1.63-2.81) | 183 (8.8) | 2.74 (2.34-3.14) | 2.17 (1.66-2.84) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 2014 | 156 (8.1) | 2.35 (1.98-2.72) | 2.02 (1.52-2.68) | 169 (8.3) | 2.54 (2.16-2.93) | 2.07 (1.57-2.72) | 176 (8.4) | 2.65 (2.26-3.04) | 2.10 (1.60-2.75) |
| 2015 | 183 (9.5) | 2.74 (2.34-3.14) | 2.36 (1.79-3.11) | 187 (9.2) | 2.80 (2.40-3.20) | 2.28 (1.74-2.98) | 192 (9.2) | 2.88 (2.47-3.28) | 2.28 (1.74-2.97) |
| 2016 | 209 (10.8) | 3.14 (2.71-3.56) | 2.70 (2.06-3.54) | 220 (10.8) | 3.30 (2.87-3.74) | 2.68 (2.06-3.50) | 222 (10.6) | 3.33 (2.89-3.77) | 2.64 (2.03-3.43) |
| 2017 | 195 (10.1) | 3.00 (2.58-3.42) | 2.58 (1.96-3.40) | 202 (9.9) | 3.11 (2.68-3.54) | 2.53 (1.93-3.30) | 203 (9.7) | 3.13 (2.70-3.56) | 2.47 (1.90-3.22) |
| **Overall** | 1929 | 1.96 (1.87-2.04) | | 2033 | 2.06 (1.97-2.15) | | 2091 | 2.12 (2.03-2.21) | |
| | | | | | | | | | |
| **Year** | | | | | | | | | |
| 2003-2007 | 386 (20.0) | 1.24 (1.11-1.36) | 1 | 410 (20.2) | 1.31 (1.19-1.44) | 1 | 427 (20.4) | 1.37 (1.24-1.50) | 1 |
| 2008-2012 | 636 (33.0) | 1.85 (1.71-2.00) | 1.50 (1.32-1.70) | 669 (32.9) | 1.95 (1.80-2.10) | 1.48 (1.31-1.68) | 688 (32.9) | 2.01 (1.86-2.16) | 1.46 (1.30-1.65) |
| 2013-2017 | 907 (47.0) | 2.74 (2.56-2.91) | 2.21 (1.96-2.49) | 954 (46.9) | 2.88 (2.70-3.06) | 2.19 (1.95-2.46) | 976 (46.7) | 2.94 (2.76-3.13) | 2.15 (1.92-2.41) |

## 3.4 Discussion

In this population-level incidence estimate of PPCM from the UK, including 225 women in Scotland and 2091 women in England, the crude incidence rate of PPCM was 2.02 (95% CI 1.76-2.29) per 10,000 deliveries (or 1 in 4950) in Scotland over 20 years, and 2.12 (95% CI 2.03-2.21) per 10,000 deliveries (or 1 in 4717) in England over 15 years. In Scotland, the incidence was notably higher in older women (those over 32 years). Examining the sensitivity and specificity of different combinations of ICD-10 codes in the Scottish cohort demonstrated that the ICD-10 code for PPCM (O903) had a high specificity (93-94%), but low sensitivity (33-42%) when certain exclusions were applied. Combining this code with codes for non-specific cardiomyopathies (I420, I428, I429) and heart failure (I50) was highly sensitive.

The incidence of PPCM varies markedly by geographical location, with rates as high as 1 in 100 deliveries in certain parts of Nigeria[5, 30], and as low as 1 in 20,000 in Japan[36]. The largest body of published research is from North America, where incidence rates range from 1 in 1000-5000[7, 8, 25-27, 9, 12, 13, 20-24]. Such contrasting rates are likely explained by a number of factors; differences in study design, with some studies conducted in a single-centre and only few at population-level, non-consecutive inclusion, lack of validation or use of a standardised definition (particularly in those which utilised administrative or 'big data' sources), or the absence of a formal definition of PPCM altogether. As demonstrated in Table 1-2 in the Introduction chapter, in those studies which use ICD coding to identify cases of PPCM, there is variability in the codes included. True differences attributable to genetic, ethnic and cultural diversity may also play a part. It is possible that the incidence of PPCM is underestimated globally, since women are often only diagnosed when signs and symptoms are severe enough to warrant hospital admission. It seems like that there may be a proportion of women who have less severe cardiac dysfunction which remains undiagnosed (perhaps even for years).

In Europe, there are only two country-level studies reporting incidence - one from Denmark and one from Sweden, with an incidence in Sweden double that of Denmark (1 in 5719 and 1 in 10,149 deliveries, respectively)[18, 19]. The discordance between these two studies, despite the countries neighbouring one

another, may be driven by differences in methods and inclusion criteria applied in each. In the study from Sweden, administrative datasets were combined and incidence was calculated from 1997-2010. Cases were not validated against a standardised definition requiring confirmation of the presence of LV systolic impairment and systematic, adjudicated exclusion of other causes for heart failure. Furthermore, the cohort included in the Swedish study was not comprised exclusively of women with PPCM, but also included women with diagnostic codes corresponding to alternative types of cardiomyopathy, such as hypertrophic cardiomyopathy and restrictive cardiomyopathy. If the incidence was calculated for those women with the ICD-10 code for PPCM, the estimate would have changed to 1 in 29,326 (47 cases in 1,378,351 deliveries). The authors conclude that this is likely to be an underestimation of the true incidence since an audit of a subset of the cohort showed that alternative ICD-10 codes for cardiomyopathy and heart failure were used more often that a code for PPCM. In keeping with this, in the current study, only 50% of the final cohort had a PPCM ICD-10 code at any time. The PPCM ICD-10 code (O903) had a high specificity, but low sensitivity. In the study from Denmark, potential cases of PPCM were identified from administrative datasets, and cases were validated against the European Society of Cardiology PPCM Study Group definition. The stringent exclusion of women, after review of the clinical details, is likely to explain the lower incidence rate there compared to Sweden.

The findings in this study are the first of their kind, with no previous published data on PPCM from the UK. Over the 20- and 15-year study periods in Scotland and England, respectively, the overall incidence rates in both countries were similar at approximately 1 in 5000 deliveries. Despite comparable study methodology, including case review and validation, the incidence was double that seen in Denmark. There are a number of possible explanations for this. First is the inclusion of unvalidated cases in the present study, unlike the Danish study, in which women with records that were unable to be reviewed (n=12) were consequently excluded. If, in fact, these women had met the definition of PPCM, the reported incidence in Denmark would have been much higher at 1 in 8480 (73 cases in 619,084 deliveries). Second is the less stringent inclusion criteria applied in the present study, also including women with mild LV dysfunction, as well as those diagnosed up to 2 years postpartum (although the majority of women included were diagnosed within 1 year). When the subgroup

of women with at least moderate LV dysfunction were examined, the incidence was closer to that in Denmark (1 in 7092 deliveries). Third is the possibility that true epidemiological differences exist between the different regions and that PPCM is more common in the UK than in Denmark and Sweden. In the present study, the incidence of PPCM was higher in women aged above 32 years. Comparing age with other European studies, women with PPCM in Scotland and England were a similar age to those in Sweden and Denmark, with the mean age of all women across the studies being 31-33 years. In other studies from Europe (not population-level), the mean age of women in a German PPCM registry[66], and in a single-centre case-series in the Republic of Ireland[147], was 34 years. There could also be regional differences in the prevalence of comorbidities which predispose a woman to PPCM.

The present study also established an upward trend in incidence over time in Scotland and England. Only a small number of studies have reported temporal trends in PPCM[8, 12, 33]. The upward trend in incidence may be due to risk factors for the condition becoming more common, such as obesity or hypertensive disorders, increasing maternal age, or a greater frequency of twin pregnancies (Chapter 4 of this thesis will focus on factors associated with PPCM in the Scottish population). Although age at diagnosis rose in Scotland, it remained relatively static in England, despite an increasing prevalence. There is also the possibility that the change in incidence rates over time reflects a greater awareness of the condition amongst health care providers looking after pregnant and postpartum women. In recent years, there has been more intense focus on maternal morbidity and mortality and improving strategies to reduce adverse maternal outcomes. In the UK, the 'Saving Lives, Improving Mothers' Care' programme, which regularly reports on causes of maternal death, found that nearly a quarter of all maternal deaths were due to cardiac disease[184]. Avoiding preventable deaths by improved recognition and appropriate escalation is a major public health target. Other changes which may have resulted in increase awareness of PPCM include the introduction of the ESC PPCM Study Group definition in 2010, as well as publications providing guidance on diagnosis and management[3]. Lastly, improvements in the accuracy of discharge coding within the administrative datasets used in the study might, in part, explain this observation.

The final finding of this chapter worthy of discussion relates to the sensitivity and specificity of the ICD-10 diagnostic codes for PPCM, heart failure and DCM. The PPCM code itself was found to be highly specific, but much less sensitive, whereas also including codes for non-specific DCM and heart failure resulted in a high level of sensitivity, but a reduction in specificity. PPCM occurs in approximately 0.02% of pregnancies in the UK. In future, application of these findings may facilitate monitoring of population-level trends in incidence and outcomes for these women, using the same linked population-level administrative datasets. In this way, future epidemiological research could be conducted without the requirement for case validation.

There are some limitations of these analyses. Due to the time frame included in the study, it was not possible to validate all cases; this was largely due to older patient records having been destroyed. However, this was addressed by application of sensitivity/specificity criteria generated from reviewed cases to exclude those individuals who were unlikely to be women with 'true' PPCM. Similarly, case validation was not possible in England, but the closely aligned incidence rates are encouraging. Due to differences in methodology and disease definitions, drawing direct comparisons in incidence rates with other cohorts is difficult, but a number of sensitivity analyses were conducted to assess the impact of this. In the future, a standardised definition, with not only inclusion criteria, but also explicit exclusion criteria, will facilitate a more standardised approach to identifying women with the condition, particularly in a research context. In the future, it is likely this definition will incorporate other parameters, such as natriuretic peptide levels, and no longer include the arbitrary thresholds of LVEF (<45%) and time frame (<6 months postpartum).

## 3.5 Summary

PPCM occurred in approximately 1 in 5000 deliveries in both Scotland and England over a 20- and 15-year period, respectively. The incidence increased during the study period in both Scotland and England, although this was not a statistically significant difference in Scotland. The combination of ICD-10 codes for PPCM, dilated or 'other' cardiomyopathy and heart failure, with comprehensive exclusion codes, was highly sensitive for PPCM, while the PPCM ICD-10 code alone, O903, was highly specific. In future, these findings could be used to facilitate ongoing PPCM research at population-level, using routine administrative datasets.

# Chapter 4 Baseline characteristics and risk factors

## 4.1 Introduction and aims

There is heterogeneity in the phenotype of PPCM across the world. In the ESC PPCM Registry, the only international observational study of women with PPCM, demographics, comorbidities and clinical presentation differed across the four regions described[11]. Compared to women from other regions, women from Europe were older, more often White, had a greater prevalence of diabetes and smoking, lower parity and tended to have less evidence of congestion (peripheral and pulmonary). However, only a small proportion of women enrolled from Europe were from the UK, and recruitment was highly selective, favouring enrolment of women from specialist and/or tertiary centres, by investigators with an interest in the condition. Moreover, no studies from Europe, in which the demographics of patients may be distinct from other regions, have examined factors associated with the development of PPCM, in a systematic fashion.

The focus of this chapter is on describing the characteristics of women with PPCM in Scotland, including demographics, comorbidities, obstetric history, details of delivery, and clinical features. The second half is dedicated to the identification of factors associated with the development of PPCM in the Scottish population.

# 4.2 Methods

## *4.2.1 Study population*

Analyses were conducted in 225 women with PPCM. A total of 2240 matched controls were identified using the following criteria:

- Women with a delivery, matched to age at delivery, year of delivery ± 1 year, and health board in Scotland where the delivery took place

- Without a prior discharge diagnosis of PPCM, heart failure or cardiomyopathy (i.e. no prior admission to hospital with any of the codes used to identify possible cases)

Women who delivered at the Golden Jubilee National Hospital were matched to controls from NHS Greater Glasgow and Clyde.

Full matching criteria was possible in 217/225 (96%) women. In the remaining 8 women, the health board criterion was removed in order to identify a sufficient number of controls. In two women, 5 controls, rather than 10, were identified.

## *4.2.2 Data sources and definitions*

Table 4-1 summarises the data sources used, and Table 4-2 provides definitions used in this chapter. The methods used to categorise echocardiographic data are also shown in Table 4-2.

**Table 4-1 Data sources**

| Variable | Source(s) | Description |
|---|---|---|
| Age | SMR | Age at delivery. |
| Socioeconomic deprivation quintile | Scottish Index of Multiple Deprivation 2016 quintiles | If missing for the pregnancy or PPCM admission of interest, data obtained from an alternative admission (closest temporally available). |

| | | |
|---|---|---|
| Height and weight | SMR + patient records | Height and weight at booking visit captured as part of SMR02. If missing, data obtained from patient records where available (for cases only). |
| Smoking | SMR + patient records | Smoking status at booking visit captured as part of SMR02. If missing, data obtained from patient records where available (for cases only). Smoking defined as current or former smoker. |
| Comorbidities | SMR | Lookback for SMR admissions with ICD-9 or ICD-10 codes of interest back to 1981, prior to the index delivery. |
| Obstetric data | SMR + patient records | Captured as part of the SMR02 delivery record. If missing, data obtained from patient records where available (for cases only). |
| Clinical features and management | Patient records | E.g. clinical signs, haemodynamic support, intra-aortic balloon pump. For cases only. |
| Diagnostic tests/investigations | Patient records | E.g. laboratory, electrocardiographic and echocardiographic parameters. For cases only. |
| Timing of diagnosis | Patient records | E.g. pre- or postpartum. Timing obtained from patient records in order to ensure accuracy; for example, in the event that heart failure developed during the index maternity admission, the timing of onset in relation to the delivery would not be clear from the SMR02 dataset. |

**Table 4-2 Definitions**

| Terms | Definition |
|---|---|
| Date of end of pregnancy | The date of delivery where a delivery outcome occurred, or the date of admission to hospital in the event of a terminated pregnancy. |
| Conditions during current pregnancy | Any SMR02 admission in a 9-month lookback prior to the date of the end of pregnancy and up to 1 month afterwards.<br><br>Dates are recorded as MMYYYY; therefore, the number of months may not always be an exact equivalent number of days (e.g. '1 month' may not be exactly 30 days).<br><br>As a sensitivity analysis, a lookback of 6 months was examined to ensure obstetric diagnoses during pregnancy were not being overestimated. Of all obstetric comorbidities, this only changed the proportion of antepartum haemorrhage (by 12%). Given this generally occurs in the first trimester, so as not to underestimate the prevalence, the '9-month' lookback was used.<br><br>Women with PPCM with a termination were examined specifically to ensure that a '9 month' lookback did not erroneously identify obstetric comorbidities during the pregnancy. |
| Prior pregnancy | Any SMR02 admission prior to the time period used to define the current pregnancy (see above). |
| Date/year of diagnosis | Date of admission (MMYYYY) for the first hospitalisation with an ICD code for heart failure in any SMR record. If case validation identified that the diagnosis had been reached as an outpatient, the first subsequent hospitalisation within 6 months was used. |
| **Comorbidities** | |
| Pre-existing diabetes | ICD-9 or ICD-10 codes in any prior SMR01 record: E10-E14, 250. |
| Pre-existing hypertension | ICD-9 or ICD-10 codes in any prior SMR01 record: I10-I15, 401-405. |

| | |
|---|---|
| Cancer | ICD-9 or ICD-10 codes in any prior SMR01 record: C00-C99, 140-208. |
| Renal disease | ICD-9 or ICD-10 codes in any prior SMR01 record: N17-N19, 584-586. |
| Chronic lung disease | ICD-9 or ICD-10 codes in any prior SMR01 record: J40-J47, J60-J70, J82, J84, J92, J96.1, J99, 490-496, 500-508, 516, 517, 518.3, 518.83. |
| Cerebrovascular disease | ICD-9 or ICD-10 codes in any prior SMR01 record: I60-I69, G45, 430-438. |
| Autoimmune disease | ICD-9 or ICD-10 codes in any prior SMR01 record: G70, 358.0 (myasthenia gravis), D51.0, 281.0 (pernicious anaemia), E27.1, E27.2, 255.4 (adrenal insufficiency), K50-K51, 555, 556 (inflammatory bowel disease), M30-M36, 710 (connective tissue disorders), D68.6, 286.53 (antiphospholipid syndrome), M05-M14, 712-714 (inflammatory arthropathy), E00-E03, E05, 242-244, O90.5, 648.1 (thyroid disease), M30-M31, 446 (vasculitis). |
| Pregnancy-induced hypertension | ICD-9 or ICD-10 codes in the SMR02 record: O10-O16, 642. |
| Pre-eclampsia (includes codes for eclamspsia) | ICD-9 or ICD-10 codes in the SMR02 record: O11, O14, O15, 6424-6427. |
| Gestational diabetes | ICD-9 or ICD-10 codes in the SMR02 record: O244, 648 ± 'Diabetes' variable captured as part of SMR02. |
| Obstetric thromboembolism | ICD-9 or ICD-10 codes in the SMR02 record: I26, I80-I82, O22.3, O87.1, O88.2, 415.1, 451-453, 671.3, 671.4, 673.2. |
| Postpartum haemorrhage | ICD-9 or ICD-10 codes in the SMR02 record: O72, 666. |
| Antepartum haemorrhage | ICD-9 or ICD-10 codes in the SMR02 record: O44-O46, O20, 640, 641. |
| Prior hypertension (any) | Pre-existing hypertension or pregnancy-induced hypertension (including pre-eclampsia) in a prior pregnancy. |

| | |
|---|---|
| Prior diabetes (any) | Pre-existing diabetes or gestational diabetes in a prior pregnancy. |
| Other comorbidities ≥1 | At least one from the following: cancer, cerebrovascular disease, renal disease, autoimmune disease. |
| **Admission details/clinical features** | |
| Systolic and diastolic blood pressure | Initial measurement recorded at the time of hospital admission or development of symptoms. |
| Oxygen therapy | Delivery of any oxygen therapy, including mechanical ventilation. |
| Inotropes | Any use of adrenaline, noradrenaline, vasopressin, dobutamine. |
| Major arrhythmia at baseline | Any rhythm disturbance requiring synchronised direct current cardioversion or targeted antiarrhythmic pharmacotherapy (not including beta-blockers, calcium channel blockers or digoxin in isolation), or a non-fatal cardiac arrest. |
| Thromboembolism at baseline | Arterial: imaging suggestive of LV thrombus, radiologically confirmed arterial thrombus.<br><br>Venous: imaging suggestive of RV thrombus, radiologically confirmed venous thrombus. |
| Stroke at baseline | Radiologically confirmed stroke. |
| **Investigations** | |
| Electrocardiographic parameters | First available ECG within 48 hours of admission, or as an outpatient. All available parameters collected. |
| Laboratory parameters | First available laboratory tests at the time of hospital admission or development of symptoms. |
| Baseline echocardiogram | Defined as the diagnostic echocardiogram, confirming the presence of LV systolic dysfunction. Most comprehensive echo around the time of diagnosis used. If a missing parameter (e.g. LV end systolic diameter) was available on a repeat echo within 14 days, this was used. All available parameters collected. In n=9, the exact date of |

| | |
|---|---|
| | the baseline echocardiogram was not available and date of diagnosis was used. |
| LV function | As described in the Methods chapter. |

Except for LVEF, if an echocardiographic parameter was not reported on the baseline echocardiogram, but was reported on a subsequent echocardiogram within 14 days, that parameter was used as the baseline measurement.

### *4.2.3 Statistical analyses*

Baseline characteristics were compared using t-tests, Wilcoxon rank-sum test, and chi-squared tests, where appropriate. Missing data were not imputed and amounts in each group are displayed in the tables.

Given the strata size, factors associated with the development of PPCM were analysed using unconditional logistic regression, with each model adjusted for the three matching factors – maternal age at delivery, year of delivery (2008-2017 vs 1998-2007) and health board of maternity admission. This type of logistic regression is described in the Methods chapter. Patient characteristics were examined in univariable and multivariable models, and then stratified according to the timing of diagnosis (pre- vs postpartum) to try and minimise bias associated with modifications to obstetric plans in women known to have PPCM prior to delivery.

The discriminatory ability of each multivariable model was assessed using the C-statistic; equivalent to the area under the receiver operating characteristic curve, where a value below 0.5 indicates a poor model, a value of 0.5 indicates that the model is no better at predicting the outcome than chance, and a value of 1 means that the model perfectly predicts individuals who will and will not experience the outcome (i.e. the development of PPCM).

# 4.3 Results

## *4.3.1 Baseline demographics, comorbidities and obstetric characteristics in women with PPCM and controls*

Age, socioeconomic deprivation quintile and comorbidities of 225 women with PPCM and 2240 controls are shown in Table 4-3. The mean age of women with PPCM and controls at delivery was 32 (±6) years. Socioeconomic deprivation was greater in women with PPCM, with 34% in the most deprived quintile (1), as compared with 23% of controls (p=0.012). Compared with controls, women with PPCM were more often obese and more often had a history of smoking (current or former).

Prior hypertension, defined as any type of pre-existing hypertension, including pregnancy-induced hypertension in a prior pregnancy, was approximately twice as common in women with PPCM than in controls (17% vs 8%, p<0.001). The same was true for prior diabetes, defined as any type of pre-existing diabetes, including gestational diabetes in a prior pregnancy (9% vs 5%, p=0.007). Due to small numbers of women (n<5) with a history of cancer, renal disease, cerebrovascular disease and autoimmune disease, these were presented as a composite of at least one: other comorbidities ≥1. Women with PPCM had a greater prevalence of these comorbidities than did controls (4% vs 1%, p<0.001).

Obstetric characteristics are shown in Table 4-4. Women with PPCM more often had pregnancy-induced hypertension and pre-eclampsia (both during the index and during a prior pregnancy) than controls. The prevalences of pregnancy-induced hypertension and of pre-eclampsia during the index pregnancy in cases vs controls were: pregnancy-induced hypertension 34% vs 8%, p<0.001; pre-eclampsia 20% vs 2%, p<0.001. Gestational diabetes during the index pregnancy occurred at a similar frequency in women with PPCM and in controls (3% and 2%, respectively). Conversely, gestational diabetes during a prior pregnancy was approximately twice as common in women with PPCM than in controls (8% vs 4%, p=0.013).

Postpartum haemorrhage complicated the index pregnancy more frequently in women with PPCM than in controls (36% vs 27%, p=0.007), but the proportions of women with antepartum haemorrhage were similar (6% and7%, respectively).

Both multiparity and multiple gestation were more common in women with PPCM than in controls. Overall, 17% of women with PPCM had more than two prior pregnancies, compared with 9% of controls (p<0.001) and 8% of women with PPCM had a multigestational pregnancy, compared with 2% of controls (p<0.001). Terminations were excluded when reporting estimated gestation, induction and mode of delivery. Duration of pregnancy differed between the groups; a larger proportion of women with PPCM had an estimated gestation less than 37 weeks than did controls (26% vs 7%, p<0.001). Compared to controls, stillbirth occurred more frequently in women with PPCM (1.8% vs 0.4%, p<0.001). Overall, a similar proportion of women with PPCM required induction of labour as did controls, but women with PPCM were more often treated with prostaglandins. A C-section delivery was more common in women with PPCM than in controls, particularly an emergency C-section (36% vs 17%, p<0.001).

## Table 4-3 Baseline demographics and comorbidities in women with PPCM and controls

| | Total | Controls | PPCM | P value | Controls Missing | PPCM Missing |
|---|---|---|---|---|---|---|
| | N=2465 | N=2240 | N=225 | | | |
| Age (years) | 31.9±6.0 | 31.9±6.0 | 31.8±6.0 | 0.87 | 0 | 0 |
| Age (years) | | | | 1.00 | 0 | 0 |
| <30 | 815 (33.1) | 740 (33.0) | 75 (33.3) | | | |
| 30-34 | 748 (30.3) | 680 (30.4) | 68 (30.2) | | | |
| ≥35 | 902 (36.6) | 820 (36.6) | 82 (36.4) | | | |
| Age >32 years | 1,232 (50.0) | 1,120 (50.0) | 112 (49.8) | 0.95 | 0 | 0 |
| Deprivation quintile | | | | 0.012 | 4 | 1 |
| 1 (most deprived) | 596 (24.2) | 520 (23.3) | 76 (33.9) | | | |
| 2 | 449 (18.3) | 412 (18.4) | 37 (16.5) | | | |
| 3 | 457 (18.6) | 419 (18.7) | 38 (17.0) | | | |
| 4 | 470 (19.1) | 435 (19.5) | 35 (15.6) | | | |
| 5 | 488 (19.8) | 450 (20.1) | 38 (17.0) | | | |
| Deprivation quintile 1 | 596 (24.2) | 520 (23.3) | 76 (33.9) | <0.001 | 4 | 1 |
| Body mass index (kg/m$^2$) | 26.5±6.0 | 26.3±5.8 | 28.2±7.0 | <0.001 | 823 | 29 |
| Body mass index >30kg/m$^2$ | 369 (22.9) | 301 (21.2) | 68 (34.7) | <0.001 | 823 | 29 |
| Smoking (current/former) | 796 (33.8) | 705 (33.1) | 91 (41.2) | 0.016 | 109 | 4 |
| Prior hypertension | 217 (8.8) | 179 (8.0) | 38 (16.9) | <0.001 | 0 | 0 |
| Prior diabetes | 126 (5.1) | 106 (4.7) | 20 (8.9) | 0.007 | 0 | 0 |
| Chronic lung disease | 89 (3.6) | 77 (3.4) | 12 (5.3) | 0.15 | 0 | 0 |
| Other comorbidities ≥1 | 34 (1.4) | 24 (1.1) | 10 (4.4) | <0.001 | 0 | 0 |

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Table 4-4 Baseline obstetric characteristics in women with PPCM and controls

| | Total | Controls | PPCM | P value | Controls Missing | PPCM Missing |
|---|---|---|---|---|---|---|
| | N=2465 | N=2240 | N=225 | | | |
| Gestational diabetes | 51 (2.1) | 44 (2.0) | 7 (3.1) | 0.25 | 0 | 0 |
| Gestational diabetes, prior | 107 (4.3) | 90 (4.0) | 17 (7.6) | 0.013 | 0 | 0 |
| PIH | 259 (10.5) | 182 (8.1) | 77 (34.2) | <0.001 | 0 | 0 |
| PIH, prior | 211 (8.6) | 173 (7.7) | 38 (16.9) | <0.001 | 0 | 0 |
| Pre-eclampsia | 94 (3.8) | 50 (2.2) | 44 (19.6) | <0.001 | 0 | 0 |
| Pre-eclampsia, prior | 57 (2.3) | 42 (1.9) | 15 (6.7) | <0.001 | 0 | 0 |
| APH, current | 169 (6.9) | 156 (7.0) | 13 (5.8) | 0.50 | 0 | 0 |
| PPH, current | 696 (28.2) | 615 (27.5) | 81 (36.0) | 0.007 | 0 | 0 |
| Parity >1 | 618 (25.2) | 550 (24.6) | 68 (30.2) | 0.066 | 8 | 0 |
| Parity >2 | 230 (9.4) | 192 (8.6) | 38 (16.9) | <0.001 | 8 | 0 |
| Parity >3 | 103 (4.2) | 81 (3.6) | 22 (9.8) | <0.001 | 8 | 0 |
| Multiple gestation* | 59 (2.4) | 41 (1.8) | 18 (8.2) | <0.001 | 0 | 5 |
| Pregnancy outcome | | | | <0.001 | 0 | 0 |
| Live birth | 2,448 (99.3) | 2,232 (99.6) | 216 (96.0) | | | |
| Stillbirth | 12 (0.5) | 8 (0.4) | 4 (1.8) | | | |
| Termination | 5 (0.2) | 0 (0.0) | 5 (2.2) | | | |
| Estimated gestation (weeks)* | 39 (38-40) | 40 (38-40) | 38 (36-40) | <0.001 | 4 | 5 |
| Estimated gestation <37weeks* | 205 (8.3) | 149 (6.7) | 56 (25.5) | <0.001 | 4 | 5 |
| Induction of labour* | 634 (26.1) | 572 (25.7) | 62 (30.5) | 0.13 | 16 | 22 |
| Medical induction of labour* | 546 (22.5) | 491 (22.1) | 55 (27.1) | 0.10 | 20 | 22 |
| Oxytocics* | 251 (10.3) | 228 (10.3) | 23 (11.3) | 0.63 | 16 | 22 |
| Prostaglandins* | 441 (18.2) | 392 (17.6) | 49 (24.1) | 0.021 | 16 | 22 |
| Mode of delivery of baby 1* | | | | <0.001 | 0 | 5 |
| Vaginal | 1,654 (67.2) | 1,555 (69.4) | 99 (45.0) | | | |
| Elective caesarean | 348 (14.1) | 307 (13.7) | 41 (18.6) | | | |
| Emergency caesarean | 458 (18.6) | 378 (16.9) | 80 (36.4) | | | |

**Terminations excluded*
*PIH = pregnancy-induced hypertension; APH = antepartum haemorrhage; PPH = postpartum haemorrhage*
*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

### *4.3.2 Baseline demographics, comorbidities and obstetric characteristics in women with PPCM, by year and age*

**Stratified by year of delivery**

There were no statistically significant differences in age at delivery, or the prevalence of obesity, smoking, prior hypertension or prior diabetes according to year of delivery (2008-2017 vs 1998-2007) (Table 4-5). Women with PPCM in the latter half of the study were more frequently in the most deprived deprivation quintile.

Pregnancy-induced hypertension and pre-eclampsia (during the index pregnancy) were less common in women who delivered in 2008-2017, as compared with 1998-2007 (Table 4-6). There were no differences between years in the prevalence of antepartum haemorrhage or postpartum haemorrhage, parity, multiple gestation, in estimated gestation (or prematurity [estimated gestation <37 weeks]), induction, or mode of delivery.

## Table 4-5 Baseline demographics and comorbidities in women with PPCM, by year of delivery

| | Total | 1998-2007 | 2008-2017 | P value | 1998-2007 Missing | 2008-2017 Missing |
|---|---|---|---|---|---|---|
| | N=225 | N=98 | N=127 | | | |
| Age (years) | 31.8±6.0 | 31.8±5.9 | 31.8±6.1 | 0.98 | 0 | 0 |
| Age (years) | | | | 0.58 | 0 | 0 |
| <30 | 75 (33.3) | 32 (32.7) | 43 (33.9) | | | |
| 30-34 | 68 (30.2) | 33 (33.7) | 35 (27.6) | | | |
| ≥35 | 82 (36.4) | 33 (33.7) | 49 (38.6) | | | |
| Age >32 years | 112 (49.8) | 48 (49.0) | 64 (50.4) | 0.83 | 0 | 0 |
| Deprivation quintile | | | | 0.26 | 0 | 1 |
| 1 (most deprived) | 76 (33.9) | 26 (26.5) | 50 (39.7) | | | |
| 2 | 37 (16.5) | 18 (18.4) | 19 (15.1) | | | |
| 3 | 38 (17.0) | 21 (21.4) | 17 (13.5) | | | |
| 4 | 35 (15.6) | 16 (16.3) | 19 (15.1) | | | |
| 5 | 38 (17.0) | 17 (17.3) | 21 (16.7) | | | |
| Deprivation quintile 1 | 76 (33.9) | 26 (26.5) | 50 (39.7) | 0.039 | 0 | 1 |
| Body mass index (kg/m$^2$) | 28.2±7.0 | 27.9±8.0 | 28.4±6.4 | 0.68 | 26 | 3 |
| Body mass index >30kg/m$^2$ | 68 (34.7) | 22 (30.6) | 46 (37.1) | 0.35 | 26 | 3 |
| Smoking (current/former) | 91 (41.2) | 37 (39.4) | 54 (42.5) | 0.64 | 4 | 0 |
| Prior hypertension | 38 (16.9) | 20 (20.4) | 18 (14.2) | 0.22 | 0 | 0 |
| Prior diabetes | 20 (8.9) | 12 (12.2) | 8 (6.3) | 0.12 | 0 | 0 |

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Table 4-6 Baseline obstetric characteristics in women with PPCM, by year of delivery

| | Total | 1998-2007 | 2008-2017 | P value | 1998-2007 Missing | 2008-2017 Missing |
|---|---|---|---|---|---|---|
| | N=225 | N=98 | N=127 | | | |
| PIH | 77 (34.2) | 47 (48.0) | 30 (23.6) | <0.001 | 0 | 0 |
| Pre-eclampsia | 44 (19.6) | 31 (31.6) | 13 (10.2) | <0.001 | 0 | 0 |
| APH | 13 (5.8) | 7 (7.1) | 6 (4.7) | 0.44 | 0 | 0 |
| PPH | 81 (36.0) | 31 (31.6) | 50 (39.4) | 0.23 | 0 | 0 |
| Parity >1 | 68 (30.2) | 30 (30.6) | 38 (29.9) | 0.91 | 0 | 0 |
| Parity >2 | 38 (16.9) | 18 (18.4) | 20 (15.7) | 0.60 | 0 | 0 |
| Parity >3 | 22 (9.8) | 12 (12.2) | 10 (7.9) | 0.27 | 0 | 0 |
| Multiple gestation* | 18 (8.2) | 10 (10.4) | 8 (6.5) | 0.29 | 2 | 3 |
| Estimated gestation (weeks)* | 38 (36-40) | 38 (35-39) | 39 (37-40) | 0.062 | 2 | 3 |
| Estimated gestation <37weeks* | 56 (25.5) | 27 (28.1) | 29 (23.4) | 0.42 | 2 | 3 |
| Induction of labour* | 62 (30.5) | 30 (33.3) | 32 (28.3) | 0.44 | 8 | 14 |
| Medical induction of labour* | 55 (27.1) | 29 (32.2) | 26 (23.0) | 0.14 | 8 | 14 |
| Oxytocics* | 23 (11.3) | 12 (13.3) | 11 (9.7) | 0.42 | 8 | 14 |
| Prostaglandins* | 49 (24.1) | 27 (30.0) | 22 (19.5) | 0.082 | 8 | 14 |
| Mode of delivery of baby 1* | | | | 0.97 | 2 | 3 |
| Vaginal | 99 (45.0) | 44 (45.8) | 55 (44.4) | | | |
| Elective caesarean | 41 (18.6) | 18 (18.8) | 23 (18.5) | | | |
| Emergency caesarean | 80 (36.4) | 34 (35.4) | 46 (37.1) | | | |

**Terminations excluded*
*PIH = pregnancy-induced hypertension; APH = antepartum haemorrhage; PPH = postpartum haemorrhage*
*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

**Stratified by age**

There were no differences in socioeconomic deprivation quintile or in the prevalence of smoking according to age categories (≤32 years and >32 years) (Table 4-7). Older women had a higher BMI as compared to younger women (29 [±7] kg/$m^2$ vs 27 [±7] kg/$m^2$, p=0.035). Prior hypertension and prior diabetes (values could not be shown due to small numbers) were more common in older women than in younger women.

The frequencies of pregnancy-induced hypertension and of pre-eclampsia during the index pregnancy were similar irrespective of age grouping (Table 4-8). Multiparity was more common in older women than in younger women, but both groups had a similar frequency of multiple gestation. There were no differences in other obstetric characteristics examined, including estimated gestation, induction of labour, and mode of delivery.

## Table 4-7 Baseline demographics and comorbidities in women with PPCM, by age

| | Total | ≤32 years | >32 years | P value | ≤32 years Missing | >32 years Missing |
|---|---|---|---|---|---|---|
| | N=225 | N=113 | N=112 | | | |
| Age (years) | 31.8±6.0 | 27.0±4.1 | 36.7±2.9 | <0.001 | 0 | 0 |
| Deprivation quintile | | | | 0.24 | 0 | 1 |
| 1 (most deprived) | 76 (33.9) | 41 (36.3) | 35 (31.5) | | | |
| 2 | 37 (16.5) | 23 (20.4) | 14 (12.6) | | | |
| 3 | 38 (17.0) | 19 (16.8) | 19 (17.1) | | | |
| 4 | 35 (15.6) | 16 (14.2) | 19 (17.1) | | | |
| 5 | 38 (17.0) | 14 (12.4) | 24 (21.6) | | | |
| Deprivation quintile 1 | 76 (33.9) | 41 (36.3) | 35 (31.5) | 0.45 | 0 | 1 |
| BMI ($kg/m^2$) | 28.2±7.0 | 27.2±7.2 | 29.3±6.8 | 0.035 | 13 | 16 |
| BMI >30$kg/m^2$ | 68 (34.7) | 29 (29.0) | 39 (40.6) | 0.087 | 13 | 16 |
| Smoking (current/former) | 91 (41.2) | 48 (43.6) | 43 (38.7) | 0.46 | 3 | 1 |
| Prior hypertension | 38 (16.9) | 12 (10.6) | 26 (23.2) | 0.012 | 0 | 0 |
| Prior diabetes | - | - | - | <0.001 | 0 | 0 |

*BMI = body mass index*
*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Table 4-8 Baseline obstetric characteristics in women with PPCM, by age

| | Total | ≤32 years | >32 years | P value | ≤32 years Missing | >32 years Missing |
|---|---|---|---|---|---|---|
| | N=225 | N=113 | N=112 | | | |
| PIH | 77 (34.2) | 36 (31.9) | 41 (36.6) | 0.45 | 0 | 0 |
| Pre-eclampsia | 44 (19.6) | 19 (16.8) | 25 (22.3) | 0.30 | 0 | 0 |
| APH | 13 (5.8) | 7 (6.2) | 6 (5.4) | 0.79 | 0 | 0 |
| PPH | 81 (36.0) | 35 (31.0) | 46 (41.1) | 0.11 | 0 | 0 |
| Parity >1 | 68 (30.2) | 24 (21.2) | 44 (39.3) | 0.003 | 0 | 0 |
| Parity >2 | 38 (16.9) | 9 (8.0) | 29 (25.9) | <0.001 | 0 | 0 |
| Parity >3 | 22 (9.8) | 5 (4.4) | 17 (15.2) | 0.007 | 0 | 0 |
| Multiple gestation* | 18 (8.2) | 10 (9.1) | 8 (7.3) | 0.62 | 3 | 2 |
| Estimated gestation (weeks)* | 38 (36-40) | 38.5 (37-40) | 38 (36-39) | 0.20 | 3 | 2 |
| Estimated gestation <37weeks* | 56 (25.5) | 24 (21.8) | 32 (29.1) | 0.22 | 3 | 2 |
| Induction of labour* | 62 (30.5) | 31 (29.8) | 31 (31.3) | 0.82 | 9 | 13 |
| Medical induction of labour* | 55 (27.1) | 28 (26.9) | 27 (27.3) | 0.96 | 9 | 13 |
| Oxytocics* | 23 (11.3) | 9 (8.7) | 14 (14.1) | 0.22 | 9 | 13 |
| Prostaglandins* | 49 (24.1) | 27 (26.0) | 22 (22.2) | 0.53 | 9 | 13 |
| Mode of delivery of baby 1* | | | | 0.095 | 3 | 2 |
| Vaginal | 99 (45.0) | 57 (51.8) | 42 (38.2) | | | |
| Elective caesarean | 41 (18.6) | 16 (14.5) | 25 (22.7) | | | |
| Emergency caesarean | 80 (36.4) | 37 (33.6) | 43 (39.1) | | | |

**Terminations excluded*
*PIH = pregnancy-induced hypertension; APH = antepartum haemorrhage; PPH = postpartum haemorrhage*
*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

### *4.3.3 Baseline clinical features in women with PPCM*

Baseline clinical data are reported only in women with a validated diagnosis of PPCM (i.e. case records were available to collect these data) (n=202, n=181 for electrocardiographic data) and are shown in Table 4-9. The majority of women (82%) were diagnosed after delivery. Median heart rate was 109bpm (IQR 90-125) and 73% of women had a heart rate above 90bpm. Median systolic and diastolic blood pressures were 134mmHg (IQR 120-154) and 85mmHg (IQR 73-100), respectively.

At the time of hospitalisation, 48% of women required oxygen therapy (including mechanical ventilation) and 71% received intravenous loop diuretic therapy. Overall, 30% of women were admitted to an intensive care unit, 24% were intubated and mechanically ventilated and 4% required renal replacement therapy. Pharmacological haemodynamic support (defined as any use of adrenaline, noradrenaline, vasopressin or dobutamine) was used in 15% of women.

Any thromboembolic event (arterial, venous or a radiologically confirmed stroke) was identified in 13% of women during the index hospitalisation with PPCM and a LV thrombus in 4%. A major arrythmia (defined as a rhythm disturbance requiring synchronised direct current cardioversion or antiarrhythmic pharmacotherapy, or non-fatal cardiac arrest) occurred in 7% of women.

Median haemoglobin was 114g/l (IQR 101-126), white cell count was $12x10^9$/l (IQR 9-15) and platelet count was $283x10^9$/l (IQR 205-387) (Table 4-13). Median creatinine was 68µmol/l (IQR 57-83) and serum albumin was 31g/l (IQR 26-35).

A total of 181 women had available electrocardiographic data (80% of the total cohort / 90% of those with a validated diagnosis of PPCM) (Table 4-9). Most women (95%) were in sinus rhythm at presentation. The remainder had either a supraventricular arrhythmia (including atrial fibrillation), an indeterminate narrow complex tachycardia or a broad complex tachycardia. In total, 14% of women had a bundle branch block and in 34% the QTc duration was greater than 470ms. In addition to bundle branch block, the prevalence of abnormal R wave progression (defined as an R wave height in lead V3 ≤ 3mm and an R wave height

in lead V2 ≤ the R wave height in lead V3) was 30%, and of ST-T-wave changes was 37%. Two or more ventricular ectopic beats were present on the ECG in 8%. Any ECG abnormality, defined as either bundle branch block, a QTc duration >470ms, ventricular ectopy, abnormal R wave progression, or ST-T wave changes, was evident in 78% of women (i.e. 22% had a normal ECG).

Echocardiographic confirmation of LV systolic dysfunction was available in 202 (90%) of women (Table 4-9). In 5 (2%) women with a baseline echocardiogram, it was not possible to categorise the severity of LV dysfunction (for example, LV function was documented as 'impaired', but without more specific qualitative, or any quantitative, assessment). In total, a quantitative assessment of LVEF was available in 129 (64%) women with available echocardiographic data at baseline; in the remaining women, a standardised LVEF was assigned based on a qualitative assessment of mild (50%), moderate (40%) or severe (25%), as described in the Methods chapter. The median time between baseline echocardiogram and the date of the index admission was 2 days (IQR -1-3). Mean LVEF in women with PPCM was 35% (±11) with a similar median value of 36% (IQR 25-43). In 48% of women, LV systolic function was severely impaired (LVEF ≤35%). Overall, 79% of women had a LVEF ≤45%). The mean LV end diastolic diameter was 57mm (±8). The LV end diastolic diameter was severely dilated (≥62mm[169]) in 26% of women.

**Table 4-9 Baseline clinical features in women with PPCM**

| | Total | Missing |
|---|---|---|
| **Clinical findings** | **N=202** | |
| Timing of diagnosis | | 0 |
| Postpartum | 165 (81.7) | |
| Prepartum | 37 (18.3) | |
| Heart rate (bpm) | 108 (90-125) | 16 |
| Heart rate >90 bpm | 136 (73.1) | 16 |
| SBP (mmHg) | 134 (120-154) | 23 |
| DBP (mmHg) | 85 (73-100) | 25 |
| Oxygen therapy | 88 (47.8) | 18 |
| Intravenous diuretic therapy | 132 (70.6) | 15 |
| Intensive care | 60 (29.7) | 0 |
| Intubation and ventilation | 48 (23.9) | 1 |
| Renal replacement therapy | 7 (3.6) | 5 |
| Pharmacological haemodynamic support | 29 (14.9) | 7 |
| Stroke or thromboembolism, index admission | 26 (12.9) | 0 |
| LV thrombus, index admission | 8 (4.0) | 0 |
| Major arrhythmia, index admission | 15 (7.4) | 0 |
| **Laboratory tests** | **N=202** | |
| Haemoglobin (g/l) | 114 (101-126) | 11 |
| Haematocrit (%) | 0.35 (0.31-0.38) | 16 |
| White blood cells (x10^9/l) | 11.6 (9.1-14.6) | 11 |
| Lymphocytes (x10^9/l) | 1.8 (1.2-2.3) | 15 |
| Neutrophils (x10^9/l) | 8.7 (6.4-12.1) | 15 |
| Platelets (x10^9/l) | 283 (205-378) | 12 |
| Serum sodium (mmol/l) | 139 (137-141) | 9 |
| Serum potassium (mmol/l) | 4.2 (4.0-4.5) | 9 |
| Serum creatinine (µmol/l) | 68 (57-83) | 9 |
| Serum urea (mmol/l) | 4.4 (3.3-5.5) | 10 |
| Serum albumin (g/l) | 31 (26-35) | 17 |
| Bilirubin (µmol/l) | 8 (6-13) | 18 |
| Alanine aminotransferase (iu/l) | 23 (14-44) | 19 |
| **Electrocardiogram** | **N=181** | |
| Sinus rhythm | 172 (95.0) | 0 |
| PR interval (ms) | 138 (126-152) | 8 |
| QRS duration (ms) | 83 (76-94) | 1 |
| Bundle branch block | 26 (14.4) | 1 |
| QTc duration (ms) | 451 (425-483) | 4 |
| QTc >470ms | 60 (33.9) | 4 |
| Abnormal R wave progression | | 3 |
| No/bundle branch block | 125 (70.2) | |

| | | |
|---|---|---|
| Yes | 53 (29.8) | |
| ST-T wave change | | 2 |
| No/bundle branch block | 112 (62.6) | |
| Yes | 67 (37.4) | |
| Ectopy (≥2 ventricular ectopic beats) | 14 (7.8) | 2 |
| Any ECG abnormality | 138 (77.5) | 3 |
| **Echocardiogram** | **N=202** | |
| LVEF (%) mean | 35±11 | 5 |
| LVEF (%) median | 36 (25-43) | 5 |
| LVEF ≤45% | 155 (78.7) | 5 |
| LV impairment | | 0 |
| Severe (or LVEF ≤35%) | 96 (47.5) | |
| Moderate (or LVEF 36-44%) | 55 (27.2) | |
| Mild (or LVEF 45-50%) | 46 (22.8) | |
| Unquantified impairment | 5 (2.5) | |
| LVEDD (mm) | 57±8 | 28 |
| LVEDD (mm) | | 28 |
| ≤53 | 58 (33.3) | |
| 54-57 | 38 (21.8) | |
| 58-61 | 33 (19.0) | |
| ≥62 | 45 25.9) | |

*SBP = systolic blood pressure; DBP = diastolic blood pressure; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter*
*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

### *4.3.4 Factors associated with the development of PPCM*

**All women**

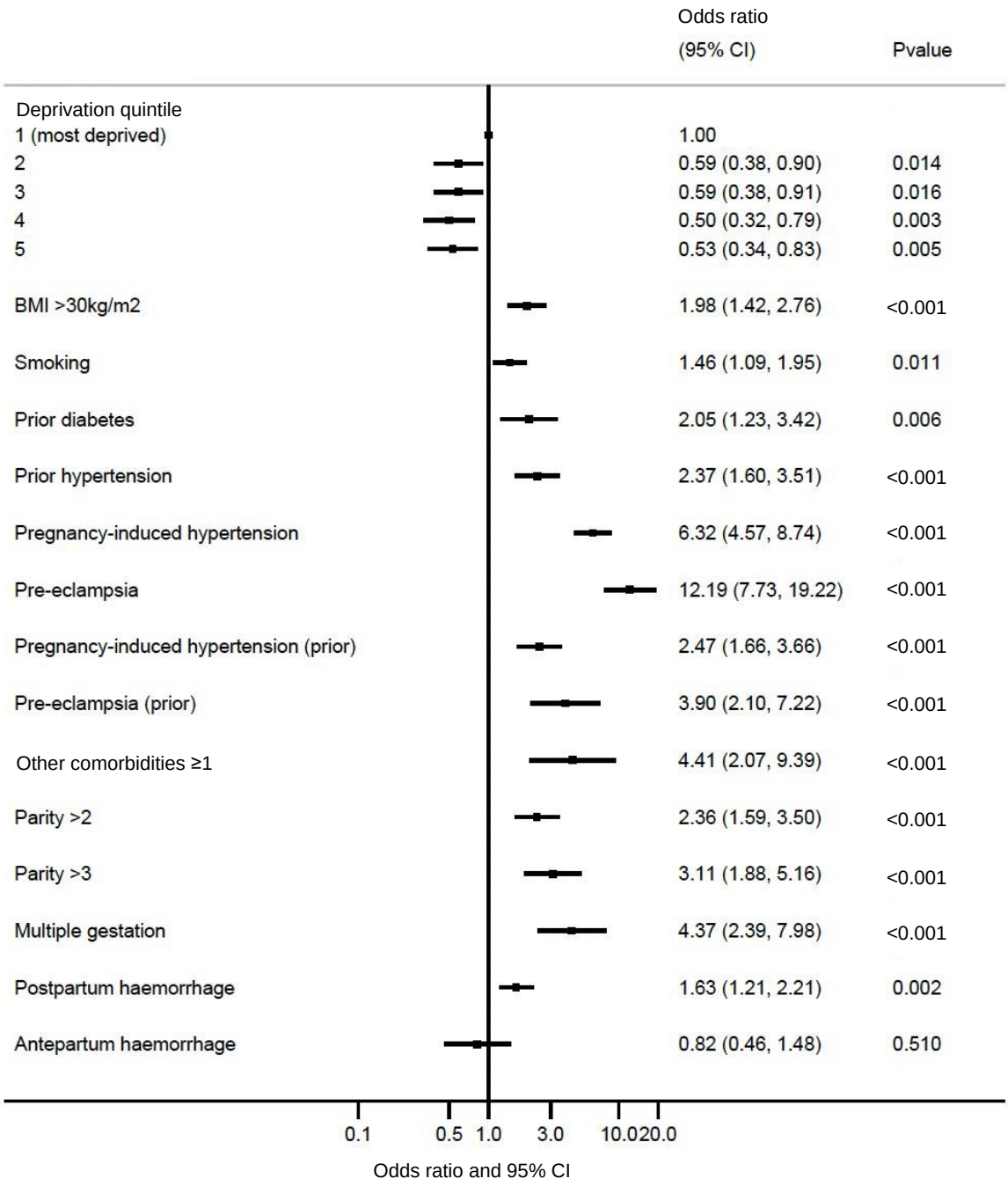
*Univariable analysis*

First, baseline demographic variables and obstetric factors were examined in a logistic regression model including each variable in turn, adjusted for maternal age, year of delivery (2008-2017 vs 1998-2007) and health board of maternity admission. Associations between these factors and the development of PPCM are displayed in Figure 4-1. A higher socioeconomic deprivation quintile (i.e. less deprived) was associated with a lower likelihood of developing PPCM. Obesity (BMI>30kg/$m^2$), smoking, a history of diabetes, a history of hypertension, pregnancy-induced hypertension in the index pregnancy and pre-eclampsia in the index pregnancy, multiparity, multiple gestation and postpartum haemorrhage were all associated with a greater likelihood of developing PPCM. The characteristics with the greatest magnitude of association were: pre-eclampsia (OR 12.19, 95% CI 7.73-19.22) and pregnancy-induced hypertension (OR 6.32, 95% CI 4.57-8.74).

*Multivariable analysis*

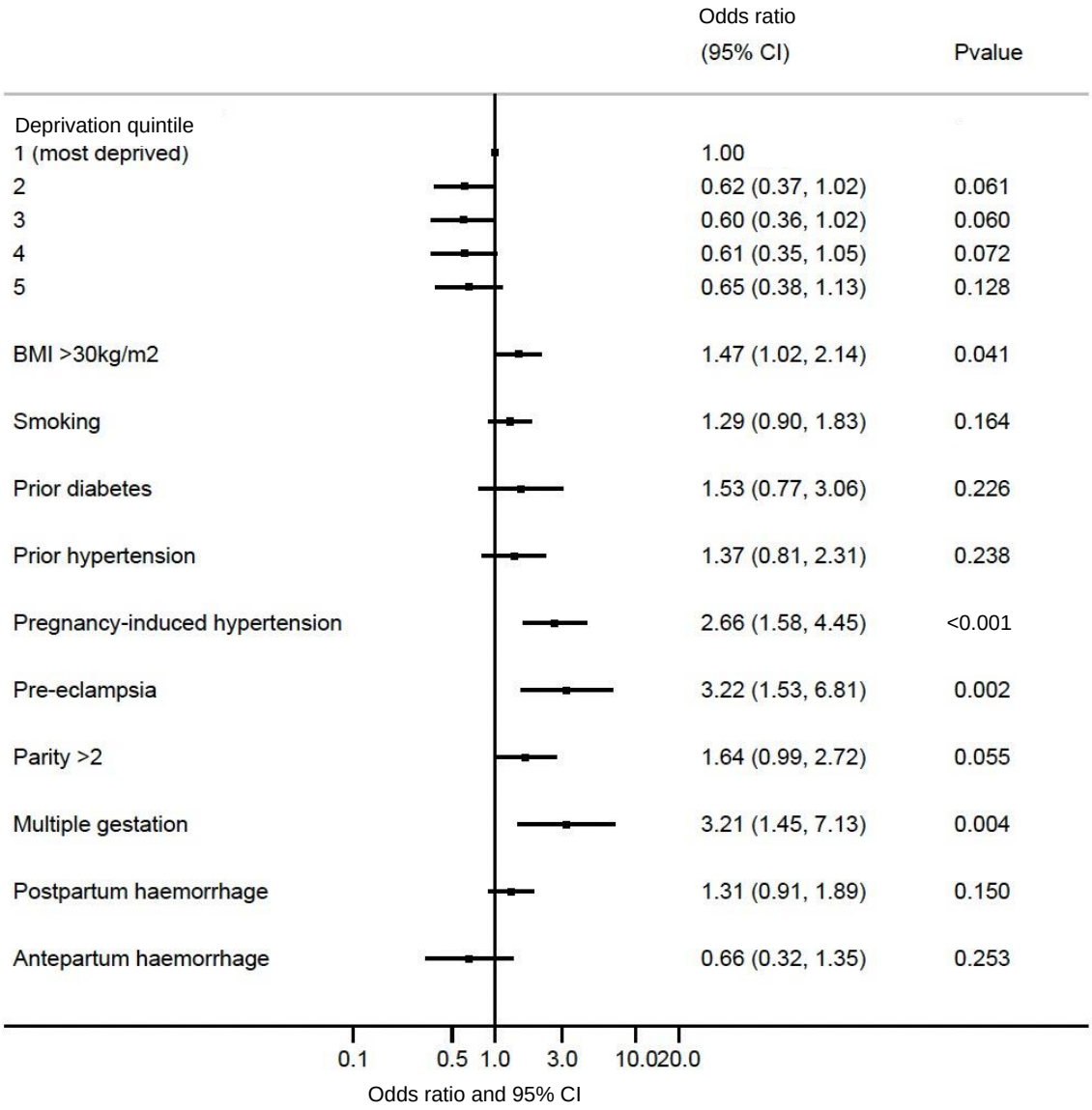
Next, the variables identified in the univariable analysis were examined in a multivariable model (n=1582 with complete data in final model), with the exception of pregnancy-induced hypertension and pre-eclampsia in a prior pregnancy (since they were both a component of the prior hypertension variable), parity >3 (due to collinearity with parity >2) and the comorbidity composite (due to very small numbers). The model was adjusted for age at delivery, year of delivery (1998-2007 vs 2008-2017) and health board. Independent associations are displayed in Figure 4-2. Obesity (OR 1.47, 95% CI 1.02-2.14), pregnancy-induced hypertension (OR 2.66, 95% CI 1.58-4.45), pre-eclampsia (OR 3.22, 95% CI 1.53-6.81) and multiple gestation (OR 3.21, 95% CI 1.45-7.13) were independently associated with a greater likelihood of developing PPCM. The C-statistic for the model was 0.72 (95% CI 0.68-0.77).

**Figure 4-1 Factors associated with the development of PPCM (univariable)**




*Adjusted for maternal age, year of delivery* (1998-2007 vs 2008-2017) *and health board.*

**Figure 4-2 Factors associated with the development of PPCM (multivariable)**




*Adjusted for maternal age, year of delivery (1998-2007 vs 2008-2017) and health board.*
*N=1582 with complete data in final model*

**Women diagnosed postpartum**

*Univariable analysis*

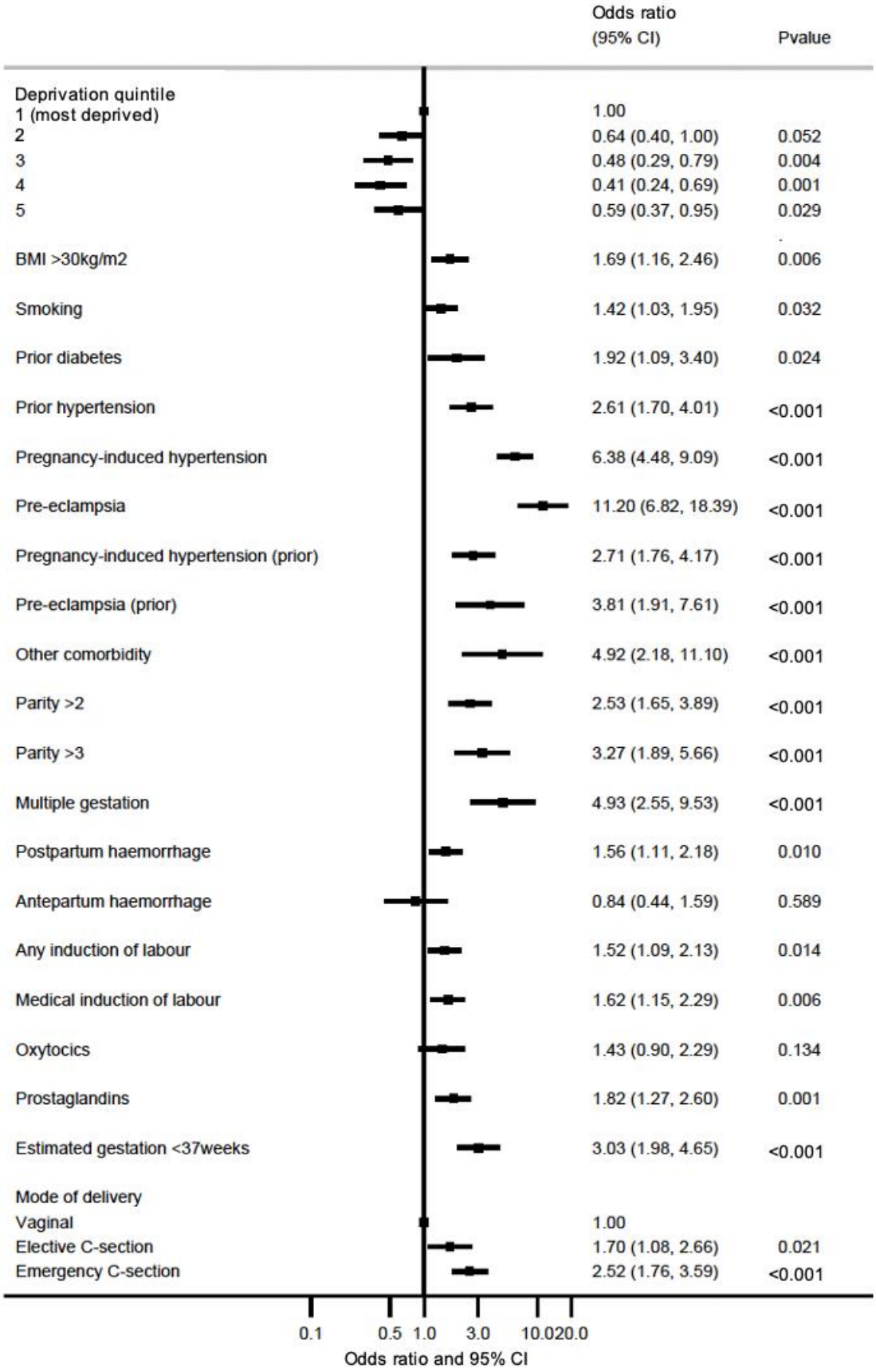
Given that certain obstetric factors may be directly related to the presence of established cardiac disease in a pregnant woman (for example, inducing delivery early, certain modes of delivery), analysis of specific obstetric associations were conducted separately in women who were assigned a diagnosis of PPCM after delivery. The timing of diagnosis could not be determined in 2 women, who were excluded. The diagnosis was postpartum in 182/223 (82%) women. Only controls for these 182 women were included.

Generally, the findings were similar to those in the whole cohort (Figure 4-3). With respect to the additional obstetric factors examined, medical induction of labour was associated with a greater likelihood of developing PPCM, driven by an association with the use of prostaglandins (OR 1.82, 95% CI 1.27-2.60), as was premature delivery (estimated gestation <37 weeks) (OR 3.03, 95% CI 1.98-4.65). C-section delivery was also associated with a greater likelihood of developing PPCM when compared to vaginal delivery; the magnitude of the association was larger for emergency (OR 2.52, 95% CI 1.76-3.59), than it was for elective (OR 1.70, 95% CI 1.08-2.66).

*Multivariable analysis*

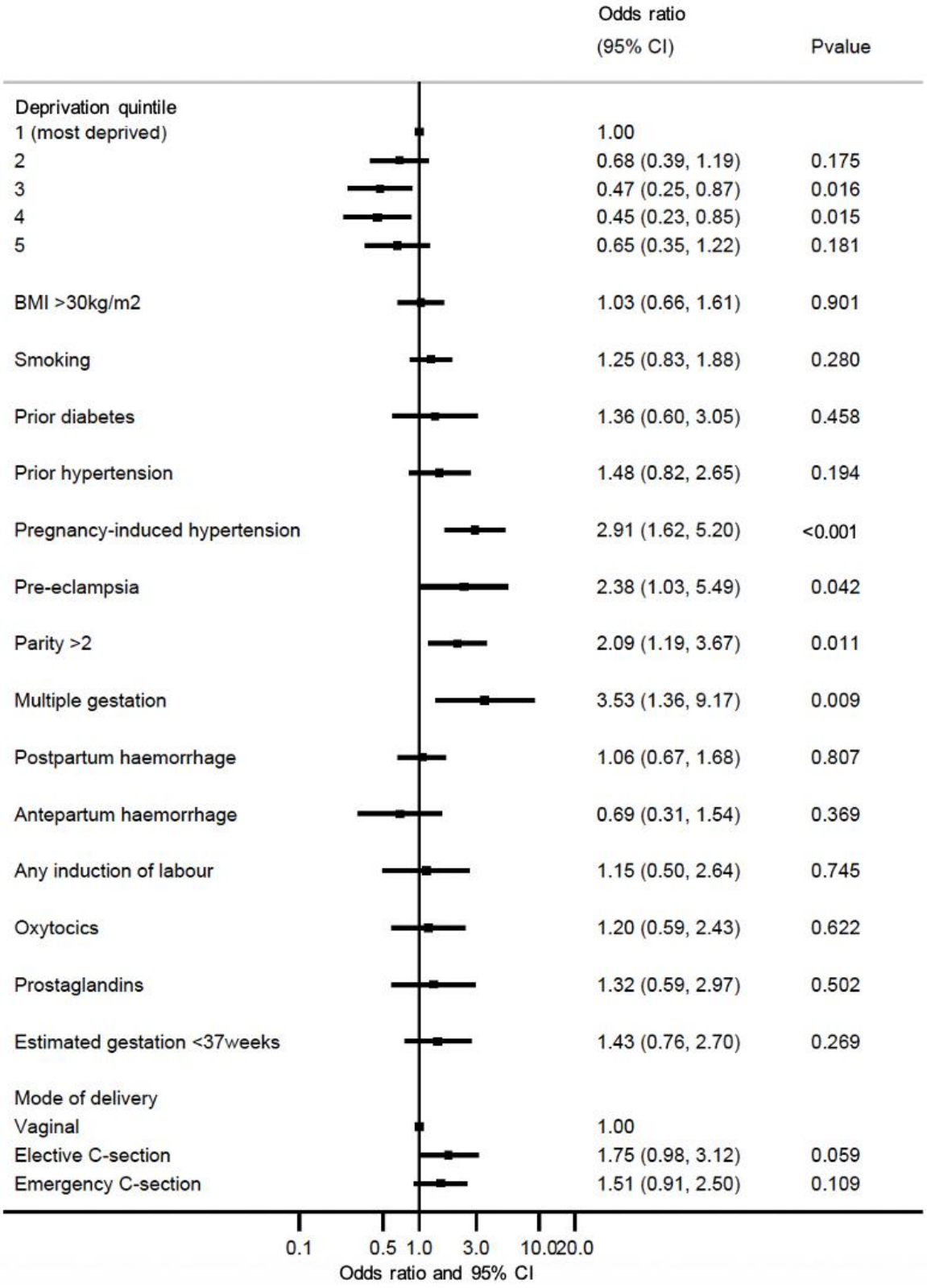
In keeping with the prior multivariable analysis, pregnancy-induced hypertension and pre-eclampsia in a prior pregnancy, parity >3 and the comorbidity composite were excluded, as was medical induction of labour (instead, the two components, oxytocics and prostaglandins, were included separately). In women diagnosed postpartum, pregnancy-induced hypertension, pre-eclampsia, multiparity and multiple gestation were independently associated with a greater likelihood of developing PPCM (n=1254 with complete data in final model) (Figure 4-4). There was no association with induction of labour, use of oxytocics or prostaglandins, estimated gestation <37weeks or mode of delivery. The C-statistic for the model was 0.74 (95% CI 0.70-0.79).

**Figure 4-3 Factors associated with the development of PPCM in women diagnosed postpartum (univariable)**




*Adjusted for maternal age, year of delivery* (1998-2007 vs 2008-2017) *and health board.*

**Figure 4-4 Factors associated with the development of PPCM in women diagnosed postpartum (multivariable)**




*Adjusted for maternal age, year of delivery (1998-2007 vs 2008-2017) and health board.*
*N=1254 with complete data in final model*

## 4.4 Discussion

The phenotype of women in Scotland with PPCM and factors associated with developing the condition are defined in this chapter. Notably, the mean age of women at delivery was 32 years, pre-eclampsia occurred in 20% of women, just under half of women had severe LV dysfunction at baseline, just over three-quarters had an abnormal ECG and approximately a third were admitted to an intensive care unit at the time of diagnosis. Thromboembolic complications or stroke occurred in 13% of women at the time of presentation and 4% of women were found to have LV thrombus. Several factors were independently associated with the development of PPCM in the Scottish population, including hypertensive disorders, multiparity and multiple gestation. In women diagnosed postpartum, none of the delivery-specific factors examined were associated with an increased likelihood of developing the condition.

Patient characteristics and associations identified in this Scottish cohort of women with PPCM are generally in keeping with those of other cohorts. Pre-eclampsia occurred in 20% of women with PPCM in this study, an estimate similar to that reported in one systematic review which included 22 studies, with a pooled prevalence of 22%[17]. Pre-eclampsia was associated with a 3-fold increase in the likelihood of developing PPCM, after adjustment. In women with PPCM in Europe, pre-eclampsia has been found to occur in approximately 1 in 4 women[11]. The relationship between hypertensive disorders of pregnancy and PPCM is not fully understood. Pre-eclampsia is thought to be a disorder of placental function, driven by impaired remodelling of the spiral artery, resultant ischaemia and excess circulation of antiangiogenic factors[54]. Angiogenic imbalance and endothelial dysfunction have been identified in both pre-eclampsia and in PPCM, suggesting that there may be an overlap between conditions[53, 185]. It is possible that pregnancy-induced hypertensive disorders and PPCM are part of a shared disease-spectrum, or that pregnancy-induced hypertensive disorders are a risk factor for the development of PPCM, or that they are distinct causes of heart failure. There remains a paucity of evidence in our understanding of the relationship and the subject warrants dedicated prospective research. My analysis of women with PPCM in the ESC PPCM Registry according to the presence of absence of gestational hypertensive disorders found that women with concomitant pre-eclampsia presented with more severe symptoms and

more frequent signs of heart failure than women without hypertension, despite having better baseline cardiac function[186]. Women with PPCM and pre-eclampsia also had a greater likelihood of LV recovery (but more frequent adverse neonatal outcomes), than women with PPCM without hypertension. This is, perhaps, suggestive of two somewhat distinct groups of patients with PPCM – those with a hypertensive phenotype and those with a more 'conventional' DCM phenotype. Other findings from that study which further support such a hypothesis were less frequent bundle branch block, biventricular dysfunction, and family history of cardiomyopathy in women with gestational hypertensive disorders than in women without.

Further characteristics associated with the development of PPCM worthy of discussion include multiparity and multiple gestation. Although the exact mechanism of these associations is unclear, like pre-eclampsia, they may be vascular in origin. In normal pregnancy, soluble fms-like tyrosine kinase 1 (sFlt-1, an antagonist of vascular endothelial growth factor) is released from the placenta, with levels peaking at delivery and returning to normal soon after delivery[55]. Upregulation of sFlt-1, which occurs in pre-eclampsia and in multigestational pregnancies, leads to endothelial dysfunction, hypertension, reduced capillary density and oedema [53, 55, 56, 73]. Upregulation of sFlt-1 has also been shown to occur in women with PPCM, with a greater elevation corresponding to more severe heart failure symptoms[48, 53, 187]. Greater haemodynamic change and CV demand in a multigestational pregnancy may also be relevant[74, 75]. One proposed explanation for the association between multiparity and PPCM is through cumulative upregulation of antiangiogenic factors with each additional pregnancy[17]. Multiparity has also been shown to be associated with adverse cardiac remodelling in women without PPCM[76, 77].

A further novel finding of this analysis was the relationship between level of socioeconomic deprivation and PPCM. This has not before been studied. Unadjusted analysis showed there was a lower likelihood of developing PPCM as the level of socioeconomic deprivation reduced. However, this finding was attenuated after adjustment for other baseline differences (i.e. the association was explained by other patient factors).

Given this study is mostly a reflection of hospitalised (acute) heart failure, rather than ambulatory heart failure, it was perhaps unsurprising that the proportions of women requiring intravenous loop diuretic therapy (70%), admission to intensive care (30%) and pharmacological haemodynamic support (15%) were high. Although clinical details such as these are infrequently described in the PPCM literature, these findings are generally in keeping with previous reports[18, 33, 113, 123]. One notable difference was the slightly higher proportion of women with a thromboembolic event or stroke in this study (13%). Previous reports of thromboembolism range from 2-7% [10, 11, 92, 188]. There may be regional variation in the extent of investigation and work up of peripartum women with breathlessness that could account for differences observed. These data suggest that a high index of suspicion of thromboembolic events is warranted and consideration should be given to investigations to diagnose the presence of these conditions.

Electrocardiographic abnormalities in women with PPCM have been a focus of interest in recent years. Approximately 70% of women had at least one electrocardiographic abnormality evident in prior reports[189-192]. Moreover, it has been shown that two of more of a heart rate threshold of ≥100bpm, the presence of ST-T wave abnormalities, and a QRS duration of ≥110ms have a sensitivity of 85% in PPCM[190]. Although it was not possible to perform a similar analysis in the current study in the absence of control ECG data, 78% of women with PPCM had at least one of the following abnormalities: bundle branch block, QTC >470ms, ≥2 ventricular ectopic beats, ST-T wave changes or abnormal R wave progression. The incidence of left bundle branch block in an unselect population of ambulant patients with chronic heart failure is around 10%[193] and in this study the prevalence of any kind of bundle branch block was similar (14%). Future research could focus on evaluating the efficacy of the electrocardiogram (± natriuretic peptide testing) as a screening tool during pregnancy, and the potential significance of electrocardiographic abnormalities noted during the routine clinical care of pregnant women must not be overlooked.

There are limitations to these analyses that must be considered. The large time period included meant that not all clinical records were available for all patients, which resulted in incomplete data. This tended to be due to differing

policies for record retention across health boards in Scotland. In order to be able to draw direct comparisons between control and cases, the majority of demographic data examined were derived from administrative datasets, each with their own limitations with respect to coding accuracy and completeness (described in more detail in the Methods chapter). In some instances, administrative data were supplemented with data collected from patient records, such as in the event that delivery took place at the Golden Jubilee National Hospital as a delivery (SMR02) record is not generated in this setting. It was not possible to predetermine which patient records would be unavailable until stores were searched at each health board. Comorbidities examined were based upon ICD coding, rather than standardised definitions, but it was reassuring to see prevalence estimates very similar to those expected (for example, pre-eclampsia and gestational diabetes). Due to the nature of the data sources, only prespecified characteristics could be examined (i.e. those routinely captured in SMR01 and SMR02 datasets) and it is likely that there are other important factors not accounted for in these analyses. Given the retrospective nature of the study and the lack of standard echocardiographic protocols across centres, it was not possible to obtain a quantitative assessment of LV function in all patients at the time of presentation. Inclusion and analyses of LV systolic function on the basis of qualitative echocardiographic data (e.g. normal, mildly, moderately or severely impaired) has been done before[194].

## 4.5 Summary

Gestational hypertensive disorders, multiparity and multiple gestation were independently associated with the development of PPCM in this Scottish cohort. Although socioeconomic deprivation was also relevant, this appeared to be explained by baseline comorbidities, rather than deprivation itself. These factors, in combination with other clinical findings, such as electrocardiographic abnormalities, should further prompt health care professionals to consider PPCM in women around the time of pregnancy. Although outside the scope of the current study, future research should focus on the feasibility and efficacy of screening tools for at-risk groups women.

# Chapter 5 Outcomes and subsequent events

## 5.1 Introduction and aims

This chapter focusses on clinical outcomes for women with PPCM in Scotland. Rates of death and rehospitalisation are reported, including those due to any cause and a CV cause. These are compared to rates for controls (see Methods). In women with PPCM, a number of disease-specific outcomes are also examined, including rates of cardiac device implantation (implantable cardioverter defibrillator or cardiac resynchronisation therapy), mechanical circulatory support and cardiac transplantation. Finally, the frequency and timing of LV recovery, and subsequent deterioration in cardiac function following LV recovery, will be examined. Outcomes at 30 days, 6 months, 1 year, 5 years and 10 years are reported. Factors associated with adverse outcomes and with LV recovery will be determined.

## 5.2 Methods

### *5.2.1 Study population*

Outcomes were analysed in women with PPCM and compared to those for controls. Four women were excluded from outcome analyses due to errors in dates used for record linkage (for example, one patient had a date of death prior to the date of admission) or because the heart failure admission in the dataset was not the within 6 months of the true date of diagnosis (where this was confirmed through review of patient records).

### *5.2.2 Data sources and definitions*

Outcome data were obtained from a combination of linked administrative data on subsequent adult general hospitalisations (i.e. non-maternity admissions) from the SMR01 scheme, linked mortality data from the Scottish death registry and data collected directly from patient records. Table 5-1 summarises the data sources and definitions used in this chapter. All data from available follow-up echocardiograms were collected for each patient and were categorised in the same way as at baseline, as detailed in Table 4-2 in Chapter 4.

**Table 5-1 Data sources and definitions for subsequent events/outcomes**

| Variable | Source(s) | Description/definition |
|---|---|---|
| All-cause death | NRS death registry | Death due to any cause. |
| CV death | NRS death registry | Main cause of death with ICD-10 codes relating to a CV condition: I00-I90, O903 (PPCM), O994 (diseases of the circulatory system complicating pregnancy, childbirth and the puerperium). |
| All-cause rehospitalisation | SMR01 | Subsequent SMR01 hospital admission, for any cause. |
| CV rehospitalisation | SMR01 | Subsequent hospital admission with ICD-10 codes relating to a CV condition in the primary or secondary discharge diagnostic position: I00-I99, O903 (PPCM). |
| First subsequent non-maternity rehospitalisation | SMR01 | Primary discharge diagnostic code in the first episode of the first subsequent hospital admission.<br><br>CV: I00-I99<br><br>PPCM: O903<br><br>Obstetric/gynaecological: O00-O99 (except O903), N70-N99, Z30-Z39<br><br>Respiratory: J00-J99<br><br>Gastrointestinal: K00-K93<br><br>Injury/poisoning/complications of health care: S00-S99, T00-T98 |
| Stroke | SMR01 + patient records | Subsequent hospital admission with ICD-10 codes in any discharge diagnostic position: I60-I64. |

| | | |
|---|---|---|
| | | Events were cross-checked with data collected from patient records and events included if not captured in SMR dataset. |
| Thromboembolism | SMR01 + patient records | Subsequent hospital admission with ICD-10 codes in any discharge diagnostic position: K55.0, I74, N28.0, I26, I80-I82, O22.3 O87.1, O88.2.<br><br>Events were cross-checked with data collected from patient records and events included if not captured in SMR dataset. |
| Advanced heart failure procedures | SMR01 + patients records | Subsequent procedure codes:<br><br>Intra-aortic balloon pump: K561<br><br>Ventricular assist device or intra-aortic balloon pump: K54, K56<br><br>Cardiac transplantation K01, K02<br><br>Events were cross-checked with data collected from patient records and events included if not captured by OPCS coding. |
| Implantable cardioverter defibrillator | Patient records | Implantation of a primary or secondary prevention ICD. |
| Cardiac resynchronisation therapy | Patient records | Implantation of a CRT-pacemaker or defibrillator. |
| LV recovery/decline | Patient records | All data from available follow-up transthoracic echocardiograms collected. Echocardiography databases reviewed where available. In n=7, only the month of the echocardiogram was available (e.g. the echo data were |

| | | |
|---|---|---|
| | | included in a dictated clinic letter without providing the exact date), and the 15th of the month was used. |

**LV recovery**

Complete LV recovery was defined as a LVEF ≥55%, given that the definition of PPCM used in this study was a threshold of 50%. A further three definitions were also examined: partial LV recovery, defined as a LVEF >50%; LV improvement, defined as an increase in LVEF of ≥10%; and LV improvement or complete recovery, defined as an increase in LVEF ≥10% or LVEF ≥55%. Women who died prior to recovery were categorised as unrecovered, but were categorised as recovered if death occurred after recovery. Only women with an echocardiogram at baseline and at least one additional echocardiogram were included in analyses of recovery.

LV decline was defined as a reduction in LVEF of >10% (from the LVEF at the point of complete recovery) and to <50%[108]. Time to decline was calculated from the date of complete recovery. As a sensitivity analyses, rates were examined using a definition that required two consecutive echocardiograms to fulfil the decline criteria (unless the final echocardiogram for a patient, then only one required).

**Medications**

Medications following the end date of the pregnancy were linked from the national Prescribing Informations System (PIS) database, which allows linkage of dispensed community medications from 2009 onwards. The formulary codes used to identify medications are listed in the Methods chapter.

## *5.2.3 Statistical analyses*

Rates of events of clinical outcomes were calculated using the date of index hospitalisation (defined as the start date of the episode of care during which the

diagnosis was assigned) for women with PPCM, the date of baseline echocardiogram for echocardiographic outcomes (e.g. LV recovery) and the date of delivery for controls. The date of delivery was not used for women with PPCM as this would have skewed hospitalisation outcomes, since they were often identified through a subsequent hospitalisation with heart failure (which would be considered 'baseline'). The end date was the date of the event (defined as the start date of the episode of care during which the event occurred, or the date of operation, or the date of death) or, if no event occurred, the censor date (31st December 2017 for clinical outcomes; 31st December 2019 for echocardiographic outcomes). When analysing echocardiographic outcomes, women who had a cardiac transplantation were classified as unrecovered and censored at the date of cardiac transplantation.

Event rates were expressed per 1000 person-years follow-up. Rate ratios and 95% confidence intervals were calculated using the method proposed by Rothman et al, which is described in the Methods chapter, in section 2.7.2. Cumulative incidences were displayed graphically using Kaplan-Meier survival curves. Comparisons were examined using log-rank tests.

Where numbers of events allowed, outcomes for women with PPCM were analysed at 30 days, 6 months, 1 year, 5 years and 10 years from the date of admission to hospital. Only women with complete follow-up were analysed at each time point.

Counts and rates of total (recurrent) hospitalisations were examined, and associations between baseline characteristic and recurrent hospitalisations were modelled using negative binomial regression, offset by follow-up time. Maternal age (≤32 years vs >32 years) and year of year of delivery (2008-2017 vs 1998-2007) were included in all models. The following variables were also included in the multivariable model: socioeconomic deprivation quintile, smoking, pregnancy-induced hypertension, obesity (BMI>30kg/$m^2$) and baseline LVEF ≤35%.

**Prognostic markers**

Prognostic markers were examined in relation to the following clinical outcomes: 1) CV death or CV rehospitalisation; and 2) complete LV recovery (LVEF ≥55%) at 1 year.

CV death or CV rehospitalisation was modelled using Cox proportional hazards regression and LV recovery using logistic regression. In each case, predictor variables were first examined in a univariable fashion. A select number of candidate variables were then taken forward for multivariable analysis. The strongest independent predictors were identified using a backward stepwise selection process, with 2-sided p value <0.1 as the initial significance level for retaining the variable in the model. Missing data were not imputed; complete case analysis was used.

## 5.3 Results

In total, 4 women and their controls were excluded from all analyses, except LV recovery (see above reasons).

Median duration of follow-up of the 221 women with PPCM included in the analyses of death and hospitalisation was 8.3 years (IQR 4.0-12.9) with a total of 1,911 person-years of follow-up. A minimum of 5-year follow-up was available in 157 (71%) women and a minimum of 10-year follow-up in 95 (43%).

Event rates and frequencies of all-cause death, CV death, all-cause rehospitalisation, CV rehospitalisation and a composite of all-cause death or all-cause rehospitalisation and CV death or CV rehospitalisation at 30 days, 6 months, 1 year, 5 years and 10 years and at any time are shown in Tables 5-2 and 5-3. Only women with the potential for complete follow-up at each time point were included (i.e. only women diagnosed prior to 31 Dec 2007 were included in the 10-year follow up group). Each outcome will be discussed more detail.

### *5.3.1 Death and rehospitalisation in women with PPCM and controls*

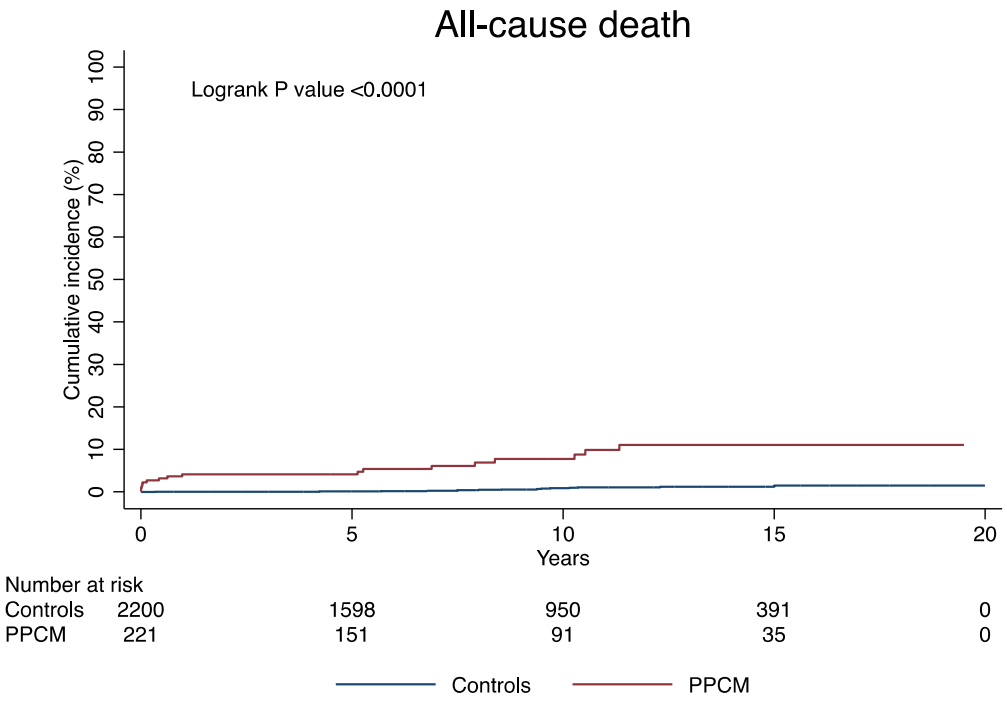
**All-cause death**

A total of 17 (7.7%, 95% CI 4.8-12.1) women with PPCM died from any cause during the study period, with a corresponding rate of 8.9 per 1000 person-years (95% CI 5.5-14.3) (Table 5-2).

The rate of all-cause death in women with PPCM was 12-times that of controls (rate ratio 11.98, 95% CI 5.98-23.99) (Table 5-2 and Figure 5-1).

The proportions of women with PPCM who died from any cause at 30 days, 6 months, 1 year, 5 years were: 2.3 % (95% CI 0.9-5.3), 2.8% (95% CI 1.2-6.0), 3.8% (95% CI 1.9-7.4) and 3.8% (95 % CI 1.7-8.3), respectively (Table 5-3).

**Figure 5-1 Cumulative incidence of all-cause death in women with PPCM and controls**

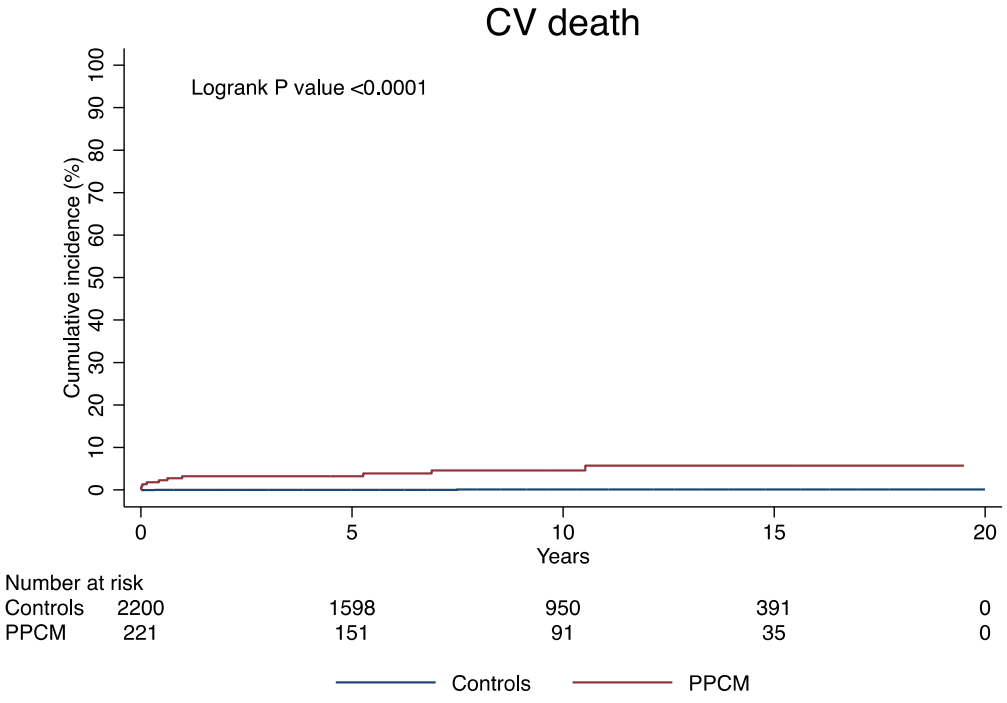


**CV death**

A total of 10 (4.5%, 95% CI 2.4-8.2) women with PPCM died from a CV cause. The corresponding event rate was 5.2 per 1000 person-years (95% CI 2.8-9.7) (Table 5-2).

Numbers, proportions and rates of CV death for controls, and also at specific follow-up times in women with PPCM were not reported due to small numbers, but the cumulative incidence in women with PPCM and controls is shown in Figure 5-2.

**Figure 5-2 Cumulative incidence of CV death in women with PPCM and controls**



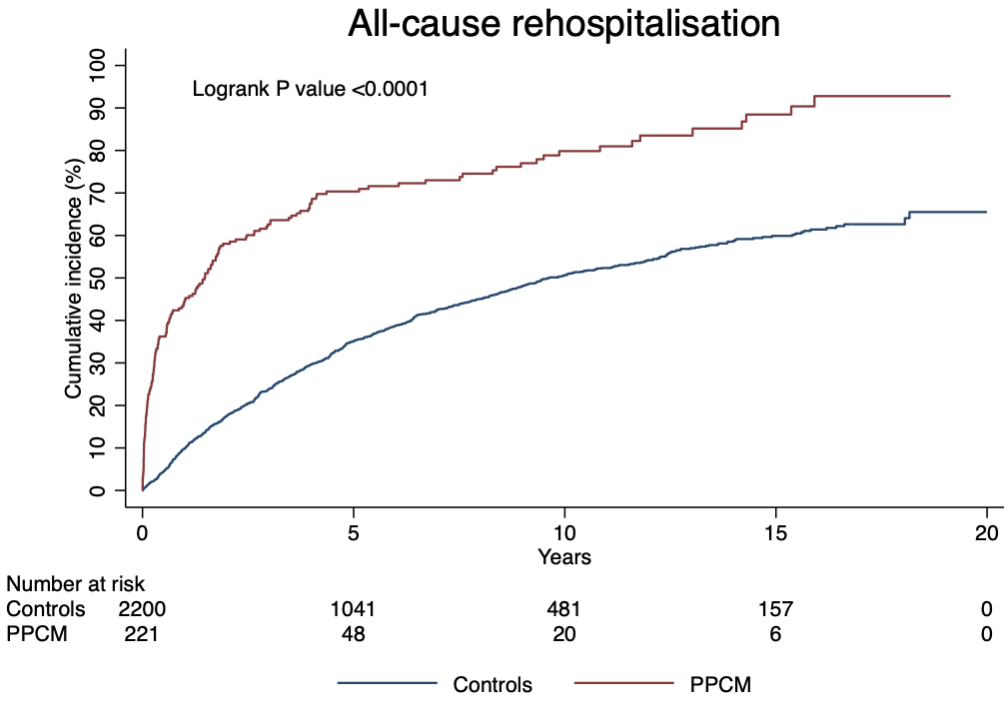
**All-cause rehospitalisation**

A total of 166 (75.1%, 95% CI 69.0-80.4) women with PPCM were rehospitalised for any cause, with a corresponding event rate of 243.6 per 1000 person-years (95% CI 209.2-283.6) (Table 5-2).

The rate of rehospitalisation for any cause in women with PPCM was 3-times that of controls (rate ratio 3.36, 95% CI 2.58-4.36) (Table 5-2 and Figure 5-3).

The proportions of women with PPCM rehospitalised for any cause were: at 30 days, 16.7% (95% CI 12.4-22.3); at 6 months, 35.5% (95% CI 29.4-42.1); at 1 year, 43.6% (95% CI 37.0-50.4); at 5 years, 66.9% (95% CI 59.1-73.8); at 10 years, 77.9% (95% CI 68.3-85.2%) (Table 5-3).

**Figure 5-3 Cumulative incidence of rehospitalisation for any cause in women with PPCM and controls**



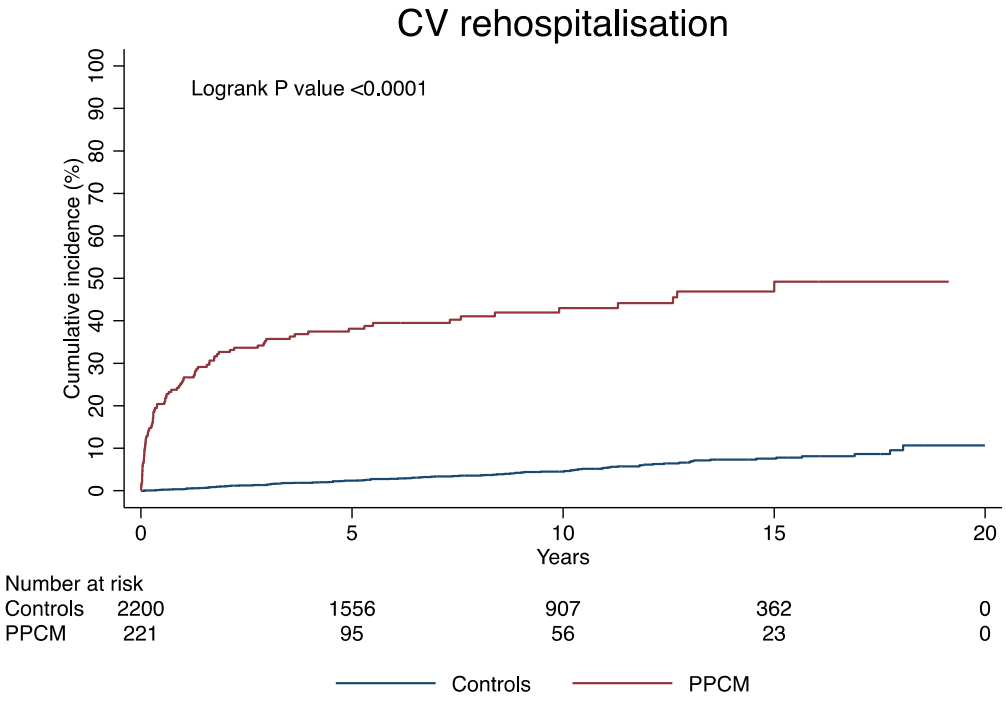
### CV rehospitalisation

Rehospitalisation for a CV cause occurred in a total of 89 (40.3%, 95% CI 34.0-46.9) women with PPCM, with a corresponding event rate of 70.1 per 1000 person-years (95% CI 57.0-86.3) (Table 5-2).

The rate of CV rehospitalisation in women with PPCM was 14-times that of controls (rate ratio 13.58, 95% CI 10.22-18.06) (Table 5-2 and Figure 5-5).

Numbers, proportions and rates of CV rehospitalisation at specific follow-up times in women with PPCM were not reported due to small numbers, but the cumulative incidence in women with PPCM and controls is shown in Figure 5-4.

**Figure 5-4 Cumulative incidence of rehospitalisation for a CV cause in women with PPCM and controls**



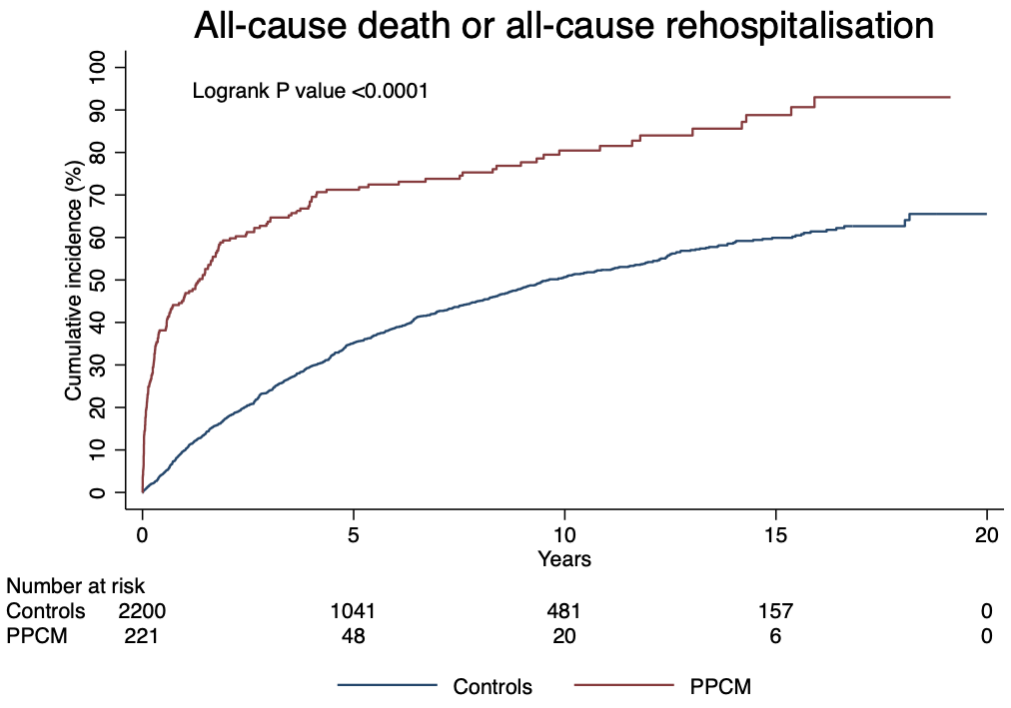
**All-cause death or all-cause rehospitalisation**

The composite of all-cause death or all-cause rehospitalisation occurred in 172 (77.8%, 95% CI 71.8-82.8) women with PPCM, with a corresponding event rate of 252.4 per 1000 person-years (95% CI 217.4-293.1) (Table 5-2).

The rate of all-cause death or all-cause rehospitalisation in women with PPCM was 3-times that of controls (rate ratio 3.47, 95% CI 2.68-4.51) (Table 5-2 and Figure 5-5).

The proportions of women with PPCM who died from or were rehospitalised for any cause were: at 30 days, 19.0% (95% CI 14.3-24.8); at 6 months, 37.8% (95% CI 31.6-44.5); at 1 year, 46.0% (95% CI 39.3-52.8); at 5 years, 69.4% (95% CI 61.7-76.2); and at 10 years, 78.9% (95% CI 69.5-86.1) (Table 5-3).

**Figure 5-5 Cumulative incidence of all-cause death or all-cause rehospitalisation in women with PPCM and controls**



**CV death or CV rehospitalisation**

The composite of CV death or CV rehospitalisation occurred in 93 (42.1%, 95% CI 35.7-48.7) women with PPCM, with a corresponding event rate of 73.3 per 1000 person-years (95% CI 59.8-89.8) (Table 5-2).

The rate of CV death or CV rehospitalisation in women with PPCM was 14-times that of controls (rate ratio 14.06, 95% CI 10.61-18.62) (Table 5-2 and Figure 5-6).

The proportions of women with CV death or CV rehospitalisation were 10.4% (95% CI 7.0-15.2) at 30 days, 21.7% (95% CI 16.7-27.2) at 6 months, 27.5% (95% CI 21.9-33.9) at 1 year, 38.2% (95% CI 30.9-46.1) at 5 years and 38.9% (95% CI 29.6-49.2) at 10 years (Table 5-3).

**Figure 5-6 Cumulative incidence of CV death or CV rehospitalisation in women with PPCM and controls**

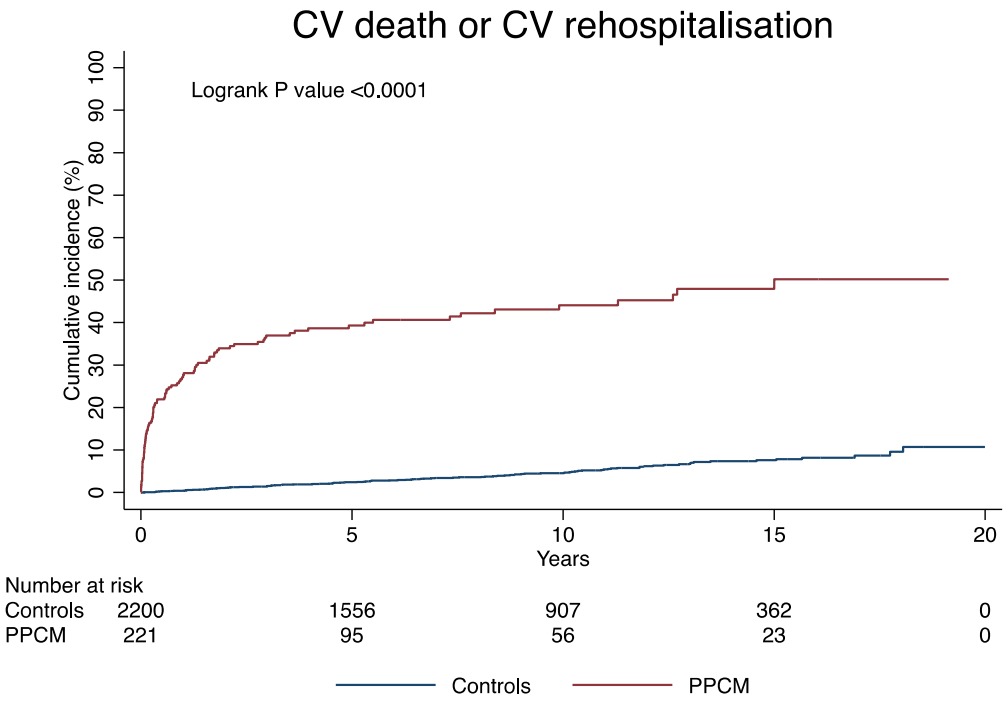


**Table 5-2 Frequency and rates of death and rehospitalisation in women with PPCM and controls from 1998-2017**

| | PPCM N=221 | Controls N=2210 | Rate ratio (95% CI) |
|---|---|---|---|
| **All-cause death** | | | |
| No. | 17 | 15 | |
| % (95% CI) | 7.7 (4.8-12.1) | 0.7 (0.4-1.1) | |
| Rate per 1000 person-years (95% CI) | 8.9 (5.5-14.3) | 0.7 (0.4-1.2) | 11.98 (5.98-23.99) |
| **CV death** | | | |
| No. | 10 | <5 | |
| % (95% CI) | 4.5 (2.4-8.2) | | |
| Rate per 1000 person-years (95% CI) | 5.2 (2.8-9.7) | | - |
| **All-cause rehospitalisation** | | | |
| No. | 166 | 971 | |
| % (95% CI) | 75.1 (69.0-80.4) | 44.1 (42.1-46.2) | |
| Rate per 1000 person-years (95% CI) | 243.6 (206.2-283.6) | 72.6 (68.1-77.3) | 3.36 (2.58-4.36) |
| **CV rehospitalisation** | | | |
| No. | 89 | 101 | |
| % (95% CI) | 40.3 (34.0-46.9) | 4.6 (3.8-5.5) | |
| Rate per 1000 person-years (95% CI) | 70.1 (57.0-86.3) | 5.2 (4.2-6.3) | 13.58 (10.22-18.06) |
| **All-cause death or all-cause rehospitalisation** | | | |
| No. | 172 | 972 | |
| % (95% CI) | 77.8 (71.8-82.8) | 44.2 (42.1-46.3) | |
| Rate per 1000 person-years (95% CI) | 252.4 (217.4-293.1) | 72.6 (68.2-77.4) | 3.47 (2.68-4.51) |
| **CV death or CV rehospitalisation** | | | |
| No. | 93 | 102 | |
| % (95% CI) | 42.1 (35.7-48.7) | 4.6 (3.8-5.6) | |
| Rate per 1000 person-years (95% CI) | 73.3 (59.8-89.8) | 5.2 (4.3-6.3) | 14.06 (10.61-18.62) |

**Table 5-3 Frequency and rates of death and rehospitalisation in women with PPCM at 30 days, 6 months, 1 year, 5 years and 10 years**

| | 30 days N=221 | 6 months N=217 | 1 year N=211 | 5 years N=157 | 10 years N=95 |
|---|---|---|---|---|---|
| **All-cause death** | | | | | |
| No. | 5 | 6 | 8 | 6 | <5 |
| % (95% CI) | 2.3 (0.9-5.3) | 2.8 (1.2-6.0) | 3.8 (1.9-7.4) | 3.8 (1.7-8.3) | |
| **All-cause rehospitalisation** | | | | | |
| No. | 37 | 77 | 92 | 105 | 74 |
| % (95% CI) | 16.7 (12.4-22.3) | 35.5 (29.4-42.1) | 43.6 (37.0-50.4) | 66.9 (59.1-73.8) | 77.9 (68.3-85.2) |
| **All-cause death or all-cause rehospitalisation** | | | | | |
| No | 42 | 82 | 97 | 109 | 75 |
| % (95% CI) | 19.0 (14.3-24.8) | 37.8 (31.6-44.5) | 46.0 (39.3-52.8) | 69.4 (61.7-76.2) | 78.9 (69.5-86.1) |
| **CV death or CV rehospitalisation** | | | | | |
| No. | 23 | 47 | 58 | 60 | 37 |
| % (95% CI) | 10.4 (7.0-15.2) | 21.7 (16.7-27.7) | 27.5 (21.9-33.9) | 38.2 (30.9-46.1) | 38.9 (29.6-49.2) |

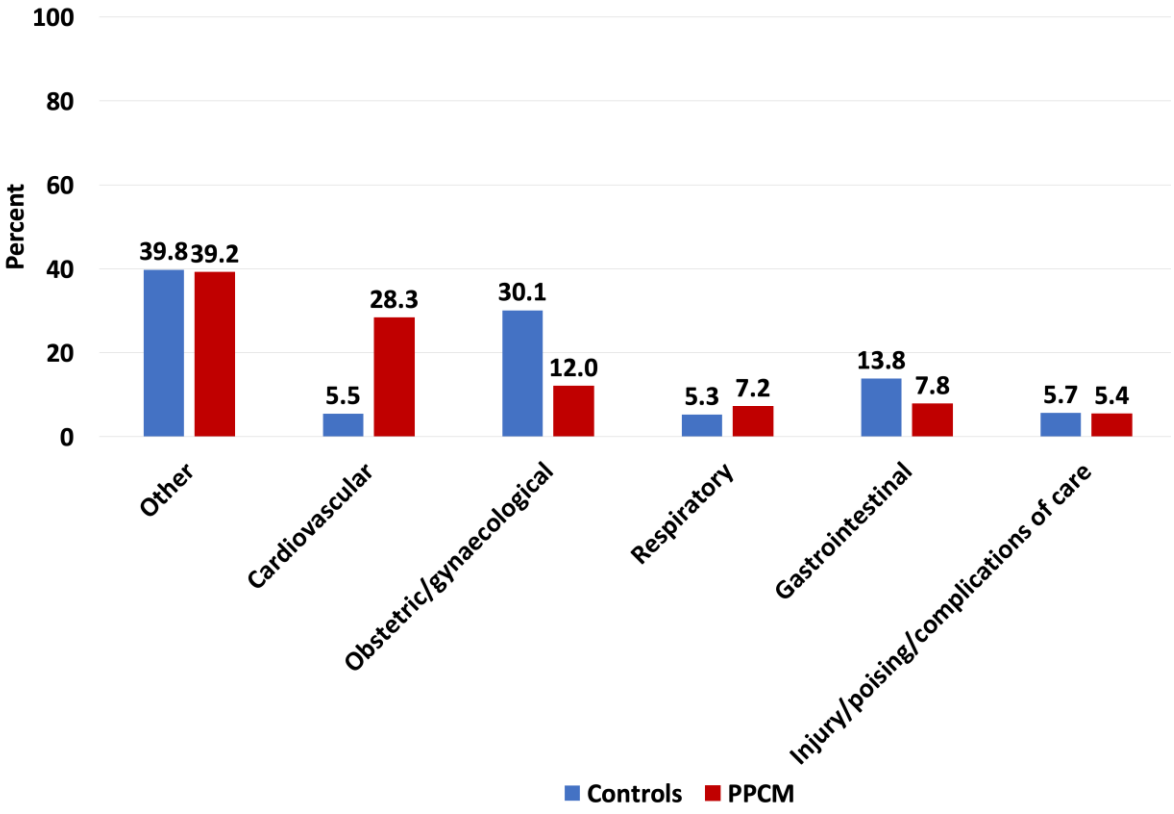
*Only women with the potential to have complete follow-up at each time point were included.*

### *5.3.2 First subsequent non-maternity hospitalisation*

The cause of the first subsequent non-maternity hospital admission (defined as the primary ICD-10 discharge code in the first episode of the first subsequent hospital attendance) was CV in 28% of women with PPCM and in 5% of controls (Figure 5-7).

As a sensitivity analysis, the definition of 'CV' was expanded to include PPCM, and also cardiac signs and/or symptoms (e.g. breathlessness, syncope, oedema), cardiac procedures (e.g. diagnostic cardiac investigations) and admissions related to the management of a cardiac device. With this expanded definition, a CV cause accounted for 46% of first subsequent hospitalisations in women with PPCM and for 8% in controls.

**Figure 5-7 Causes of first subsequent non-maternity hospitalisation in women with PPCM and controls**



### *5.3.3 Recurrent rehospitalisations and total length of stay*

After the index presentation, there were a total of 894 subsequent rehospitalisations for any cause among 221 women with PPCM, resulting in a total of 2621 days in hospital (Table 5-4). Overall, 21% of women had a single subsequent rehospitalisation and 54% had two or more. A total of 12% of women had at least two subsequent rehospitalisations within 6 months, 20% within 1 year, 45% within 5 years and 56% within 10 years. The cumulative numbers of days spent in hospital were 653 by 6 months, 821 by 1 year, 1733 by 5 years and 2227 by 10 years. Examining subsequent rehospitalisations for a CV cause, there were a total of 245 subsequent rehospitalisations. At least two further CV rehospitalisations occurred in 23% of women overall, in 4% by 6 months, in 7% by 1 year, in 19% by 5 years and in 25% by 10 years.

Due to the way data were extracted, the definition of 'CV' used to identify recurrent CV rehospitalisations described here did not include the ICD-10 code specifically for PPCM (O903), unlike the analyses of first CV rehospitalisation presented in the earlier section. However, a sensitivity analysis of subsequent rehospitalisations including a PPCM code (in the primary or secondary diagnostic discharge position) showed that there were only ten additional subsequent rehospitalisations with a PPCM discharge code among 10 women, that were not captured through the co-presence of a CV ('I') code also in the primary or secondary diagnostic position.

**Table 5-4 Total subsequent hospitalisations in women with PPCM**

| | **All N=221** No. (%) | **6 months N=217** No. (%) | **1 year N=211** No. (%) | **5 years N=157** No. (%) | **10 years N=95** No. (%) |
|---|---|---|---|---|---|
| **All-cause** | | | | | |
| 0 | 55 (24.9) | 140 (64.5) | 119 (56.4) | 52 (33.1) | 21 (22.1) |
| ≥1 | 166 (75.1) | 77 (35.5) | 92 (43.6) | 105 (66.9) | 74 (77.9) |
| ≥2 | 119 (53.8) | 26 (12.0) | 42 (19.9) | 71 (45.2) | 53 (55.8) |
| Total number | 894 | 128 | 200 | 565 | 753 |
| Total stay – days | 2621 | 653 | 821 | 1733 | 2227 |
| **CV** | | | | | |
| 0 | 135 (61.1) | 175 (80.6) | 159 (75.4) | 101 (64.3) | 59 (62.1) |
| ≥1 | 86 (38.9) | 42 (19.4) | 52 (24.6) | 56 (35.7) | 36 (37.9) |
| ≥2 | 50 (22.6) | 9 (4.1) | 15 (7.1) | 30 (19.1) | 24.0 (25.3) |
| Total number | 245 | 58 | 77 | 170 | 225 |

**Risk of recurrent hospitalisations**

There was no statistically significant difference in age-adjusted (≤32 years vs >32 years) rates of recurrent hospitalisations between 2008-2017 and 1998-2007, neither for hospitalisations for any cause, nor for hospitalisations for a CV cause (any cause IRR 1.34, 95% CI 0.92-1.96; CV cause IRR 1.74, 95% CI 0.96-3.16) (Table 5-5).

On multivariable analysis, including year of delivery (2008-2017 vs 1998-2007), age (≤32 years vs >32 years), socioeconomic deprivation quintile, smoking (current or former), obesity (BMI>30kg/$m^2$), pregnancy-induced hypertension and baseline LVEF ≤35%, the rate of recurrent hospitalisations for any cause was greater in women who delivered in 2008-2017 than in those who delivered in 1998-2007 (IRR 1.76, 95% CI 1.17-2.64) and in women with a smoking history compared to those without (IRR 2.02, 95% CI 1.35-3.02).

The findings were similar when examining the rate of recurrent hospitalisations for a CV cause (women who delivered in 2008-2017 vs. those who delivered in 1998-2007 IRR 1.96, 95% CI 1.04-3.70; women with a smoking history vs. those without IRR 2.86, 95% CI 1.55-5.26). One additional finding was a lower rate of recurrent CV hospitalisation in women in the least deprived quintile, as compared to women in the most deprived quintile (IRR 0.24, 95% 0.09-0.64).

**Table 5-5 Risk of recurrent hospitalisations in women with PPCM**

| | Any cause | | CV cause | |
|---|---|---|---|---|
| | IRR (95% CI) | P value | IRR (95% CI) | P value |
| **Age and year adjusted** | | | | |
| N=221 with complete data in final model | | | | |
| **Year** | | | | |
| 1998-2007 | 1.00 | | 1.00 | |
| 2008-2017 | 1.34 (0.92-1.96) | 0.128 | 1.74 (0.96-3.16) | 0.070 |
| **Age** | | | | |
| ≤32 years | 1.00 | | 1.00 | |
| >32 years | 1.50 (1.03-2.20) | 0.036 | 1.04 (0.57-1.89) | 0.907 |
| **Multivariable model** | | | | |
| N=180 with complete data in final model | | | | |
| **Year** | | | | |
| 1998-2007 | 1.00 | | 1.00 | |
| 2008-2017 | 1.76 (1.17-2.64) | 0.006 | 1.96 (1.04-3.70) | 0.039 |
| **Age** | | | | |
| ≤32 years | 1.00 | | 1.00 | |
| >32 years | 1.14 (0.77-1.70) | 0.508 | 0.75 (0.41-1.38) | 0.357 |
| **Deprivation quintile** | | | | |
| 1 (most deprived) | 1.00 | | 1.00 | |
| 2 | 1.06 (0.61-1.85) | 0.825 | 0.85 (0.36-2.02) | 0.714 |
| 3 | 0.85 (0.46-1.56) | 0.591 | 1.03 (0.43-2.46) | 0.955 |
| 4 | 0.77 (0.42-1.42) | 0.403 | 0.84 (0.34-2.07) | 0.697 |
| 5 | 0.65 (0.36-1.18) | 0.158 | 0.24 (0.09-0.64) | 0.005 |
| **Smoking** | | | | |
| No | 1.00 | | 1.00 | |
| Yes | 2.02 (1.35-3.02) | 0.001 | 2.86 (1.55-5.26) | 0.001 |
| **Body mass index** | | | | |
| ≤30kg/$m^2$ | 1.00 | | 1.00 | |
| >30kg/$m^2$ | 1.32 (0.87-2.01) | 0.194 | 1.25 (0.66-2.37) | 0.491 |
| **Pregnancy-induced hypertension** | | | | |
| No | 1.00 | | 1.00 | |
| Yes | 0.88 (0.57-1.36) | 0.565 | 1.06 (0.54-2.07) | 0.873 |
| **LVEF** | | | | |
| >35% | 1.00 | | 1.00 | |
| ≤35% | 0.98 (0.67-1.44) | 0.914 | 1.35 (0.75-2.45) | 0.314 |

*IRR = incidence rate ratio; LVEF = left ventricular ejection fraction*

### *5.3.4 Other subsequent events: advanced heart failure procedures, stroke and thromboembolism*

Table 5-6 shows the proportion of women with advanced heart failure outcomes, stroke and thromboembolic events. Median duration of follow-up of the 221 women with PPCM included in the analyses of other subsequent events was the same as that for death and rehospitalisation: 8.3 years (IQR 4.0-12.9) with a total of 1,911 person-years of follow-up. A minimum of 5-year follow-up was available in 157 (71%) women and a minimum of 10-year follow-up in 95 (43%). The advanced heart failure procedures examined were: insertion of intra-aortic balloon pump, VAD, ECMO, or cardiac transplantation. Due to small numbers, in line with NHS NSS requirements for reporting small numbers, a composite of VAD/ECMO and cardiac transplantation was reported.

Overall, the composite outcome of CV death, intra-aortic balloon pump, VAD, ECMO or cardiac transplantation occurred in 10% (95% CI 7-15) of women; 7% (95% CI 4-12) had an intra-aortic balloon pump and 4% (95% CI 2-7) had either VAD, ECMO or cardiac transplantation. The rate of CV death, intra-aortic balloon pump, VAD, ECMO or cardiac transplantation was 12.6 per 1000 person-years (95% CI 8.4-18.9) and the cumulative incidence is shown in Figure 5-8.

A subsequent stroke or thromboembolic event occurred in 8% (95 %CI 5-12); this did not include events that occurred during the index admission. The cumulative incidence of stroke or thromboembolism is shown in Figure 5-9.

**Table 5-6 Other subsequent events in women with PPCM**

| | N=221 |
|---|---|
| **CV death, IABP, VAD, ECMO or cardiac transplantation** | |
| No. | 23 |
| % (95% CI) | 10.4 (7.0-15.2) |
| Rate per 1000 person-years (95% CI) | 12.6 (8.4-18.9) |
| **Intra-aortic balloon pump** | |
| No. | 16 |
| % (95% CI) | 7.2 (4.5-11.5) |
| **VAD, ECMO or cardiac transplantation** | |
| No. | 8 |
| % (95% CI) | 3.6 (1.8-7.1) |
| **Stroke after index presentation** | |
| No. | 7 |
| % (95% CI) | 3.2 (1.5-6.5) |
| Rate per 1000 person-years (95% CI) | 3.8 (1.8-7.9) |
| **Thromboembolism after index presentation** | |
| No. | 14 |
| % (95% CI) | 6.3 (3.8-10.4) |
| Rate per 1000 person-years (95% CI) | 7.6 (4.5-12.9) |
| **Stroke or thromboembolism after index presentation** | |
| No. | 17 |
| % (95% CI) | 7.7 (4.8-12.1) |
| Rate per 1000 person-years (95% CI) | 9.4 (5.8-15.1) |

**Figure 5-8 Cumulative incidence of CV death, IABP, VAD, ECMO or cardiac transplantation**

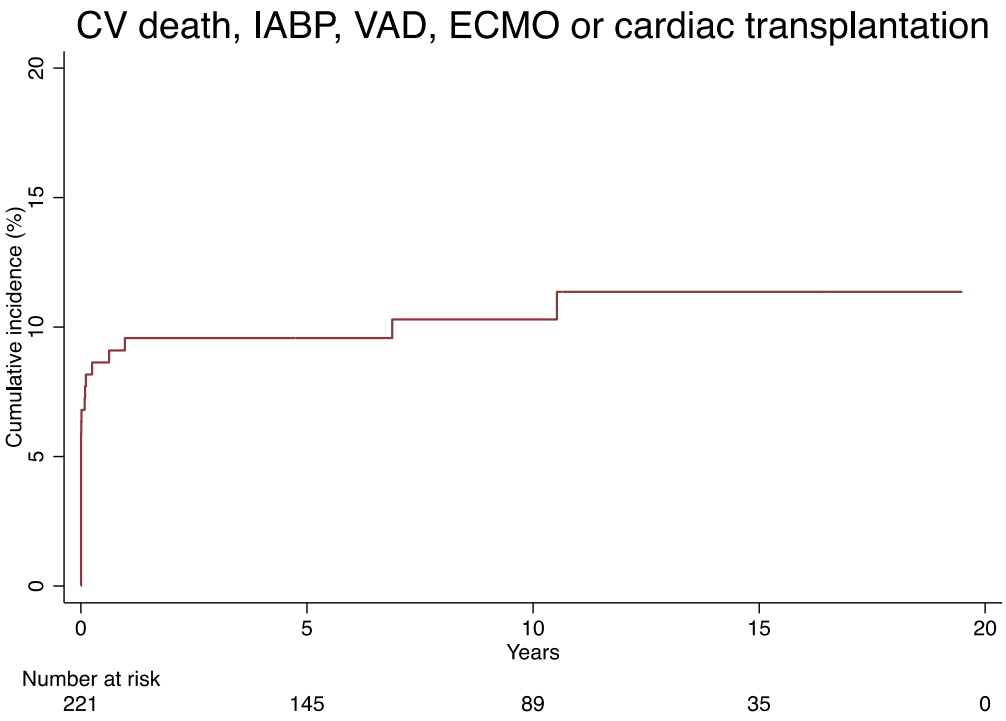
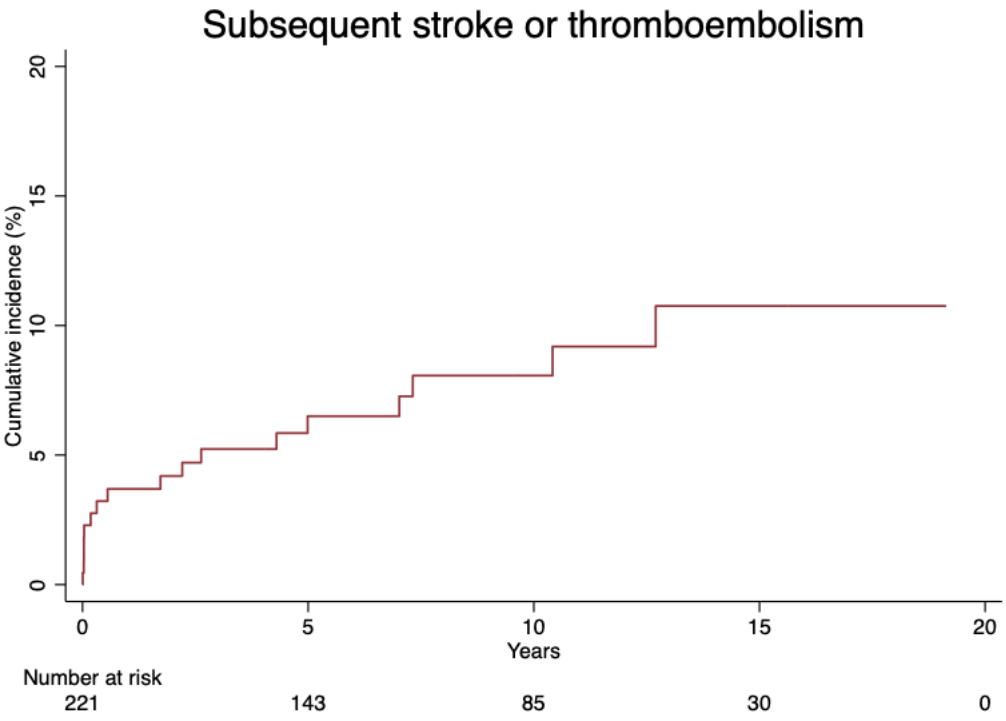



**Figure 5-9 Cumulative incidence of subsequent stroke or thromboembolism**



### *5.3.5 Implantable cardiac devices*

Of 218 women with data on implantable cardiac devices, 20 (9%, 95% CI 6-14) received either an implantable cardioverter defibrillator or cardiac resynchronisation therapy, 7 (3%, 95% CI 2-7) cardiac resynchronisation therapy and 18 (8%, 95% CI 5-13) an implantable cardioverter defibrillator (either alone or as part of cardiac resynchronisation therapy) (Table 5-7). Of those who received an implantable cardioverter defibrillator, it was a primary prevention device in 61% and a secondary prevention device in 39%. The rate of implantable cardiac devices was 11.4 per 1000 patient-years (95% CI 7.4-17.7) and the cumulative incidence is shown in Figure 5-10.

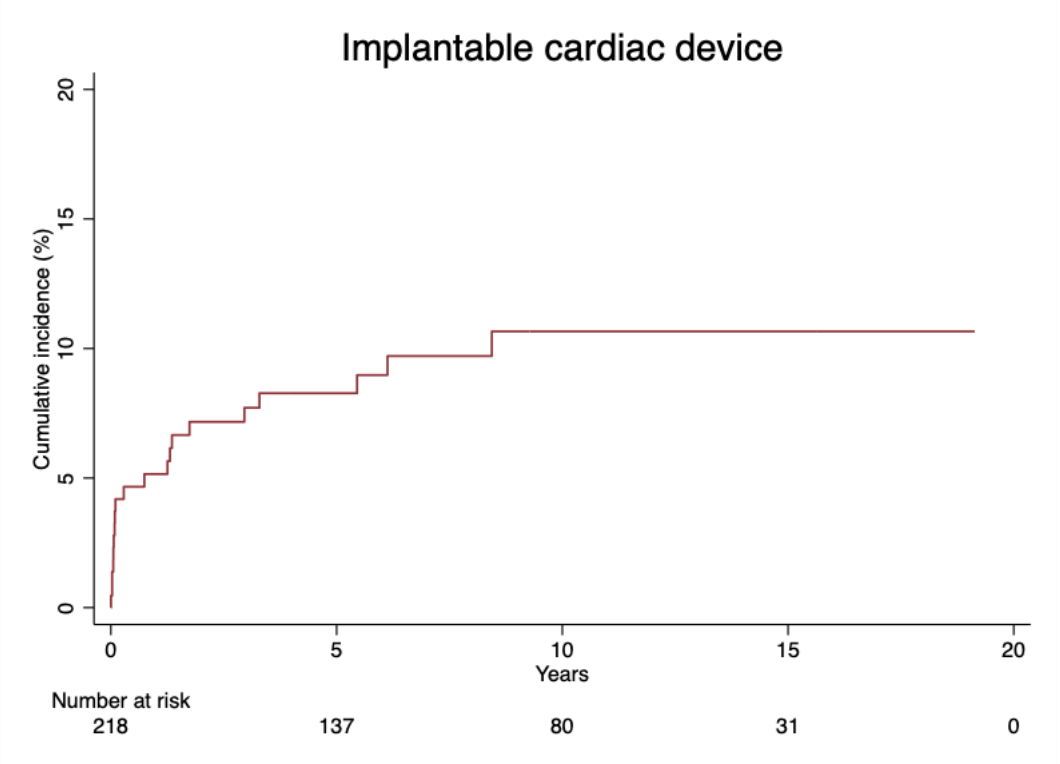
In total, 17 women had an implantable cardioverter defibrillator and had available outcome data, with a total of 159.5 person-years of follow-up. Of these, 29% received appropriate shock therapy.

**Table 5-7 Implantable cardiac devices in women with PPCM**

| | **N=218** |
|---|---|
| **Implantable cardiac device*** | |
| No. | 20 |
| % (95% CI) | 9.2 (6.0-13.8) |
| Rate per 1000 person-years (95% CI) | 11.4 (7.4-17.7) |
| **Cardiac resynchronization therapy** | |
| No. | 7 |
| % (95% CI) | 3.2 (1.5-6.6) |
| **Implantable cardioverter defibrillator** | |
| No. | 18 |
| % (95% CI) | 8.3 (5.3-12.8) |
| **Implantable cardioverter defibrillator type** | |
| Primary prevention – no (%) | 11 (61.1) |
| Secondary prevention – no. (%) | 7 (38.9) |
| **Appropriate shock therapy (n=17 with data)** | 5 (29.4) |

**Implantable cardioverter defibrillator or cardiac resynchronisation therapy*

**Figure 5-10 Cumulative incidence of implantable cardiac devices in women with PPCM**



### *5.3.6 Left ventricular recovery*

Recovery was analysed in 197 women with an echocardiogram at baseline and at least one additional echocardiogram (88% of the total cohort / 98% of those with a baseline echocardiogram). In these women, data from a total of 1408 echocardiograms were collected over a median of 9.7 years (IQR 5.8-14.2), totalling 2,024 person-years of echocardiographic follow-up. Overall, quantitative assessment of LVEF was available in 1062 (75%) echocardiograms. In the remainder, LVEF was assigned according to whether the qualitative assessment was normal (60%), borderline (55%), mildly impaired (50%), moderately impaired (40%) or severely impaired (25%) (in the same way as at baseline, as detailed in Chapter 4).

The median number of echocardiograms per woman was 6 (IQR 4-9). All women could be included in analyses of 6-month and 1-year LV recovery outcomes, since the censor date for echocardiographic outcomes was 2 years after the last possible inclusion of a case (echo censor date 31 December 2019). A total of 167 women had minimum 5-year echocardiographic follow-up and 99 minimum 10-year echocardiographic follow-up or had died within these times.

The main definition of complete LV recovery was a LVEF ≥55% on transthoracic echocardiogram. Given the variation of definitions of LV recovery in the published literature, a further three alternative definitions were examined as sensitivity analyses. The definitions used were:

1) Complete LV recovery: LVEF ≥55%
2) Partial LV recovery: LVEF >50%
3) LV improvement: increase in LVEF of ≥10%
4) LV improvement or complete LV recovery: increase in LVEF ≥10% or LVEF ≥55%

The 5 women without clear quantification of the degree of severity of LV systolic dysfunction at baseline were excluded from the definitions including an improvement of LVEF ≥10% (i.e. numbers 3 and 4).

**Complete LV recovery**

Complete LV recovery occurred in 76% (95% CI 67-81) of women overall (Table 5-9). The median time to complete LV recovery was 214 days (IQR 66-694). The rate of complete LV recovery was 225.6 per 1000 person-years (95% CI 192.1-264.9) and the cumulative incidence is shown in Figure 5-11.

A total of 34% (95% CI 27-40) women had complete recovery within 6 months and 47% (95% CI 40-54) within 1 year (Table 5-8). The proportions of women with complete LV recovery within 5 years and within 10 years were 71% (95% CI 64-77) and 76% (95% CI 67-83), respectively.

**Figure 5-11 Cumulative incidence of complete LV recovery**

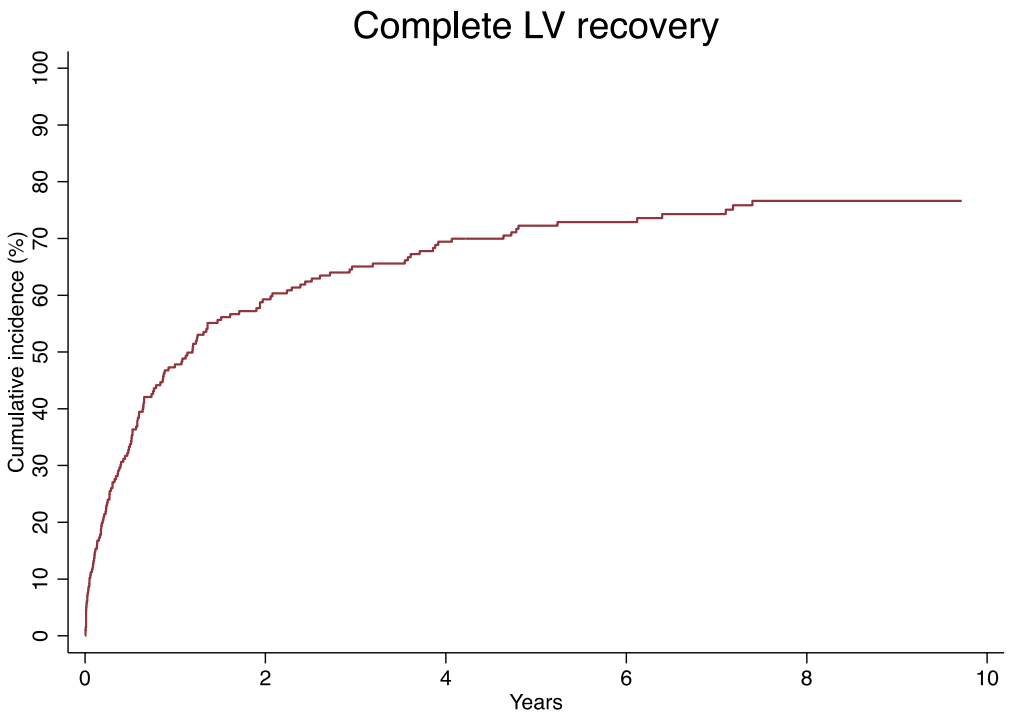


**Table 5-8 LV recovery in women with PPCM**

| | All N=197 | Within 6 months N=197 | Within 1 year N=197 | Within 5 years N=167 | Within 10 years N=99 |
|---|---|---|---|---|---|
| **Complete LV recovery** | | | | | |
| No. | 149 | 66 | 93 | 118 | 75 |
| % (95% CI) | 75.6 (69.1-81.2) | 33.5 (27.2-40.4) | 47.2 (40.3-54.2) | 70.7 (63.3-77.1) | 75.8 (66.2-83.3) |
| Rate per 1000 person-years (95% CI) | 225.6 (192.1-264.9) | | | | |
| **Partial LV recovery** | | | | | |
| No. | 161 | 80 | 108 | 132 | 80 |
| % (95% CI) | 81.7 (75.7-86.5) | 40.6 (33.9-47.7) | 54.8 (47.8-61.7) | 79.0 (72.2-84.6) | 80.8 (71.7-87.5) |
| Rate per 1000 person-years (95% CI) | 302.4 (259.1-352.9) | | | | |
| **LV improvement*** | | | | | |
| No. | 168 | 100 | 128 | 138 | 85 |
| % (95% CI) | 85.3 (79.6-89.6) | 52.1 (45.0-59.1) | 66.7 (59.7-73.0) | 85.2 (78.8-89.9) | 88.5 (80.4-93.6) |
| Rate per 1000 person-years (95% CI) | 463.7 (398.6-539.4) | | | | |
| **LV improvement or complete LV recovery*** | | | | | |
| No. | 172 | 105 | 135 | 141 | 87 |
| % (95% CI) | 89.3 (84.2-93.0) | 54.7 (47.6-61.6) | 70.3 (63.4-76.4) | 87.0 (80.9-91.4) | 90.6 (82.8-95.1) |
| Rate per 1000 person-years (95% CI) | 538.2 (463.5-624.9) | | | | |

**Excluding n=5 women without quantification of severity of LV systolic dysfunction at baseline*

**Alternative definitions of LV recovery**

Partial LV recovery occurred in 82% (95% CI 76-87) of women, LV improvement in 85% (95% CI 80-90) and LV improvement or complete recovery in 89% (95% CI 84-93) (Table 5-8). The corresponding rates per 1000 person-years were: partial LV recovery 302.4 (95% CI 259.1-352.9), LV improvement 463.7 (95% CI 398.6-539.4) and LV improvement or complete recovery 538.2 (95% CI 463.5-624.9). The cumulative incidences of LV recovery according to these three alternative definitions are shown in Figures 5-12 to 5-14.

The median time to partial LV recovery was 187 days (IQR 57-496), to LV improvement was 151 days (IQ 34-578) and to LV improvement or complete recovery was 135 days (IQR 30-437).

**Figure 5-12 Cumulative incidence of partial LV recovery**

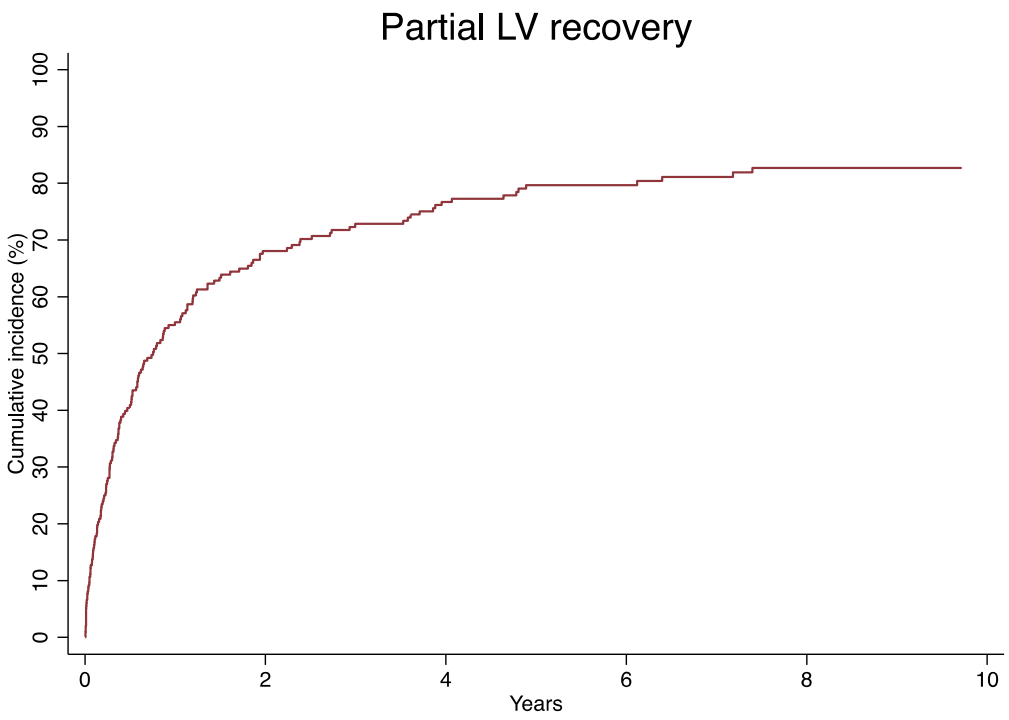
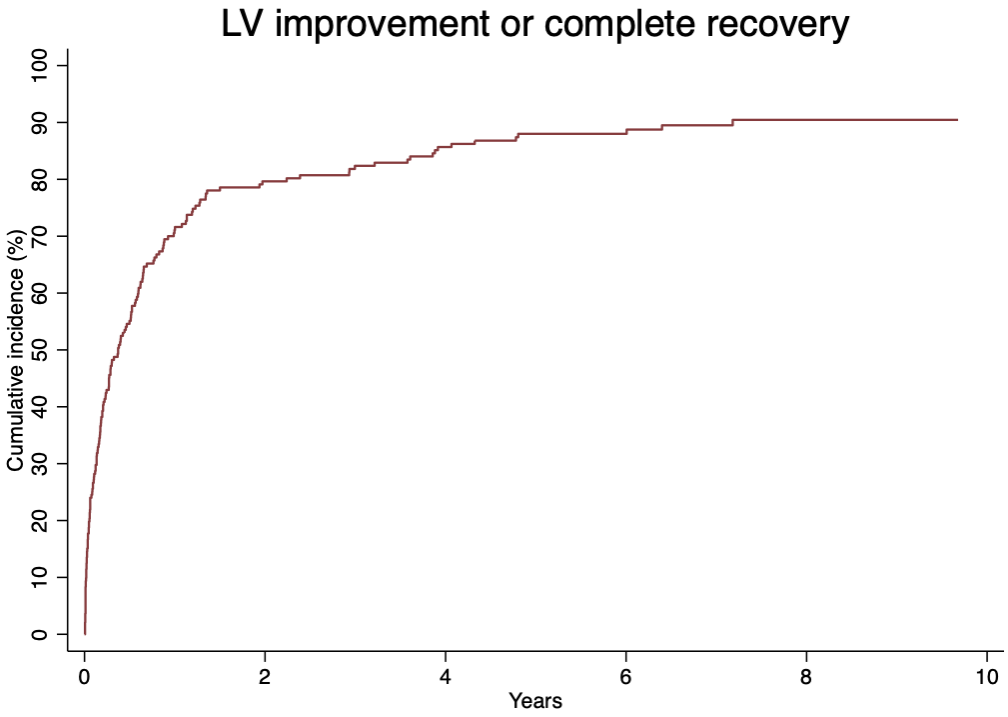


**Figure 5-13 Cumulative incidence of LV improvement**


**Figure 5-14 Cumulative incidence of LV improvement or complete recovery**



## CV death and CV rehospitalisation in women with and without complete LV recovery

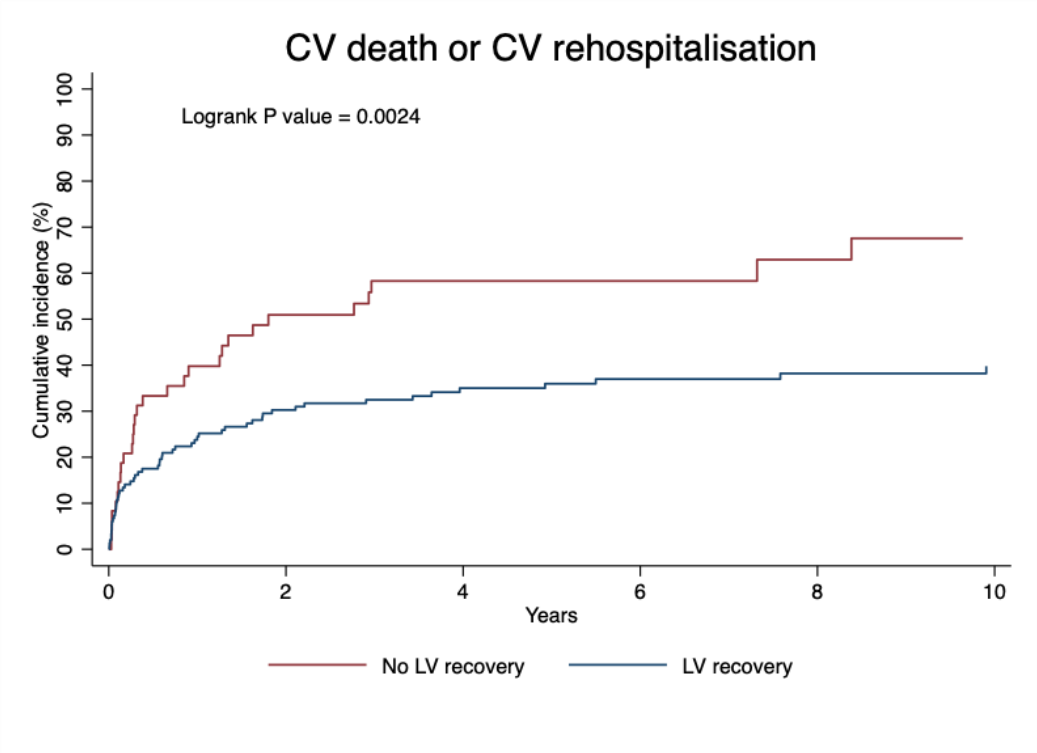
The numbers/proportions of women with and without complete LV recovery who experienced a CV death or CV rehospitalisation were 57/149, 38% (95% CI 31-46) and 29/48, 60% (95% CI 46-73), respectively (Table 5-9). The rate of CV death or CV hospitalisation was 63.6 per 1000 person-years (95% CI 49.1-82.5) in women with LV recovery and 186.5 per 1000 person-years (95%CI 129.6-268.4) in women without LV recovery. Women without LV recovery had a rate of CV death or CV rehospitalisation 3-times that of women with LV recovery (rate ratio 2.93, 95% CI 1.87-4.58). Figure 5-15 shows the cumulative incidence of CV death or CV rehospitalisation according to whether not women went on to have complete LV recovery.

**Table 5-9 CV death or CV rehospitalisation in women with PPCM with and without LV recovery**

| | LV recovery N=149 | | | No LV recovery N=48 | | | |
|---|---|---|---|---|---|---|---|
| | **No.** | **% (95% CI)** | **Rate per 1000 person-years (95% CI)** | **No.** | **% (95% CI)** | **Rate per 1000 person-years (95% CI)** | **IRR (95% CI)** |
| CV death or CV rehospitalisation | 57 | 38.3 (30.7-46.3) | 63.6 (49.1-82.5) | 29 | 60.4 (45.7-73.4) | 186.5 (129.6-268.4) | 2.93 (1.87-4.58) |

*IRR = incidence rate ratio*

**Figure 5-15 Cumulative incidence of CV death or CV rehospitalisation according to LV recovery**



### *5.3.7 LV decline following recovery*

The frequency and rate of subsequent LV decline was examined in the 149 women with complete LV recovery. Of those, 30% (95% CI 23-38) had a subsequent decline in LV function, defined as a decrease in LVEF of >10% and to below 50% on at least one subsequent transthoracic echocardiogram (Table 5-10).

Using a definition which required these criteria to be fulfilled on two consecutive echocardiograms, unless fulfilled on the final echocardiogram for a patient, the corresponding proportion was 13% (95% CI 9-20). This was termed 'sustained LV decline'.

The median time to LV decline from the date of full LV recovery was 492 days (IQR 102-1441) (or 1.3 years) and to sustained LV decline was 1041 days (IQR 366-2206) (or 2.9 years). Rates of LV decline and of sustained LV decline per 1000 person-years were 40.3 (95% CI 30.1-54.0) and 15.5 (95% CI 10.0-24.0), respectively. The cumulative incidences are shown in Figures 5-16 and 5-17.

**Table 5-10 Subsequent LV decline following complete LV recovery in women with PPCM**

| | **All N=149** |
|---|---|
| **LV decline** | |
| No. | 45 |
| % (95% CI) | 30.2 (23.3-38.1) |
| Rate per 1000 person-years (95% CI) | 40.3 (30.1-54.0) |
| **Sustained LV decline** | |
| No. | 20 |
| % (95% CI) | 13.4 (8.8-20.0) |
| Rate per 1000 person-years (95% CI) | 15.5 (10.0-24.0) |

**Figure 5-16 Cumulative incidence of LV decline**

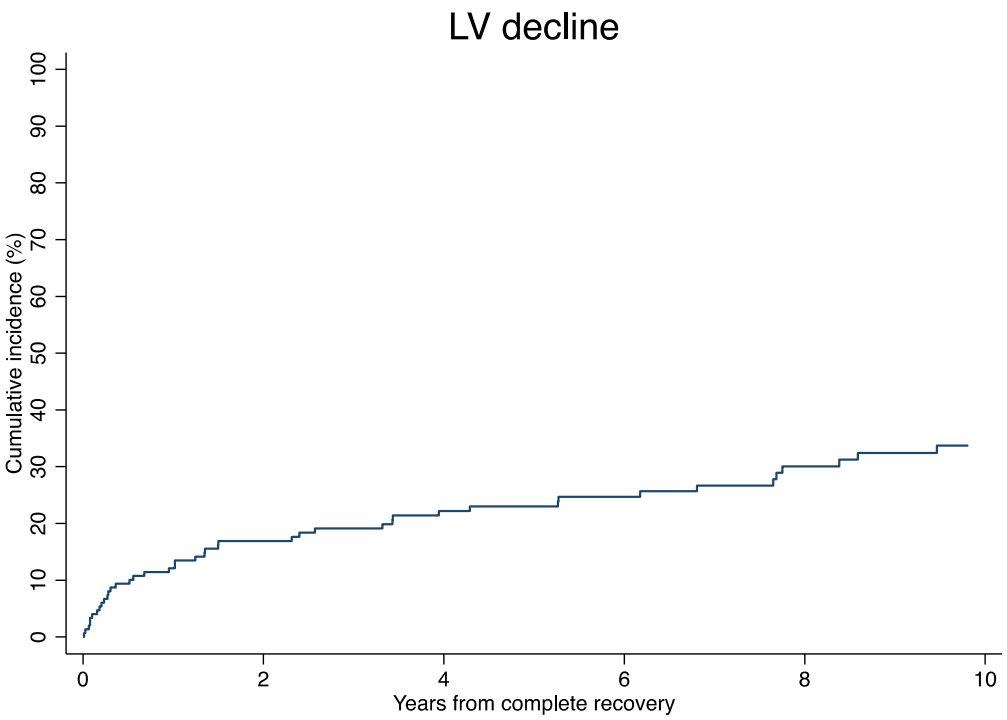
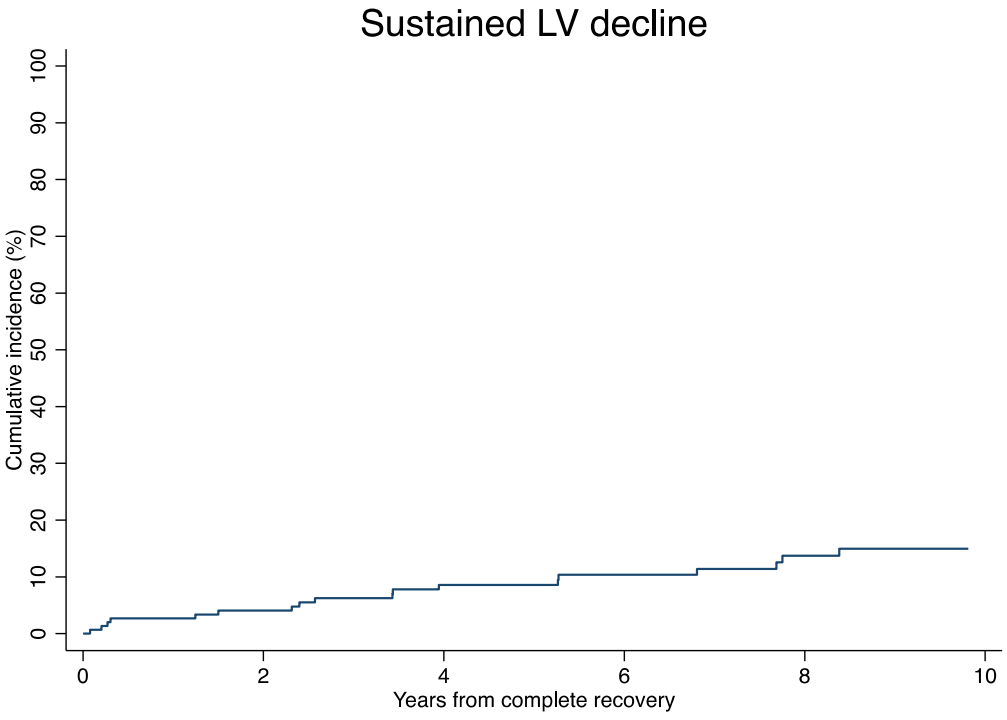



**Figure 5-17 Cumulative incidence of sustained LV decline**



### *5.3.8 Medical therapy*

CV medical therapy at 6 months following the date of the index admission to hospital with PPCM (i.e. the time of diagnosis) is shown in Table 5-11. Data were available for 112 women as the prescribing dataset could only be linked from 2009 onwards. A total of 57.1%, 66.1% and 46.4% were on a beta-blocker, ACE inhibitor or angiotensin receptor blocker, and mineralocorticoid receptor antagonist, respectively. Just under half of women (46.4%) were prescribed a loop diuretic and approximately 1 in 5 women (19.6%) an oral anticoagulant.

Due to small numbers, a more detailed breakdown of medications prescribed was not possible.

**Table 5-11 Community prescriptions of CV medications at 6 months after the index hospitalisation**

| | Total N=112 | Missing |
|---|---|---|
| Beta-blocker | 64 (57.1) | 0 |
| Renin-angiotensin modulator* | 74 (66.1) | 0 |
| Mineralocorticoid receptor antagonist | 31 (27.7) | 0 |
| Loop diuretic | 52 (46.4) | 0 |
| Digoxin | 5 (4.5) | 0 |
| Antiplatelet | 9 (8.0) | 0 |
| Oral anticoagulant | 22 (19.6) | 0 |

**ACE inhibitor, ARB, renin inhibitor or sacubitril-valsartan*
*Data are presented as n (%) for categorical measures.*

### *5.3.9 Prognostic markers*

Associations between the patient characteristics and the following outcomes were examined:

1) CV death or CV rehospitalisation
2) Recovery of LV function (LVEF ≥55%) within 1 year

Clinically relevant candidate variables included in each of the multivariable analyses are shown in Table 5-12.
White cell, lymphocyte and neutrophil count, serum creatinine and serum albumin were log transformed for inclusion in the univariable models.

**Table 5-12 Candidate variables included in the multivariable models**

| |
|---|
| Age (years) |
| Smoking |
| Most socioeconomically deprived quintile |
| BMI >30kg/m$^2$ |
| Pre-eclampsia |
| Parity >2 |
| Heart rate (bpm) |
| Systolic blood pressure (mmHg) |
| Bundle branch block |
| QTc duration (ms) |
| LVEF (%) |
| LVEDD (mm) |

*BMI = body mass index; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter*

**CV death or CV rehospitalisation**

CV death or CV rehospitalisation occurred in 93/221 (42%) women. Women with CV death or CV rehospitalisation more often smoked (current or former), had a greater prevalence of prematurity (estimated gestation <37 weeks), more frequently had bundle branch block, had a longer QTc duration, a lower LVEF at baseline, a larger LV end diastolic diameter, and had a higher lymphocyte count and serum creatinine (Table 5-13).

In an unadjusted Cox regression analysis, the following characteristics were associated with an increased risk of CV death or rehospitalisation: smoking, multiparity, bundle branch block, a greater QTc duration and larger LV end diastolic diameter, whereas a higher LVEF at baseline was associated with a lower risk (Figure 5-18).

Candidate variables listed in Table 5-12 were examined in a multivariable Cox regression analysis using backward selection and a p value <0.1 to retain the variable in the model (n=140 with complete data in final model). The following variables were most strongly associated with a greater risk of CV death or rehospitalisation: QTc duration (per 10ms increase), smoking, greater socioeconomic deprivation and the presence of a bundle branch block on baseline electrocardiogram (Table 5-14).

## Table 5-13 Characteristics of women with and without CV death or CV rehospitalisation

| | No CV death or rehosp. N=128 | CV death or rehosp. N=93 | P value | No CV death or rehosp. Missing | CV death or rehosp. Missing |
|---|---|---|---|---|---|
| Age (years) | 31.9±6.3 | 32.2±5.5 | 0.77 | 0 | 0 |
| Deprivation quintile 1 | 36 (28.3) | 37 (39.8) | 0.075 | 1 | 0 |
| PIH | 48 (37.5) | 28 (30.1) | 0.25 | 0 | 0 |
| Pre-eclampsia | 30 (23.4) | 14 (15.1) | 0.12 | 0 | 0 |
| Prior hypertension | 18 (14.1) | 17 (18.3) | 0.40 | 0 | 0 |
| Prior diabetes | 9 (7.0) | 11 (11.8) | 0.22 | 0 | 0 |
| BMI >30kg/$m^2$ | 39 (35.5) | 26 (31.7) | 0.59 | 18 | 11 |
| Smoking (current/former) | 41 (32.8) | 49 (53.3) | 0.003 | 3 | 1 |
| Parity >2 | 17 (13.3) | 21 (22.6) | 0.070 | 0 | 0 |
| Estimated gestation (weeks) | 38 (35-40) | 38 (37-40) | 0.45 | 2 | 2 |
| Estimated gestation <37weeks | 40 (31.7) | 16 (17.6) | 0.019 | 2 | 2 |
| Systolic blood pressure (mmHg) | 138 (120-158) | 131 (112-150) | 0.084 | 24 | 18 |
| Heart rate (bpm) | 107 (90-120) | 110 (88-128) | 0.19 | 22 | 15 |
| Sinus rhythm | 103 (96.3) | 73 (92.4) | 0.25 | 21 | 14 |
| PR interval (ms) | 140 (127-156) | 134 (124-148) | 0.16 | 26 | 24 |
| QRS duration (ms) | 80 (74-89) | 88 (80-100) | <0.001 | 23 | 20 |
| Bundle branch block | 8 (7.6) | 18 (23.7) | 0.002 | 23 | 17 |
| QTc duration (ms) | 441 (420-474) | 463 (438-495) | 0.003 | 23 | 23 |
| Abnormal R wave progression | | | 0.67 | 23 | 20 |
| No/bundle branch block | 75 (71.4) | 50 (68.5) | | | |
| Yes | 30 (28.6) | 23 (31.5) | | | |
| ST-T wave change | | | 0.55 | 23 | 20 |
| No/bundle branch block | 63 (60.0) | 47 (64.4) | | | |
| Yes | 42 (40.0) | 26 (35.6) | | | |
| Any ECG abnormality | 75 (71.4) | 64 (87.7) | 0.010 | 23 | 20 |
| LVEF (%) | 36.6±10.4 | 32.0±11.1 | 0.004 | 18 | 9 |
| LVEF ≤45% | 81 (73.6) | 72 (85.7) | 0.041 | 18 | 9 |
| LVEF ≤35% | 45 (40.9) | 49 (58.3) | 0.016 | 18 | 9 |
| LVEDD (mm) | 56.0±7.6 | 59.1±7.2 | 0.008 | 28 | 22 |
| Haemoglobin (g/l) | 114 (100-125) | 115 (104-130) | 0.21 | 19 | 10 |
| White blood cells (x10^9/l) | 11.8 (9.1-14.6) | 11.5 (9.2-15.0) | 0.77 | 19 | 10 |
| Lymphocytes (x10^9/l) | 1.7 (1.1-2.0) | 1.9 (1.3-2.5) | 0.018 | 21 | 13 |
| Neutrophils (x10^9/l) | 9.1 (6.1-12.1) | 8.3 (6.5-11.7) | 0.78 | 21 | 13 |
| Platelets (x10^9/l) | 271 (201-375) | 291 (225-422) | 0.12 | 20 | 10 |
| Serum creatinine (μmol/l) | 66 (55-80) | 72 (61-86) | 0.042 | 17 | 10 |
| Serum albumin (g/l) | 30 (25-35) | 31 (27-37) | 0.39 | 23 | 12 |

*PIH = pregnancy-induced hypertension BMI = body mass index; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter*

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Figure 5-18 Unadjusted risk of CV death or CV rehospitalisation

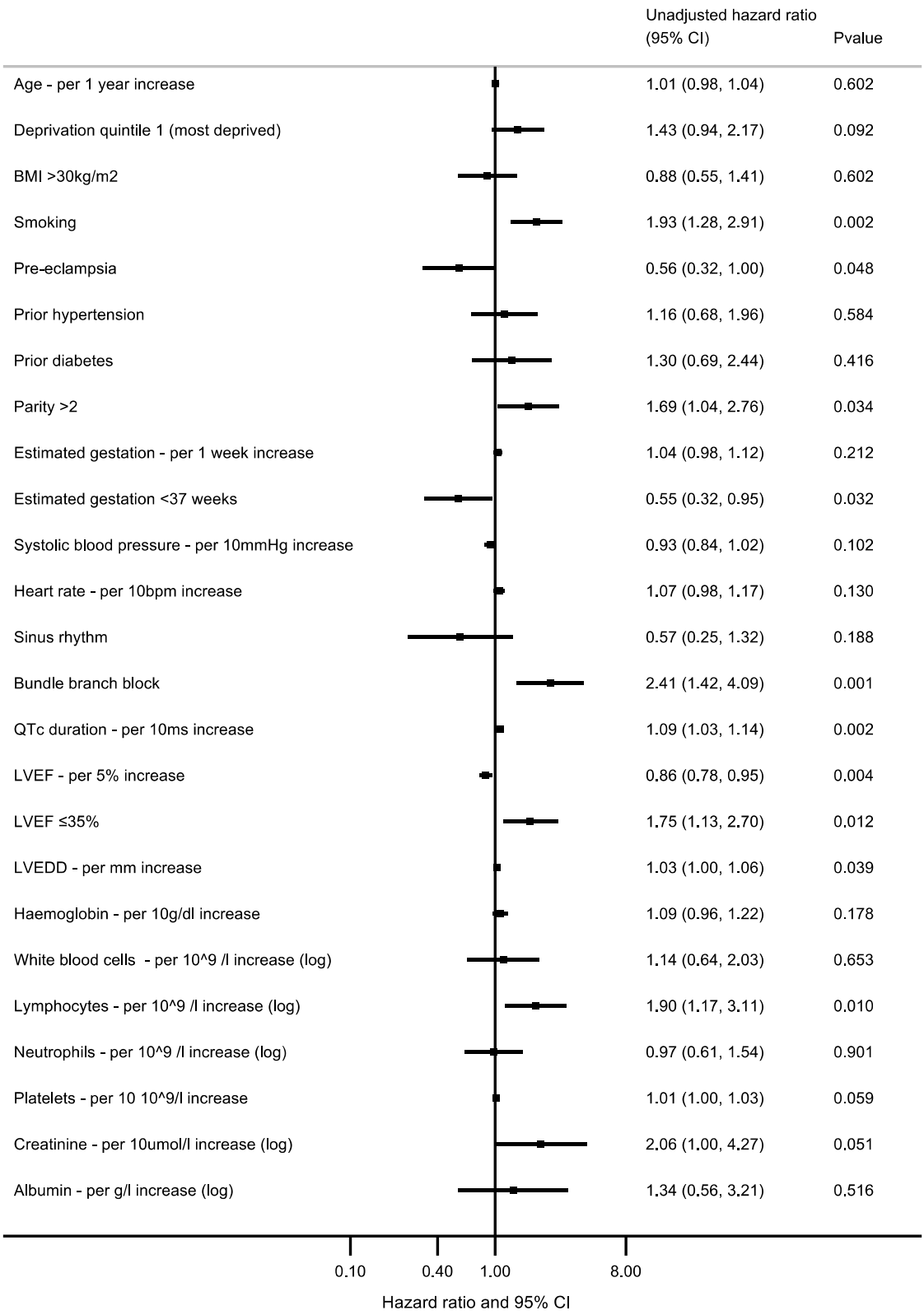


**Table 5-14 Characteristics most strongly associated with CV death or CV rehospitalisation**

| | Hazard ratio (95% CI) | P value |
|---|---|---|
| QTc duration (per 10ms increase) | 1.09 (1.02-1.17) | 0.010 |
| Smoking | 1.89 (1.09-3.27) | 0.023 |
| Deprivation quintile 1 (most deprived) | 1.77 (1.02-3.07) | 0.041 |
| Bundle branch block | 1.93 (1.01-3.71) | 0.047 |

*N=140 with complete data in final model*

## LV recovery

A total of 93/197 (47%) women with a baseline echocardiogram had complete LV recovery within 1 year. Table 5-15 shows characteristics of women with and without complete LV recovery within 1 year. Women with recovery had a lower heart rate, a shorter QTc duration, a higher baseline LVEF and a smaller LV end diastolic diameter.

Similar associations were seen when unadjusted odds of complete LV recovery were examined in a logistic regression model (Figure 5-19).

The candidate variables listed in Table 5-12 were examined in a multivariable logistic regression analysis using backward selection and a p value <0.1 to retain the variable in the mode (n=140 with complete data in final model). Only LV end diastolic diameter was associated with likelihood LV recovery (greater diameter with lower likelihood) (Table 5-16).

## Table 5-15 Characteristics of women with and without LV recovery within 1 year

| | No LV recovery | LV recovery | P value | No LV recovery Missing | LV recovery Missing |
|---|---|---|---|---|---|
| | N=104 | N=93 | | | |
| Age (years) | 32.5±5.6 | 30.9±6.3 | 0.058 | 0 | 0 |
| Deprivation quintile 1 | 39 (37.9) | 31 (33.3) | 0.51 | 1 | 0 |
| PIH | 30 (28.8) | 32 (34.4) | 0.40 | 0 | 0 |
| Pre-eclampsia | 16 (15.4) | 19 (20.4) | 0.36 | 0 | 0 |
| Prior hypertension | 16 (15.4) | 13 (14.0) | 0.78 | 0 | 0 |
| Prior diabetes | 11 (10.6) | 6 (6.5) | 0.30 | 0 | 0 |
| BMI >30kg/$m^2$ | 35 (36.5) | 28 (32.6) | 0.58 | 8 | 7 |
| Smoking (current/former) | 45 (44.1) | 34 (37.4) | 0.34 | 2 | 2 |
| Parity >2 | 20 (19.2) | 12 (12.9) | 0.23 | 0 | 0 |
| Estimated gestation (weeks) | 38 (37-40) | 39 (36-40) | 0.94 | 1 | 3 |
| Estimated gestation <37weeks | 21 (20.4) | 25 (27.8) | 0.23 | 1 | 3 |
| Systolic blood pressure (mmHg) | 135 (119-154) | 132 (120-151) | 0.71 | 12 | 9 |
| Heart rate (bpm) | 112 (97-128) | 103 (89-120) | 0.036 | 8 | 7 |
| Sinus rhythm | 94 (95.9) | 81 (94.2) | 0.59 | 6 | 7 |
| PR interval (ms) | 136 (124-150) | 138 (129-152) | 0.21 | 15 | 12 |
| QRS duration (ms) | 84 (78-96) | 82 (76-94) | 0.36 | 13 | 8 |
| Bundle branch block | 17 (18.5) | 8 (9.3) | 0.078 | 12 | 7 |
| QTc duration (ms) | 455 (432-493) | 440 (423-475) | 0.027 | 16 | 8 |
| Abnormal R wave progression | | | 0.71 | 15 | 8 |
| No/bundle branch block | 63 (70.8) | 58 (68.2) | | | |
| Yes | 26 (29.2) | 27 (31.8) | | | |
| ST-T wave change | | | 0.36 | 14 | 8 |
| No/bundle branch block | 59 (65.6) | 50 (58.8) | | | |
| Yes | 31 (34.4) | 35 (41.2) | | | |
| Any ECG abnormality | 72 (80.9) | 62 (72.9) | 0.21 | 15 | 8 |
| LVEF (%) | 32.4±11.5 | 37.1±9.7 | 0.003 | 4 | 1 |
| LVEF ≤45% | 81 (81.0) | 70 (76.1) | 0.41 | 4 | 1 |
| LVEF ≤35% | 57 (57.0) | 36 (39.1) | 0.013 | 4 | 1 |
| LVEDD (mm) | 58.7±7.7 | 55.7±7.4 | 0.009 | 18 | 8 |
| Haemoglobin (g/l) | 110 (99-128) | 117 (104-125) | 0.46 | 7 | 4 |
| White blood cells (x10^9/l) | 11.5 (9.1-14.6) | 11.8 (9.2-14.7) | 0.67 | 7 | 4 |
| Lymphocytes (x10^9/l) | 1.9 (1.3-2.3) | 1.6 (1.1-2.0) | 0.088 | 11 | 4 |
| Neutrophils (x10^9/l) | 8.4 (6.4-12.1) | 9.4 (6.4-12.2) | 0.47 | 11 | 4 |
| Platelets (x10^9/l) | 295 (222-422) | 280 (204-355) | 0.098 | 7 | 5 |
| Serum creatinine (μmol/l) | 69 (59-83) | 68 (57-81) | 0.89 | 6 | 3 |
| Serum albumin (g/l) | 31 (27-36) | 31 (25-35) | 0.61 | 11 | 6 |

*PIH = pregnancy-induced hypertension; BMI = body mass index; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter*

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Figure 5-19 Unadjusted odds of LV recovery

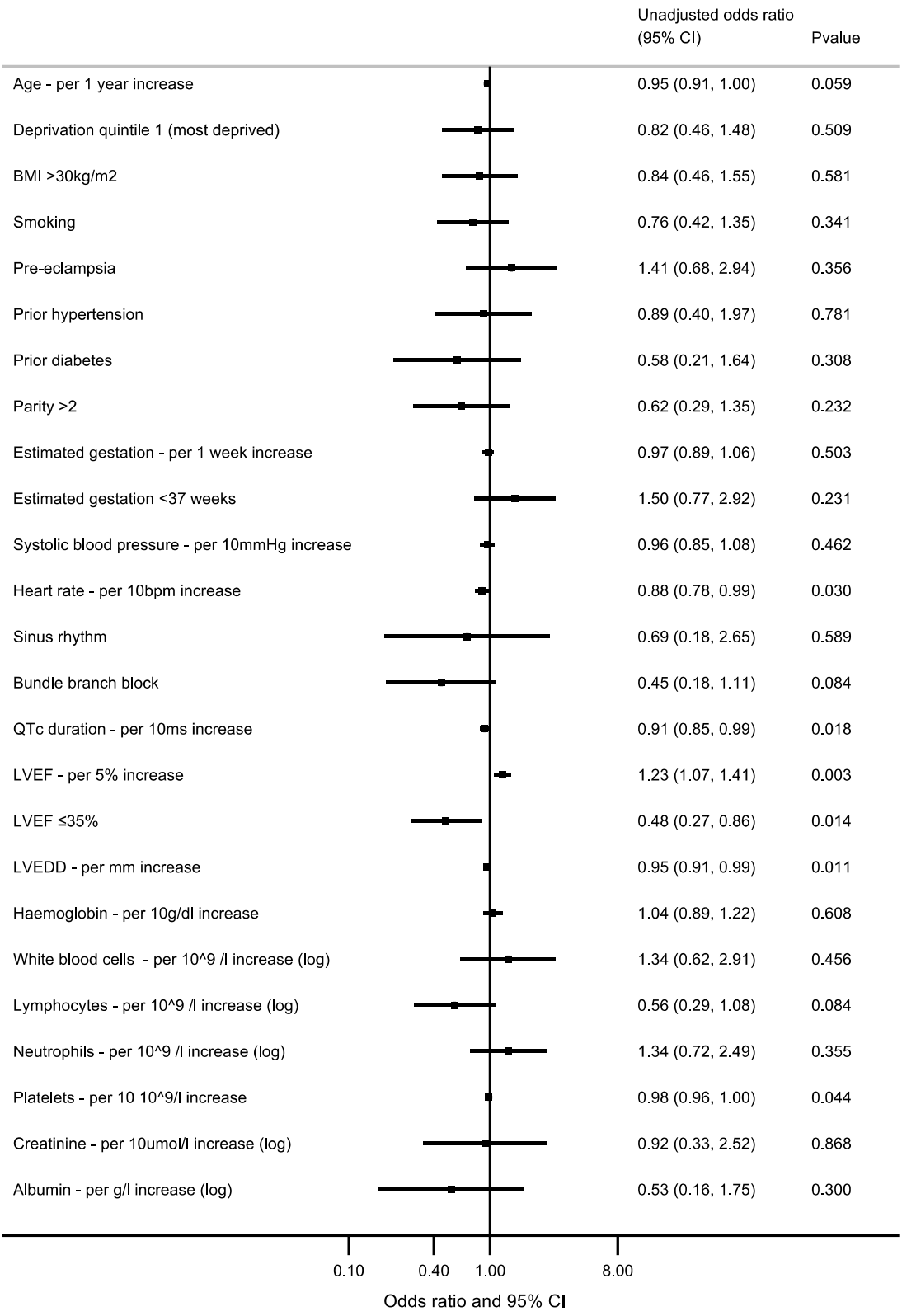


**Table 5-16 Characteristics most strongly associated with LV recovery**

| | Odds ratio (95% CI) | P value |
|---|---|---|
| LVEDD - per mm increase | 0.94 (0.89-0.98) | 0.007 |

*LVEDD = left ventricular end diastolic diameter*
*N=140 with complete data in final model*

## 5.4 Discussion

This chapter describes short- and long-term outcomes for women with PPCM in Scotland over a median follow-up of 8.3 years (9.7 years for echocardiographic outcomes). Overall, 8% of women died, at least one further admission to hospital for any cause and for a CV cause occurred in 75% and 40% of women, respectively. Advanced heart failure procedures (mechanical circulatory support or cardiac transplantation) were required in 4% of women, and 8% had a subsequent stroke or thromboembolism. Similarly, 8% of women received an implantable cardioverter defibrillator. Complete LV recovery occurred in 76% of women over the whole study period (34% within 6 months; 47% within 1 year), and, of those who recovered, 13% had sustained decline of LV systolic function after recovering.

The rate of all-cause mortality was 8.9 per 1000 person-years (95% CI 5.5-14.3), with a case-fatality of 2% at 30 days, 3% at 6 months, and 4% at 1 and 5 years. Reports of early mortality — generally studies reporting in-hospital outcomes using data from the Nationwide Inpatient Sample in North America — suggest death occurs in approximately 1-2% of women, as seen in this Scottish cohort[12, 14, 24, 25, 110, 111, 195]. Similarly, case-fatality at 6 months (3%) and 1 year (4%) in the current study was comparable to that reported in other European studies (2% in Germany at 6 months[66]; 3% in Denmark at 1 year[18]; 4% in European patients enrolled into the ESC PPCM Registry at 6 months[11]). Outcomes vary markedly by region, with case-fatality as high as 19% in Nigeria[103], and 15% in South Africa[83, 85], India[116], and Haiti[6]. It is likely that ethnicity is not only a risk factor for the development of PPCM, but also a prognostic marker. Black women appear to have a worse outcome than women of other races — a trend which is also evident in regions other than sub-Saharan Africa[70, 104]. Sociodemographic factors and access to health services are likely to play a role, as well as genetic and physiological differences. Too few women were non-Caucasian to be able to examine the impact of ethnicity in the Scottish population.

There are only a small number of studies reporting outcomes beyond 5 years for women with PPCM, despite the young age, relative to the general heart failure population, at which they are diagnosed. This is most likely because of how uncommon the condition is, limiting the ability to provide long-term prospective

follow-up. In Scotland, the capacity to link administrative datasets throughout the course of an individual's life allows for a long period of follow-up to be achieved retrospectively. In the current study, a minimum of 10-year follow-up was available in 95 women for clinical outcomes and in 99 women for echocardiographic outcomes. In the current study, case-fatality at 5 years was 4%, but could not be reported at 10 years due to a small number of events (n<5) in the subgroup with complete 10-year follow-up. In 10 contemporary studies (published from the year 2000 onwards), collectively including a total of 495 women (with a range of 10-100 women in each study), and reporting outcomes at between 5 and 9 years, case-fatality ranged from 0-23%[20, 26, 71, 144, 150, 151, 153-155, 196]; the highest case-fatality was reported in women from India and the lowest in women from Germany. Conversely, in 3 European studies, outcomes were better, with 0-4% case-fatality. This is more in keeping with the findings from the current study, despite inclusion of women with a higher LVEF at baseline[150, 151, 154].

Originally, data back to 1986 were provided for the current study, with the aim of reporting outcomes beyond 10 years for some women; however, the inability to validate the majority of cases prior to 1998 rendered this unfeasible. Furthermore, the rapidly expanding pool of evidence-based heart failure therapies over the past two decades may have limited the applicability of such old data to patients with PPCM treated with more contemporary therapies.

Although death is uncommon in patients with PPCM in Western Europe, the condition is associated with substantial morbidity. In the current study, recurrent CV rehospitalisations (i.e. at least two further CV hospitalisation) occurred in 23% of women. Rates of recurrent hospitalisation have not been reported in previous PPCM studies. Traditionally, methods of reporting morbidity in heart failure have focussed only on 'first' events, although in recent years there has been a shift towards examining total, or first and recurrent events, particularly with respect to hospitalisation. This approach is more effective at capturing the full burden of disease and more accurately reflects the entirety of its impact. In chronic heart failure clinical trial populations, approximately 5% of patients have at least two hospitalisations [197], but in observational studies, and in patients recently hospitalised with heart failure, repeated readmissions are more common and may occur in as many as 40-50% of patients[198, 199]. Recurrent

hospitalisations have been shown to occur less frequently in women than in men[197, 200]. In the current study, more than 1 in 5 women had at least two subsequent CV hospitalisations during the whole study and approximately 1 in 14 within 1 year, highlighting the extent of morbidity associated with the condition.

Another key finding was that of a high frequency of LV recovery. Like mortality, reported rates of LV recovery differ widely depending on region. Moreover, there is no universally accepted definition of LV recovery in PPCM, with thresholds of 45-55% being used, generally without consideration of symptom-burden or NYHA class and no requirement for biomarker assessment. Given the retrospective nature of the current study, clinical assessment of the patient was not available at the time of the follow-up echocardiogram and, historically, monitoring of natriuretic peptides was not routinely performed. In the current study, a threshold of 55% (rather than 50%) was chosen to define complete LV recovery for two reasons: first, because the study included women with a LVEF up to 50%, and second, because an LVEF of 50% is not generally accepted as normal. A recent study found that women with pregnancy associated heart failure with preserved ejection fraction (HFpEF) had significantly worse obstetric outcomes than women without heart failure[201]. Sensitivity analyses were conducted in order to assess the impact of using different definitions of LV recovery, also including using a threshold of 50%. Complete LV recovery occurred in 76% of women overall (34% within 6 months, 47% within 1 year, 71% within 5 years and 76% within 10 years) and partial LV recovery in 82% (41% within 6 months, 55% within 1 year, 79% within 5 years and 81% within 10 years). The highest reported rates of recovery at 1 year are from the North American IPAC Registry, in which 72% of women recovered, defined as LVEF ≥50%. In the IPAC study, more than 80% of women were treated with a beta-blocker and angiotensin-converting enzyme or angiotensin receptor blocker and were prospectively followed-up. There is likely to be more aggressive optimisation of therapy at an earlier stage with rigorous prospective follow-up, compared to ‘real life’ practice reflected in observational data. Although the traditional view has been that majority of LV recovery in PPCM occurs in the first year following diagnosis, there is existing evidence from studies with longer follow-up, and now corroborated by the findings from the current study, that recovery can continue to occur beyond this time. The highest prevalence reported in small studies with follow-up extending beyond 5 years is approximately 90%[20, 202], and as many as

60% of patients who recovery may do so beyond 1 year[105]. This was also the case in the current study, with a substantial proportion of women recovering beyond 1 year.

An unanswered question in PPCM is whether or not heart failure therapies should be continued lifelong in the context of recovered LV systolic function. In the current study, 31% deteriorated following recovery and, in 13%, this was 'sustained'. Moreover, there were instances of deterioration which occurred late (beyond a year after recovery). The incidence and timing of LV decline after recovery is not well-established in PPCM. There are only small case reports reporting deterioration of cardiac function following recovery and not using a consistent definition. In one, deterioration occurred in 4 patients (2/71 with complete recovery [defined as LVEF ≥50%] and 2 with partial recovery); in the patients who had completely recovered, deterioration occurred following cessation of medical therapy, but in the patients with partial recovery, deterioration occurred despite continuing medical therapy[105]. In another, deterioration occurred in 2/20 patients with complete recovery (defined as LVEF >50%) and in one with partial recovery, although details about medical therapy were not available[92]. In a third, in 15 patients with full recovery (defined as LVEF >50%), none deteriorated at a mean follow-up of 29 months, despite all women stopping either the ACE inhibitor, or beta-blocker, or both[94]. In patients with recovered DCM more generally, in the TRED-HF study (Withdrawal of pharmacological treatment for heart failure in patients with recovered DCM), 44% of patients deteriorated within 6 months of staged withdrawal of heart failure therapies. In TRED-HF, 2/50 patients randomised to withdrawal had a history of PPCM, and of those, one deteriorated[108]. Although there remains no definitive evidence to guide decision-making about long-term treatment in women with recovered PPCM, the findings from this study highlight that recovery in PPCM is not always sustained.

One limitation of the current analyses of LV recovery was the lack of standardised echocardiographic follow-up, given its retrospective and observational nature. Recovery was described within a defined time period, but the timing of imaging differed between patients and, in some cases, may not have taken place by, or close to, a given time point examined. In addition, lack of data on long-term medical therapy meant treatment could not be described in

those women in whom subsequent deterioration occurred. In future, research should focus on identifying women at greater risk of deterioration in cardiac function following a period of recovery. In the same way, the benefit of continued medical therapy, versus withdrawal of therapy, in recovered women should be examined in a prospective and randomized fashion. A further limitation was the small number of events, making a thorough analysis of prognostic markers difficult. Only a small number of predictor variables were examined, and these were chosen due to an existing understanding of their potential clinical significance in heart failure. Smoking, a longer QTc duration, bundle branch block and greater socioeconomic deprivation were found to be most strongly associated with the CV composite of death or rehospitalisation, and a larger LV end diastolic diameter was associated with a lower likelihood of LV recovery at 1 year.

## 5.5 Summary

PPCM is associated with long-term morbidity and mortality, but also with a high frequency of recovery of cardiac function. Overall all-cause case-fatality was 8% (2% at 6 months, 3% at 1 year and 4% at 5 years) and LV recovery occurred in 76% of women (34% at 6 months, 47% at 1 year and 71% at 5 years). However, more than 1 in 7 women had sustained decline in LV systolic function following recovery. Small numbers of events limited the ability to conduct a comprehensive analysis of prognostic markers, but patient characteristics found to be associated with worse CV outcomes included smoking, a longer QTc duration, bundle branch block and greater socioeconomic deprivation. Only LV diameter was associated with LV recovery, with an inverse relationship. Future efforts should focus on identifying which women are at greatest risk in larger, prospective cohorts.

# Chapter 6 Subsequent pregnancies

## 6.1 Introduction and aims

Some women who develop PPCM may wish to consider a further pregnancy. The ESC classifies women with recovered PPCM as having a 'significantly increased risk of maternal mortality or severe morbidity' during a subsequent pregnancy (modified WHO [mWHO] class III), and those with any residual LV impairment as 'extremely high risk of maternal mortality or severe morbidity' (mWHO class IV)[49]. The ESC PPCM Study Group recommend that women with any residual LV impairment are advised against a subsequent pregnancy[107]. However, data to inform counselling have limitations, largely due to small numbers, short follow-up, or single-centre experience. The largest study of subsequent pregnancies in women with PPCM reported outcomes of 61 pregnancies[129]. Applicability of existing data is difficult due to variation in definitions of LV recovery following the original diagnosis, in some cases a lack of data on cardiac function directly prior to the pregnancy, and inconsistency in the timing of follow-up assessments and in the measures used to define a deterioration.

The aim of this chapter is to describe characteristics of, and clinical outcomes for, women with PPCM with a subsequent pregnancy and compare them to those without. There will also be a focus on obstetric, maternal and neonatal characteristics and outcomes in women with PPCM and a subsequent pregnancy, and how they compare with those for controls with a subsequent pregnancy.

## 6.2 Methods

### *6.2.1 Study population*

The frequencies of subsequent pregnancies were examined in women with PPCM and in controls. Outcomes were analysed in two ways: first comparing women with PPCM (subsequent pregnancy vs no subsequent pregnancy), then comparing women with a subsequent pregnancy (PPCM vs controls). As in Chapter 5, 4 women with PPCM were excluded from the analyses of the main outcomes due to inaccurate linked time-to-event data. Where a PPCM case was excluded, the controls for that case were also excluded.

### *6.2.2 Data sources and definitions*

Subsequent pregnancies were identified using the following methods, as detailed in Section 2.4.2 of the Methods chapter:
- A delivery outcome in SMR02 (maternity)
- An abortive outcome in SMR02 (maternity)
- An ICD discharge code or OPCS operation code relating to either a delivery or abortion in SMR01 or SMR02, not already identified (using the same ICD-10 and OPCS codes listed in the Methods chapter, Table 2-3).

Subsequent pregnancies were identified through the SMR02 (maternity) dataset for both cases and controls. In addition, the SMR01 dataset was also screened for subsequent pregnancies in women with PPCM in order not to miss deliveries that took place at the national cardiac centre (since a delivery there would not automatically generate a maternity record).

All baseline characteristics were defined in the same way and used the same data sources as in Chapter 4 (see Tables 4-1 and 4-2). All clinical outcomes and outcomes relating to LV function were defined in the same way and used the same data sources as in Chapter 5 (see Table 5-1).

The end date of the subsequent pregnancy was the date of delivery where a delivery outcome occurred, or the date of admission to hospital in the event of an abortive outcome. For the purposes of identifying the most recent

transthoracic echocardiogram performed prior to the start of the subsequent pregnancy, the start date of the first subsequent pregnancy was estimated by subtracting the estimated gestation (number of weeks multiplied by 7) from date of the end of pregnancy. For terminations, for which the estimated gestation is not always known/recorded, the estimated gestation was assumed to be 10 weeks.

### *6.2.3 Statistical analyses*

Comparisons of means, medians and frequencies were made using t tests, Wilcoxon rank-sums and chi-squared tests where appropriate.

Rates of events of clinical outcomes in women with PPCM were calculated using the date of index hospitalisation (defined as the start date of the episode of care during which the diagnosis was assigned) for women with PPCM. The end date was the date of the event (defined as the start date of the episode of care during which the event occurred, or the date of operation, or the date of death) or, if no event occurred, to the censor date (31$^{st}$ December 2017). Event rates were expressed per 1000 person years follow-up. Rate ratios and 95% confidence intervals were calculated using the method proposed by Rothman et al, which is described in the Methods chapter, in section 2.7.2. Cumulative incidences were displayed graphically using Kaplan-Meier survival curves. Comparisons were examined using log-rank tests.

Associations between obstetric characteristics/outcomes and between an adverse neonatal outcome composite of prematurity (estimated gestation <37 weeks), low birth weight (<2500g), termination, stillbirth or early neonatal death (death within 7 days of delivery) in a first subsequent pregnancy were examined using univariable and multivariable binary logistic regression. Each model was adjusted for maternal age, year of pregnancy outcome, (dichotomised; 2008-2017 vs 1998-2007) and health board. Early neonatal death (death within 7 days of delivery) was chosen as this was a variable included in the maternity dataset (SMR02) and did not rely on adequate linkage to the NRS death registry. This meant that some children, who were otherwise excluded from analyses of longer-term outcomes due to problems with record linkage, could be included.

## 6.3 Results

### *6.3.1 Characteristics of women with PPCM with and without a subsequent pregnancy*

Overall, 36/225 (16%) women with PPCM had at least one further pregnancy, with 44 subsequent pregnancies. A total of 8/225 (4%) women with PPCM had two further pregnancies. Among controls, 747/2240 (33%) women had a total of 963 subsequent pregnancies.

The median time from the end of the index pregnancy to the end of the first subsequent pregnancy was 34 months (IQR 22-58) in women with PPCM. Since the specific date of delivery is included in the maternity datasets, whereas the start of pregnancy is not, the end of first subsequent pregnancy (rather than start) was used.

Table 6-1 shows patient characteristics at baseline (i.e. at the time of the original PPCM diagnosis) in women with PPCM according to whether or not they went on to have a subsequent pregnancy. Compared to women without a subsequent pregnancy, women with a subsequent pregnancy were younger, more often from the most socioeconomically deprived quintile, had shorter QRS and QTc durations and had a higher LVEF.

**Table 6-1 Characteristics of women with PPCM (at index presentation) with and without a subsequent pregnancy**

| | Total | No SSP | SSP | P value | No SSP Missing | SSP Missing |
|---|---|---|---|---|---|---|
| | N=225 | N=189 | N=36 | | | |
| Age (years) | 31.8±6.0 | 32.8±5.6 | 26.6±5.2 | <0.001 | 0 | 0 |
| Deprivation quintile 1 (most deprived) | 76 (33.9) | 53 (28.2) | 23 (63.9) | <0.001 | 1 | 0 |
| Body mass index (kg/m$^2$) | 28.2±7.0 | 28.5±7.1 | 26.7±6.7 | 0.20 | 25 | 4 |
| Smoking (current/former) | 91 (41.2) | 74 (39.8) | 17 (48.6) | 0.33 | 3 | 1 |
| Prior hypertension | 38 (16.9) | 33 (17.5) | 5 (13.9) | 0.60 | 0 | 0 |
| PIH | 77 (34.2) | 67 (35.4) | 10 (27.8) | 0.37 | 0 | 0 |
| Pre-eclampsia | 44 (19.6) | 38 (20.1) | 6 (16.7) | 0.63 | 0 | 0 |
| Parity >1 | 68 (30.2) | 58 (30.7) | 10 (27.8) | 0.73 | 0 | 0 |
| Multiple gestation* | 18 (8.2) | 16 (8.6) | 2 (5.9) | 0.59 | 3 | 2 |
| Estimated gestation (weeks)* | 38 (36-40) | 38 (37-40) | 38 (35-40) | 0.77 | 3 | 2 |
| Mode of delivery, baby 1* | | | | 0.078 | 3 | 2 |
| Vaginal | 99 (45.0) | 79 (42.5) | 20 (58.8) | | | |
| Caesarean | 121 (55.0) | 107 (57.5) | 14 (41.2) | | | |
| Heart rate (bpm) | 108 (89-125) | 110 (90-125) | 103 (83-127) | 0.36 | 32 | 6 |
| SBP (mmHg) | 135 (120-154) | 135 (120-155.5) | 130 (120-145) | 0.29 | 33 | 11 |
| DBP (mmHg) | 86 (73-100) | 87 (73-100) | 83 (75-96) | 0.57 | 34 | 12 |
| Oxygen therapy | 89 (47.8) | 76 (48.1) | 13 (46.4) | 0.87 | 31 | 8 |
| Intravenous diuretic therapy | 132 (70.6) | 117 (73.1) | 15 (55.6) | 0.064 | 29 | 9 |
| Intensive care | 62 (30.1) | 54 (31.6) | 8 (22.9) | 0.31 | 18 | 1 |
| QRS duration (ms) | 82 (76-94) | 84 (76-96) | 80 (72-84) | 0.033 | 37 | 7 |
| QTc duration (ms) | 450 (425-483) | 454 (429-484) | 426 (412-452) | 0.002 | 39 | 8 |
| LVEF (%) | 34.6±10.8 | 33.7±11.0 | 39.1±8.8 | 0.007 | 26 | 2 |
| LVEDD (mm) | 57.2±7.6 | 57.6±7.6 | 55.4±7.6 | 0.20 | 40 | 11 |

**Terminations excluded*

*SSP = subsequent pregnancy; PIH = pregnancy-induced hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter*

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

### *6.3.2 Death and rehospitalisation in women with PPCM with and without a subsequent pregnancy*

One woman with a subsequent pregnancy was excluded from these analyses due to inaccuracy with data linkage as previously described. Overall, all-cause death or all-cause rehospitalisation occurred in 30 (86%) women with PPCM with a subsequent pregnancy and in 141 (76%) women with PPCM without a subsequent pregnancy (Table 6-2). The numbers (%) of women with a CV death or CV rehospitalisation were: 19 (54%) with a subsequent pregnancy and 74 (40%) without.

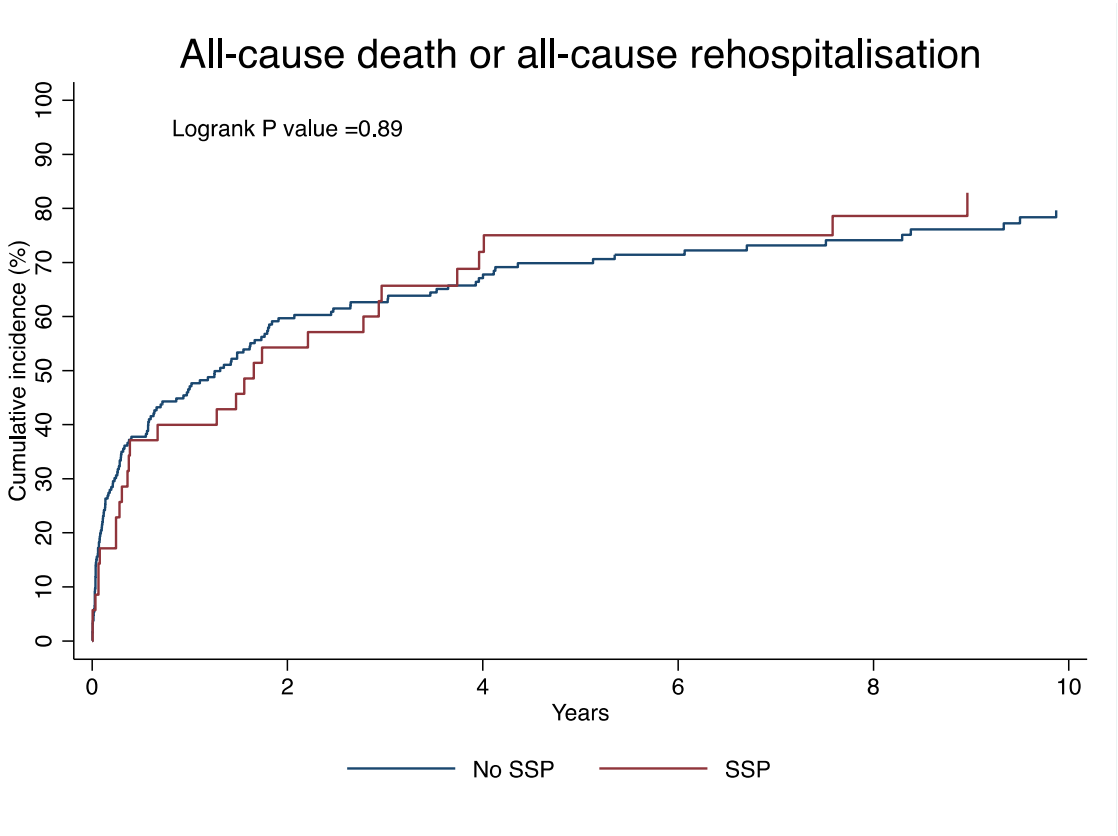
Rates of all-cause death or all-cause rehospitalisation were similar in women with and without a subsequent pregnancy (Table 6-2). The cumulative incidence of all-cause death or all-cause rehospitalisation is shown in Figure 6-1.

**Table 6-2 Death and rehospitalisation in women with PPCM with and without a subsequent pregnancy**

| | No SSP<br><br>N=186 | SSP<br><br>N=35 | Rate ratio (95% CI) |
|---|---|---|---|
| **All-cause death or all-cause rehospitalisation** | | | |
| No. | 141 | 30 | |
| % (95% CI) | 75.8 (69.1-81.5) | 85.7 (69.2-94.1) | |
| Rate per 1000 person-years (95% CI) | 254.4 (215.7-300.0) | 230.0 (160.8-329.0) | 0.90 (0.61-1.34) |

*SSP = subsequent pregnancy*

**Figure 6-1 Cumulative incidence of all-cause death or all-cause rehospitalisation in women with PPCM with and without a subsequent pregnancy**



### *6.3.3 Obstetric characteristics associated with a subsequent pregnancy in women with PPCM and controls*

Of the 44 subsequent pregnancies that occurred in women with PPCM, 39 (89%) resulted in a live birth and the remaining 5 (11%) in either a therapeutic or spontaneous termination (Table 6-3). Pregnancy-induced hypertension occurred in 16% of subsequent pregnancies, antepartum haemorrhage in 16% and postpartum haemorrhage in 41%. Estimated gestation was <37 weeks in 33% of all pregnancies, excluding terminations, and in 32% of pregnancies induction of labour was required. The mode of delivery (of the first subsequent delivery) was a C-section in 61% of live deliveries.

Compared to controls, women with PPCM more often had a termination (therapeutic or spontaneous) of a subsequent pregnancy, and more often had pregnancy-induced hypertension (16% vs 6%, p=0.018) and postpartum haemorrhage (41% vs 18%, p<0.001). Of those subsequent pregnancies which did not end in termination, women with PPCM also had a shorter duration of pregnancy, more often with an estimated gestation <37 weeks (33% vs 5%, p<0.001) and C-section delivery (61% vs 18%, p<0.001).

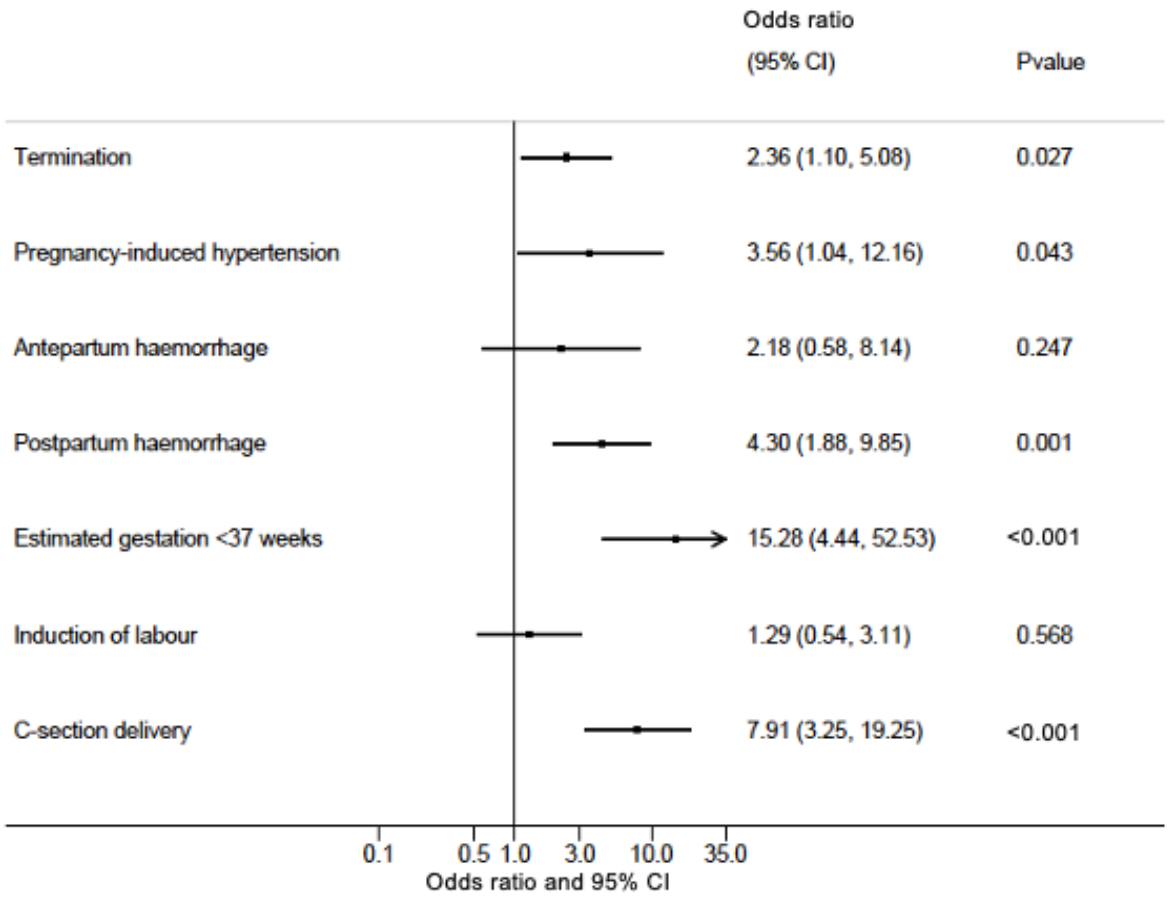
Figure 6-2 shows the likelihood of each obstetric characteristic being present during a first subsequent pregnancy for women with PPCM as compared with controls, adjusted for maternal age, year (2008-2017 vs 1998-2007) and health board of maternity admission. Compared with controls, women with PPCM were significantly more likely to have a termination (either spontaneous or therapeutic) (OR 2.36, 95% CI 1.10-5.08), pregnancy-induced hypertension (OR 3.56, 95% CI 1.04-12.16), postpartum haemorrhage (OR 4.30, 95% CI 1.88-9.85), premature delivery (estimated gestation <37weeks) (OR 15.28, 95% CI 4.44-52.53) and a Caesarean-section delivery (OR 7.91, 95% CI 3.25-19.25).

## Table 6-3 Obstetric characteristics during a subsequent pregnancy

| | Total | Controls | PPCM | P value | Controls Missing | PPCM Missing |
|---|---|---|---|---|---|---|
| | N=285 | N=241 | N=44 | | | |
| Age (years) | 29.5±4.7 | 29.4±4.6 | 30.1±5.3 | 0.37 | 0 | 0 |
| Outcome of SSP | | | | 0.049 | 0 | 0 |
| Live delivery | 270 (94.7) | 231 (95.9) | 39 (88.6) | | | |
| Termination | 15 (5.3) | 10 (4.1) | 5 (11.4) | | | |
| PIH | 21 (7.4) | 14 (5.8) | 7 (15.9) | 0.018 | 0 | 0 |
| APH | 27 (9.5) | 20 (8.3) | 7 (15.9) | 0.11 | 0 | 0 |
| PPH | 62 (21.8) | 44 (18.3) | 18 (40.9) | <0.001 | 0 | 0 |
| Estimated gestation (weeks)* | 39 (38-40) | 40 (39-40) | 37 (36-39) | <0.001 | 10 | 5 |
| Estimated gestation <37 weeks* | 25 (9.3) | 12 (5.2) | 13 (33.3) | <0.001 | 10 | 5 |
| Induction of labour* | 75 (28.0) | 63 (27.4) | 12 (31.6) | 0.59 | 11 | 6 |
| Medical induction of labour* | 64 (24.0) | 53 (23.1) | 11 (28.9) | 0.44 | 12 | 6 |
| Mode of delivery of baby 1* | | | | <0.001 | 10 | 5 |
| Vaginal | 204 (75.6) | 189 (81.8) | 15 (38.5) | | | |
| Caesarean (any) | 66 (24.4) | 42 (18.2) | 24 (61.5) | | | |

**Terminations excluded*
*PIH = pregnancy-induced hypertension; APH = antepartum haemorrhage; PPH = postpartum haemorrhage*
*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Figure 6-2 Forest plot of obstetric characteristics during a first subsequent pregnancy (women with PPCM vs controls, univariable)




*Adjusted for maternal age, year of delivery and health board.*

### *6.3.4 Clinical outcomes associated with a subsequent pregnancy in women with PPCM*

There were 42 subsequent pregnancies with 6-month follow-up, 39 with 1-year follow-up and 20 with 5-year follow-up. A composite CV endpoint of CV death, mechanical circulatory support and cardiac transplantation was examined. No women experienced the composite CV endpoint during pregnancy or up to 5 years following pregnancy (Table 6-4). The proportion of pregnancies associated with a CV hospitalisation were: 5/42 (12%) at 6 months, 6/39 (15%) at 1 year and 5/20 (25%) at 5 years (Table 6-4). It was not possible to report CV hospitalisation during the pregnancy due to the inability to link records to the start of a pregnancy (which does not generate an admission).

LV function prior to the start of the first subsequent pregnancy was examined. The most recent echocardiogram was a median of 11 months (IQR 2-19) prior to the start of the first subsequent pregnancy in 33 women with an echocardiogram reporting LV function (qualitatively or quantitatively). The start of pregnancy was estimated using the date of the end of pregnancy minus estimated gestation. Prior to the start of the first subsequent pregnancy, 42% of women had a LVEF <55%, 27% had a LVEF <50% and 15% had a LVEF <45% (Table 6-4).

**Table 6-4 Maternal outcomes associated with a subsequent pregnancy**

| | |
|---|---|
| **All SSPs** | |
| **Composite CV endpoint** | |
| During pregnancy to 6 months postpartum (n=42 SSPs) | 0 (0) |
| During pregnancy to 1 year postpartum (n=39 SSPs) | 0 (0) |
| During pregnancy to 5 years postpartum (n=20 SSPs) | 0 (0) |
| **Subsequent CV hospitalisation** | |
| 6 months postpartum (n=42 SSPs) | 5 (11.9) |
| 1 year postpartum (n=39 SSPs) | 6 (15.4) |
| 5 years postpartum (n=20 SSPs) | 5 (25.0) |
| **First SSP** | |
| LVEF <55% prior to first SSP (n=33) | 14 (42.2) |
| LVEF <50% prior to first SSP (n=33) | 9 (27.3) |
| LVEF <45% prior to first SSP (n=33) | 5 (15.2) |

*LVEF = left ventricular ejection fraction; SSP = subsequent pregnancy*
*Data are presented as n (%) for categorical measures.*

### *6.3.5 Neonatal outcomes associated with a subsequent pregnancy in women with PPCM and controls*

There were a total of 45 babies during 44 subsequent pregnancies in women with PPCM. In 5 (11%) cases, the outcome was a spontaneous or therapeutic termination (Table 6-5). Of the remaining 40 live deliveries, 60% were boys, 63% were delivered via Caesarean section, 18% had low birth weight (<2500g), the median APGAR score at 5 minutes was 9 (IQR 9-9) and 15% were admitted to a neonatal unit.

Compared to babies born during a subsequent pregnancy in controls, babies born during a subsequent pregnancy in women with PPCM were more often delivered by Caesarean section (63% vs 19%, p<0.001) and more often had low birth weight (18% vs 5%, p=0.004). An adverse neonatal outcome composite of prematurity (estimated gestation <37 weeks), low birth weight (<2500g), termination, stillbirth or early neonatal death (death within 7 days of delivery) was analysed. An adverse neonatal outcome occurred in 44% of PPCM subsequent pregnancies and in 11% of matched control subsequent pregnancies (p<0.001).

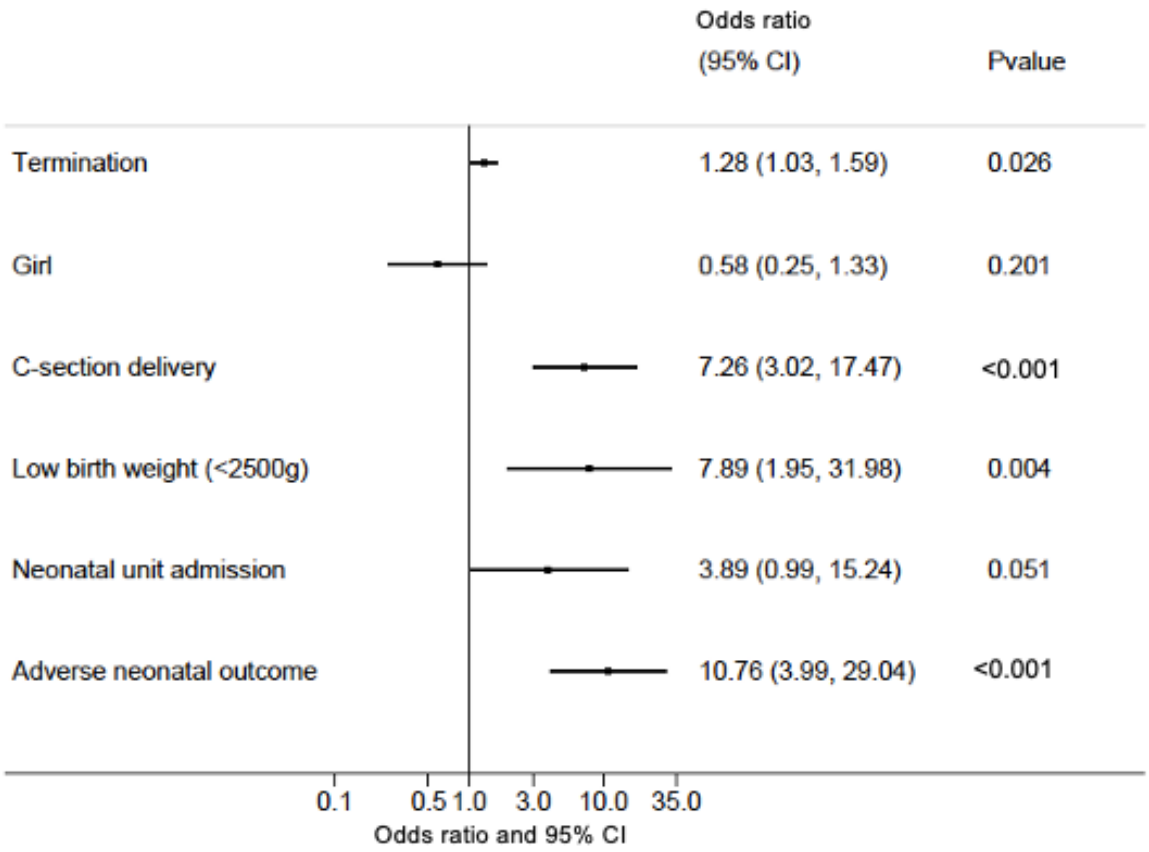
Figure 6-3 shows the likelihood of each neonatal outcome occurring during a first subsequent pregnancy for children born to women with PPCM as compared with children born to controls, adjusted for maternal age, year (2008-2017 vs 1998-2007) and health board of maternity admission. Compared with control children, PPCM children were significantly more likely to have low birth weight (<2500g) (OR 7.89, 95% CI 1.95-31.98) and an adverse neonatal outcome (OR 10.76, 95% CI 3.99-29.04).

## Table 6-5 Neonatal outcomes during a subsequent pregnancy

| | Total N=289 | Control children N=244 | PPCM children N=45 | P value | Controls Missing | PPCM Missing |
|---|---|---|---|---|---|---|
| Pregnancy outcome | | | | 0.051 | 0 | 0 |
| Live birth | 274 (94.8) | 234 (95.9) | 40 (88.9) | | | |
| Termination | 15 (5.2) | 10 (4.1) | 5 (11.1) | | | |
| Sex | | | | 0.24 | 10 | 5 |
| Boy | 141 (51.5) | 117 (50.0) | 24 (60.0) | | | |
| Girl | 133 (48.5) | 117 (50.0) | 16 (40.0) | | | |
| Mode of delivery | | | | <0.001 | 10 | 5 |
| Vaginal | 205 (74.8) | 190 (81.2) | 15 (37.5) | | | |
| Caesarean (any) | 69 (25.2) | 44 (18.8) | 25 (62.5) | | | |
| Birthweight (grams) | 3350 (3000-3730) | 3410 (3060-3780) | 3076 (2795-3320) | <0.001 | 10 | 6 |
| Low birth weight (<2500g) | 19 (7.0) | 12 (5.1) | 7 (17.9) | 0.004 | 10 | 6 |
| APGAR score at 5 minutes | 9 (9-9) | 9 (9-9) | 9 (9-9) | 0.047 | 16 | 6 |
| Neonatal unit admission | 21 (7.8) | 15 (6.6) | 6 (15.0) | 0.068 | 16 | 5 |
| Adverse neonatal outcome | 48 (16.6) | 28 (11.5) | 20 (44.4) | <0.001 | 0 | 0 |

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

## Figure 6-3 Forest plot of neonatal outcomes during a first subsequent pregnancy (PPCM vs control children, univariable)




*Adjusted for maternal age, year of delivery and health board.*

## 6.4 Discussion

In this chapter, characteristics of and outcomes for women with PPCM with a subsequent pregnancy are described and compared to a) those for women with PPCM without a subsequent pregnancy and b) those for controls with a subsequent pregnancy. Overall, 36 (16%) women with PPCM and 747 (33%) controls had at least one subsequent pregnancy. Women with PPCM and a subsequent pregnancy were younger and more socioeconomically deprived than those without. Overall, rates of all-cause death or all-cause rehospitalisation were similar in women with PPCM irrespective of whether or not they went on to have a subsequent pregnancy. No women died from a CV cause, or required mechanical circulatory support or cardiac transplantation during a subsequent pregnancy or in the following 5 years. CV hospitalisation after the subsequent pregnancy occurred in 12% at 6 months, 15% at 1 year and 26% at 5 years. Compared to controls, women with PPCM were more likely to have a termination, pregnancy-induced hypertension, postpartum haemorrhage, premature delivery and Caesarean-section during a subsequent pregnancy. An adverse neonatal outcome was more likely in women with PPCM than in controls during a subsequent pregnancy.

The safety of a future pregnancy is an important component of informed counselling for a woman with PPCM. Despite this, studies examining outcomes for women during a subsequent pregnancy, and exploring which factors might be associated with an adverse outcome, are generally lacking and are limited by being small. A total of 23 published studies, summarised in Table 1-4 in the Introduction chapter, report data on subsequent pregnancies; these include between 2-56 women with between 1-61 deliveries. The highest reported mortality was 56% and 48% in a series of 9 and 29 women in India and Burkina Faso, respectively [132, 144]. Outcomes elsewhere are generally better. In the three largest studies, 0-7% of women died and all who did began the subsequent pregnancy with residual LV dysfunction[125, 128, 203]. Generally, causes of death (i.e. CV vs non-CV) are not described. Only 4 previous studies have reported death during a subsequent pregnancy for women from Europe and, in each case, only ≤16 participants were included. Case-fatality in these studies ranged from 0-25%. It is difficult to draw comparisons when numbers included are small. In the current study, 15% of pregnancies were associated with a CV hospitalisation

during the 1st year after pregnancy, but there did not appear to be an upfront risk of all-cause death or all-cause rehospitalisation in women at the time of presentation according to whether or not they went on to have a subsequent pregnancy. Importantly, there were no major adverse events (defined as CV death, requirement for mechanical circulatory support or cardiac transplantation).

In their 2018 guidelines for the management of CV diseases during pregnancy, the ESC risk stratifies PPCM into one to two group: mWHO III or mWHO IV, depending on whether or not there is residual LV dysfunction. Caution should be applied when using this as a tool for women with PPCM for a number of reasons. First, the definition of residual LV dysfunction is not provided. Second, the ESC provides an estimate of the risk of a maternal cardiac event of 19-27% for mWHO III and of 40-100% for mWHO IV, but these estimates are not derived specifically from studies of women with PPCM. Third, they do not incorporate influential differences such as region, race and provision of/access to dedicated cardio-obstetric maternity services. Data relevant to patients cared for within a particular service, in a particular demographic, are important. Counselling regarding a future pregnancy must be appropriate. Previously, there has been no evidence-base to underpin such discussions in the UK. The current data suggest that event rates are lower in women with PPCM and a subsequent pregnancy than those suggested by the ESC, although due to small numbers, exploration of the impact of LVEF, and of other patient factors, was not possible. In addition to residual cardiac dysfunction, determinants of outcomes are likely to include a range of factors, such as: methods of pre-pregnancy counselling and planning, mode and frequency of assessment of cardiac function during withdrawal of fetotoxic heart failure treatments, intensity of surveillance during pregnancy, and the provision of cardio-obstetric care. It is not possible to encompass all of this into a single measure of prognostication that can be applied universally.

Foetal/neonatal outcomes associated with a subsequent pregnancy are also an important consideration. Compared with control subsequent pregnancies, PPCM subsequent pregnancies were around 8 times more likely to result in low birth weight (<2500g) and around 11 times more likely to have an adverse neonatal outcome (a composite of prematurity [estimated gestation <37 weeks], low birth weight [<2500g], termination, stillbirth or early neonatal death [death within 7

days of delivery]) during a subsequent pregnancy. In studies of subsequent pregnancies, miscarriage or foetal death is reported in 0-40% of cases[104, 128, 141]. No specific recommendations are given in the ESC guidelines or PPCM Study Group position papers about how best to counsel a woman with PPCM regarding risks to the baby during a subsequent pregnancy. Nonetheless, they do advocate that counselling should acknowledge the risk of complications for the offspring[49]. Because of small numbers of subsequent pregnancies and of adverse neonatal events, it was not possible to identify factors associated with a greater likelihood of an adverse neonatal outcome in this context.

There are some limitations of this chapter for discussion. Natriuretic peptides were not routinely measured during the study period and are likely to be important in determining risk, although there are no existing studies examining the utility of NT-proBNP as a prognostic tool during a subsequent pregnancy specifically in PPCM. Data supporting the use of NT-proBNP in estimating risk in women with CV disease more generally do exist, but the evidence base is largely for women with congenital heart disease[204, 205]. With respect to imaging, small studies have suggested a potential role for stress echocardiography and evaluation of contractile reserve, but this has not been validated in a prospective cohort[129, 134]. In the future, routine use of more sophisticated imaging modalities (e.g. global longitudinal strain, cardiac magnetic resonance imaging) in women with PPCM with apparent normalization of LV systolic function may help identify women at higher risk of relapse, but this is not current standard practice. In the TRED-HF (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy) study, late gadolinium enhancement on cardiac magnetic resonance imaging, and changes in global longitudinal and circumferential strain were not associated with relapse[108]. On the other hand, global radial strain was lower at baseline in patients with relapse, as compared to those without. Another limitation relates to the possible underestimation of terminations. particularly in controls, if it did not require a hospital admission. Admission for termination may be more likely in women with comorbidities such as heart disease than in those without. There were no ways in which to account for this, and exclusion of such events would have disregarded important outcomes in women with PPCM. It was not possible to report CV hospitalisation (and therefore heart failure hospitalisation) during pregnancy due to an inability to link records during pregnancy (records could be

linked to the end of pregnancy as this generated a hospital admission to link to). A further limitation related to the inability to examine factors associated with an adverse outcome in women or their children during a subsequent pregnancy due to small overall numbers of pregnancies and events; larger studies are required for this. In particular, small numbers of women with reduced LVEF limited conclusions which could be drawn about this group with respect to risk of a subsequent pregnancy.

## 6.5 Summary

Women with PPCM and a subsequent pregnancy were younger and more socioeconomically deprived than those without. No women with PPCM died from a CV cause, or required mechanical circulatory support or cardiac transplantation during a subsequent pregnancy or up to 5 years postpartum, but CV hospitalisation occurred in 15% of pregnancies within the 1st year of delivery. Compared with controls, women with PPCM were more likely to have a termination, pregnancy-induced hypertension, postpartum haemorrhage, premature delivery and Caesarean-section during a subsequent pregnancy. Subsequent PPCM pregnancies had a more than 10-times greater likelihood of an adverse neonatal outcome than a subsequent matched control pregnancy.

# Chapter 7 Child outcomes

## 7.1 Introduction and aims

Previous research into PPCM has largely focussed on the mother rather than the child. Our understanding of the impact on children born to women with PPCM is limited, and the literature is summarised in the Introduction chapter. The information provided by these is basic, largely focusing on outcomes such as birth weight, gestational age and, only in some cases, neonatal mortality. In general, across all studies, babies born to women with PPCM are smaller, more frequently premature and have lower APGAR scores than control babies, whereas data on neonatal mortality are inconclusive[13, 14, 20, 21, 23].

Few European data exist. There is one study from Sweden and, although it includes women with PPCM, they are one component of a larger cohort of women with undefined heart failure or cardiomyopathy around the time of pregnancy[19]. Similar to other case-control studies, babies born to women with heart failure had a lower birth weight, were more often small for gestational age and had a lower gestational age at delivery, when compared to control children in this study. In the global ESC PPCM Registry, death occurred in 5% of all neonates[11]. In European patients enrolled into this registry, neonatal death occurred in 2% and low birth weight (defined as birth weight <2500 grams) in 25%.

Only one study has examined outcomes for children beyond the neonatal period, reporting a remarkably high case-fatality of 64% at 1 year among 22 infants in Haiti[156]. Haiti is a low-income Caribbean nation with considerable maternal and infant mortality; in that study, the cause of death in all infants was malnutrition. These data are clearly not applicable to regions with differing population demographics, and social and health-related infrastructure.

In this penultimate chapter, the focus is on morbidity and mortality in babies born to women with PPCM and how this compares with babies born to the matched maternal controls. Events specific to delivery and the neonatal period are examined, as well as mortality and morbidity, including the incidence of cardiovascular disease, throughout childhood.

## 7.2 Methods

### *7.2.1 Study population*

Outcomes were examined in all children born to women during the index presentation of PPCM with available data and compared to children born to controls. If a PPCM child could not be linked, and thus follow-up data were not obtainable, the corresponding control children were also excluded from the analysis.

### *7.2.2 Data sources and definitions*

Table 7-1 summarises the data sources and definitions used in this chapter. More detail on ICD codes and OPCS codes used to define CV disease is included in Appendix 2. Delivery data for neonates (e.g. birth weight, APGAR scores) were obtained from the maternal SMR02 record, which contains a 'Baby Record Section' for recording of information about the neonate at the time of delivery. For children born to cases (but not controls), if data were missing (e.g. if the delivery did not generate an SMR02 record in the event it took place during a non-maternity episode), data collected directly from patient records were used to supplement the dataset.

In Scotland, data relating to a neonatal inpatient stay (i.e. a transfer to neonatal care following delivery) was captured through the SMR11 scheme prior to 2003 and has been captured through the Scottish Birth Record since. Data relating to infant morbidity beyond the neonatal period were derived using data on hospitalisations through the SMR01 scheme and data on community prescriptions of medications through the Prescribing Information System registry. Mortality data for children were obtained from two National Records of Scotland registries: 1) death registry and 2) stillbirth and infant death registry.

Children born to women with PPCM were labelled 'PPCM children' and those born to controls as 'control children'.

**Table 7-1 Data sources and definitions of child outcomes**

| Variable | Source(s) | Description/definition |
|---|---|---|
| Neonatal delivery data | SMR02 + mother's records | Captured as part of the mother's SMR02 delivery record. If missing, data obtained from mother's records where available. |
| Death | NRS death registry and stillbirth and infant deaths registry | Death due to any cause.<br><br>When a specific cause of death was examined, this was the main cause of death recorded on the death certificate. |
| Hospitalisations | SMR01 | Subsequent hospital admission for any cause, excluding the neonatal period.<br><br>When a specific cause was examined, this was defined as the presence of a discharge code in any diagnostic position. |
| **ICD-10 disease codes and OPCS-4 procedural codes used to define disease groups** | | |
| CV | SMR01 | ICD-10: I00-I90, Q20-Q28, P29<br><br>OPCS-4: K and L codes |
| Respiratory | SMR01 | ICD-10: J00-J99, P20-P28<br><br>OPCS-4: E codes |
| Gastrointestinal | SMR01 | ICD-10: K00-K99, P75-P78<br><br>OPCS-4: G, H and J codes |
| Infection | SMR01 | ICD-10: A00-A99, P35-P39, G00-G01 |
| Congenital anomalies | SMR01 | ICD-10: Q00-Q99 (excluding Q20-Q28) |

| | | |
|---|---|---|
| (non-CV) | | |
| **Medications** | | |
| Community prescriptions | Prescribing Information System registry | Medications codes used:<br><br>Gastrointestinal 010, cardiovascular 020, respiratory 030, central nervous system 040, antimicrobial 050, endocrine 060, immunomodulator 080, musculoskeletal 100, eye 110, ear nose throat 120, skin 130 |

### *7.2.3 Statistical analyses*

Comparisons of means, medians and frequencies were made using t tests, Wilcoxon rank-sums and chi-squared tests where appropriate.

Rates were calculated from the date of birth. The end date was the date of the event; this was the date of admission to hospital (the first hospitalisation during which the relevant disease code was assigned in any diagnostic position), or date of death, or censor date (31st December 2017) if no event occurred. Event rates were expressed per 1000 person years follow-up. Rate ratios and 95% confidence intervals were calculated using the method proposed by Rothman et al, which is described in the Methods chapter, in section 2.7.2.

Cumulative incidences were displayed graphically using Kaplan-Meier survival curves. Comparisons were examined using log-rank tests.

Counts of total (recurrent) hospitalisations were examined and differences in the rate of recurrent hospitalisation between PPCM children and control children was modelled using negative binomial regression, offset by follow-up time. When analysing total hospitalisations within a specified time period, only children with complete follow-up were studied (i.e. for 1-year outcomes, only children born prior to 2017 were included).

**Prognostic markers**

Factors associated with an adverse neonatal outcome composite of prematurity (estimated gestation <37 weeks), low birth weight (<2500g), stillbirth or early neonatal death (death within 7 days of delivery) were examined using univariable and multivariable binary logistic regression. The multivariable model was also adjusted for year of delivery/birth (dichotomised; 2008-2017 vs 1998-2007).

# 7.3 Results

## *7.3.1 Neonatal outcomes*

Pregnancies which ended in a termination were excluded from the analyses, as were the controls for these women. Delivery outcomes were available for a total of 239 PPCM children and 2231 control children (Table 7-2).

Stillbirth or early neonatal death (within 7 days of delivery) was more common in PPCM children, as compared to controls (2.7% vs 0.6%, p<0.001). PPCM children were more often premature than control children (estimated gestation at delivery <37 weeks in 28% vs 7%, p<0.001), weighed less (low birth weight [<2500g] in 21% vs 7%, p<0.001) and had lower APGAR scores.

The requirement for invasive ventilation was greater in PPCM children than in control children; overall, 7% of PPCM children were intubated and ventilated, as compared with 1% of control children (p<0.001). Just over one third of PPCM children (34%) were admitted to a neonatal unit, as compared with 10% of control children (p<0.001). At the time of the discharge from the maternity unit, 20% of PPCM children remained an inpatient (vs. 5% of control children).

An adverse neonatal outcome composite of prematurity (estimated gestation <37 weeks), low birth weight (<2500g), stillbirth or early neonatal death (death within 7 days of delivery) occurred in 32% of PPCM children and in 10% of control children (p<0.001).

## Table 7-2 Neonatal outcomes in PPCM and control children

| | Total N=2470 | Control children N=2231 | PPCM Children N=239 | P value | Control children Missing | PPCM children Missing |
|---|---|---|---|---|---|---|
| Sex | | | | 0.18 | 0 | 0 |
| Boy | 1,249 (50.6) | 1,138 (51.0) | 111 (46.4) | | | |
| Girl | 1,221 (49.4) | 1,093 (49.0) | 128 (53.6) | | | |
| Estimated gestation (weeks) | 39 (38-40) | 40 (38-40) | 38 (36-40) | <0.001 | 4 | 0 |
| Estimated gestation <37weeks | 234 (9.5) | 166 (7.5) | 68 (28.5) | <0.001 | 4 | 0 |
| Mode of delivery | | | | <0.001 | 0 | 0 |
| Vaginal | 1,627 (65.9) | 1,526 (68.4) | 101 (42.3) | | | |
| Elective caesarean | 371 (15.0) | 322 (14.4) | 49 (20.5) | | | |
| Emergency caesarean | 472 (19.1) | 383 (17.2) | 89 (37.2) | | | |
| Birthweight (grams) | 3410 (3036-3780) | 3430 (3080-3780) | 3145 (2620-3680) | <0.001 | 2 | 5 |
| Low birth weight (<2500g) | 202 (8.2) | 152 (6.8) | 50 (21.4) | <0.001 | 2 | 5 |
| APGAR score at 5 minutes | 9 (9-9) | 9 (9-9) | 9 (9-9) | <0.001 | 37 | 13 |
| APGAR score at 5 minutes | | | | <0.001 | 37 | 13 |
| 8-10 | 2,351 (97.1) | 2,146 (97.8) | 205 (90.7) | | | |
| 6-7 | 44 (1.8) | 31 (1.4) | 13 (5.8) | | | |
| ≤5 | 25 (1.0) | 17 (0.8) | 8 (3.5) | | | |
| Invasive ventilation | 34 (1.6) | 19 (1.0) | 15 (7.1) | <0.001 | 253 | 29 |
| Neonatal unit admission | 289 (12.0) | 209 (9.6) | 80 (34.5) | <0.001 | 51 | 7 |
| Status at maternity discharge | | | | <0.001 | 0 | 16 |
| Discharged | 2,268 (92.4) | 2,095 (93.9) | 173 (77.6) | | | |
| Inpatient | 166 (6.8) | 122 (5.5) | 44 (19.7) | | | |
| Stillbirth/early neonatal death | 20 (0.8) | 14 (0.6) | 6 (2.7) | | | |
| Adverse neonatal outcome | 289 (11.8) | 214 (9.6) | 75 (32.2) | <0.001 | 6 | 6 |

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

### *7.3.2 Mortality*

Long-term mortality data were available for 216 PPCM children and 1985 control children. In the event outcome data were not available for a PPCM child (i.e. the child was not linkable across datasets), children from all controls matched to the mother of that child were also excluded from the analyses. The median follow-up time for all children was 9.1 years (IQR 4.9-13.4), with a total of 20,295 person-years of follow-up. The median follow-up time for PPCM children alone was 8.8 years (IQR 4.2-13.2), with a total of 1946 person-years of follow-up.

Including stillbirths, death from any cause occurred in 8 (3.7%, 95% CI 1.9-7.3) PPCM children and in 16 (0.8%, 95% CI 0.5-1.3) control children (Table 7-3). The all-cause mortality rates per 1000 person-years in PPCM and control children, were 4.1 (95% CI 2.1-8.2) and 0.9 (95% 0.5-1.4), respectively, with a mortality rate ratio of 4.72 (2.02-11.02). The cumulative incidence of child mortality is shown in Figure 7-1.

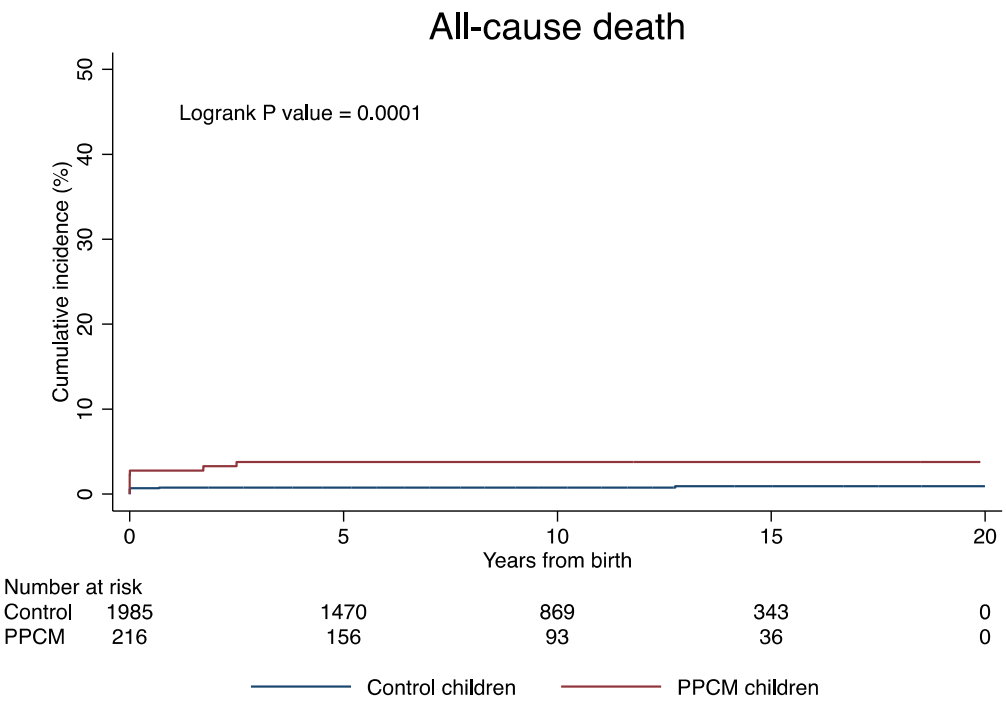
Due to the small numbers of infant deaths, cause of death was not reported (in line with NHS NSS requirements for reporting small numbers).

**Table 7-3 All-cause mortality in PPCM and control children**

| | Control children N=1985 | | | PPCM children N=216 | | | |
|---|---|---|---|---|---|---|---|
| | **No.** | **% (95% CI)** | **Rate per 1000 person-years (95% CI)** | **No.** | **% (95% CI)** | **Rate per 1000 person-years (95% CI)** | **MRR (95% CI)** |
| All-cause death | 16 | 0.8 (0.5-1.3) | 0.9 (0.5-1.4) | 8 | 3.7 (1.9-7.3) | 4.1 (2.1-8.2) | 4.72 (2.02-11.02) |

*MRR = mortality rate ratio*

**Figure 7-1 Cumulative all-cause mortality in PPCM and control children**



### *7.3.3 Morbidity*

**Incidence of disease**

Morbidity (disease incidence) was measured using hospitalisations beyond the neonatal period. Incidence rates of CV disease, respiratory disease, infection, non-CV congenital anomalies and gastrointestinal disease for PPCM children and control children are shown in Table 7-4. CV disease was defined as any general hospital admission (SMR01 record) with an ICD-10 code for circulatory disease, a CV congenital anomaly, perinatal CV disorder, or cardiac/vascular surgery (detailed in Appendix 2).

CV disease occurred more frequently in PPCM children than in control children (4.2%, 95% CI 2.2-7.8 vs 1.3%, 95% CI 0.9-1.9). The corresponding incidence rates per 1000 person-years were 4.8 (95% CI 2.5-9.1) in PPCM children and 1.4 (95% CI 1.0-2.1) in control children, with an incidence rate ratio of 3.3 (95% CI 1.6-7.1). The cumulative incidence of CV disease is shown in Figure 7-2.

Non-CV congenital anomalies also occurred more frequently in PPCM children than in control children: 8.2 (95% CI 5.0-13.7) per 1000 person-years in PPCM children vs 4.2 (95% CI 3.4-5.3) per 1000 person-years in control children, with an incidence rate ratio of 2.0 (95% CI 1.1-3.4). The cumulative incidence of non-CV congenital anomalies is shown in Figure 7-3.

The incidences of respiratory disease, infection and gastrointestinal disease were similar in PPCM and control children (Table 7-4 and Figures 7-4-7-6).

## Table 7-4 Disease incidence in PPCM and control children

| | Control children N=1985 | | | PPCM children N=216 | | | |
|---|---|---|---|---|---|---|---|
| | No. | % (95% CI) | Rate per 1000 person-years (95% CI) | No. | % (95% CI) | Rate per 1000 person-years (95% CI) | IRR (95% CI) |
| CV disease | 26 | 1.3 (0.9-1.9) | 1.4 (1.0-2.1) | 9 | 4.2 (2.2-7.8) | 4.8 (2.5-9.1) | 3.32 (1.56-7.08) |
| Non-CV congenital anomalies | 75 | 3.8 (3.0-4.7) | 4.2 (3.4-5.3) | 15 | 6.9 (4.2-11.2) | 8.2 (5.0-13.7) | 1.96 (1.13-3.42) |
| Respiratory disease | 352 | 17.7 (16.1-19.5) | 22.3 (20.1-24.8) | 48 | 22.2 (17.1-28.3) | 29.8 (22.5-39.6) | 1.34 (0.99-1.81) |
| Gastrointestinal disease | 265 | 13.4 (11.9-14.9) | 16.1 (14.3-18.1) | 37 | 17.1 (12.6-22.8) | 22.4 (16.2-30.9) | 1.39 (0.99-1.96) |
| Infection | 72 | 3.6 (2.9-4.5) | 4.0 (3.2-5.1) | 8 | 3.7 (1.9-7.3) | 4.2 (2.1-8.4) | 1.04 (0.50-2.17) |
| Hospitalisation for any cause | 915 | 46.1 (43.9-48.3) | 78.9 (74.0-84.2) | 116 | 53.7 (47.0-60.3) | 111.7 (93.1-133.9) | 1.41 (1.17-1.72) |

*IRR = incidence rate ratio*

**Figure 7-2 Cumulative incidence of CV disease in PPCM and control children**

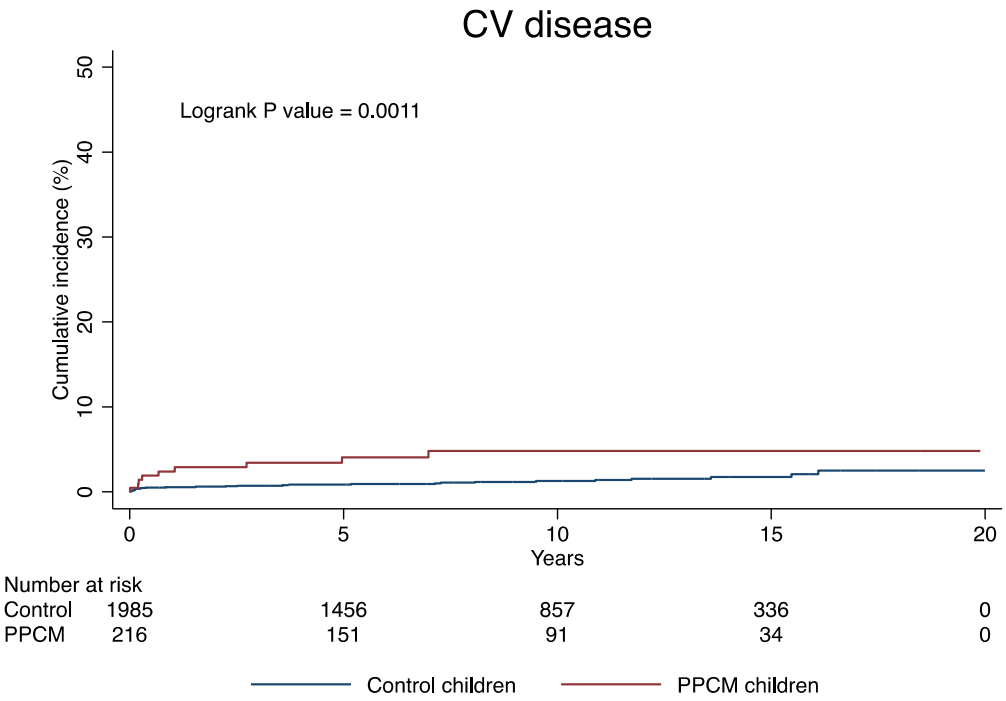



**Figure 7-3 Cumulative incidence of non-CV congenital anomalies in PPCM and control children**

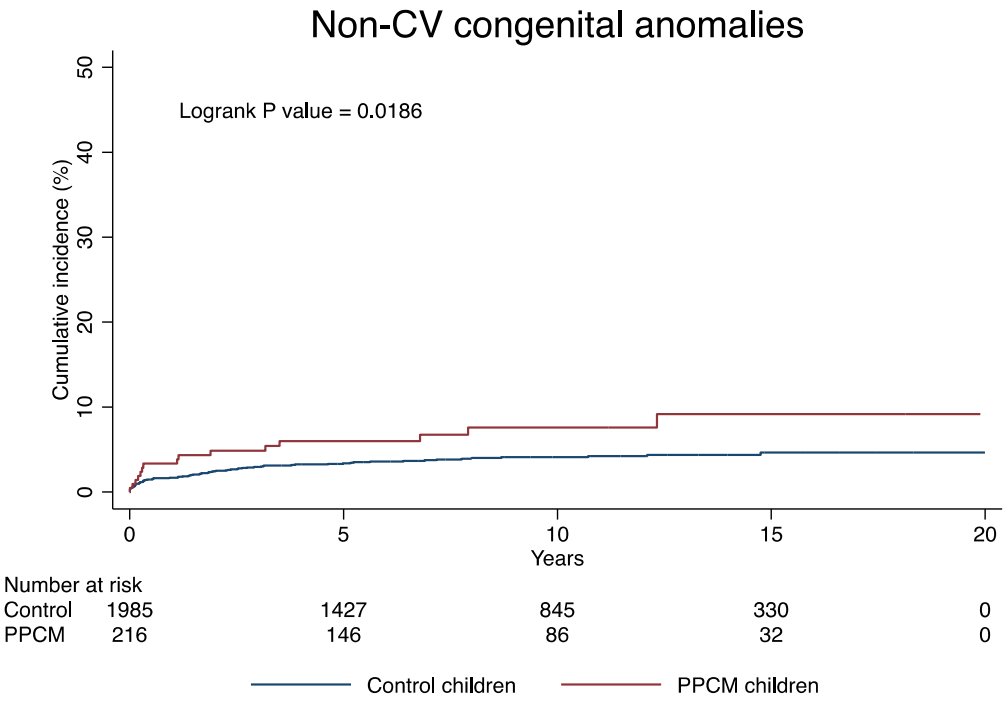


**Figure 7-4 Cumulative incidence of respiratory disease in PPCM and control children**

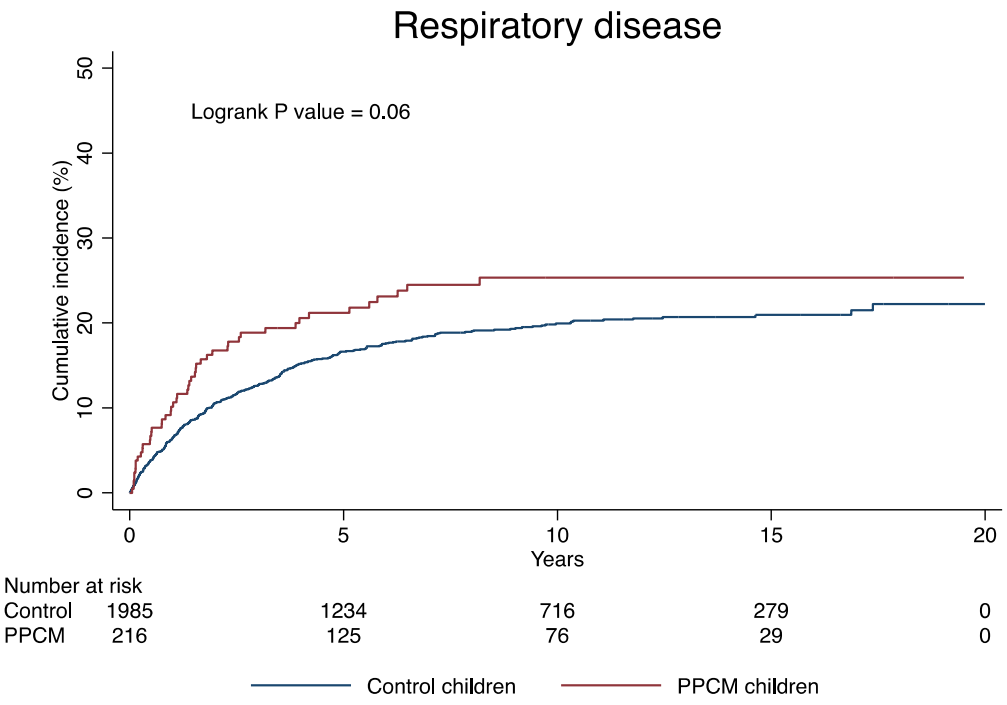



**Figure 7-5 Cumulative incidence of gastrointestinal disease in PPCM and control children**

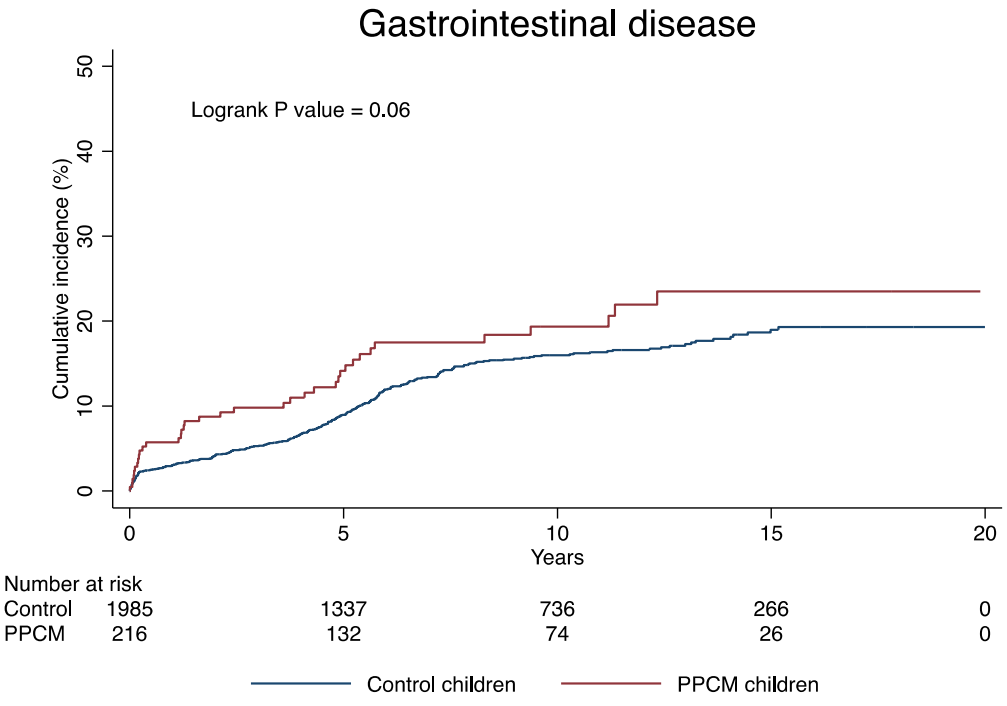
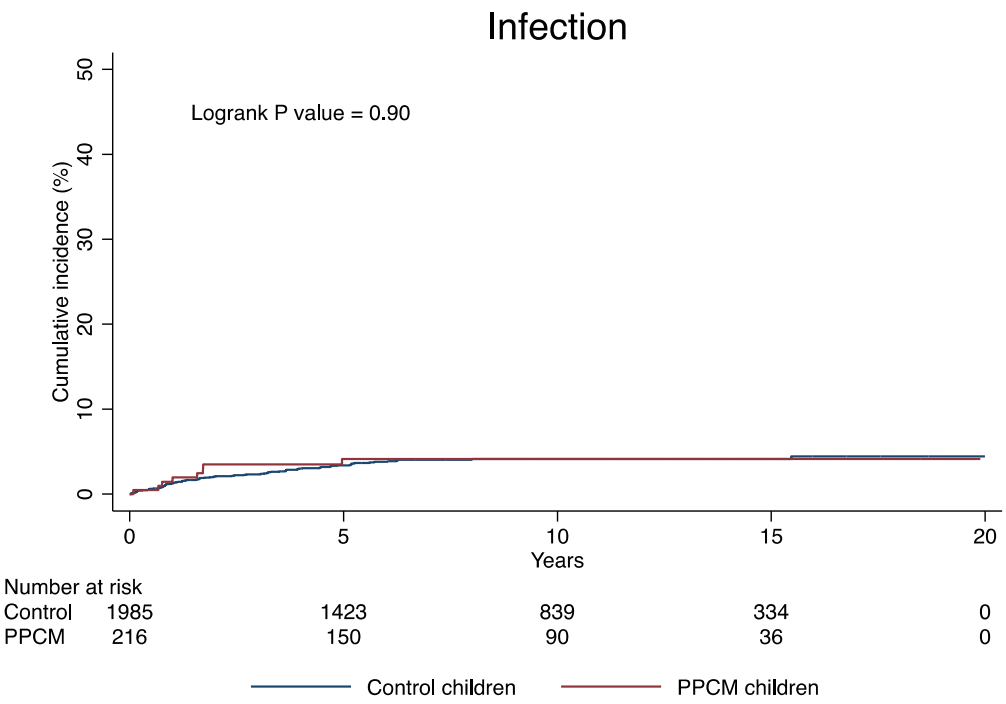


**Figure 7-6 Cumulative incidence of infection in PPCM and control children**

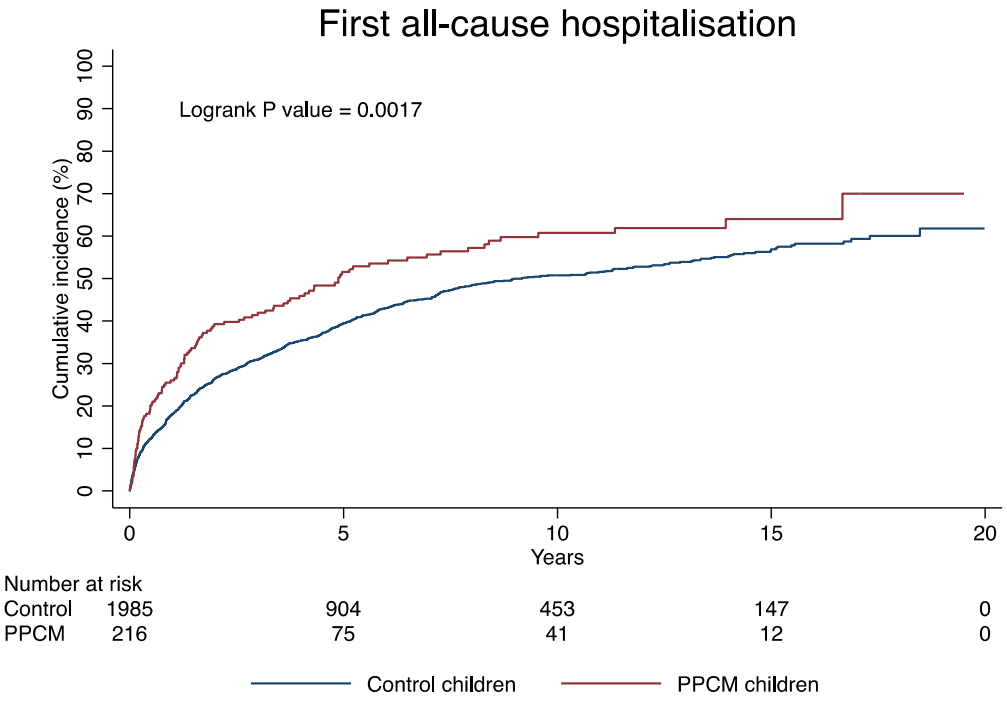


**All-cause hospitalisation**

The rate of a first hospitalisation for any cause per 1000 person-years was greater in PPCM children than in control children: 111.7 (95% CI 93.1-133.9) and 78.9 (95% CI 74.0-84.2), respectively (Table 7-4 and Figure 7-7). The rate of hospitalisation for any cause in PPCM children was 1.41 (95% CI 1.17-1.72) times that for control children (Table 7-4).

The median time to a first hospitalisation beyond the neonatal period was 412 days (IQR 83-1229) in PPCM children and 588 days (IQR 156-1639) in control children.

**Figure 7-7 Cumulative incidence of first hospitalisation for any cause in PPCM and control children**



**Medical therapy**

Medication data were available for children born from April 2009 onwards. As with the analyses of long-term outcomes, in the event data were not available for a PPCM child, children from all controls were also excluded from the analyses.

Medications were examined at 5 years from the date of birth in children with complete follow-up at each time point (n=49 PPCM children; n=428 control children). There were no differences between PPCM children and control children in the frequencies of prescriptions of any classes of medications (Table 7-5).

**Table 7-5 Community prescriptions in PPCM and control children at aged 5 years**

| | Total N=477 | Control children N=428 | PPCM children N=49 | P value | Missing |
|---|---|---|---|---|---|
| CV | 4 (0.8) | 3 (0.7) | 1 (2.0) | 0.33 | 0 |
| Respiratory | 340 (71.3) | 305 (71.3) | 35 (71.4) | 0.98 | 0 |
| Gastrointestinal | 237 (49.7) | 213 (49.8) | 24 (49.0) | 0.92 | 0 |
| CNS | 386 (80.9) | 345 (80.6) | 41 (83.7) | 0.60 | 0 |
| Antimicrobial | 396 (83.0) | 354 (82.7) | 42 (85.7) | 0.60 | 0 |
| ENT | 239 (50.1) | 213 (49.8) | 26 (53.1) | 0.66 | 0 |
| Ophthalmological | 272 (57.0) | 244 (57.0) | 28 (57.1) | 0.99 | 0 |
| Musculoskeletal | 248 (52.0) | 222 (51.9) | 26 (53.1) | 0.87 | 0 |
| Dermatological | 410 (86.0) | 369 (86.2) | 41 (83.7) | 0.63 | 0 |
| Endocrine | 85 (17.8) | 79 (18.5) | 6 (12.2) | 0.28 | 0 |

*CV = cardiovascular; CNS = central nervous system; ENT = ear nose throat.*

*Data are presented as n (%) for categorical measures*.

### *7.3.4 Recurrent hospitalisations*

Children who died within the first 7 days following delivery (including stillbirths) were excluded from analyses of recurrent hospitalisations. Only children with complete follow-up at each time point were examined (6 months n=213 PPCM children and n=1936 control children; 1 year n=207 PPCM children and n=1901 control children; 5 years n=164 PPCM children and n=1486 control children; 10 years n=101 PPCM children and n=883 control children; all n=216 PPCM children and n=1985 control children).

The median cumulative length of stay for all hospitalisations beyond the neonatal period was similar in PPCM children and control children (3 days [IQR 1-6] vs 2 days [IQR 1-5], respectively, p=0.91).

At 6 months, 1 and 5 years, the proportions of PPCM children with at least one hospitalisation were greater than those for control children: at 6 months 20% vs 12% (p=0.001); at 1 year 27% vs 18% (p=0.002); at 5 years 52% vs 39% (p<0.001). However, by 10 years a similar proportion of PPCM and control children had had at least one hospitalisation (57% vs 48%, p=0.09) (Table 7-6). The proportion of PPCM children with at least two hospitalisation was 3% at 6 months, 9% at 1 years, 21% at 5 years and 26% at 10 years.

Overall, recurrent hospitalisations were more common in PPCM children than in control children, with a rate 1.3-times greater for PPCM children than for control children (IRR 1.31, 95% CI 1.01-1.69).

## Table 7-6 Recurrent hospitalisations for any cause in PPCM and control children

| | All | | | 6 months | | | 1 year | | | 5 years | | | 10 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Control children N=1985** | **PPCM children N=216** | **P value** | **Control children N=1936** | **PPCM children N=213** | **P value** | **Control children N=1901** | **PPCM children N=207** | **P value** | **Control children N=1486** | **PPCM children N=164** | **P value** | **Control children N=883** | **PPCM children N=101** | **P value** |
| ≥1 – no. (%) | 915 (46.4) | 116 (55.2) | 0.015 | 235 (12.2) | 42 (20.3) | 0.001 | 340 (18.0) | 54 (26.9) | 0.002 | 568 (38.6) | 83 (52.5) | <0.001 | 417 (47.9) | 54 (56.8) | 0.099 |
| ≥2 – no. (%) | 518 (26.3) | 68 (32.4) | 0.058 | 49 (2.5) | 7 (3.4) | 0.48 | 95 (5.0) | 18 (9.0) | 0.020 | 239 (16.2) | 34 (21.5) | 0.091 | 198 (22.8) | 25 (26.3) | 0.43 |
| ≥3 – no. (%) | 286 (14.5) | 42 (20.0) | 0.034 | 15 (0.8) | 2 (1.0) | 0.78 | 37 (2.0) | 6 (3.0) | 0.33 | 121 (8.2) | 18 (11.4) | 0.17 | 98 (11.3) | 16 (16.8) | 0.11 |
| Total no. | 2422 | 332 | | 314 | 52 | | 524 | 85 | | 1512 | 210 | | 2084 | 279 | |
| **IRR (95% CI)** | 1.31 (1.01-1.69) | | | 1.64 (1.06-2.54) | | | 1.59 (1.07-2.37) | | | 1.60 (1.16-2.20) | | | 1.34 (0.95-1.87) | | |

*IRR = incidence rate ratio*

*Data are presented as n (%) for categorical measures.*

## *7.3.5 Prognostic markers*

**Adverse neonatal outcome**

An adverse neonatal outcome, defined as a composite of prematurity (estimated gestation <37 weeks), low birth weight (<2500g), stillbirth or early neonatal death (death within 7 days of delivery), occurred in 75 (32%) of children with PPCM. Table 7-7 shows maternal and foetal characteristics according to whether or not an adverse neonatal occurred, among PPCM children.

The median birthweight of infants with an adverse neonatal outcome was 2165g (IQR 1560-2590), and of those without was 3385g (IQR 3000-3906) ($p<0.002$). Infants with an adverse neonatal outcome were more often girls, had lower APGAR scores, more often required invasive ventilation, were more frequently from a multigestational pregnancy and one which required induction, and were more often born to a mother with pregnancy-induced hypertension (in the current pregnancy), pre-eclampsia (in the current pregnancy) or prior diabetes (either pre-existing diabetes or previous gestational diabetes)

There were no differences in maternal age, socioeconomic deprivation quintile, or in the prevalence of other maternal factors such as obesity (BMI >30kg/$m^2$), smoking, or multiparity in neonates with and without an adverse outcome. Maternal LVEF at baseline, LV end diastolic diameter and electrocardiographic parameters were also similar irrespective of neonatal outcome, whereas maternal platelet count and maternal serum albumin levels were lower in those with an adverse neonatal outcome than in those without.

## Table 7-7 Maternal and infant characteristics in PPCM children with and without an adverse neonatal outcome

| | Total<br>N=233 | No adverse neonatal outcome<br>N=158 | Adverse neonatal outcome<br>N=75 | P value | Missing |
|---|---|---|---|---|---|
| **Infant** | | | | | |
| Birthweight (grams) | 3100 (2597-3670) | 3385 (3000-3906) | 2165 (1560-2590) | <0.001 | 5 |
| Sex | | | | 0.002 | 0 |
| Boy | 106 (45.5) | 83 (52.5) | 23 (30.7) | | |
| Girl | 127 (54.5) | 75 (47.5) | 52 (69.3) | | |
| APGAR score 5 minutes | 9 (9-9) | 9 (9-9) | 9 (8-9) | 0.004 | 13 |
| Invasive ventilation | 15 (7.3) | 3 (2.1) | 12 (20.0) | <0.001 | 27 |
| **Maternal** | | | | | |
| Age (years) | 32±6 | 31±6 | 32±6 | 0.25 | 0 |
| Deprivation quintile | | | | 0.52 | 1 |
| 1 (most deprived) | 74 (31.9) | 46 (29.3) | 28 (37.3) | | |
| 2 | 42 (18.1) | 29 (18.5) | 13 (17.3) | | |
| 3 | 41 (17.7) | 28 (17.8) | 13 (17.3) | | |
| 4 | 34 (14.7) | 22 (14.0) | 12 (16.0) | | |
| 5 | 41 (17.7) | 32 (20.4) | 9 (12.0) | | |
| Body mass index >30kg/$m^2$ | 69 (34.0) | 45 (31.7) | 24 (39.3) | 0.29 | 30 |
| Smoking (current/former) | 90 (39.3) | 63 (40.1) | 27 (37.5) | 0.71 | 4 |
| PIH | 88 (37.8) | 50 (31.6) | 38 (50.7) | 0.005 | 0 |
| Pre-eclampsia | 52 (22.3) | 28 (17.7) | 24 (32.0) | 0.014 | 0 |
| Prior hypertension | 40 (17.2) | 26 (16.5) | 14 (18.7) | 0.68 | 0 |
| Prior diabetes | 19 (8.2) | 9 (5.7) | 10 (13.3) | 0.047 | 0 |
| Parity >1 | 69 (29.6) | 49 (31.0) | 20 (26.7) | 0.50 | 0 |
| Parity >2 | 37 (15.9) | 26 (16.5) | 11 (14.7) | 0.73 | 0 |
| Parity >3 | 22 (9.4) | 14 (8.9) | 8 (10.7) | 0.66 | 0 |
| Multiple gestation | 37 (15.9) | 12 (7.6) | 25 (33.3) | <0.001 | 0 |
| PPH | 91 (39.1) | 58 (36.7) | 33 (44.0) | 0.29 | 0 |
| Induction of labour | 64 (29.1) | 58 (37.2) | 6 (9.4) | <0.001 | 13 |
| SBP (mmHg) | 136 (120-156) | 135 (120-150) | 148 (120-165) | 0.15 | 47 |
| Heart rate (bpm) | 107 (88-125) | 110 (89-125) | 104 (86-126) | 0.65 | 40 |
| QRS duration (ms) | 82 (76-94) | 82 (76-93) | 82 (74-94) | 0.75 | 46 |
| Bundle branch block | 24 (12.6) | 17 (12.8) | 7 (12.3) | 0.92 | 43 |
| QTc duration (ms) | 447 (423-479) | 447 (423-478) | 449 (425-484) | 0.92 | 48 |
| Any ECG abnormality | 141 (75.8) | 99 (76.2) | 42 (75.0) | 0.87 | 47 |
| LVEF (%) | 35±11 | 35±11 | 35±11 | 0.93 | 31 |
| LVEDD (mm) | 57±8 | 58±7 | 56±8 | 0.23 | 53 |
| Haemoglobin (g/l) | 114 (100-126) | 114 (99-127) | 111 (102-125) | 0.49 | 34 |
| White blood cells (x10^9/l) | 12 (9-15) | 12 (9-15) | 12 (10-14) | 0.48 | 34 |
| Lymphocytes (x10^9/l) | 2 (1-2) | 2 (1-2) | 2 (1-2) | 0.18 | 40 |
| Neutrophils (x10^9/l) | 9 (6-12) | 9 (6-12) | 9 (6-12) | 0.79 | 40 |
| Platelets (x10^9/l) | 283 (205-391) | 298 (225-395) | 252 (180-378) | 0.026 | 35 |
| Serum creatinine (µmol/l) | 68 (57-83) | 69 (57-81) | 66 (53-85) | 0.30 | 32 |
| Serum albumin (g/l) | 30 (25-35) | 31 (26-37) | 30 (23-34) | 0.047 | 40 |

*PIH = pregnancy-induced hypertension; PPH = postpartum haemorrhage; SBP = systolic blood pressure; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end diastolic diameter*

*Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.*

*Univariable analysis*

On univariable analysis, the following characteristics were associated with a greater likelihood of an adverse neonatal outcome in PPCM children: female infant sex (OR 2.50, 95% CI 1.40-4.48), pregnancy-induced hypertension (OR 2.22, 95% CI 1.26-3.90), pre-eclampsia (OR 2.18, 95% CI 1.16-4.12) and multiple gestation (OR 6.08, 95% CI 2.85-13.00).

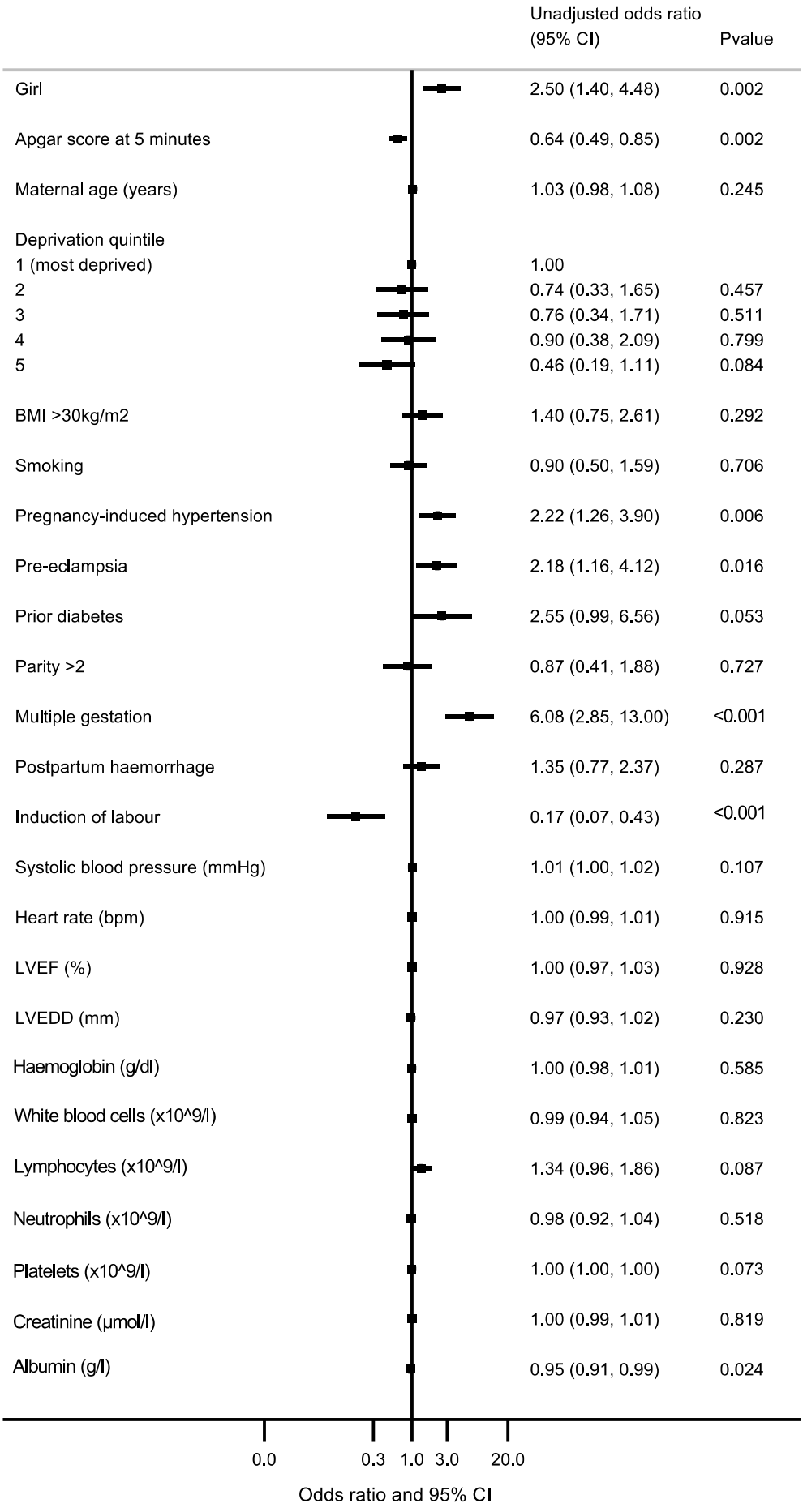
The following characteristics were associated with a lower likelihood of an adverse neonatal outcome: higher APGAR score at 5 minutes (OR 0.64, 95% CI 0.49-0.85), induction of labour (OR 0.17, 95% CI 0.07-0.43) and a higher maternal serum albumin at the time of diagnosis (OR 0.95, 95% CI 0.91-0.99) (Figure 7-8).

*Multivariable analysis*

A limited number of obstetric candidate variables were examined given the number of events . The following variables were included in the model (n=202 with complete data in final model): infant sex, socioeconomic deprivation (most deprived quintile vs not), maternal age at delivery, maternal obesity (body mass index >30kg/$m^2$), maternal smoking (current/former), multigestational pregnancy, pre-eclampsia, prior history of hypertension, multiparity (more than 2 prior pregnancies). The model was also adjusted for year of delivery (1998-2007 vs 2008-2017).

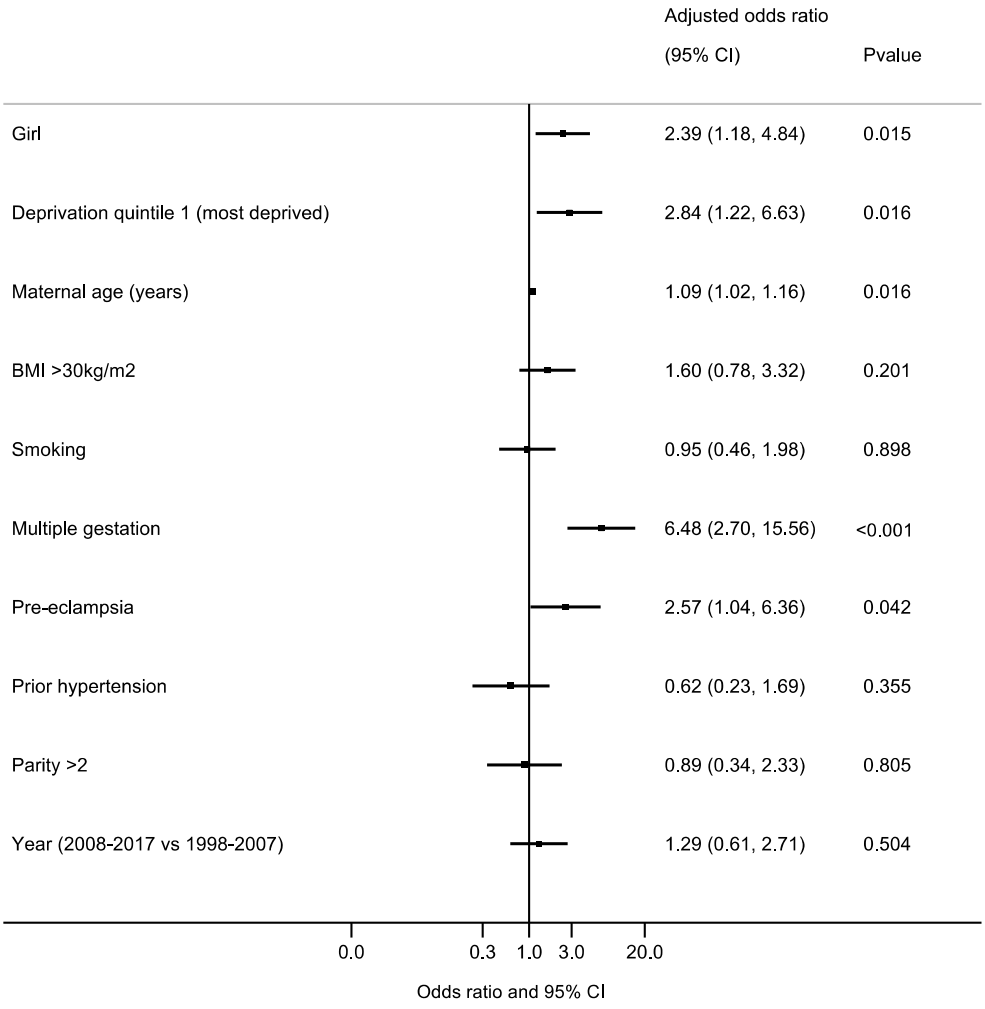
Female infant sex (OR 2.39, 95% CI 1.18-4.84), greater socioeconomic deprivation (OR 2.84, 95% CI 1.22-6.63), increasing maternal age (per 1 year) (OR 1.09, 95% CI 1.02-1.16), multiple gestation (OR 6.48, 95% CI 2.70-15.56) and pre-eclampsia (OR 2.57, 95% CI 1.04-6.36) were independently associated with a greater likelihood of an adverse neonatal outcome (Figure 7-9).

## Figure 7-8 Factors associated with an adverse neonatal outcome (univariable)




*All but sex and APGAR score are maternal factors.*

## Figure 7-9 Factors associated with an adverse neonatal outcome (multivariable)




*All but sex are maternal factors.*
*N=202 with complete data included in final model*

## 7.4 Discussion

These analyses have identified that children born to women with PPCM in Scotland had worse clinical outcomes than children born to controls, over a median follow-up of 9.1 years. Not only were neonatal outcomes worse, including a greater prevalence of prematurity, low birth weight and lower APGAR scores, but the overall mortality rate was 5-times higher than that for control children (0.9, 95% CI 0.5-1.4 and 4.1, 95% CI 2.1-8.2 per 1000 person-years). However, in both groups, the majority of deaths occurred very early (i.e. stillbirths and neonatal death within the first 7 days of delivery). Notably, PPCM children also had a 3-times higher incidence of CV disease, as compared to control children (1.4, 95% CI 1.0-2.1 and 4.8, 95% CI 2.5-9.1 per 1000 person-years).

A small number of studies have reported outcomes in infants born to women with PPCM. Birth weight and APGAR scores were lower than in controls, as well as a greater prevalence of prematurity, are consistent findings between those which have and the current study[11, 13, 19, 20, 23]. Overall, case-fatality in neonates from mothers with PPCM ranges from 0%-5% in the published literature[11, 14, 21, 23, 153], with the exception of one study from Haiti, in which the frequency of neonatal death was considerably higher at 12%[156]. It is unclear whether or not stillbirths were included in these figures. In the current study, stillbirth or neonatal death occurred in 2.7% of PPCM children. This is the first report of infant mortality in PPCM from the UK and the third from Europe. In the ESC PPCM Registry, although neonatal death was greater overall (5%), there was significant regional variation in outcomes, with lower case-fatality in 186 infants in Europe (1.6%). In a population-level study including 66 neonates in Denmark, neonatal death occurred in 1.5% of infants[18]. These estimates may be slightly lower than that in the current study due to their exclusion of stillbirths and more contemporary study period.

A strength of the current analyses is the duration of follow-up available for infants. Only one prior case series, from Haiti, has reported infant outcomes beyond the neonatal period[156]. Overall, 64% of infants (14/22) were reported to have died at 1 year post-delivery. In all cases, the cause death was associated with malnutrition. Major demographic, economic and health-related differences

make it impossible to apply these data to countries within Western Europe, such as the UK. Linkage of routine data in Scotland allowed follow-up of infants included to the end of the study period (31st December 2017). Median follow-up for all children in this study was 9.1 years (IQR 4.9-13.4). Importantly, extension of follow-up beyond the neonatal period showed that later deaths were uncommon.

These findings suggest an elevated risk for PPCM infants during the obstetric and neonatal period. Reasons for this are likely to be multifactorial. Conditions which co-exist in mothers who develop PPCM, such as pre-eclampsia and multigestational pregnancy, are known to be associated with adverse foetal outcomes in women without PPCM[206]. Indeed, in the ESC PPCM Registry, women with PPCM and pre-eclampsia had a 2.8 times greater likelihood of an adverse neonatal outcome than women with PPCM without gestational hypertensive disease, even after adjustment for differences in baseline cardiac function, region, maternal body mass index and serum creatinine[186]. Early recognition of factors such as these, and treatment where indicated, is paramount. It has also been shown that lower maternal stroke volume and cardiac output may be associated with worse foetal outcomes in women with heart disease[207, 208].

Approximately 1 in 3 PPCM children experienced an adverse neonatal outcome (defined as a composite of prematurity [estimated gestation <37 weeks], low birth weight [<2500g], stillbirth or early neonatal death [death within 7 days of delivery]). Female sex, greater socioeconomic deprivation, increasing maternal age, multiple gestation and pre-eclampsia were found to be independently associated with a greater likelihood of an adverse neonatal outcome. Other than the ESC PPCM Registry, no prior studies have evaluated predictors of infant outcomes in PPCM using multivariable regression analysis. Given the small numbers of events, the selection of candidate predictor variables included was limited to those with clinical relevance and/or statistical significance in the univariable model. Since the components of the adverse neonatal outcome composite included outcomes at the time of delivery, other delivery-related factors (such as mode of delivery or induction of labour) were not examined, as these may have been directly influenced by the clinical status of the foetus.

A further novel finding is that of a greater incidence of CV disease in PPCM children relative to control children (3.3 times higher). This has not before been examined in a cohort of women with PPCM. The condition has previously been shown to be a genetic disease in around 1 in 7 women. In two studies, approximately 15% of women with PPCM were found to harbour defects in genes known to cause dilated cardiomyopathy, with the majority being variants in the gene coding the protein titin (TTN)[68, 69]. In the earlier of these two studies, which included 79 women recruited from the IPAC study, in whom phenotypic and genetic data were available, the presence of a TTN variant was associated with a lower prevalence of hypertension and a lower LVEF at 1 year[68]. Conversely, in the more contemporary and larger study (n=469 with phenotypic and genetic data), the proportions of women with hypertension and with recovery at 1 year were similar in those with and without a TTN variant. In each, the total number with a TTN variant was small (n=11 and n=45)[69]. Differences in phenotype and outcomes according to the presence or absence of pre-eclampsia may exist. Women with PPCM without pre-eclampsia have been shown to have clinical features more closely aligned with those seen in 'idiopathic' dilated cardiomyopathy than those with pre-eclampsia, including larger LV diameters, more frequent bundle branch block on ECG, a greater prevalence of biventricular dysfunction, a greater reported frequency of a family history of dilated cardiomyopathy and less frequent recovery of cardiac function[186]. Currently there are no guideline-recommendations regarding genetic testing and screening of first-degree relatives in PPCM. In the future, it is possible that routine genetic testing (with or without family screening) in all women with PPCM may enhance timely detection and management of CV disease in children. Discussion about inherited risk in children is also an essential part of pre-pregnancy counselling in women with established CV disease[49].

Limitations of these analyses include the lack of hospitalisation data from the early neonatal period, such as details of a neonatal unit admission after delivery. In Scotland, prior to 2003, neonatal data were captured only for babies who required a neonatal unit inpatient stay, or those with congenital anomalies. From 2003 onwards, this was replaced by the Scottish Birth Record, which now records neonatal data on all children. However, these are not audited datasets, data completeness is highly variable, and there are differences in engagement with data submission over time and across NHS health boards. For these reasons,

the SMR11 and Scottish Birth Record datasets were not used. Therefore, estimates of disease incidence do not include a diagnosis assigned during an early neonatal inpatient stay if the diagnosis does not feature during a later hospitalisation for that child (i.e. in the SMR01 dataset). However, it is plausible that a diagnosis assigned during the neonatal period, which never features again during the child's life, may be less relevant (perhaps with the exception of infection). An additional limitation was the lack of data regarding other variables which may be of prognostic significance; for example, maternal natriuretic peptide levels, particularly in the context of pre-eclampsia, a state which is associated with elevation in levels of B-type natriuretic peptides[209]. Finally, due to small numbers of PPCM children with incident CV disease, factors associated with its development could not be explored.

## 7.5 Summary

Approximately 1 in 3 children born to women with PPCM had an adverse neonatal outcome, with 4% case-fatality (including stillbirths) and a mortality rate approximately 5 times that of children born to controls. The majority of infants deaths occurred early. Female sex, greater deprivation, increasing maternal age, multiple gestation and pre-eclampsia were associated with an increased likelihood of an adverse neonatal outcome (a composite of stillbirth, early neonatal death, low birth weight and prematurity). Children born to women with PPCM also had an approximately 3-times greater incidence of CV disease than children born to controls.

# Chapter 8 Discussion

## 8.1 Summary of findings

My aim was to provide a comprehensive account of the epidemiology of PPCM in Scotland, at population-level, over an extended period. The objectives included describing patient characteristics and outcomes for women with PPCM (including those related to a subsequent pregnancy) and their children. Through a nested case-control study, factors associated with the development of the condition were identified, and outcomes for women with PPCM and their children were compared to those for women without heart failure or cardiomyopathy.

This section will link back to areas originally identified as gaps in the knowledge in the Introduction chapter, section 2.1.1.

**Incidence of PPCM in the UK**

This study is the first to provide an estimate of the incidence of PPCM in the UK, with validation of Scottish cases in 90%. In both Scotland and England, PPCM occurred in approximately 1 in 5000 deliveries (1 in 4950 in Scotland; 1 in 4717 in England).

The incidence of PPCM around the world varies dramatically and this is summarised in Table 1-2 in the Introduction chapter. In some regions, such as Nigeria, PPCM appears to be much more common, occurring in as many as 1 in 100 deliveries[30]. The lowest estimate of incidence reported in the literature is in Japan, at around 1 in 20,000 deliveries[36]. Although true differences are likely to exist, a major difficulty with drawing direct comparisons stems from important differences in the methods used to identify cases (e.g. cardiac imaging vs no cardiac imaging; retrospective vs prospective; population-level vs single/multicentre; consecutive vs non-consecutive inclusion; administrative data vs clinical data; validated cases vs International Classification of Disease coding; explicit exclusion criteria vs ambiguous exclusion criteria). Strengths of this study include consecutive capture of hospitalised cases at population level, validation of cases through direct review of patient records across Scottish health boards and the application of explicit exclusion criteria with respect to

alternative aetiologies. For those patients without available records, the combination of ICD discharge codes resulting in optimal sensitivity for PPCM was applied and cases only included if this combination was present.

An important consideration is that any reported incidence could be under- or overestimated. In this study, underestimation could occur due to the possibility that a woman never had a hospitalisation relating to PPC and was therefore not captured. Only hospital discharges were screened due to limitations of the outpatient SMR dataset (SMR00). Underestimation could also occur due to underdiagnosis of the condition. Historically, the overlap of signs and symptoms of cardiac disease with those of pregnancy (e.g. breathlessness) has made distinguishing between pathology and normal physiology challenging. Women are often only diagnosed when signs and symptoms are severe enough to warrant hospital admission and it thus seems plausible that there may be a proportion of women who have less severe cardiac dysfunction which remains undiagnosed. More contemporary diagnostic modalities and techniques, including hand-held echocardiography and natriuretic peptide testing, have helped make this distinction clearer. Ultimately, the diagnosis can only be reached if it is considered; education and awareness amongst healthcare professionals caring for peripartum women are paramount to improving this. Overestimation is also possible. There may be ambiguity about the likely aetiology in some situations, such as sepsis or bleeding. Clear diagnostic criteria, with explicit exclusion criteria, are required to standardise the diagnosis. Overestimation of the incidence in the current study seems unlikely given the rigorous exclusion of women with likely alternative aetiologies and adjudication of borderline cases with a second cardiologist.

International criteria suggest an arbitrary LVEF of below 45% is necessary in order to diagnose PPCM[3]. What does this mean for women with an LVEF that is subnormal, but above this threshold? Indeed, it has been shown that a ‘normal’ LVEF for women is actually higher than that for men[210]. In this study, all women with a reduction in systolic function (mildly impaired or worse) were included. Despite this, outcomes were similar to those seen in other European studies which applied the more stringent cut-off, suggesting that this group of women are just as important. In the future, inclusion of women with a milder degree of cardiac dysfunction, along with thresholds of natriuretic peptide levels, will help

us better understand the complex spectrum of LV dysfunction around the time of pregnancy. PPCM with a HFpEF phenotype has been proposed[211-213]. Here, the interplay between cardiac dysfunction and comorbidities such as obesity, hypertension and diabetes, which were more prevalent in women with PPCM than controls in this study, may be even more relevant. In the current study, only 47 women with echocardiographic data had an LVEF above 45% (or equivalent qualitative assessment) and so outcomes were not reported separately for this group. Interestingly, prevalences of comorbidities associated with HFpEF, such as diabetes or hypertensive disorders, were not greater in this study as compared with others which only included patients with LVEF <45%. More research is required into this unique subgroup.

Incidence of disease is perhaps most relevant to the population in which it was estimated and to those individuals who are at risk of developing it. The accepted definition of a rare disease is one which affects fewer than 1 in 2000 individuals[214]. Although technically a rare disease in Scotland, it is likely PPCM is more common in certain subgroups, i.e. those with risk factors. In this study, factors independently associated with an increased likelihood of developing the condition included pregnancy-induced hypertension, pre-eclampsia, multiparity and multiple gestation. The study design did not allow for incidence to be examined specifically in subgroups such as these, which would have required the denominator to comprise all women in the population with the risk factor of interest. It was possible to examine the incidence according to maternal age, and it was greater in older women. Indeed, in the later part of the study, PPCM occurred in 3.66 per 10,000 deliveries (or 1 in 2732) in women over the age of 32 years. With this in mind, is there a case for screening certain at-risk groups of women for asymptomatic LV dysfunction (and/or those with clinical features not always recognised as potentially abnormal, such as breathlessness or tachycardia) and, if so, could this modify risk? Screening programmes are underpinned by the notion that pre-clinical identification of a disease can lead to better health outcomes through targeted intervention[215]. The appropriateness of a screening programme is generally evaluated through principles proposed by Wilson & Jungner[216], which are not discussed in detail in this thesis. Identifying cardiac dysfunction may allow modifications to the delivery plan, such as more judicious intravenous fluid administration, avoidance of tocolytic therapies and earlier delivery. Beyond obstetric management, treatment of asymptomatic LV

dysfunction with heart failure therapies (those safe during pregnancy) reduces the incidence of heart failure and ameliorates LV remodelling[217-219]. Furthermore, in women with PPCM, delayed diagnosis and later presentation have been shown to be associated with worse outcomes[92, 220].

**Long term outcomes**

In total, 8% of women died over a median follow-up of 8.3 years, and 76% had 'LV recovery' over a median follow-up of 9.7 years. Long-term follow-up (i.e. beyond 5 years) is uncommon in published studies of PPCM, as discussed in the Introduction chapter, and summarised in Table 1-5. There are case reports of deaths occurring up to 8 years postpartum[26, 29, 92, 104]. In this study, the cumulative incidence curve depicting all-cause death showed that events continued to occur up to and even beyond 10 years from the index hospitalisation in women with PPCM. Due to small numbers, details on the causes of death could not be discussed, although the primary cause of death was CV in the majority of cases. Similarly, recovery of cardiac function (or at least normalisation of ejection fraction) continued to occur beyond 1 year postpartum. Notably, a sustained decline in LV function occurred in 13% of women who had fully recovered, with a continued rise in the incidence of sustained decline to 10 years after recovery. Although overall numbers of women with sustained decline were small (n=20), these data would suggest that, for some women, recovered PPCM is not 'cured' and that long term follow-up after recovery may be warranted. There are three main points of discussion raised by these findings.

The first relates to the definition and quantification of LV recovery. In PPCM, this has traditionally been based solely on an LVEF threshold of greater than 50% or 55%. LV recovery is, of course, more complex than this, with attenuation of adverse LV remodelling also involving changes in LV volumes and neurohumoral activation[221]. In the prospective TRED-HF (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy) study, recovered patients were defined as: a) those without symptoms, b) an LVEF of ≥50%, c) an LV end diastolic volume indexed to body surface area within the normal range on cardiac magnetic resonance imaging and d) plasma NT-proBNP concentration <250 ng/L[108]. Abnormalities in global longitudinal strain

have been shown to persist despite improvements in LVEF in women with PPCM and may be more reliable in risk stratification than LVEF alone[121, 222-224]. A reduction in contractile reserve has also been demonstrated in a small number of women with PPCM with otherwise normal echocardiographic measures of LV function[134, 225, 226]. In the current study, a more comprehensive definition of LV recovery was not possible, largely because of its retrospective nature and lack of routine measurements of biomarkers in clinical practice during the study period. In the future, research should focus on incorporating biomarker thresholds and more sophisticated imaging modalities into the definition of LV recovery. This may also aid more accurate characterisation of women at greater risk of subsequent decline in cardiac function. Genetics may also be important, although there was no association between the presence of a TTN variant and the risk of deterioration following withdrawal of therapy in the TRED HF study[108]. In the current study, women with sustained decline after recovery more often had a history of prior hypertension, had a greater prevalence of multiparity, a longer QRS duration, a lower LVEF and larger LVEDD at baseline.

The second relates to pharmacological treatment of a recovered patient. Expert opinion on cessation of medical therapy in this setting is divided[107]. Unfortunately, it was not possible to temporally link changes in pharmacological therapy to either recovery of LV function or to sustained decline after recovery in these analyses. Withdrawal of medical therapy may be detrimental in nearly half of patients with recovered DCM[108]. In PPCM specifically, data are sparse and conflicting, with reports of both deterioration and stability after cessation of heart failure therapies[94, 105]. The safety and effects of withdrawal of treatments in recovered PPCM remain unknown.

The third point relates to the propensity for adverse CV outcomes later in life. This is particularly relevant in women with pregnancies complicated by gestational hypertensive disorder. Pregnancy-induced hypertension occurred in 39% of women enrolled in the ESC PPCM Registry[11] and in 34% in the current study. Hypertensive disorders of pregnancy have been shown to be associated with an increased risk of heart failure, as well as coronary artery disease, stroke, diabetes, hyperlipidaemia and chronic kidney disease in the decades following pregnancy[227, 228]. In the current study, the incidence of CV death or CV rehospitalisation in women with PPCM was 14 times that of controls, and CV

events occurred years later even in women with complete recovery of LV function. HFpEF may be an important consideration. HFpEF is associated with a high prevalence of hypertension and important alterations in cardiac structure and physiology are present in women with pre-eclampsia[229-231]. Furthermore, pre-eclampsia is associated with an elevated risk of developing essential hypertension, which is common in HFpEF[231]. HFpEF is also more common in women than in men, and it is possible that pregnancy itself is a risk factor for adverse CV outcomes later in life[232]. Healthy pregnancies are associated with an increase in LV mass and volume, changes in longitudinal function and diastolic dysfunction, though not with a reduction in ejection fraction[233-236]. Furthermore, multiparity, which is more common in both PPCM and pre-eclampsia than uncomplicated pregnancies, is associated with greater risk of adverse cardiac remodelling later in life[76, 77].

**Subsequent pregnancies**

Although 15% of women with PPCM and a subsequent pregnancy (n=36, 15% of women) had a CV hospitalisation in the 1st year after pregnancy, there were no occurrences of the CV composite (defined as CV death, mechanical circulatory support or cardiac transplantation). Neonatal outcomes were worse than those for controls. Women who went on to have a subsequent pregnancy tended to be younger, more socioeconomically deprived and had features suggestive of a less severe cardiomyopathy (e.g. higher LVEF). Given the retrospective nature of the study, dedicated echocardiographic assessment of LV function was not performed directly prior to each subsequent pregnancy. Nevertheless, 33 women had had an echocardiogram at a median of 11 months prior to the first subsequent pregnancy. Of these, 15% (n=5) had at least moderately impaired LV systolic function. An adverse neonatal outcome (defined as prematurity [estimated gestation <37 weeks], low birth weight [<2500g], termination, stillbirth or early neonatal death [death within 7 days of delivery]) was more likely in women with PPCM than in controls during the first subsequent pregnancy.

Reports of outcomes relating to a subsequent pregnancy in women with PPCM are sparse. Relevant studies are summarised in the Introduction chapter in Table 1-4. Across 23 studies, case-fatality ranged from 0-56%. Deaths occurred

exclusively in women without recovery of cardiac function prior to the subsequent pregnancy. Only 4 studies include women from European countries, and, in each, only 12-16 women were included[43, 102, 131, 136]. In 2 of these studies (including women in Denmark and Germany), no women died, whereas in a further study from Germany, a quarter of women died. In the final study (including women from Germany, Scotland and South Africa enrolled in the ESC PPCM Registry), a breakdown of case-fatality by country was not provided. The current analysis of subsequent pregnancies in the Scottish population give rise to a number of discussion points.

It has identified characteristics of women in this population who most often go on to have a subsequent pregnancy. This is important in shaping pre-pregnancy counselling in women with PPCM and ensuring those most likely to conceive again have access to appropriate information and support. While it is perhaps unsurprising that women with a subsequent pregnancy were younger with a less severe phenotype (probably explained by more intense counselling of women with a more severe phenotype against a subsequent pregnancy), it is noteworthy that socioeconomic deprivation also appeared to be relevant. Greater socioeconomic deprivation has been shown to be associated with a greater risk of adverse maternal and perinatal outcomes and with barriers to perinatal care[237, 238]. Data from the 2017-2019 MBRRACE-UK report (Saving Lives, Improving Mothers' Care) showed that 40% of maternal deaths were in women from the most deprived group[239]. Ensuring that those women with PPCM most likely to go on to have a further pregnancy receive appropriate counselling and follow-up is vital, and these data highlight which women may benefit most from additional support or services.

It also suggests that major adverse outcomes (such as CV death) are unlikely to occur, even in women with persistent cardiac dysfunction prior to a subsequent pregnancy. The modified WHO classification places women with previous PPCM and any residual LV impairment into the highest risk category (group IV: 'extremely high risk of maternal mortality or severe morbidity'). It is important that, while women are counselled appropriately regarding risk, they are supported to make an informed decision about a further pregnancy. In the future, a better understanding of the PPCM sub-phenotypes (e.g. inherited DCM vs pre-eclampsia vs 'HFpEF') will allow risk stratification and prognostication to

be more finely tuned. It seems plausible that women with gene positive DCM might have a greater propensity for future deterioration than women with a transient reduction in LV systolic function related to pre-eclampsia and that a 'one rule fits all' approach proposed by the WHO is not appropriate. However, currently no data exist to underpin this. How best to risk stratify women with respect to a subsequent pregnancy remains unclear. Contractile reserve, quantified using stress echocardiography, has shown promise in very small numbers of women[203].

Finally, the adverse outcomes seen in neonates relating to a subsequent pregnancy require consideration. Infants of PPCM mothers during a subsequent pregnancy had a more than 10-fold greater likelihood of an adverse neonatal outcome as compared to infants of controls during a subsequent pregnancy. Dissecting the relationship between maternal LVEF and an adverse neonatal outcome during a subsequent pregnancy showed that baseline LVEF (i.e. at the index presentation) was lower in mothers of neonates with an adverse outcome during a subsequent pregnancy than in those without. It appeared that pre-subsequent pregnancy LVEF was less relevant, although the number of women with a subsequent pregnancy in this study was small, and a large, prospective study would be required to further explore this and other factors which might be influential. Just one previous study has examined subsequent pregnancies in a case-control fashion, but only pregnancy outcome was reported (delivery vs termination)[20]. In that study, termination of a subsequent pregnancy was around 4 times more common in women with PPCM than in controls. The novel neonatal data provided by the current study highlight the need for close foetal surveillance during a subsequent pregnancy. They may also serve to guide information-giving for women with PPCM in Scotland in the future.

**Outcomes for children of women with PPCM**

Children born to women with PPCM (during the index pregnancy) had worse clinical outcomes than those born to controls, including more frequent adverse neonatal events, a higher mortality rate and a greater incidence of CV disease over a median follow-up of 9.1 years (8.8 years for PPCM children alone). The few published data on child outcomes are summarised in Table 1-6 in the Introduction chapter. The data linkage system in Scotland enables linkage of a

child to its mother throughout the entirety of its life. Because of this, this study provides a comprehensive account of outcomes for infants of women with PPCM and is the first to examine long-term outcomes and the incidence of CV disease. There is only one study describing outcomes beyond the neonatal period (conducted in Haiti, n=25 children, 64% case-fatality at 1 year)[156].

An adverse neonatal outcome, defined as a composite of prematurity (estimated gestation <37 weeks), low birth weight (<2500g), stillbirth or early neonatal death (death within 7 days of delivery) occurred in approximately a third of PPCM infants and was around 3 times more prevalent than in control infants. There are some limitations to the application of this finding clinically, given that the majority of women with PPCM are diagnosed after delivery (in this study, more than 80%). Neonatal complications may serve as a 'reg flag' for clinicians to consider a diagnosis of PPCM, particularly in those women with symptoms or signs such as breathlessness, oedema or tachycardia.

All-cause death also occurred significantly more often in PPCM children than in control children, with a mortality rate almost 5-fold higher, largely explained by a greater prevalence of stillbirths. A strength of this study was the ability to achieve a long period of follow-up, at population-level, through record linkage. Doing so showed that few deaths occurred beyond the neonatal period, and this was true in both PPCM and control children. These data may provide some basis to inform mothers in Scotland about the longer-term risk to their child. In future, larger studies of children born to women with PPCM are required to better understand factors which may be associated with mortality beyond the neonatal period. In this study, the total number of deaths was small.

A novel finding of this study was the approximately 3-times greater incidence of CV disease in PPCM children relative to control children. CV risk in children born to women with PPCM has never before been described. Here, the definition of incident CV disease was the first hospitalisation beyond the neonatal period with a discharge ICD-10 code for CV disease or congenital heart disease. In Scotland, data capture does occur in the neonatal period, previously through SMR11 and now through the Scottish Birth Record, but contribution of data is not standardised across health boards and the quality and quantity of data entry is variable. Because of this, these datasets were not used. However, it seems likely

that any significant cardiac condition would result in hospitalisation or day-case contact beyond the neonatal period. Familial PPCM and DCM have been reported in women with PPCM[62, 240]. In the ESC PPCM Registry, 4% of women reported a family history of DCM and 1% of PPCM[186]. In a study of 48 women with PPCM in Denmark, 23% had a first degree relative with heart failure (vs 10% in the control population) and 29% had a sibling with any CV diagnosis (vs 16% in the control population)[241]. In the last decade, two genetic studies have shown that approximately 15% of women harbour a truncating gene variant associated with DCM — predominantly TTN[68, 69]. Referral for genetic testing in women with PPCM is not yet routine in Scotland, nor is it mandated in international guidelines, but awareness is growing among clinicians. Again, education is crucial to improving this. Genetic data were collected during review of patient records in the current study, but uptake of genetic testing was very variable depending on region and access to genetic services, and the type of testing offered evolved substantially during the study period; as such, it was challenging to meaningfully interpret these data. If complete and comprehensive genetic data were available, genotypic and phenotypic associations could have been explored (e.g. do women with a genetic variant have a lower prevalence of pre-eclampsia, or worse LV function, or more LV dilatation, a higher proportion of ECG abnormalities, or a greater occurrence of arrhythmia at baseline?) and any differences with respect to outcomes could have been examined (e.g. do women with a genetic variant have a lower rates of LV recovery, or higher rates of CV hospitalisation, or worse outcomes during a subsequent pregnancy?).

Although appropriate genetic investigation is important for the mother, particularly with respect to LV recovery, consideration of treatments and prognostication, it is also important for offspring. Identifying children at greater risk of developing a CV phenotype may provide an opportunity for earlier clinical screening, closer surveillance, and more timely initiation of beneficial treatments. The findings from this study, together with what is understood about the genetic basis of PPCM, emphasise the importance of clinicians considering the hereditary nature of cardiac disease in women with PPCM and their children. Data such as these are also important for pre-pregnancy counselling in subsequent pregnancies, which should feature tailored discussions about mechanisms of inheritance and risk to offspring.

## 8.2 Limitations

As with any observational study conducted using routine 'real-world' administrative data, there are inherent limitations. Using administrative data is one of the few approaches which enables consecutive capture of individuals with a certain condition at population-level. However, missingness occurs to a greater extent than it does in prospective studies, and this was the case for both the administrative datasets used and for data collection from patient records. For some patients, complete patient records were missing. Where possible, obstetric/delivery data collected from patient records replaced missing data in the administrative datasets. Since case identification did not occur exclusively via the SMR02 (maternity) datasets, some women identified as having PPCM did not have an SMR02 record; for example, delivery at the Golden Jubilee National Hospital, the tertiary cardiac centre for the country, does not routinely generate an SMR02 record. For this reason, missing data occurred less frequently in controls, who were specifically identified through SMR02 delivery records with high levels of completeness. Certain variables are known to have low levels of completeness in SMR datasets, in particular ethnicity, which was therefore excluded from this study. However, 96% of Scotland's population is White, so it seems unlikely that any robust conclusions could be drawn from an analysis of ethnicity in 225 women.

Administrative datasets also include a finite and pre-specified set of variables. There may be other factors associated with the development of PPCM, or with prognosis, which could not be investigated in this study. The small cohort size also limited the ability to conduct more extensive analyses of patient characteristics associated with outcomes in multivariable regression models.

Data accuracy, meaning the accuracy with which a code is transcribed from a patient record to the database and not the accuracy of the clinician at reaching the diagnosis, is another consideration when using datasets such as these. In Scotland, auditing of the SMR datasets is routine, and data accuracy, as discussed in the Methods chapter, is generally high, in particular for CV diagnostic codes (e.g. heart failure accuracy is 91%). In the SMR02 datasets, all the routine obstetric variables included, except maternal height and weight, had an accuracy of >80%. In addition, the accuracy of coding of common conditions

in SMR02 is very high (e.g. hypertension 95%, PPH 99%). Administrative datasets do not allow identification of people moving out of the country, but data from NRS show that only around 55,000-75,000 people (or 1-2% of the population) have emigrated from Scotland over the last two decades.

A further limitation is that this study only captures women with a hospitalisation around the time of pregnancy. Whether or not some women were diagnosed as an outpatient, without a hospitalisation with a discharge diagnosis relating to heart failure/cardiomyopathy/PPCM temporally related to pregnancy, is unknown. However, it seems likely that this is uncommon and that most peripartum women with features of PPCM (e.g. breathlessness, palpitations, chest pain, oedema, tachycardia, hypoxia) would be referred for urgent hospital assessment, particularly since differential diagnoses in this context include pulmonary embolism, or acute aortic or coronary events. The same applies to the prevalence of 'non-acute' comorbidities, such as hypertension or diabetes, which are only captured if they feature as a discharge ICD code during a hospitalisation, and future events such as subsequent terminations, which are only captured if they result in a hospitalisation.

The retrospective nature of collecting echocardiographic data and the variability with which a quantitative assessment of LVEF was provided in the scan reports meant that not all women had LVEF recorded at specific time points. Instead, the last available echocardiogram was used and, where only qualitative assessment was provided, a standardised LVEF was assigned. Overall, a quantitative measure of LVEF was available from 75% of all echocardiograms included in the echocardiographic outcome analyses (n=1408).

Lastly, when analysing outcomes for women with PPCM, the start time used was diagnosis and not delivery. This introduces bias when drawing comparisons with controls, for whom the start time was delivery, by creating a period of 'immortality' in the time between delivery and diagnosis for women with PPCM. This approach was chosen in order to produce data which would be most clinically relevant for patients with the condition and clinicians treating them, i.e. the likelihood of a particular outcome occurring from the point at which the diagnosis is established.

## 8.3 Future research

There is a lot still to understand about PPCM. The first step towards this is to define the true incidence of new-onset LV dysfunction in relation to pregnancy, and to characterise the phenotypes of women in whom it occurs. This would require a large, prospective study recruiting consecutive women without a history of significant cardiac disease, with interval assessment of cardiac structure and function, and natriuretic peptide testing throughout pregnancy and the postpartum period. A study designed in this way would also provide important information regarding:

1. Normal changes during healthy pregnancies, particularly with respect to natriuretic peptide levels, about which much less is known during pregnancy and existing data are not consistent[209, 242–245].
2. The phenotype of women with new HFrEF during pregnancy, which may help elucidate the mechanisms through which PPCM may develop. It is a clearly heterogenous condition, and, in the future, a better understanding of how to identify and treat it relies on a better understanding of the interplay between the many different possible risk factors and aetiologies.
3. The incidence and phenotype of women with new 'HFpEF' during pregnancy, by combining data on diastolic function and natriuretic peptide levels.
4. The incidence of cardiac dysfunction in certain subgroups of women, such as older women, or those with gestational hypertension, obesity, multiparity or a multigestational pregnancy, which, in turn, could lead to a pilot programme of screening in women at greatest risk.
5. A clear definition of PPCM, which can be applied universally and will allow a uniform approach to identifying women for inclusion in future studies. By doing so, applicability of data will improve.
6. Long-term morbidity and mortality (for the mother and child) in a precisely defined cohort with PPCM (either through prospective data capture or record linkage).

Next, efforts should focus on developing a more robust definition of cardiac recovery in women with PPCM. As modalities for assessing cardiac function evolve (e.g. strain analysis, stress testing, biomarker testing), these are likely to be incorporated into the evaluation of recovery. This may also be relevant to

prognostication, particularly with respect to the identification of women at greater risk of subsequent decline in cardiac function.

Finally, determination of the sensitivity and specificity of certain combinations of ICD discharge codes for identifying women with PPCM in administrative datasets in Scotland provides an opportunity for ongoing epidemiological research nationally, and indeed across the whole of the United Kingdom. This method can be applied in the future to examine trends in incidence and risk factors as population demographics change. The incidence in certain at-risk groups (e.g. women with pre-eclampsia) could be examined in this way. Outcomes can continue to be monitored and may inform long-term follow-up, treatment and provision of health services for women with the condition.

## 8.4 Conclusions

The main findings of this study can be summarised as follows:

The incidence of PPCM in Scotland over a 20-year period was 1 in 4950 deliveries and was similar in England. In Scotland, the incidence of PPCM was greater in women over the age of 32 years. Among 225 women with PPCM (and 2240 matched controls), obesity, gestational hypertensive disorders, multiparity and multiple gestation were independently associated with the development of PPCM in this Scottish cohort. Socioeconomic deprivation was also relevant, although this appeared to be explained by other baseline factors studied.

Over a median follow-up of 8.3 years (9.7 years for echocardiographic outcomes), 8% of women with PPCM died, 40% were rehospitalised at least once for a CV cause and 23% had at least two further CV hospitalisations (i.e. recurrent hospitalisations). Rates of all-cause mortality and of CV death or CV rehospitalisation in women with PPCM were 12- and 14-times that of controls. Complete LV recovery occurred in 76% of women throughout the whole study period (47% within 1 year), and, of those who recovered, 13% had sustained decline of LV systolic function despite initial recovery, at a median of 2.9 years after recovery.

Women with PPCM with a subsequent pregnancy were younger and more socioeconomically deprived than those without. Clinical outcomes examined were similar in women with PPCM irrespective of whether or not they went on to have a subsequent pregnancy. Although 15% of women had a CV hospitalisation in the 1$^{st}$ year after pregnancy, no women had a CV death or required mechanical circulatory support or cardiac transplantation up to 5 years following a subsequent pregnancy.

Approximately 1 in 3 children born to women with PPCM had an adverse neonatal outcome, with 4% case-fatality (including stillbirths) and a mortality rate approximately 5-times that of children born to controls. Children born to women with PPCM also had an approximately 3-times greater incidence of CV disease than children born to controls.

# Appendix 1 STROBE (STrengthening the Reporting of OBservational studies in Epidemiology)

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

| | | |
|---|---|---|
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

# Appendix 2 ICD and OPCS codes used to define maternal and child CV outcomes

| | | |
|---|---|---|
| **Mothers** | | |
| I00-I02 | Acute rheumatic fever | |
| I05-I09 | Chronic rheumatic heart disease | |
| I10-I15 | Hypertensive diseases | |
| I20-I25 | Ischaemic heart disease | |
| I26-I28 | Pulmonary heart disease and diseases of pulmonary circulation | |
| I30-I52 | Other forms of heart disease | E.g. Pericardial diseases, myocardial diseases, non-rheumatic valvular disease, endocarditis, arrhythmias, heart failure |
| I60-I69 | Cerebrovascular diseases | |
| I70-I79 | Diseases of arteries, arterioles and capillaries | E.g. Aneurysms, arterial thromboembolism |
| I80-I89 | Diseases of veins, lymphatic vessels and lymph nodes | E.g. Venous thromboembolism, varices |
| I95-I99 | Other and unspecified disorders of the circulatory system | |
| O903 | PPCM | |
| O994 | Diseases of the circulatory system complicating pregnancy, childbirth and the puerperium | Included in CV death not CV hospitalisation |
| **Children** | | |
| Q20-Q28 | Congenital malformations of cardiac chambers and connections | |
| P290 | Neonatal cardiac failure | |
| P291 | Neonatal cardiac dysrhythmia | |
| P292 | Neonatal hypertension | |
| P293 | Persistent foetal circulation | |

| | | |
|---|---|---|
| P294 | Transient myocardial ischaemia of the newborn | |
| P298 | Other CV disorders originating in the perinatal period | |
| P299 | Unspecified CV disorder originating in the perinatal period | |
| I00-I02 | Acute rheumatic fever | |
| I05-I09 | Chronic rheumatic heart disease | |
| I10-I15 | Hypertensive diseases | |
| I20-I25 | Ischaemic heart disease | |
| I26-I28 | Pulmonary heart disease and diseases of pulmonary circulation | |
| I30-I52 | Other forms of heart disease | E.g. Pericardial diseases, myocardial diseases, non-rheumatic valvular disease, endocarditis, arrhythmias, heart failure |
| I60-I69 | Cerebrovascular diseases | |
| I70-I79 | Diseases of arteries, arterioles and capillaries | E.g. Aneurysms, arterial thromboembolism |
| I80-I89 | Diseases of veins, lymphatic vessels and lymph nodes | E.g. Venous thromboembolism, varices |
| I95-I99 | Other and unspecified disorders of the circulatory system | |
| OPCS K | Cardiac intervention | All surgical and percutaneous cardiac interventions |
| OPCS L | Vascular interventions | All surgical and percutaneous vascular interventions |

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