The occurrence and risk factors for first venous thromboembolism in and around pregnancy: Population based cohort studies using primary and secondary care data from the United Kingdom

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Abstract

Background: Venous thromboembolism (VTE) in one of the leading causes of maternal morbidity and mortality in high income countries. However there is a surprising shortage of evidence which allows us to accurately predict which women are at high risk which has hindered prevention to date. Therefore the aim of this thesis is to measure the occurrence of and risk factors for VTE during the antepartum and postpartum periods.

Methods: Electronic health records from women of childbearing age (15-44 years) were identified from two separate databases; The Health Improvement Network (THIN) between 1995 and 2009 and the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) between 1997 and 2010. Five separate studies were then carried out to study the incidence and risk factors for VTE during antepartum and postpartum periods. In studies 1 and 2 I used the THIN database to assess the incidence of and risk factors for VTE during antepartum and postpartum periods separately. Studies 3, 4 and 5 incorporated the CPRD-HES linked data which enabled me to get better ascertainment of VTE and its potential risk factors. Using these data I externally validated my VTE definition which was followed by investigating the impact of non-delivery related hospitalisations on the incidence of antepartum VTE. I also examined the risk factors for postpartum VTE using a conceptual hierarchical analysis approach along with their impact on the timing of VTE during specific periods of postpartum. All results were presented in the form of absolute rates (AR) per 100,000 person-years and incidence rate ratios (IRR) were calculated using Poisson regression with adjustment for relevant covariates.

Results: In THIN, there were a total of 1.7 million women of which 280,451 experienced 376,154 pregnancies resulting in live or stillbirths whereas the

CPRD-HES linked data contained information on over 240,000 pregnancies among 204,929 women. Overall VTE rates were highest in the first few weeks postpartum. Women in their third trimester of antepartum were at a 5 fold increased risk of first VTE compared to their time outside pregnancy whereas in the first and second trimesters this rate was only marginally higher. However the use of CPRD-HES linked database gave me estimates of VTE risk with better precision in and around pregnancy that were comparable to the existing literature. For my risk factor analysis I found that the strongest risk factor for VTE during the antepartum period was hospitalisation corresponding to a 17-fold increase (IRR=17.7 95%CI=7.7-39.6) compared to time outside hospital. The rate of VTE was also high during the 28 days post-discharge (IRR=5.9; 95%CI=3.5-10.0; AR=646). These factors were not confounded by pregnancy related characteristics and complications, pre-existing medical co-morbidities or demographic or life style related characteristics.I also found that postpartum, women whose pregnancies resulted in stillbirth were at a 6-fold (IRR=6; 95%CI 3.17-14.6; AR=2570) increased risk of VTE. Those with caesarean delivery (elective or emergency), pre-term birth or postpartum haemorrhage had a 2-fold or higher risk of postpartum VTE compared to their respective baseline (AR>600/100,000 person-years). These findings were consistent across both the THIN and CPRD-HES linked databases with respect women's risk factors for VTE. Finally the risk of VTE remains consistently high up to first six weeks postpartum (>700/100,000 person-years) for pregnancies of women complicated with BMI>30kg/m^2 or caesarean delivery whereas risk of VTE was only high in the first three weeks postpartum (>1300/100,000 person-years) in those with pre-term birth or postpartum haemorrhage.

Conclusion: I have provided some of the most precise estimates of absolute rates of VTE in and around pregnancy for better understanding of risks. The

overall rate of antepartum VTE is substantially increased during non-delivery related hospitalisations and this increase is sustained in the 28 days post-discharge. Postpartum, delivery associated characteristics and complications including, stillbirth, caesarean delivery, BMI>30Kg/m^2 postpartum haemorrhage are important risk factors for VTE particularly during the first three weeks postpartum. My analysis provides valuable information to clinicians for better decision making in terms of identifying high risk pregnant and postpartum women who may require some form of thromboprophylaxis

Lists of publications

Peer reviewed publications

- Sultan AA, Tata LJ, West J, Fiaschi L, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk factors for first venous thromboembolism around pregnancy: A population-based cohort study from the United Kingdom. Blood. 2013; **121**(19): 3953-61.

- Sultan AA, Grainge MJ, West J. The incidence of first venous thromboembolism in and around pregnancy using linked primary and secondary care data: A population based cohort study from England and comparative meta-analysis. Plos One. 2013; **8**(7):e70310

- Sultan AA, Tata LJ, West J, Fleming KM, Nelson-Piercy C, Grainge MJ, Risk of first venous thromboembolism in hospitalised pregnant women. BMJ. (In Press)

Conference presentations (Oral)

- Sultan AA, West J, Tata L, Fleming K, Grainge M, Nelson-Piercy C. The risk of venous thromboembolism in and around pregnancy: A population-based cohort study. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2011; **96**(Suppl S1): Fa4-Fa5. (Best oral presentation)

- Sultan AA, Tata L, West J, Fiaschi L, Fleming K, Nelson-Piercy C. Risk Factors for First Venous Thromboembolism in and around Pregnancy: A Population Based Cohort Study from the United Kingdom. *J Epidemiol Community Health*. 2012; **66**(Suppl 1): A37-A.

- Sultan AA, Tata L, West J, Fiaschi L, Fleming K, Nelson-Piercy C. Risk Factors for First Venous Thromboembolism in and around Pregnancy: A Population Based Cohort Study from the United Kingdom. International Society of Obstetric Medicine Conference. 2012

Conference presentation (poster)

- Sultan AA, West J, Tata L, Fleming K, Grainge M, Nelson-Piercy C. The risk of venous thromboembolism in and around pregnancy: A population-based cohort study. Journal of Epidemiology & Community Health; **65**(Suppl 1): P2-346

- Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Impact of hospitalisation on antepartum VTE using primary and secondary care data: A population based cohort study from England. BJOG; **120**(Suppl 1): EPI.125

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The Health Improvement Network (THIN) data were obtained from Cegedim Strategic Data for Medical Research and were initially processed by Mr Chris Smith. Dr. Linda Fiaschi created the pregnancy cohort in THIN which involved extracting mother's pregnancy information and linking it to child record. Some of the Read codes used in this thesis were obtained from Dr. Laila Tata's initial work on pregnancy related complications. The Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistic (HES) linked data used in this thesis were acquired through Dr. Joe West's Clinical Research Fellowship. Dr. Colin Crooks extracted data from the server and did the initial data cleaning. Dr. Kate Fleming and Professor Catherine Nelson-Piercy provided invaluable methodological and clinical input throughout the project. I sincerely would like to thank them for all their important contributions.

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List of Abbreviations

VTE= Venous Thromboembolism

DVT= Deep Vein Thrombosis

PE= Pulmonary Embolism

THIN= The Health Improvement Network

GPRD= General Practice Research Database

CPRD=Clinical Practice Research Datalink

HES= Hospital Episode Statistics

ONS= Office for National Statistics

CMACE= Centre of Maternal and Childhood Enquiries

BMI= Body Mass Index

LMWH= Low molecular Weight heparin

UFH= Unfractionated Heparin

RCOG: Royal College of Obstetricians and Gynaecologist

IQR= Inter Quartile Range

CI= Confidence Interval

AMR= Acceptable Mortality Reporting

BNF= British National Formulary

ICD= International Classification of Diseases

GP= General Practitioner

UK= United Kingdom

USA= United States of America

IBD= Inflammatory Bowel Disease

NHS= National Health Service

SLE= Systemic Lupus Erythematosus

ACCP= American College of Chest Physicians

OPCS= Operating and Procedure Code Supplement

NN4B= NHS number for babies

HG= Hyperemesis Gravidarum

1 Introduction

1.1 Introduction to venous thromboembolism

Thromboembolism is a detached intravascular mass mainly originating from some part of the detached thrombus that gets dislodged in the general circulation subsequently obstructing the blood flow in the vessels causing tissue and organ damage[1]. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two main clinical manifestations of venous thromboembolism (VTE). It is estimated that VTE is responsible for 100,000[2] and 25,000[3] annual deaths in United States and United Kingdom respectively many of which are potentially preventable. Data from primary care in the UK suggests that the short term mortality associated with DVT is 1.4% which increases to 23% when manifested as PE.[4] Sudden death, heart failure or cardiovascular collapse may occur if more than 60% of the pulmonary circulation is obstructed.[1] While PE is more likely to be fatal than DVT, treatment for both conditions is quite similar.[5] The risk factors for VTE have been well documented in the general population (Table 1-1).[6] For instance, those patients who undergo hip or knee replacement surgery or suffer a spinal cord injury or any major trauma are more than 10 times more likely to develop VTE following surgery/injury. For young women, pregnancy is also considered to be a higher risk period for VTE. For instance, the antepartum period is considered to be a weak risk period for VTE (odds ratio<2, compared to non-pregnant women), whereas the postpartum period is considered a moderate risk period (odds ratio 2-9). However, the evidence on which these estimates are based dates back to 1988 when diagnostic modalities were less prevalent potentially leading to underestimation VTE incidence in general and in pregnancy. Additionally many previous studies only looked at fatal VTE (mainly PE) thus overlooking non-fatal DVT which is more frequent during pregnancy and is associated with considerable morbidity.

Table 1-1: Risk factors for venous thromboembolisms as categorised by Anderson et al[6]

Strong risk factors (odds ratio>10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Moderate risk factor (odds ratio 2 – 9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/postpartum
Previous venous thromboembolism
Thrombophilia
Weak risk factor (odds ratio <2)
Bed rest 3 days
Immobility due to sitting
Increasing age
Laparoscopic surgery
Obesity
Pregnancy/ antepartum
Varicose veins

1.2 VTE in pregnancy: The medical burden

Venous thromboembolism in one of the leading causes of maternal mortality in most developed countries causing around 1.1[7] deaths in the USA and 0.7 deaths[8] in the UK per 100,000 pregnancies. Whilst, the Centre for maternal and Child Enquiries (CMACE) report highlighted that annual maternal deaths from PE have significantly decreased from 33 (between 2003 and 2005) to 16 (between 2006 and 2008)[8] in the UK, the considerable morbidity associated with non-fatal VTE should not be overlooked. Overall previous evidence suggests that VTE occurs in 1-3 per 1000 full term pregnancies[9, 10] with case fatality of 1.7-3% and 0.2% for PE and DVT respectively.[11, 12] The reason behind the increased risk of VTE in pregnancy was described more than a century ago in the form of Virchow's triad[13] which describes the three main

factors which pre-dispose to thrombosis, namely a change in blood composition, venous stasis and changes in blood vessel structure. Pregnancy is associated with all of those factors starting from the alteration in clotting factors especially factor V and VIII. In some cases resistance to proteins C and S may also develop. Secondly, progesterone mediated venous stasis begins in early pregnancy and peaks during the 36th week of gestation. Thirdly, blood vessels are prone to get damaged during vaginal or caesarean delivery which can further increase the risk.

1.3 Diagnosis of VTE in pregnancy

Clinical assessment and diagnosis of VTE can be challenging as many of the signs and symptoms including leg oedema, dyspnoea and tachycardia of VTE often resemble to those of a normal pregnancy.[5] The incidence of isolated DVT is more common in pregnancy which further complicates its diagnosis as it can mostly present as back and abdominal pain with or without oedema of the lower limbs.[5, 14] For DVT, the diagnostic gold standard historically has been contrast venography which was an invasive procedure and has now been replaced by ultrasonography. For suspected DVT, Doppler ultrasound is the preferred mode of investigation with 94% specificity and 97% sensitivity.[5, 15] For pulmonary embolism, a chest x-ray is often non-conclusive and may point towards other potential causes of hypoxia and breathlessness. Depending on hospital policy and x-ray findings, various imaging techniques may be employed including CT pulmonary angiogram, echocardiogram and MRI each of which has varying degree of accuracy and exposure to radiation.[5] These have largely replaced other tests such as the ventilation-perfusion scan and invasive pulmonary angiography which were previously used for PE diagnosis.

1.4 Treatment of VTE during pregnancy

According to the Royal College of Obstetricians and Gynaecologists (RCOG)[16] guidelines on acute management of thrombosis, Low Molecular Weight Heparin (LMWH) is considered as the treatment of choice for management due to its proven safety and efficacy in pregnancy. In clinically suspected DVT or PE, treatment with LMWH should be initiated until the diagnosis is excluded by objective means, unless strongly contraindicated. For treatment of VTE during pregnancy, LMWH should be administered subcutaneously twice a day. The dose should be titrated against the woman's weight. Due to the adverse effect on the foetus, the use of oral anticoagulants (eg. warfarin) is contraindicated during pregnancy. Therapeutic anticoagulant therapy should be continued for the remainder of the pregnancy and for at least 6 weeks postpartum until at least 3 months of treatment has been given in total. Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy after discussion about the need for regular blood tests for monitoring of warfarin, particularly during the first 10 days of treatment. Neither heparin nor warfarin is contraindicated in breast feeding therefore women may be converted from LMWH to warfain 5-7 days after delivery.

1.5 *Thromboprophylaxis*

1.5.1 UK's thromboprophylaxis guideline in pregnancy and its impact on maternal mortality: The last 60 years

The UK's thromboprophylaxis guidelines and its impact on maternal mortality is summarised by Drife[17] and the CMACE reports[8, 18, 19] (Table 1-2). The first advance in preventing deaths from venous thromboembolism in pregnant women was in the early 1960s when the importance of early mobilization after normal delivery was recognized leading to the abolishment of enforced bed rest after childbirth. The use of anticoagulants was very poor at that

time and was considered as a matter of clinical judgement. For instance only 12 (9%) of the overall 129 deaths which occurred due to PE between 1961 and 1963 were among women who received any form of anticoagulation.

Overall deaths from pulmonary embolism have declined significantly between 1952 and 1975 (from 138 to 38 maternal deaths) probably reflecting better case management and diagnostic procedures. After that time it was realised that risk factors (such as obesity, advanced maternal age and parity) play an important role particularly in women who were put on bed rest during or after pregnancy due to existing co-morbidities and who underwent operative procedures. There was a further reduction in the overall deaths from PE between 1979 and 1981 (28 maternal deaths) which could reflect greater awareness of thromboembolism in pregnancy and wider use of anticoagulants in general. Furthermore the concept of thromboprophylaxis also emerged in those with a previous known history of deep vein thrombosis or pulmonary embolism.

After 1991 VTE deaths preceding caesarean section became a major concern which led to the publication of Royal College of Obstetrician and Gynaecologists (RCOG) guidelines of thromboprophylaxis for operative procedures in 1995. The guidelines for the first time gave a clear risk assessment profile for thromboembolism in caesarean section which was based on stratifying risk groups as low, moderate and high based on certain factors. Furthermore, it also gave recommendations for thromboprophylaxis during the antepartum and postpartum periods in those with a history for thromboembolism. However the guidelines were constrained to caesarean section and did not give recommendations for prophylaxis after vaginal delivery. This may have resulted in decreased mortality after caesarean section from 15 (1994-96) to 4 (1997-99) whereas death from VTE after

vaginal delivery remained constant during that time (10 maternal deaths). Deaths due to VTE once again increased between 2003 and 2005 with the rise in both antepartum and postpartum deaths which increased focus towards the publication of the RCOG's[20] first comprehensive guidelines on thromboprophylaxis during pregnancy, labour and after vaginal delivery in 2004. The guidelines not only recommended antepartum and postpartum thromboprophylaxis for women with previous thromboembolic disorders but also incorporated risk factors to identify the highest risk women for whom anticoagulants were recommended. They advised that all women should undergo routine assessment for thromboembolic disease ideally before or in early pregnancy and that antenatal anticoagulation should begin as soon as possible where required. A notable and statistically significant decrease in mortality from thromboembolism occurred between 2006 and 2008 when compared with the previous three-year period (2003-5) with venous thromboembolism being no longer the leading cause of maternal mortality in the most recent CMACE report.[8] This suggests that mortality associated with VTE can be prevented with better understanding of its risk factors and targeting of prophylaxis. However currently there is no evidence evaluating the overall incidence of VTE during the antepartum and postpartum periods before and after publication of RCOG guidelines for thromboprophylaxis.

Table 1-2: Maternal deaths and the use of anticoagulant for thromboprophylaxis in past 60 years.

Year	Maternal deaths*◇	Interventions to reduce VTE associated deaths
1952	Total VTE deaths: 138 Antepartum death: 4 Vaginal delivery deaths: 104 C-section deaths: 30	
1961	Total VTE deaths: 129 Antepartum death : 36 Vaginal delivery deaths: 66	
1963		Concept of early ambulation after delivery developed however the use of anticoagulant was still regarded as a matter of clinical judgement. No guideline or recommendation existed for the use of anticoagulants for thromboprophylaxis
1973	Total VTE deaths: 38 15 women were obese 20% were on oestrogen	
1975		Risk factors such as age, parity and operative procedures were recognised as risk factors for VTE. No guideline or recommendation existed for the use of anticoagulants for thromboprophylaxis
1979	Total VTE deaths: 28	
1981		ROCG recommendation for thromboprophylaxis for those with previously proven DVT or PE
1991	Total VTE deaths: 30 Antepartum deaths: 12 Vaginal delivery death: 13 C-section death: 4	
1993	Total VTE deaths: 46 Antepartum deaths: 15 Vaginal delivery death: 10 C-section death: 15	Publication of RCOG recommendation of risk assessment and thromboprophylaxis in gynaecology and obstetrics. Only applied to C-section and not to vaginal delivery
1996	Total VTE deaths: 31 Antepartum deaths: 13 Vaginal delivery death: 10 C-section death: 4	The RCOG recommendations were publicised and the need for national guidelines on thromboprophylaxis after normal delivery were identified
1999	Total VTE deaths: 25 Antepartum deaths: 4 Vaginal delivery death: 7 C-section death: 9	The RCOG first comprehensive guideline on the management of thromboembolic disease in pregnancy and puerperium (2001)
2002	Total VTE deaths: 33 Antepartum deaths: 11 Vaginal delivery death: 8 C-section death: 7	The RCOG first comprehensive guideline on thromboprophylaxis during pregnancy, labour and after vaginal delivery (2004)
2005	Total VTE deaths: 16 Antepartum deaths: 3 Vaginal delivery death: 2 C-section death: 6	
2008		Updated RCOG guideline on thromboprophylaxis during pregnancy, labour and after vaginal delivery (2009)

Maternal deaths are derived from CMACE reports

◇Stratified maternal deaths may not sum up to total maternal deaths as deaths associated with miscarriages/terminations were excluded or if the information on deaths by antepartum and postpartum was not provided.

1.5.2 Thromboprophylaxis guidelines today

In 2004 the first comprehensive guidelines[20] issued by the RCOG on thromboprophylaxis during pregnancy and the postpartum were introduced which were updated in 2009 (Figure 1-1 and Figure 1-2). The guidelines suggest that the need for thromboprophylaxis should be assessed with regards to antepartum and postpartum separately and categorized pregnant and postpartum women as high, intermediate or low risk based on certain clinical risk factors. These guidelines recommend prophylaxis with low molecular weight heparin, for at least 6 weeks postpartum in the highest risk women and for 7 days in a much larger proportion of women considered to be at intermediate risk (those with 3 or more risk factors). Although a lower proportion of women will be considered at risk during the antepartum period (those with 2 or more risk factors or 3 if admitted to hospital) which may account for about 3-8% (for PE) of the total pregnant women[11], the advice for those who are at risk is to initiate thromboprophylaxis as early in pregnancy as practical and to continue throughout pregnancy.[21]

Figure 1-1: Current risk assessment and management of VTE in antenatal period[21]

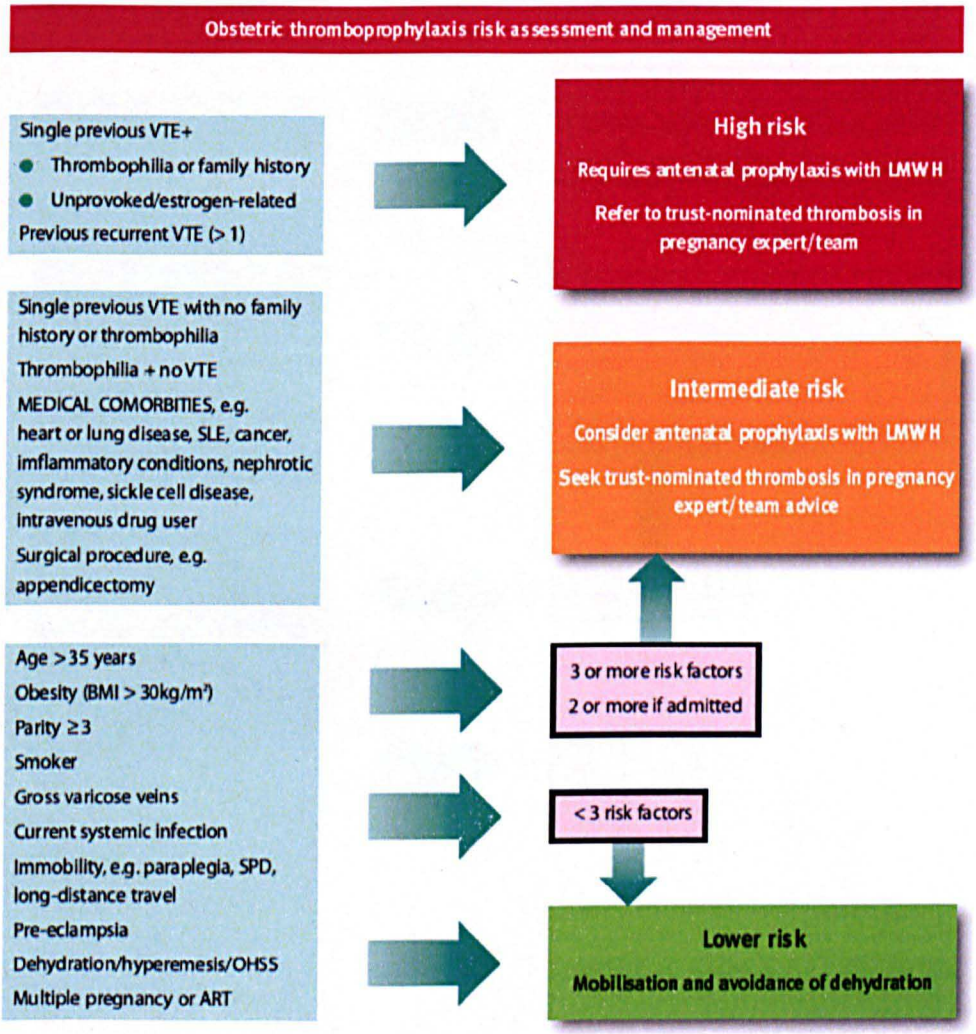
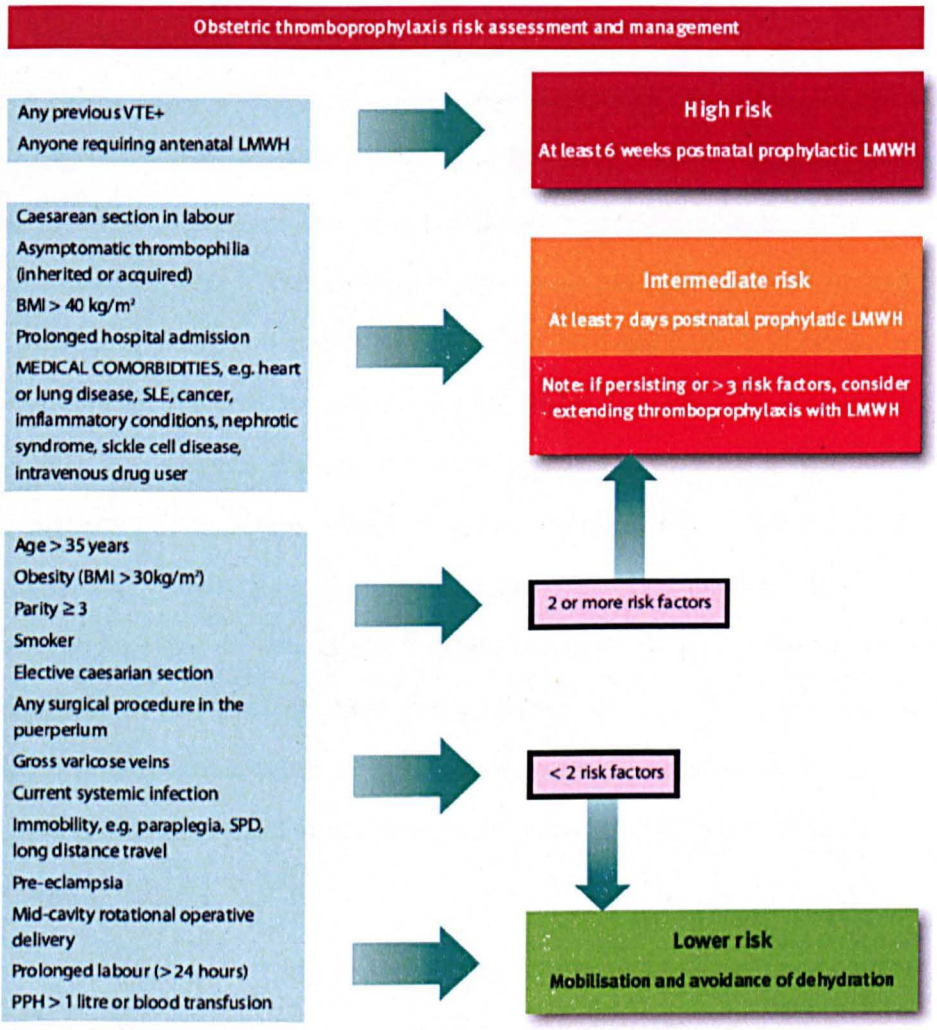


Figure 1-2: Current risk assessment and management of VTE during antenatal and postnatal period[21]



1.6 Agents used for thromboprophylaxis

1.6.1 Low molecular weight heparin

Despite the scarcity of supportive data from randomised controlled trials or large prospective observational studies, low molecular weight heparin (LMWH) is now commonly used for thromboprophylaxis during pregnancy instead of unfractionated heparin.[22] This change in practice is particularly based on large trials conducted in the non-pregnant population. It is considered as effective[23] as unfractionated heparin but more safe. For instance a systematic review by Sinson et al.[24] evaluated the use of LMWH during pregnancy and reported a 2.7% occurrence of minor bleed and no major haemorrhage episodes associated with LMWH use. Another similar systematic review[25] of 2,777 pregnancies reported no episodes of heparin induced thrombocytopenia and a low incidence of osteoporotic fractures (0.04%) and allergic skin reactions (1.8%). The study also reported the risk of major haemorrhage to be 2% which was primarily related to obstetric causes that could not be attributed to LMWH use.

1.6.2 Unfractionated heparin

Unfractionated heparin (UFH) is used for both prevention and treatment of venous thromboembolism and has a shorter half-life than LMWH.[22] It may be occasionally be used during the time around delivery in cases where there is very high risk of thrombosis and when there is reluctance to use LMWH (regional anaesthesia).[21] The risk of major bleeding associated with the use of UFH among pregnant women is documented to be 2%. Compared to LMWH, the risk of heparin induced thrombocytopenia (HIT) is higher in those who receive UFH (0 versus 3%).[26] Long term use of UFH has also been linked to increased risk of osteoporosis and fracture. For instance, previous studies

have highlighted vertebral fracture occurs in 2-3% of those receiving long term UFH therapy with a significant bone density reduction reported in up to 30% of women.[22, 27, 28]

1.6.3 Warfarin

Warfarin use during pregnancy is only limited to the cases where the use of heparin is not suitable such as pregnant women with mechanical heart valves. This is due to the fact that warfarin crosses the placenta and has teratogenic potential. There is evidence of higher risk of complication associated with warfarin use including spontaneous miscarriages, stillbirths, maternal haemorrhage and congenital malformation.[21]

1.7 Literature search

Sections 1.8 to 1.12 provide a comprehensive overview of the current literature on incidence of VTE and risk factors in and around pregnancy. In order to identify previous studies describing the incidence of VTE in and around pregnancy, I carried out a systematic literature review. I searched Medline and Embase for the period January 1960 to January 2013 to identify observational studies which estimated the rate of VTE among pregnant and puerperal women. Search terms to identify studies and those relating to VTE were adapted from a previous systematic review on the incidence of VTE in people with cancer[29] These were combined with an adapted version of the Cochrane Pregnancy Group search strategy to identify studies relating to pregnancy.[30] The final Medline and Embase search terms are presented in Appendix 1 and Appendix 2 respectively (full results from a systematic review and meta-analysis of these studies are contained within chapter 4). A separate search strategy was carried out using the Medline database to identify studies focussing on risk factors of VTE during pregnancy using terms such as "pregnancy", "risk factors" and "venous thromboembolism" between 1960 and 2013.

1.8 Incidence of VTE in and around pregnancy

The incidence of VTE in and around pregnancy varies considerably in the existing literature. Reported rates vary from 28 to 86 per 100,000 pregnancies in the antepartum and 28-128 per 100,000 pregnancies in the postpartum period. The estimates from those studies are summarised in Table 1-3. These data also support the belief that VTE risk is highest around delivery and in the first two weeks postpartum.[31-33] There is greater controversy surrounding the period of greatest antenatal risk with some studies reporting the highest risk in the first trimesters,[34, 35] others have

reported an increased risk confined to the second and third trimester and a further study reporting a bimodal distribution where risks were highest in the first and third trimesters.[32] The wide variation in the estimates might be due to differences in the study designs and populations studied. Some limitations of previous studies are presented below:

1.8.1 Use of number of pregnancies as the denominator

Most studies have used number of pregnancies as the denominator when calculating the incidence rate instead of person-years. This approach does not take into account the difference in antepartum versus postpartum duration thus, making the risks in those respective periods non comparable. Theoretically, if we assume VTE effects 1 in every 1000 women during pregnancy and 1 in every 1000 women postpartum, periods which last for 280 and 42 days respectively (as most studies assess up to six weeks postpartum), then this equates to a VTE rate of 133 per 100,000 person-years during the antepartum and 800 per 100,000 person-years during the postpartum. Therefore assuming that the overall number of events was the same in both periods, the risk of VTE per unit of time would be much higher in the postpartum and using pregnancies as baseline does not capture this.

Table 1-3: Incidence of VTE in and around pregnancy per 100,000 pregnancies* presented in previous studies in order of publication

Author	Country	Study period	Study design and methodology	Number of Pregnancies (birth outcome)*	Overall VTE rate/100,00 pregnancies*	Antepartum/postpartum rates/100,000 pregnancies*	Trimester Rate/100,000 pregnancies*
Sultan[36]	United Kingdom	1984-2004	Population based retrospective cohort. VTE cases were identified using primary care data validated by evidence of anticoagulation	207,327 (live birth only)	101	Antepartum=45 Postpartum=56	First=6 Second=9 Third=30
Vikrus[37]	Denmark	1995-2005	Population based retrospective cohort. Cases were identified from a national patient registry using ICD-10 codes. VTE diagnoses in this registry have been previously validated against medical records	819,751 (live birth, stillbirth or miscarriages)	86	Antepartum=59 Postpartum=27	First=7 Second=9 Third=43
O'Connor[38]	United States	2003-2008	Cross sectional study. Cases were identified from a single hospital. Cases were objectively confirmed by diagnostic tests	33,311 (not specified)	222	Antepartum=108 Postpartum=114	First=30 Second=27 Third=51
Liu[12]	Canada	1991-2006	Cross sectional study. Cases were identified using hospital discharge database using ICD-10 codes	3,852,569 (live or stillbirths)	121	Antepartum=56 Peripartum=74 Postpartum=46	-----
Jacobsen[32]	Norway	1990-2003	Cross sectional study. Cases were	613,847	100	Antepartum=49	First=10

Author	Country	Study period	Study design and methodology	Number of Pregnancies (birth outcome)*	Overall VTE rate/100,00 pregnancies*	Antepartum/postpartum rates/100,000 pregnancies*	Trimester Rate/100,000 pregnancies*
			identified from patient and birth register. Cases were validated for a subset of data by diagnostic tests	(Pregnancies reaching 23 weeks of gestation)		Postpartum=51	Second=10 Third=29
Lindqvist[39]	Sweden	1990-2005	Cross sectional study. Cases were identified from a single hospital. Cases were objectively confirmed by diagnostic tests	51,968 (not specified)	-----	Postpartum=71	-----
Sharma[40]	Australia	1999-2006	Cross sectional study. Cases were identified from a single hospital. Not all VTE cases were objectively confirmed. Included some probable and possible VTEs	6,987 (not specified)	114	Antepartum=100 Postpartum=14	First=71 Third=28
Larsen[41]	Denmark	1980-2001	Cross sectional study. Cases were identified from a single county.	71,729 (live or stillbirths)	179	Antepartum=85 Postpartum=94	-----
James[7]	United States	2000-2001	Cross-sectional study. Cases were identified from national inpatient sample which covers around 100 hospitals using ICD-10 codes.	8,330,927 (live or stillbirths)	172	Antepartum=86 Postpartum=85	-----

Author	Country	Study period	Study design and methodology	Number of Pregnancies (birth outcome)*	Overall VTE rate/100,00 pregnancies*	Antepartum/postpartum rates/100,000 pregnancies*	Trimester Rate/100,000 pregnancies*
Heit[31]	United States	1966-1995	Population based cohort. Potentially fertile women were prospectively followed in a single county. Not all VTE cases were objectively confirmed. Included some probable and possible VTEs	50,080 (Live or stillbirths)	199	Antepartum=71 Postpartum=128	Second=27 Third=40
Haggaz[9]	Sudan	1999-2000	Cross sectional study. Cases were identified from a single hospital. Cases were objectively confirmed.	14,210 (not specified)	380	Antepartum=56 Postpartum=323	-----
Soomro[42]	Saudi Arabia	1986-1998	Cross sectional study. Cases were identified from a single hospital. Cases were objectively confirmed.	39,757 (not specified)	125	Antepartum=42 Postpartum=83	First=17 Second=12 Third=12
Chan[43]	China	1998-2000	Cross sectional study. Cases were identified from a single hospital. Cases were objectively confirmed by diagnostic tests	16,993 (live, stillbirths or miscarriages)	188	Antepartum=47 Postpartum=141	First =17 Second=17 Third=11
Ros[33]	Sweden	1987-1995	Population based retrospective cohort. Cases were identified using inpatient registry using ICD-9 codes	1,003,489 (Pregnancies reaching 28 weeks of gestation)	-------	Postpartum=28	Third=18

Author	Country	Study period	Study design and methodology	Number of Pregnancies (birth outcome)*	Overall VTE rate/100,00 pregnancies*	Antepartum/postpartum rates/100,000 pregnancies*	Trimester Rate/100,000 pregnancies*
Simpon[10]	United Kingdom	1988-1997	Cross sectional study in which cases were identified using ICD codes from hospital database	395,335 (live or stillbirths)	90	Antepartum=26 Postpartum=64	------
Gherman[34]	United States	1978-1996	Cross sectional study. Cases were identified from a single hospital. Cases were objectively confirmed by diagnostic tests	268,525 (not specified)	61	Antepartum=40 Postpartum=21	First=9 Second=22 Third=10
Lindqvist[44]	Sweden	1990-1993	Cross sectional study. Cases were identified from Swedish birth and patient registry	479,422 (Pregnancies reaching 28 weeks of gestation)	130[b]	Antepartum=64 Postpartum=62	-----
McColl[45]	United Kingdom	1985-1996	Cross sectional study. Cases were identified using national health service data. Cases were objectively confirmed by diagnostic tests	72,201 (live or stillbirths)	85	Antepartum=56 Postpartum=29	
Anderson[46]	Denmark	1984-1994	Cross sectional study. Cases were identified using inpatient registry. Cases were objectively confirmed by diagnostic	63,300 (not specified)	85	Antepartum=52 Postpartum=33	------

Author	Country	Study period	Study design and methodology	Number of Pregnancies (birth outcome)*	Overall VTE rate/100,00 pregnancies*	Antepartum/postpartum rates/100,000 pregnancies*	Trimester Rate/100,000 pregnancies*
			tests				
Macklon[47]	United Kingdom	1981-1991	Cross sectional study where cases were identified from medical records at a single hospital. Cases were objectively confirmed by diagnostic tests	645,663 (live or stillbirths)	111	-----	-----
James[48]	United States	1989-1994	Cross sectional study. Cases were identified from a single unit which were confirmed using diagnostic tests	30,040 (Live births)	53	Antepartum=26 Postpartum=16	-----

*birth outcome considered in the study population

1.8.2 Non-specification of type of pregnancy outcomes studied

Most studies have only assessed risks in pregnancies that have ended in a live (or still) birth[7, 10, 12, 49] and few studies have specified the length of gestation or whether only certain gestational lengths were included.[31, 44, 50] In the most recent CMACE report, 2 of the 16 deaths from pulmonary embolism occurred in the 1st trimester following miscarriage.[8] By only considering pregnancies which reach full term, these important and occasionally fatal events may be overlooked. In particular, it will not allow us to assess whether first trimester risks will differs for pregnancies that reach full term compared to those with non-live outcomes such as miscarriages, terminations or stillbirths.

1.8.3 Reliance on International Classification of Disease (ICD) codes for defining VTE

Studies solely reliant on ICD codes without any objective confirmation or other source of validation might not provide accurate estimates. A code assigned for suspected VTE which was later not confirmed by objective means might lead to overestimation of the incidence especially in the third trimester of pregnancy as many VTE associated clinical symptoms overlap with changes associated with a normal pregnancy. These include pregnancy related changes of increased intra-abdominal pressure, obesity and decreased venous return associated with lower extremity oedema can be associated with a false-positive diagnosis of VTE.[34] For instance, of all studies conducted on VTE incidence during the antepartum period that have utilised data up to or before 2005, the studies where VTE outcome was not validated[7, 31, 44] have reported the highest estimates ranging from 86 to 115 per 100,000 person-years. This is higher than studies where VTE outcome was validated (53-76 per 100,000 person-years during the same time period; later discussed in Chapter 4).

1.8.4 Ascertainment of VTE

Both diagnosis and management of VTE have changed considerably over the course of time. Technology has improved in recent years allowing for more accurate diagnosis. This has been accompanied by the greater appreciation of prophylaxis measures in patients with increased risk of VTE. The first probably means that the older studies have a greater likelihood of misclassification of VTE, while the second means that there will be some expectation that rates might have decreased. The latter may also be countered by possibly more older mothers today than 30 years ago and perhaps also by increased prevalence of risk factors today (for example obesity[51]). This would make overall comparison of incidence estimates from previous studies less meaningful with today's rates.

It is also important to note that changes in diagnostic modalities and case management over time might have lead to over diagnosis of VTE cases in more recent years. For instance, Wiener et al.[52] in their time trend analysis for pulmonary embolism in the USA concluded that with the introduction of new and improved diagnostic techniques there was an increase in the incidence of PE with reduction in PE associated mortality (8% reduction in mortality), suggesting over diagnosis of clinically insignificant events. Despite the fact that this previous study had a number of limitations (reliance on death certificate for PE diagnosis, no identifier to track individual after hospital discharge and confounding by calendar year) this phenomenon might particularly affect pregnant women who are exposed to more frequent contact with health care professionals during and after their pregnancy compared to women in the general population.

Few recent studies (post 2005) have quantified the incidence of VTE during the antepartum and postpartum period where the VTE cases were either confirmed by objective means (diagnostic tests) or using a registry where VTE cases were previously validated. Whilst estimates from those studies are broadly similar for the antepartum (ranging from 95 to 144 per 100,000 person-years), there are wide variations in the rate of VTE during the postpartum period (ranging from 124 to 969 per 100,000 person-years). Most of those estimates are based on small numbers which do not provide adequate precision when examining risk of VTE during the specific antepartum and postpartum periods. Moreover the wide variation in the reported rate of VTE during the postpartum may partially be explained by the thromboprophylaxis practice post-delivery, the duration and frequency of which may vary by country. For instance the UK's current RCOG thromboprophylaxis guidelines also extend to those women who have undergone normal vaginal delivery when accompanied by certain risk factors as opposed to US American College of Chest Physicians (ACCP) guidelines which are only restricted to post caesarean section women with additional risk factors. Secondly studies utilising data from a single centre may potentially miss out postpartum VTE (particularly DVT) diagnosed and managed solely in primary care or any other facility especially during the postpartum period. For instance Vikrus et al[37] utilising data from an in-patient registry, quantified the incidence of VTE during the antepartum and postpartum periods and reported the rate of VTE to be 107 and 304 per 100,000 person-years respectively. Despite the fact that their study utilised prospectively collected data with large follow-up where VTE diagnosis was previously validated, the use of hospital admission date as the date of diagnosis may have potentially caused misclassification between antepartum and postpartum VTE events around the time of delivery for maternity admissions taking place before delivery which were also complicated by VTE during the postpartum period. This may have

led to slight underestimation of postpartum VTE incidence with the added potential of missing out DVTs diagnosed and managed in primary care.

1.9 Risk factors for VTE in and around pregnancy

Many of the recent UK guidelines are hampered by the lack of contemporary; UK-population based estimates from the studies of sufficient size leading to wide variation in the absolute and relative risks of VTE. Moreover, studies exploring risk factors for VTE such as age, parity, BMI, smoking provide inconsistent estimates, There are few important points to consider about the evidence surrounding the risk factors of VTE:

1.9.1 Type of evidence

To date there have been number of studies which have explored risk factors for VTE in the pregnant population. Risk factors highlighted in previous studies are summarised as Table 1-4, Table 1-5 and Table 1-6. Most of those studies can broadly be categorised as either registry based, or hospital based studies. Registry based studies analyse information collected from more than one centre over time. Whilst such studies are based on large sample size, they often suffer from VTE validation issues (previously highlighted) and are only able to analyse a few risk factors simultaneously. This is because the information recorded on any one patient is limited. For instance, Lindqvist et al[44] in their registry based study analysed more than 470,000 pregnancies and found that caesarean section deliveries were associated with a 5 fold increased risk compared to normal vaginal deliveries during the postpartum. However they were not able to analyse other important risk factors such as BMI, birth outcome, length of gestation and pre-existing medical co-morbidities which may have confounded their association to a certain extent. Furthermore, most of the previous registry based studies have lumped antepartum and postpartum VTE together for their risk factor analysis despite evidence of differences in overall level of risk and risk factor profiles in these two periods (Table 1-4). On the other hand hospital based studies provide

more in-depth information on VTE outcomes and potential risk factors but are based on insufficient statistical power to provide meaningful estimates. For instance Chan et al[43] looked a wide range of pregnancy related factors which were individually scrutinised but their analysis was based on only 25 VTE events which may have potentially led to type 2 error (i.e. failure to reject a false null hypothesis.

1.9.2 Lack of contemporary UK based evidence

Whilst there is lack of contemporary UK based studies on the VTE risk factors in and around pregnancy, Jacobsen et al[53] addressed some of the limitations of previously highlighted registry and hospital based studies by conducting a case-control study in Norway where cases where recruited from 18 different hospitals through a Norwegian Patient Register. These were when individually scrutinised for wide range of potential risk factors and were compared to their respective controls. However, their controls (recruited from a single hospital) were systematically different from the general population (with respect to mode of delivery, pre-eclampsia, multiple pregnancies and other factors) which may have biased their estimates. For instance their controls had more emergency and planned caesarean sections than the general population which may have biased their estimates towards the null as evident by there being no statistically significant association between elective caesarean section and VTE. Despite of the above stated limitations, studies highlighted in Table 1-5 and Table 1-6 provide the best available evidence of the risk factors of VTE in pregnant and postpartum women. However, most of them utilise data up to 2004 which also has its implications (Section 1.8.4). Therefore in general there is a lack of contemporary studies especially from the UK

1.9.3 Implications for the thromboprophylaxis guidelines

1.9.3.1 Reliance on CMACE report

The current guidance for thromboprophylaxis is reliant on expert consensus and CMACE reports.[8] Whilst CMACE reports are useful in that they provide information on the most serious VTEs occurring among women from the UK, as they only consider fatal events they cannot be a good source of evidence for identifying risk factors for VTE. For instance, these reports have consistently identified that the women who die from VTE are either ≥35 years of age, have high BMI or are immobile as reflected in the current prophylaxis guidelines. This does not indicate independent or causal associations as these findings could be due to chance (as they were based on only handful of cases) or confounding. These gaps in knowledge might lead to exaggeration of the impact of the risk factor leading to un-necessarily high use of anticoagulants (which is expensive, inconvenient and uncomfortable to administer[54]) in the large number of women who will exhibit one or more of these factors. It may also underestimate the relative importance of other risk factors.

1.9.3.2 Unknown risk factors

There might also be some unknown factors influencing the risk of VTE. For instance, a population-based case-control study exploring risk factors for antepartum PE in the UK concluded that two thirds of the women with confirmed PE had no known risk factors according to the current guidelines.[11] This finding is consistent with another hospital based cross sectional study in which 36% of the women with VTE during the antepartum/postpartum periods had no clinical risk factors.[45] This either indicates that these VTE risk factors are being under recorded or there is still room for targeted thromboprophylaxis. However there is a strong possibility that the latter may

be true as information on risk factors in both previous studies was collected via structured questionnaire.

1.9.3.3 Reliance on relative risk

Whilst odds ratios and rate ratios present measures of effect for each risk factor during pregnancy, it is also important to consider the absolute risks associated with those risk factors when considering thromboprophylaxis. For instance, factor "X" maybe associated with a 5-fold increased risk of VTE during the antepartum period, which in relative terms is evidence of a strong association. However hypothetically if the risk of VTE associated with not having factor "X" is less than 0.001%, in absolute terms the additional risk associated is still only 0.005% which is not so alarming considering the number needed to treat. However currently there is a lack of studies estimating the risk factors of VTE in absolute terms.

Some of the risk factors from previous studies are summarised below which can be broadly categorised as demographic risk factors, pregnancy related characteristics, delivery related characteristics and complications and pre-existing medical co-morbidities (Table 1-4).

Table 1-4: Risk factors for VTE during pregnancy/postpartum with their respective odds ratios presented in previous studies (either where risk factors for Antepartum and Postpartum periods could not be distinguished or where combined results have been presented in addition to the separate antepartum/postpartum results).

Risk factors	Danileko-Dixon[55] et al. (VTE)*	Lindqvist et al.[44] (VTE)*	Liu et al.[12] (PE)*	James et al.[7] (VTE)*	Ros et al.[50] (PE)*	Haggaz et al.[9] (VTE)*	Chan et al.[43] (VTE)*
Demographic and life style related factors							
Obesity (BMI>30 Kg/m^2)	0.77 (0.22-2.72)[a]	-	2.7 (1.6-4.4)[+]	4.4 (3.4-5.7)[+]	-	-	-
Age≥35	1.01 (0.94-1.07)[1]	1.3 (1.0-1.7)[d]	1.0 (0.8-1.3)[+]	-	1.6 (1.1-2.2)[f]	-	-
Smoking/current smoking/tobacco use	2.37 (1.18-4.78)[b]	1.4 (1.1-1.9)[2,b]	1.5 (0.6-3.7)[+]	1.7 (1.4-2.1)[b]	1.4 (1.1-1.9)[+]	-	-
Pregnancy and delivery related characteristics and complications							
Parity							
2	-	1.5 (1.1-1.9)[e]	-	-	-	-	-
3 or more	-	2.4 (1.8-3.1)[e]	-	-	1.8 (1.1-2.8)	-	-
Mode of delivery							
Any caesarean	1.17 (0.39-3.47)[c]	3.6 (3.0-4.3)[+]	2.9 (2.4-3.5)[+]	2.1 (1.8-24)[c]	1.4 (1.1-1.9)[+]	0.22 (0.05-0.95)[+]	-
Emergency caesarean	-	-	-	-	-	-	11.7 (3.7-37.0)[c]
Elective caesarean	-	-	-	-	-	-	11.2 (4.5-27.4)[c]
Multiple gestation	7.00 (0.36-135)[+]	1.8 (1.1-3.0)[+]	1.3 (0.9-1.9)[+]	1.6 (1.2-2.1)[+]	2.3 (1.1-4.6)[+]	2.84 (1.05-7.6)[+]	1.8 (0.2-13.5)[+]
Pre eclampsia	1.00 (0.14-7.10)[+]	2.9 (2.1-3.9)[+]	1.2 (0.8-1.8)[+]	0.9 (0.7-1.0)[+]	4.8 (2.7-8.6)[3+]	0.15 (0.02-0.77)[+]	5.1 (1.2-21.7)[+]
Obstetric haemorrhage	9.00 (1.14-71.0)[+]	-	-	-	-	-	-
Hyperemesis	-	-	2.2 (0.6-7.3)[+]	2.5 (2.0-3.2)[+]	-	-	-
Pre-term birth	4.50 (0.97-20.8)[+]	-	2.1 (1.6-2.6)[+]	-	-	-	-
Stillbirth	-	-		-	-	-	-
Postpartum haemorrhage			1.3 (1.0-1.7)[+]	1.3 (1.1-1.6)[+]	-	-	-
Antepartum haemorrhage			1.0 (0.3-4.4)[+]	2.3 (1.8-2.8)[+]	-	-	-

Risk factors	Danileko-Dixon[55] et al. (VTE)*	Lindqvist et al.[44] (VTE)*	Liu et al.[12] (PE)*	James et al.[7] (VTE)*	Ros et al.[50] (PE)*	Haggaz et al.[9] (VTE)*	Chan et al.[43] (VTE)*
Infection	-	-	4.1 (3.0-5.6)	4.1 (2.9-5.7)+			
			Medical co-morbidities				
Varicose veins	2.15 (0.90-5.10)+	-	-	-	-	-	-
Diabetes			1.4 (1.0-1.8)+	2.0 (1.4-2.7)+	2.7 (1.3-5.4)+	-	-
Hypertension			1.2 (0.9-1.8)+	1.8 (1.4-2.3)+	-	-	-
Thrombophilia			2.4 (1.1-5.0)+	51.8 (38.7-69.2)+	-	-	-
Cardiac disease	-	-	43.4 (35.0-53.9)+	7.1 (6.2-8.3)+	-	-	-
Lupus				8.7 (5.8-13.0)+	-	-	-

[1]Age per 10 years, [2]>10 cigarette/day, [3]Severe eclampsia

[a] Compared to normal BMI, [b] Compared to Never smoker, [c] Compared to spontaneous vaginal delivery, [d] Compared to age 20-24 years, [e] Compared to parity 1, [f] Age<30 years

+Compared to women without the risk factor under study, *Preference given to the most fully adjusted results presented in the study

Table 1-5: Risk factors for VTE during the antepartum period with their respective odds ratios presented in previous studies

Risk factors	Simpson et al.[10] (VTE)*	Lindqvist et al.[44] (VTE)*	Jacobsen et al.[32, 53] (VTE)*	Larsen et al.[41] (VTE)*	Knight et al.[11] (PE)*
Demographic and life style related factors					
Obesity (BMI>30Kg/m^2)	1.4 (0.7-2.5)[a]	-	1.8 (1.3-2.4)[1,b]	9.7 (3.1-30.8)[h]	2.65 (1.09-4.45)[h]
Age≥35	-	1.0 (0.7-1.4)[4,f]	1.5 (1.1-2.2)[2,c]	-	0.90 (0.42-1.90)[i]
Smoking/current smoking/tobacco use	-	1.1 (0.8-2.0)[5,e]	2.1 (1.3-3.4)[3,e]	5.7 (2.5-13.2)[e]	0.89 (0.40-1.95)[e]
Pregnancy related characteristics and complications					
Parity					
2	-	1.3 (0.8-2.0)[d]	0.8 (0.5-1.2)[d]	-	4.03 (1.60-9.84)[j]
>3	-	2.8 (1.8-4.4)[d]	1.0 (0.6-1.8)[d]	-	-
Multiple gestation	4.2 (1.8-9.7)[+]	2.1 (1.0-4.6)[+]	2.7 (1.6-4.5)[+]	-	-
Assisted reproduction	-	-	4.4 (2.6-7.5)[+]	-	
Gestational diabetes	-	-	4.1 (2.0-7.5)[+]	-	
Premature rupture of membrane	-	-	0.2 (0.1-1.0)[+]	-	
Pre-eclampsia	-	0.8 (0.4-1.7)	0.5 (0.2-1.2)		

[1]BMI>25, [2]Age 35-54 years, [3] 10-30 cigarettes per day, [4]Age≥35 years, [5]≥10 Cigarettes per day,
[a] Compared to normal BMI, [b] Compared to BMI<20Kg/m^2, [c] Compared to age 25-29 years, [d] Compared to parity 1, [e] Compared to non smokers, [f] Compared to Age≤19 years, [h]Compared to BMI<25 Kg/m^2, [i]Compared to age<35 years, [j]Compared to parity 0.
[+]Compared to women without the risk factor under study
*Preference given to the most fully adjusted results presented in the study

Table 1-6: Risk factors for VTE during the postpartum period with their respective odds ratios presented in previous studies

Risk factors	Simpson et al.[10] (VTE)	Lindqvist et al.[44] (VTE)	Jacobsen et al.[32, 53] (VTE)	Lindqvist et al.[39]	Larsen et al.[41] (VTE)	Morris et al.[56] (PE)
Demographic and life style related factors						
Obesity (BMI>30Kg/m^2)	1.7 (1.2-2.4)[a]	-	2.4 (1.7-2.3)[1,e]	2.3 (1.0-4.8)[6,h]	2.8 (0.8-9.8)[j]	
Age≥35	1.4 (1.0-2.0)[b]	1.2 (0.9-1.6)[g]	0.8 (0.5-1.1)[2,a]	2.5 (0.3-18.9) [7,i]	-	1.67 (1.01-2.76)[7,i]
Smoking/current smoking/tobacco use	-	1.2 (0.8-1.7)[5,f]	3.4 (2.0-5.5)[3,f]	-	1.3 (0.6-2.7)[f]	1.17 (0.83-1.65)[f]
Pregnancy related characteristics, complications and medical co-morbidities						
Parity						
2	-	1.7 (1.2-2.4)[k]	1.2 (0.9-1.8)[k]	-	-	-
>3	-	1.8 (1.2-2.9)[k]	1.9 (1.2-3.0)[k]	-	-	1.49 (1.02-2.20)[+]
Mode of delivery						
Any caesarean	2.6 (1.5-2.7)[c]	4.9 (3.8-6.3)[c]	-	6.8 (3.4-13.2)[+]	-	3.11 (2.22-4.30)
Emergency caesarean	-	-	4.0 (3.0-5.3)[c]	-	-	-
Elective caesarean	-	-	2.7 (1.8-4.0)[c]	-	-	-
	-					
Multiple gestation	-	0.6 (0.2-1.4)[+]	-	-	-	-
Eclampsia	-	-	4.4 (1.4-14.2)[+]	-	-	-
Pre eclampsia	-	3.0 (2.4-4.4)[+]	2.8 (2.8-5.1)[+]	11.6 (4.6-29.5)[+]	-	-
Obstetric haemorrhage	-	-	4.1 (2.3-7.3)[4,+]	-	-	-
Pre-term birth	2.4 (1.6-3.5)[d]	-	-	-	-	2.18 (1.54-3.09)
Stillbirth	-	-	-	-	-	5.9(3.0-11.6)
Cardiac disease	5.4 (2.6-11.3)[+]	-	-	-	-	-

[1]BMI>25Kg/m^2, [2]Maternal age 35-54 years, [3]10-30 cigarettes per day, [4]>1000 ml blood loss, [5]≥10 cigarette per day, [6]BMI<28Kg/m^2 [7]Age>40 years,
[a]Compared to age 25-34 years, [b]Compared to normal BMI, [c]Compared to spontaneous vaginal delivery, [d]Compared to normal gestation, [e]Compared to BMI<20Kg/m^2,
[f]Compared to non-smoker, [g]Compared to age≤19 years, [h]Compared to BMI≥28Kg/m^2 [i]Compared to age ≤40 years, [j]Compared to BMI<25Kg/m^2 [k]Compared to parity 1
[+]Compared to women without the risk factor under study, *Preference given to the most fully adjusted results presented in the study

1.9.4 Basic and demographic risk factors

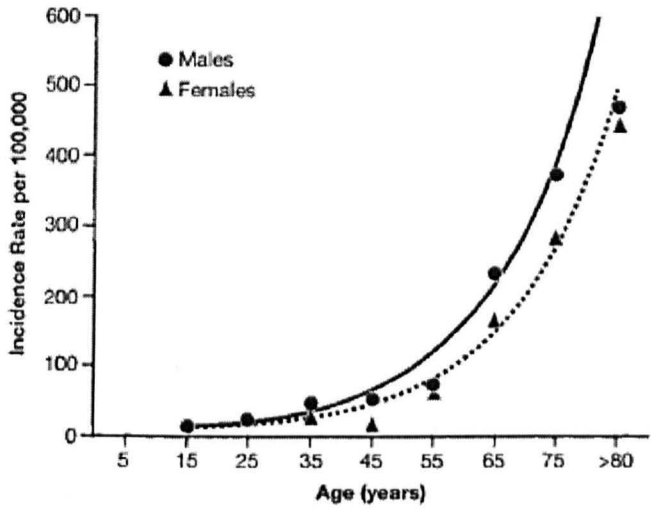
1.9.4.1 Body mass index

A high BMI has been shown to be associated with many adverse outcomes including cardiac disease, atherothrombosis disease and VTE in general medical patients.[57] A literature review by Duhl et al.[57] suggested that many aspects of obesity aggravate prothrombotic risk in pregnancy. Moreover the fibrinolytic process is also decreased. There is also a high incidence of insulin resistance syndrome also known as metabolic syndrome which inhibits the fibrinolytic process. A cross-sectional study by Sebire et al[58] highlighted that obese women are more likely to develop gestational diabetes, proteinuric pre-eclampsia, postpartum haemorrhage, genital tract infection, wound infection and are more likely to have caesarean section which may further add to the increased risk of VTE associated with obesity. To date there are many cross sectional studies conducted exploring the association between high BMI and VTE during pregnancy with most studies suggesting an increased risk of around 2-fold compared to women with normal BMI (20-24.9 kg/m^2) (Table 1-4 to Table 1-6). The current RCOG guideline for thromboprophylaxis[21] has assumed much higher risk of VTE in women who are morbidly obese (BMI>40kg/m^2) and is reflected as a separate category which is based on expert opinion. Additionally, there is a lack of evidence on how the effect of high BMI (>30Kg/m^2) on the risk of VTE is mediated by pregnancy associated complications (postpartum haemorrhage, mode of delivery etc.) and other medical co-morbidities (diabetes, hypertension etc.) by showing variation in the effect size when adjusted for those factors.

1.9.4.2 Maternal age and smoking status

The risk of VTE increases with age in the general population where an exponential increase in the risk of VTE takes place after 45 years[6] (Figure 1-3). Whilst age≥35 is considered a risk factor in the current RCOG guidelines, current evidence from primary care in the UK[36] suggests no association between age≥35 years and VTE during the antepartum and a 70% increase in the risk during the postpartum period compared to those aged 25-34 years. This finding is in concordance with other studies[10, 11, 44, 53, 56] that also failed to find a strong association of VTE with age at pregnancy. The thrombogenic potential of tobacco smoking has been recognised for more than 30 years. Early studies were poorly designed and gave inconsistent evidence however recent evidence supports this relationship in the general population.[59] There are still controversies surrounding cigarette smoking and the risk VTE during pregnancy. For instance, a population based case control study conducted by Danilenko-Dixon et al., found a 2.5 fold increased risk of VTE during pregnancy among cigarette smokers.[55] These findings contradict those presented by Liu et al.[12] in a large cross-sectional hospital based study that showed no association of tobacco use with either PE or DVT. Furthermore a cross-sectional study by Larsen et al.[41] showed no association between smoking and VTE during the antepartum but a 7-fold increased risk during the postpartum period. The wide variation in the estimates may partially be explained by the fact that most studies on the subject use hospital discharge data where smoking status is liable to be poorly recorded or not recorded at all.

Figure 1-3: Association between age and VTE[60]



1.10 Delivery associated characteristics and complications

1.10.1 Adverse pregnancy outcomes

Several adverse pregnancy outcomes have been linked to increased risk of both antenatal and postnatal VTE. For instance, pre-term birth which occurs in 7%[61] of all deliveries is known to be associated with a more than 2-fold[10] higher risk of postnatal VTE compared to pregnancies with normal gestational length. Similarly Morris et al.[56] found a 6 fold increase in the risk postpartum PE in those with stillbirths compared to pregnancies resulting in live births. To date these factors have received limited attention and are not incorporated in the current UK guidelines for thromboprophylaxis. This could be due the pre-conceived notion that the augmented risk associated with stillbirth and pre-term birth may be mediated by pre-eclampsia. While this may partially be true, 50% of stillbirths are unexplained[62] and 80% of pre-terms births occur in pregnancies not complicated by pre-eclampsia[63] which highlights the potential importance of those risk factors by themselves.

1.10.2 Caesarean mode of delivery

The need for VTE risk assessment and thromboprophylaxis in women post caesarean section has been recognised since the early 90s. Previous studies have consistently reported higher risks of VTE among women delivering by caesarean section (estimates ranging from a 17% to an 11-fold increased risk; Table 1-4 and Table 1-5) with only few studies[32, 43] going into greater detail of separating elective versus emergency caesarean.[43, 53] The impact of elective and emergency caesarean mode of delivery on VTE is also debatable. The wide variation in the reported rates may be due the difference in the study populations and data sources used. For instance Chan et al. (China) in their cross-sectional analysis of hospital discharge record from a single centre reported 11-fold increased risk of VTE for both elective and emergency caesarean section whereas Jacobsen et al. (Norway) using patient registry data reported relative risk to be 2.7-fold and 4-fold respectively. The incoherence in the reported estimates may also be due to the difference in the country's health care system and opinion about offering thromboprophylaxis to women post caesarean delivery (later discussed in chapter 4). Despite the absence of randomized controlled trials assessing the effectiveness of offering thromboprophylaxis to women post caesarean section, many guidelines[21, 64] support the use of thromboprophylaxis among those women. Finally the current RCOG guidelines for thromboprophylaxis[21] suggest 7 days thromboprophylaxis with LMWH for those who had emergency caesarean section whereas pharmacological thromboprophylaxis is only recommended for those who had elective caesarean section if accompanied by one or more additional risk factors. However these recommendations are based on scarce evidence as most prior studies fail to separate elective from emergency caesarean section.

1.10.3 Postpartum haemorrhage

Postpartum haemorrhage which affects around 10% of all pregnancies is also associated with a high relative rate of VTE. Most studies that have examined this association relied on hospital discharge data where information on both haemorrhage and VTE was extracted using ICD-10 codes around the time of delivery. Given the increased used LMWH for thromboprophylaxis during the postpartum period where the risk of postpartum haemorrhage is 1%[25], there may be particular concerns over establishing the temporal relationship of severe postpartum haemorrhage (affect 1% of all pregnancies) and VTE if they both took place during the same hospital admission. Moreover, the risk of VTE associated with postpartum haemorrhage may be the function of blood transfusion.[7]

1.11 Pregnancy related characteristics and complications

1.11.1 Parity

Parity is another established risk factor of VTE and is incorporated in the current RCOG guidelines for thromboprophylaxis. A cross sectional study by Lindqvist et al.[44] found 3-fold and 70% increased risks of VTE in those with parity 3 or more during the antepartum and postpartum periods respectively. Furthermore, a population based case-control study by Knight et al.[11] reported a 4-fold increased risk of PE even among pregnant women with parity≥1 during the antepartum period. In contrast Jacobsen at.al[53] found no association between multiparous women and VTE during the antepartum period but a 70% increased risk of VTE in those with party≥2 during postpartum. Whilst the strong positive association between parity and postnatal VTE is not clear, the wide variation in the reported estimates in previous studies may partially be explained by the characteristics of previous studies. For instance, the definition of parity differs by country and on

gestational thresholds. In the UK parity is defined as number of previous pregnancies reaching 24 weeks whereas in the US this cut off is 20 weeks. Additionally a survey conducted in the England demonstrated that clinicians and midwives often apply the term "parity" incorrectly.[65] Moreover, the study by Lindqvist et al.[44] only included pregnancies reaching a gestational age of 24 weeks or more in their analysis whereas Knight et al[11] only looked at PE.

1.11.2 Pre-eclampsia/eclampsia

Currently RCOG guideline on thromboprophylaxis considers pre-eclampsia and eclampsia as both antenatal and postnatal period risk factors. This is based on the evidence that does not allow separation between antepartum and postpartum periods. For instance, Jacobson et al.[53] in their case control study reported pre-eclampsia to be a significant postnatal risk factor (associated with 4-fold higher risk) as opposed to antenatal risk factor. The non-statistically significant association between antenatal VTE and pre-eclampsia may be due to the fairly small follow-up time period between the date of pre-eclampsia and delivery. The early onset pre-eclampsia may have different pathology than the more serious late onset of the disease as the former may be linked to prolonged immobilisation prior to delivery.

1.11.3 Hyperemesis

Hyperemesis gravidarum (HG) is defined as vomiting in pregnancy that is pernicious enough to cause weight loss, dehydration and electrolyte imbalance.[66] Estimates of severe nausea and vomiting of pregnancy vary greatly and range from 0.3% (Sweden) to 10% (China) of all pregnancies.[67] It is regarded as a risk factor for VTE in both the antepartum and postpartum periods according to the RCOG guideline for thromboprophylaxis. Dehydration and vasospasm is largely considered to be the pathogenesis behind its

increased risk associated with VTE. For instance North American cross-sectional studies[7, 12] have found a 2.5 to 4 fold increased risk of VTE associated with HG during antepartum/postpartum periods. However these estimates are based on hospital based studies which are more likely to capture pregnant women with severe forms of HG warranting hospitalisation. Secondly, it is not known whether its impact differs during the antepartum versus the postpartum period.

1.11.4 Acute systemic infection

Inflammation is the key determinant of endothelial function in both arteries and veins and the link between infection and venous thrombosis via endothelial activation has been suggested.[68] A self-controlled case series by Smeeth et al[68] using primary care data revealed a transient increased risk of VTE during the initial weeks following both urinary and respiratory infection. Similarly puerperal infection which occurs in 1-8% of pregnancies has also shown to increase the risk of VTE by 4 to 5-fold.[7, 12] However this evidence comes from hospital-based cross-sectional studies which most likely presents only the severe form of infection requiring hospitalisation and there is also a potential of missing out non-severe infection diagnosed in primary care.

1.12 Medical co-morbidities

1.12.1 Hospitalisation

Hospitalisation is considered an important risk factor in the general non-pregnant population. According to the Department of Health, each year over 25,000 people die in England from VTE as a consequence of hospital stay.[3] The All-Party Parliamentary Thrombosis Group[69] working on the prevention of VTE has recommended mandatory risk assessment for all patients admitted to

hospital.[21] The risk of VTE is not only dependent on the reason for admission but also on co-existing patient related factors and therefore the decision of whether a patient should be offered thromboprophylaxis is currently dependent on the balance between the absolute rate of thrombosis and the risk of bleeding. As most previous studies on VTE in pregnancy rely on hospital discharge data both to determine exposures and outcome it will simply not be possible to look at hospitalisation as a risk factor in its own. However, Heit et al.[70] in their population based cohort study estimated the incidence rate of VTE among hospitalised patients and compared it to non-hospitalised community residents. Overall the age and sex adjusted absolute rate of VTE among hospitalised patient was calculated to be 960 per 100,000 person-years which was more than 100 times greater than the rate in non-hospitalised community residents (incidence rate=71 per 100,000 person-years). It is not clear if a similar increase risk would be observed among pregnant women who are younger and would on average have a better health prognosis. To date there have been no studies evaluating the impact of hospitalisation or post-hospitalisation on VTE during pregnancy.

1.12.2 Previous VTE

There are number of studies suggesting increased risk of VTE during pregnancy in those with history of thrombosis. The rate of recurrence is reported between 2.4% and 10.9%[71-75] whereas rate of recurrence VTE in women who receive anticoagulation is reported to range between 0 and 2.4%.[49] Whilst a previous VTE either during or outside of pregnancy is considered an important risk factor in the current RCOG guidelines for thromboprophylaxis, most are first events which can be prevented through better understanding of its occurrence and risk factors. Additionally recurrent VTE occurs in a small proportion of pregnant women who will very likely be

cared for differently than those without a history of VTE. Furthermore the use of anticoagulants as thromboprophylaxis in those with prior history of thrombosis is arguably less controversial in the UK and therefore less relevant to current practices.

1.12.3 Thrombophilia and other inherited conditions

Thrombophilia, a condition where the blood has an increased tendency to clot is another well recognised risk factor for VTE. James et al.[7] in their cross sectional analysis of hospital discharge records found that those diagnosed with thrombophilia were 51 (95%CI 38.7-69.2) times more likely to have a VTE diagnosis during pregnancy compared to those without the condition. However Liu et al[12] found a 2 fold and 15 fold increased risk of PE and DVT respectively associated with thrombophilia. The difference in the estimates may be due to the fact that the former study failed to separate first from recurrent VTE events as the majority of thrombophilias may be diagnosed after the first VTE event. It is also important to note that a diagnosis of thrombophilia cannot be used to predict VTE as routine thrombophilia screening is not recommended for pregnant women. Furthermore, in practice testing for thrombophilia does not usually influence thromboprophylaxis in current pregnancy unless detected in a woman with a prior VTE related to a temporary risk factor who would not otherwise receive thromboprophylaxis.[21]

Evidence also suggests that prior diagnosis of varicose veins, cardiac disease, diabetes, inflammatory bowel disease, hypertension lupus have all been associated with increased risk of VTE and most of these are incorporated in the current RCOG guideline. However the absolute risks associated with these risk factors have not been studied.

1.13 Project justification

VTE is one of the leading causes of maternal mortality in high income countries and is associated with a considerable health and social economic burden. There are no up-to-date estimates of the incidence of first VTE in and around pregnancy available at a population level from the UK and data from other countries are limited. While numerous attempts have been made to understand VTE risk factors among pregnant women, there is still inconsistency and disagreement concerning which women are at highest risk of developing a first VTE during pregnancy and in the postpartum separately with limited focus on crucial risk factors such as hospitalisation and stillbirth. Most of the studies on the subject are hospital-based cross-sectional studies with no population-based cohort studies from the UK. This is combined with a lack of both national and international data about the relative impact of those risk factors with respect to the absolute risk of VTE. Only a few studies comprehensively examine factors occurring before, during and after childbirth and their impact on postpartum VTE while adequately adjusting for other confounding factors and have examined the interrelationship between factors. Additionally none of the previous studies have assessed the impact of risk factors on the incidence of VTE during specific periods of postpartum. Knowledge of the absolute risks of VTE in pregnancy and following childbirth and how recognised risk factors influence these is therefore crucial in identifying pregnant women who are most likely to benefit from thromboprophylaxis. However due to the relatively low incidence of VTE among pregnant women and uncertainties over VTE risk factors bespoke cohort studies may not be cost effective in providing robust evidence. Therefore it is more appropriate to use large routinely collected data that contain information on both exposure and outcome and can provide generalisable population based estimates. The data sources used in the work presented in this thesis provide contemporary clinical information that is

relevant to the UK population. Furthermore it will also provide international leading evidence on the absolute and relative risks of factors associated with VTE in and around pregnancy.

1.13.1 Objectives

The objectives for this thesis are:

- To determine the incidence of VTE in and around pregnancy and compare it to time outside pregnancy utilising primary care data from the UK.

- To determine the risk factors of antepartum and postpartum VTE using primary care data from the UK.

- To use the recent linkage of electronic primary and secondary care data to comprehensively assess VTE occurrence and determine which definition(s) of VTE in women of childbearing age provide estimates which are most consistent with existing literature

- To assess the impact of hospitalisation and other risk factors on the incidence of VTE during the antepartum period using linked primary and secondary care data.

- To determine the risk factors for postpartum VTE and to assess their impact on VTE in specific windows of time following delivery using linked primary and secondary care data.

1.14 Thesis outline

The subsequent chapters of this thesis contain results from five studies that were carried out to address the main research objectives of this thesis. The outline below briefly summarises the main content of each chapter. Each of the following chapters has its own background followed by methods, results, discussion and conclusion.

Chapter 2: This chapter describes the incidence of VTE in and around pregnancy utilizing The Health Improvement Network (THIN) which is a computerised primary care database from the United Kingdom. It also compares the rate of VTE during pregnancy and postpartum to that outside pregnancy.

Chapter 3: This chapter uses the same database to identify risk factors for VTE during the antepartum and postpartum periods separately in terms of absolute and relative risk.

Chapter 4: This chapter introduces and describes the recent linkage of electronic primary care records (Clinical Practice Research Datalink) with the English Hospital Episode Statistics database (HES) to comprehensively assess VTE occurrence and the best way of defining VTE in and around pregnancy.

Chapter 5: This chapter looks at the impact of hospitalisation and post-hospitalisation on the incidence of antepartum VTE using linked primary and secondary care data.

Chapter 6: This chapter identifies risk factors for VTE during the postpartum period utilising the linked primary and secondary care data. Additionally, it

evaluates the impact of those risk factors on the timing of VTE during the time around delivery and specific periods of postpartum.

Chapter 7: This chapter summarises the main findings of this thesis and suggests clinical recommendations and direction for future research.

1.15 Role of candidate

The initial idea for this PhD was conceived by Dr. Matthew J Grainge along with Dr. Joe West and Dr. Laila Jal Tata which followed on from a work initially started as an MSc project.[36] The candidate continued to further develop the project by carrying out a detailed literature review and formulating specific research questions with continuous guidance from all three supervisors. The THIN dataset used in the chapter 2 and 3 was initially processed by Mr Chris Smith. Dr. Linda Fiaschi extracted the information on potentially fertile women and created the pregnancy cohort. The pregnancy and patient cohort using the linked primary (CPRD) and secondary care (HES) used in chapter 4, 5 and 6 was created by the candidate. The candidate did an extensive literature review, also extracted information on exposure and outcomes from all three data sources, did the necessary data management and formulated and conducted statistical analyses for each chapter. Furthermore, the candidate generated all tables and figures and wrote the thesis which was read and approved by all three supervisors.

2 Incidence of VTE in and around pregnancy: An updated population based cohort study from the United Kingdom

This chapter describes the incidence of VTE in and around pregnancy utilizing The Health Improvement Network (THIN) which is a computerised primary care database from the United Kingdom. It also compares the rates of VTE during pregnancy and the postpartum to that outside pregnancy. This chapter provides an updated analysis of a study which I previously published using THIN data up to 2004.[36]

2.1 Introduction

The knowledge of the absolute and relative risk of VTE at different times around pregnancy is of crucial importance in identifying pregnant women or those who have recently delivered, who would benefit most from anticoagulant thromboprophylaxis which is known to be generally safe and highly effective [25, 76]. Equally by determining low risk periods, unnecessary thromboprophylaxis and its potential harms to both the mother and foetus could be avoided. However, clinical guidelines developed by the American College of Chest Physicians [22], the UK Royal College of Obstetricians and Gynaecologists [21], and the Society of Obstetricians and Gynecologists of Canada[77] are all limited by both the quality and quantity of the current evidence base and understandably have had to rely upon expert consensus opinion in formulating the recommendations made. One example of the existing scarcity of evidence is the lack of precise and consistent estimates of the absolute risk of VTE in and around pregnancy. Reported rates vary considerably from 28-86 per 100,000 pregnancies during the antepartum and 28-128 per 100,000 during the postpartum period [7, 10, 12, 31, 32, 34, 37, 43-46, 78]. Inconsistencies also surround the trimester of pregnancy and weeks

postpartum during which a woman is at highest risk of VTE and the extent to which age affects these risks.[31, 32, 35, 79] Fewer studies have specifically compared rates of VTE around pregnancy either with those outside of pregnancy or with those in non-pregnant women, and the evidence from these is inconsistent.[31, 37, 79] For example a case-control study by Pomp et al. demonstrated a 5 and 60-fold increased risk of VTE associated with antepartum and postpartum period respectively compared to non-pregnant women. However Vikrus et al. in their population-based cohort study demonstrated a 3.5 and 8-fold increased risk of VTE during the antepartum and postpartum periods when similar comparisons were made.

2.1.1 Study justification and aim

Accurate estimates of rates of VTE that are generalisable to the majority of pregnancies will aid both women and practitioners in their decision making surrounding the prevention of VTE. I therefore aimed to determine the absolute and relative risks of VTE in women of child bearing age around pregnancy with the primary objective of informing revisions to existing clinical guidelines.

2.2 Method

2.2.1 Data source used

The dataset used to for this study comes from The Health Improvement Network (THIN). It is a computerised primary health care database containing medical, prescription, lifestyle and socio-demographic information from individual anonymised patients from across the UK. It was initiated as a collaboration between two companies with established names in primary care computing; EPIC, an expert in the provision of the primary care patient data that is used for medical research and In Practice System (InPS) who developed and provide the widely used Vision general practice computing system. The anonymised patient data are collected from the primary care practice's Vision clinical system on a regular basis without interruption to the running general GP's system and sent to EPIC who supplies the THIN data to researchers. The basic aims of THIN are;

- To help those practices that have joined THIN improve the quality of their clinical data recording by offering training and analysis of the practice's anonymised patient data
- Create a database of anonymised primary care data to be used by academics, commercial and other research organisations to undertake studies in epidemiology, drug safety and the treatment and prevention of disease.

The version of THIN used for the second and third chapter of this thesis contained data from 429 practices with a total of 7.7 million patients of which 3 million patients were actively registered and could be prospectively followed.

2.2.2 Information contained within THIN

Upon data collection, patient's identifying information such as name, exact date of birth and National Health Service (NHS) number are removed. Although identifying information is not available to THIN, each patient in the database is assigned a new unique identifier to be used by the researcher to identify individual patients. Additional demographic information such as age and gender are also collected. THIN also contains life style related information such as smoking status and alcohol consumption recorded by the general practitioner during the course of clinical consultation. The medical and prescription records in THIN have been previously validated for pharmaco-epidemiological research.[80-82] For instance Lewis et al[82] carried out series of studies using THIN found the expected positive associations of stoke with diabetes and hypertension; of myocardial infarction with hypertension, hypercholesterolemia, obesity and smoking and of peptic ulcer with aspirin, NSAIDs and potassium. Furthermore the group also confirmed the negative association of colorectal cancer with aspirin, NSAIDs and Cox-2 inhibitors.

All medical conditions and symptoms reported by patients to the GP are recorded on the computer during a consultation. These build up a complete computerised medical history for each patient. All medical conditions in THIN are recorded in the form of Read codes. These use a hierarchal system allowing cross-referencing of the codes to International Classification of Disease (ICD-10) headings.[83] Information on secondary care referrals are also recorded in the database. Similarly, secondary care information including hospital admissions, diagnosis, and outpatient consultations is received by primary care practices and also retrospectively recorded.

Prescriptions in primary care are very well recorded as the computerised system used by GPs to enter medication is also used to print paper copies of

the prescription to be presented at the pharmacy by the patients. The computerised prescribing creates therapy records for each patient using the Multilex coding system which can be linked to the relevant chapter of the British National formulary (BNF). Prescriptions not issued from the computer, such as controlled drugs, immunisations, private prescriptions and drugs prescribed during the home visits should all be entered. However there is a possibility of under recording. Additionally drugs prescribed in secondary care or by other specialists will not appear in the THIN data unless the treatment is continued after the patient is discharged. Due to the constraints of specialist and hospital prescribing budgets many prescriptions issued outside of the GP practice will usually be enough to cover only the first 7 to 14 days.

Each THIN practice has data split into four raw standard data files from which the researcher can extract the relevant information. These can be linked together by a unique patient identifier. Table 2-1 presents the overall file structure of THIN.

Table 2-1: File structure of the data file contained in THIN

Files	Information contained
Patient	Year of birth, gender, death date, transfer out date, date of registration, registration status etc.
Clinical	Event date, Read code for medical disease diagnosis, symptoms, procedure and investigations, referral information etc.
Therapy	Date of prescription, drug code using Multilex coding system, dose, number of prescriptions, duration of prescription etc.
Additional data	This file contains additional patient information including life style related characteristics including smoking status, alcohol consumption etc.

2.2.3 Date information

The patient file contains a computerization date, Vision date and Acceptable Mortality Reporting (AMR) date. The computerization date is calculated as the date when a practice started using computerized prescriptions every day for certain consecutive months whereas the Vision date is the date when a practice switched to Vision practice management software to record consultations.

The AMR date represents the date from which a practice is expected to be reporting all-cause mortality in accordance with those derived from the Office for National Statistics (ONS) as age and sex standardised to the local practice's population. The application of this date aims to ensure that no immortal time periods are present in the data. For instance such periods may occur when a practice switches to another system and doesn't remove all deceased patients or if a practice is split some deceased as well as alive patients are transferred to the new practice.

2.2.4 Justification of using THIN

Advantage and disadvantages of using THIN

(With specific reference to VTE in pregnancy studies)

THIN is an incredible data source which is now widely used for epidemiological studies. However like all data sources there are certain limitations which should be kept in mind. The following section mentions some of the strengths and limitations of THIN and their consideration to certain extent underpins the design of studies presented in the following chapters.

Size

One of the biggest strengths of this primary care database is its size. With data on millions of patient records, it is possible to study rare diseases like VTE in pregnancy for which bespoke cohorts may not be cost effective. The large sample does not only give more precision and power to look at the incidence of VTE in narrow windows of time (e.g. trimester of antepartum) but also provides the opportunity to look at rare risk factors for VTE (e.g. postpartum haemorrhage, cardiac disease, Inflammatory Bowel Disease (IBD)) which are highlighted in subsequent chapters.

Representativeness

Whilst general practices registered with THIN are self-selected from various different areas of the UK, it's population is highly comparable to the UK population in terms of age and sex structure level at regional levels.[80] Therefore it is reasonable to assume that the study findings using THIN are generalisable to the whole of the UK population. One limitation to this generalisability is that THIN marginally under represents those practices serving more deprived populations.[84] However the impact of this may be trivial as no association has been found between PE and socio-economic status among pregnant women.[11]

Prospectively collected

For each patient registered with THIN, there is a start date which ascertains which data are prospectively or retrospectively recorded. This is of particular importance for studies where exposure recall may be biased. For instance pregnant women with VTE may be more likely to recall their history of VTE risk factors (e.g. hyperemesis, pre-pregnancy BMI, history of medical conditions) more accurately than those without thrombosis. This also gives more precise timing of both exposure and outcome.

Validated

Although THIN uses strict measures to ensure the quality of data is of the highest standard, information recorded on specific diseases can also be externally validated by third parties. The process involves requesting anonymised paper records or asking the GPs of relevant practices to fill out a questionnaire to validate medical information recorded in the electronic data. The diagnosis of VTE has been validated by this process with a positive predicted value (PPV) of 84%[85] in a similar primary care database (Clinical Practice Research Database (CPRD), some of whose practices also contribute to THIN. Similarly, fertility rates estimated from THIN are comparable to the national figures.[81]

Contemporary

The changes in diagnostic modalities over time have led to better clinical ascertainment of VTE diagnosis in the UK and in most high income countries. This is in addition to the increasing prevalence of certain VTE risk factors (e.g. body mass index) which may contribute towards the increase in the incidence of VTE. Most studies on the incidence and risk factors of VTE have used data up to 2005 which may not reflect the true incidence of VTE in more recent years since UK[21] and US[64] guidelines on thromboprophylaxis have been more comprehensively disseminated after 2004. Hence THIN provides a large component of follow-up time from more recent years which may be generalisable to the current rather than the historical clinical setting. One drawback is the increased potential for ascertainment bias which will be discussed later in this chapter.

Short duration of individual women follow-up

It is important to note that in THIN the duration of follow-up for each individual patient is short. For instance the median follow-up (of acceptable quality prospectively recorded clinical data) for potentially fertile women in THIN is approximately 3.2 years and there are no prospectively recorded data before 1987. This means that there is a potential of missing pregnancies prior 1987 which may result in incorrect information on parity and gravidity of women who do not have such data starting at the beginning of their reproductive years.

Incomplete recording

As with any routinely collected data, there is a concern that what is recorded is not determined by protocols designed for research. This means that recording of information in THIN is purely driven by a GP's and other health professionals' assessment and care of the patient in primary care. Hence the recording of data is not only incomplete but it is likely there is bias as to which data are missing. For instance, it is likely that a GP will record "a patient smokes heavily" if they know, as this may adversely affect health. However it is less likely that they would record the information that a patient is non-smoker unless they suffered from condition which might be attributable to smoking. This limitation may have been addressed to a certain extent in recent years with the introduction of Quality Outcome Framework (QOF) which is an incentive program for all general practices in the UK.[86] It rewards GPs for how well patients are cared for based on their completeness of certain clinical indicators of clinical practice quality. The QOF contains certain indicators for which a practice scores points according to their level of achievement. These indicators include cancer, cardiovascular diseases and respiratory disease. This presumably may have an impact on the completeness of recording of medical conditions. However the evidence on

whether it improves the quality of care of the patient is weak.[87] Currently, however there are no indicators for antenatal care so the extent to which biases may operate in recording around pregnancy are unknown.

2.2.5 Study population

The study time period was defined between April 1995 and July 2009 during which all women between the ages of 15 and 44 years registered with THIN were identified. All women with a medical code for VTE before the start of the observation period (history of VTE) were excluded. The study start date was defined as the latest of the woman's registration date with THIN, the practice's AMR date, first day of 1995 and the date of the women's 15th birthday. However for some practices, the Vision date was used instead of AMR date if it was recorded earlier than the latter date as it implied that information recorded in Vision is recorded in a stable and reliable way. The end date of the study was defined as the earliest date of the transfer out date, date of death, date of first VTE, date of last data collection from the practice and the woman's 45th birthday.

2.2.6 Study design

An open historic cohort design was used in the study where women between the ages of 15 and 44 years could enter and exit study at different points in time (Figure 2-1). A woman stopped contributing person time if she developed VTE, died, or was transferred out of a participating practice.

2.2.7 Exposure

The exposure in this study was defined as pregnancy including the postpartum period. Pregnancies were defined using Read codes for delivery/pregnancy which were categorised by pregnancy outcome (live birth,

stillbirth, miscarriage or termination). The total person time for each woman was divided into antepartum postpartum and time outside of pregnancy. Exposure and baseline time periods were defined as follows:

2.2.7.1 Antepartum

The antepartum period was defined as the date of the woman's last recorded menstrual period until the date of delivery. For women with no information on the gestational age at delivery, antepartum was defined as 280 days (40 weeks) prior to the date of delivery. This was subsequently divided into trimesters which were defined as follows:

First trimester: Date of conception until 90 days after conception

Second trimester: 90 days after conception until 180 days after conception

Third trimester: 180 days from conception until the date of delivery.

2.2.7.2 Postpartum

The postpartum period was defined as up to 12 weeks (84 days) following delivery and was divided as follows:

Early postpartum: The first 6 weeks (42 days) following delivery

Late postpartum: The second 6 weeks (43-84 days) following delivery. The overall postpartum period was also divided into individual weeks.

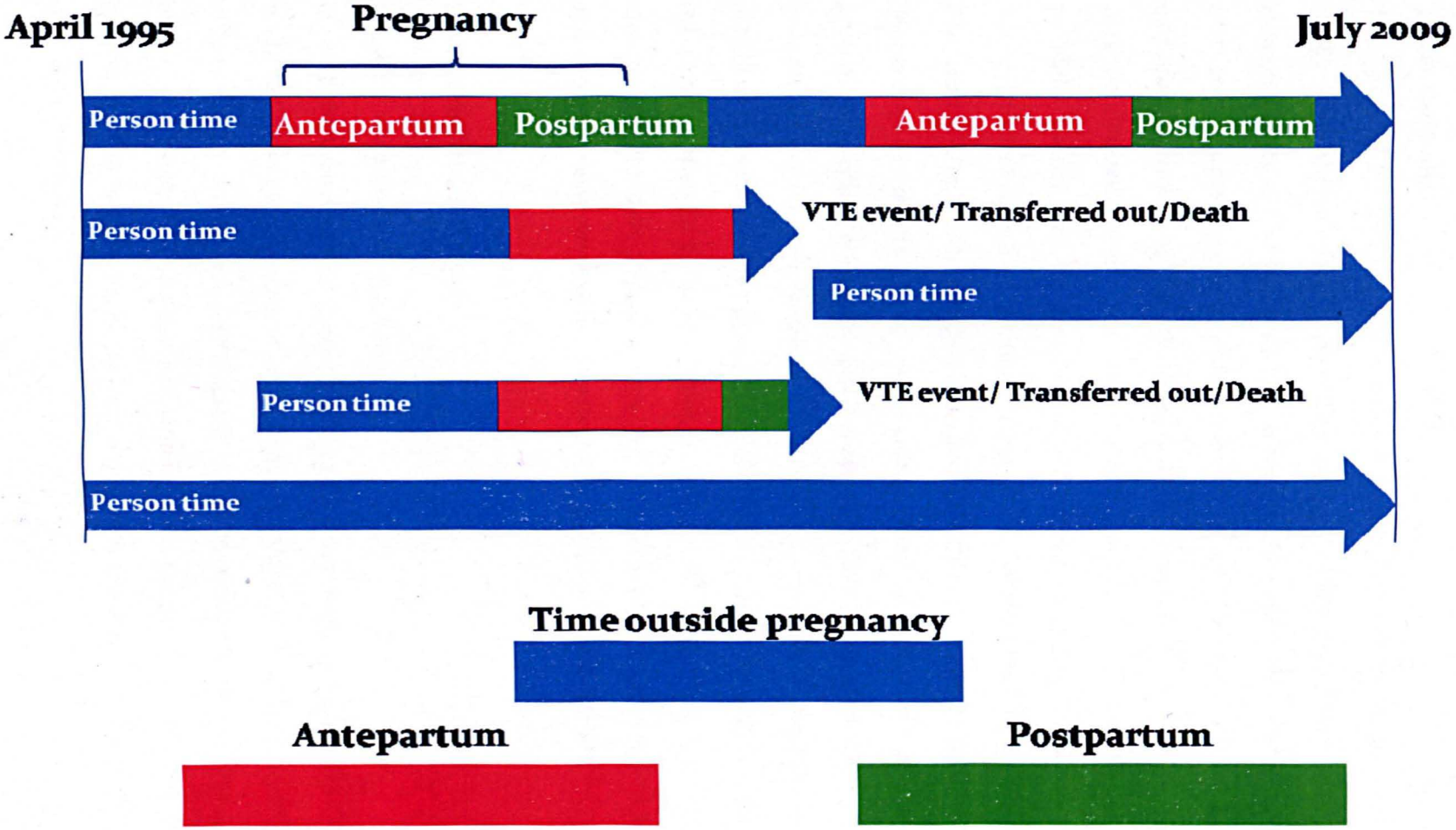
For pregnancies resulting in miscarriages and terminations, this time period was defined as the first 6 weeks following a miscarriage or termination.

2.2.7.3 Baseline period

To calculate baseline rates I used the cohort time spent outside pregnancy (including the first 12 weeks postpartum) during their registration with the general practice. For women with no recorded pregnancies this included their

entire registration during the study period between which they were 15 and 44 years of age. This time period will be referred to henceforth as "time outside pregnancy".

Figure 2-1: Study design



2.2.8 Outcome

The outcome for this study was defined as the first venous thromboembolism (VTE) including pulmonary embolism (PE) or deep vein thrombosis (DVT) experienced by a woman more than a month after her study start date. Cases and person time occurring within one month of the study start date were excluded to avoid any prevalent cases being included as incident which is a potential limitation of the data used.[18] The one month cut-off was also based on an initial examination of the dataset which revealed higher incidence of VTE during the first month of women's registration with the practice (Appendix 3). Diagnosis of VTE was based on a recorded medical code assigned by a physician (Appendix 4) supplemented by having either a recorded anticoagulant prescription (either unfractionated heparin, warfarin or low molecular weight heparin) in the 90 days following the event (Appendix 5), a medical diagnosis indicating an anticoagulant prescription which took place in the 90 days following the event (Appendix 6), death within 30 days of the event (see Appendix 7 for derivation of the date of death). Based on this, 84% of VTE cases were validated in a previous study using similar electronic primary care data (CPRD).[85]

2.2.9 Statistical analysis

2.2.9.1 Descriptive statistics

All data management and analysis was carried out using Stata version 11. The study population was described using frequencies and percentages including how different ways of validating VTE might influence incidence rates. Total person time in the study was divided into antepartum, postpartum and time outside pregnancy. The median follow up time along with the inter-quartile range (IQR) was also presented.

2.2.9.2 Calculation of Incidence

Incidence rates and 95% CIs were calculated in the antepartum, postpartum and time outside pregnancy per 100,000 person years. This was done by dividing total number of VTE events in the antepartum and postpartum period and time outside pregnancy by person-years of follow up in those respective time periods. Similarly rates per 100,000 person-years were also calculated for each trimester of the antepartum period and different periods of postpartum time (early, late, and by weeks). The calculated incidence rates were also stratified by calendar time (before and after 2004). The calendar year cut-off was based on the publication of the first RCOG comprehensive guideline for thromboprophylaxis.[20]

2.2.9.3 Calculation of incidence rate ratios

To assess the increase in the risk of VTE antepartum and postpartum, incidence rate ratios (IRR) were calculated in those respective time periods compared to time outside pregnancy using a Poisson regression model. The same baseline was used when calculating IRRs for each trimester of antepartum and different periods of postpartum compared to time outside pregnancy. The incidence rate ratios were adjusted for age and calendar year. Additionally an interaction term between pregnancy status (antepartum, postpartum and time outside pregnancy) and age group was fitted to formally test for interaction between these terms.

2.2.9.4 Sensitivity analysis

Due to specific limitations of the dataset used as previously highlighted, the following sensitivity analyses were performed.

2.2.9.4.1 Restricting the outcome definition

One limitation of using the VTE outcome definition in pregnancy in particular is the potential overestimation of some of the VTEs especially in the antepartum period where low molecular weight heparin (LMWH) can be used both as prophylaxis and therapeutically. A sensitivity analysis was therefore performed by restricting all analyses to include only those women who were prescribed either warfarin or related drugs (Fondaparinux, Lepiradin, Phenidione and Acenocoumorol) or had a medical code indicating anticoagulant therapy (but who did not have LMWH prescribed) within 90 days of the event or death within 30 days of the event. Absolute and relative rates of VTE for periods of antepartum and postpartum were calculated using methods identical to before.

2.2.9.4.2 Over diagnosis and ascertainment bias due to change in practice

Since the publication of the first comprehensive guidelines on the use of thromboprophylaxis during pregnancy and postpartum in 2004[20] it is plausible that pregnant women might be more likely to get over diagnosed (ascertainment bias) with VTE due to increased clinical awareness compared to before the guidelines. In order to assess the impact of any changes in practice relating to the diagnosis of VTE, IRRs were calculated to compare antepartum and postpartum risks with those outside pregnancy, but with results stratified by calendar time (before and after 2004).

2.2.9.4.3 Over diagnosis in pregnant women during the third trimester

It is also possible that VTE may be particularly prone to over diagnosis in the third trimester of pregnancy where pregnant women are more likely to visit clinicians. Since there is no information on the severity of disease and cause of death in the current dataset the analyses mentioned in Section 2.2.9.2 and

Section 2.2.9.3 were repeated restricted to pulmonary embolism, where over-diagnosis is assumed to be less likely

2.2.10 Ethics approval

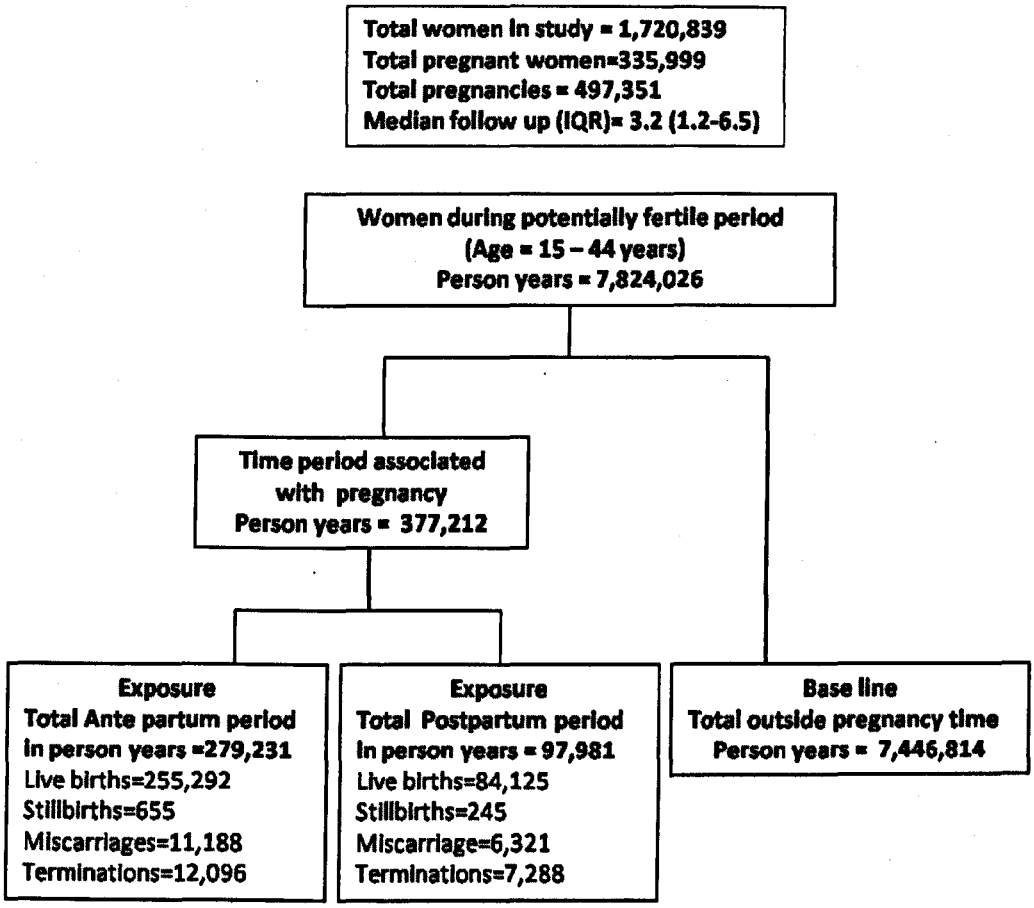
This study conducted in this and following chapter was approved by the THIN scientific advisory committee (reference number 10-002R)

2.3 Results

2.3.1 Study population

Figure 2-2 presents the basic characteristics of the study population. The study population consisted of 1,720,839 potentially fertile women (aged 15-44 years) of whom 20% experienced at least one pregnancy. There were a total of 497,351 pregnancies during the study period of which 75% ended in live births whereas 0.2% (1,152), 13% (64,167) and 11% (57,030) resulted in stillbirth, termination and miscarriage respectively. The study included over 7.8 million person-years of follow up. Around 5% of this time was associated with pregnancy which was divided into 279,231 and 97,981 person-years for antepartum and postpartum periods respectively. A total of 7.4 million person-years were associated with time outside pregnancy which included non-pregnant time periods for women experiencing at least one pregnancy and the whole period of observation for women with no recorded pregnancy during the study period. The median follow up time for each woman was 3.2 (IQR= 1.2 - 6.5) years.

Figure 2-2: Basic characteristics of the study population



2.3.2 VTE Case Confirmation

Figure 2-3 presents the total number of cases confirmed using different sources of validation. There was a total of 4,456 potential cases of VTE identified during the study period of which only 59% (2,668) were confirmed by the definition in Section 2.2.8 and met my criteria for an outcome event. Of the total cases confirmed, the majority (95%) were validated by a prescription of anticoagulants (80% warfarin and related drugs and 15% heparin) within 90 days of the event. An additional 3% of the cases were confirmed by medical codes for anticoagulant therapy for heparin or warfarin recorded within 90 days of the VTE event. Around 1% of additional VTE cases were confirmed by death recorded within 30 days of the event, the majority of which followed a PE event.

Table 2-2 presents the number of confirmed cases at different times during antepartum and postpartum periods by mode of confirmation. More than half of the antepartum VTEs were confirmed by a heparin prescription, with the highest proportions confirmed by heparin in the first and second trimesters. However in the postpartum 84% of the cases were confirmed by warfarin or related drugs whereas only 12% were confirmed by heparin. Other sources of confirmation including deaths and anticoagulant clinics codes were responsible for only a small number of additional case confirmations.

Figure 2-3: Number of cases confirmed using different sources of validation presented in a hierarchical manner

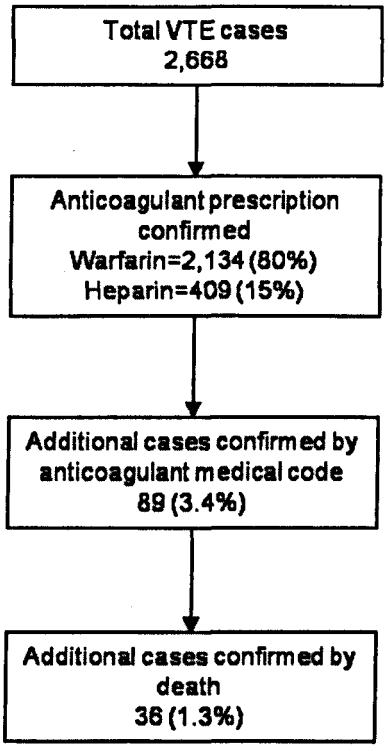


Table 2-2: Number of cases confirmed in specific time periods (number of additional cases confirmed in a hierarchical manner from left to right)

Variable	Anticoagulant prescription n(%)		Anticoagulant clinic n(%)	Death n(%)	Total n(%)
	Warfarin	Heparin			
Antepartum	49(22)	163(73)	12(5)	0 (0)	224(100)
First trimester	8 (16)	39(78)	3(6)	0(0)	50(100)
Second trimester	3(6)	40(85)	4(9)	0(0)	47(100)
Third trimester	38(30)	84(66)	5(4)	0(0)	127(100)
Postpartum	259(84)	36(12)	10(3)	1(0.3)	306(100)
Early postpartum	218(83)	33(13)	9(3)	1(0.4)	261(100)
Late postpartum	41(91)	3(7)	1(2)	0(0)	45(100)
Time outside pregnancy	1,826 (85)	210 (10)	67 (3)	35 (2)	2,138 (100)

2.3.3 Risks of VTE in pregnancy overall and by age

Table 2-3 presents the absolute rate of VTE per 100,000 person-years in and around pregnancy and outside pregnancy by age. Among all women, the rate of VTE ranged from 28 per 100,000 person years outside pregnancy (95% CI, 27-29) to 337 per 100,000 person years during the postpartum period (95% CI, 300-379). The overall rate of VTE for pregnancies resulting in live or stillbirth in and around pregnancy (including both antepartum and postpartum periods) was 146 per 100,000 person years (95% CI 134-160 per 100,000 person years). Women in the oldest age band (35-44 years) had a 38% higher rate of VTE than women aged 25-34 years during the time outside pregnancy (absolute excess risk of 0.1 per 1000 person-years). Additionally there was a 41% and 57% increased risk during antepartum and postpartum periods respectively among women aged≥35 years compared to baseline. For the time period associated with miscarriages the risk of VTE was calculated to be 35 and 126 per 100,000 person-years for antepartum and postpartum respectively. Similarly, antepartum and postpartum risks of VTE for pregnancies resulting in termination were calculated to be 41 and 178 per 100,000 person-years respectively.

Table 2-3: Rate of VTE by age and pregnancy status.

Variable	N	Rate (95%CI)	IRR (95%CI)	RD (95%CI)
Pregnancies ending in live or stillbirth				
Time outside pregnancy				
All ages	2138	28 (27-29)	-	
15-24 years	295	14 (13-16)	0.51 (0.45-0.59)	-
25-34 years	711	28 (26-30)	1.00	13 (10 to16)[¥]
35-44 years	1132	38 (36-41)	1.38 (1.26-1.52)	10 (7 to 13)[†]
Antepartum				
All ages	215	84 (73-96)	-	
15-24 years	45	73 (54-98)	0.91 (0.65-1.29)	-
25-34 years	120	79 (60-95)	1.00	6 (-19 to .3)[¥]
35-44 years	50	113 (85-148)	1.41 (1.01-1.96)	3 (-1 to 6)[†]
Postpartum				
All ages	285	337 (300-379)	-	
15-24 years	48	255 (192-339)	0.80 (0.58-1.11)	-
25-34 years	156	316 (270-370)	1.00	60 (-27 to 148)[¥]
35-44 years	81	497 (399-618)	1.57 (1.20-2.05)	180 (61 to 300)[†]
Pregnancies resulting in miscarriages				
Antepartum (all ages)	4	35 (13-95)	-	-
Postpartum (all ages)	8	126 (63-253)	-	-
Pregnancies resulting in terminations				
Antepartum (all ages)	5	41 (17-99)	-	-
Postpartum (all ages)	13	178 (103-307)	-	-

*per 100,000 person years
[¥] Increase in the risk compared to 15-25 years
[†] Increase in the risk compared to 25-34 years
IRR incidence rate ratio, CI confidence interval, VTE venous thromboembolism
RD Risk difference

2.3.4 Incidence rate ratios in and around pregnancy

Overall for pregnancies resulting in live or stillbirths a 2.9 fold (95% CI 2.53-3.36) and 11.6 fold (95% CI 10.3-13.2) increase in risk of VTE was observed during the antepartum and postpartum periods respectively compared to outside pregnancy (Table 2 4). These IRRs remained similar when stratified according to age. This was confirmed by a non-significant test for interaction between age and pregnancy status (p=0.40).

Table 2-4: Overall and age-specific Incidence Rate ratios of VTE in ante and postpartum compared to outside pregnancy

Variable	Incidence rate ratio (Unadjusted)	95%CI	Incidence rate ratio (Adjusted)	95%CI
Pregnancies resulting in live or stillbirths				
All ages				
Time outside pregnancy	1.00	-	1.00	-
Antepartum	2.9	2.54 - 3.66	2.92	2.53 - 3.36
Postpartum	11.7	10.3 - 13.3	11.6	10.3 - 13.2
15-24 years				
Time outside pregnancy	1.00	-	1.00	-
Antepartum	5.00	3.65 - 6.85	5.02	3.66 - 6.87
Postpartum	17.4	12.8 - 23.6	17.4	12.8 - 23.6
25-34 years				
Time outside pregnancy	1.00	-	1.00	-
Antepartum	2.83	2.34 - 3.44	2.82	2.33 - 3.43
Postpartum	11.2	9.46 - 13.3	11.1	9.38 - 13.2
35-44 years				
Time outside pregnancy	1.00	-	1.00	-
Antepartum	2.89	2.18 - 3.84	2.86	2.15 - 3.80
Postpartum	12.7	10.1 - 15.8	12.5	10.0 - 15.7
Pregnancies resulting in miscarriages				
All ages				
Time outside pregnancy	1.00	-	1.00	-
Antepartum	1.24	0.46 - 3.32	1.25	0.46 - 3.33
Postpartum	4.40	2.20 - 8.82	4.39	2.19 - 8.80
Pregnancies resulting in terminations				
All ages				
Time outside pregnancy	1.00	-	1.00	-
Antepartum	1.43	0.59 - 3.46	1.75	0.73 - 4.23
Postpartum	6.21	3.60 - 10.7	7.5	4.38 - 13.0

*adjusted for age and calendar year
CI confidence interval

2.3.5 Risks by trimester and weeks postpartum

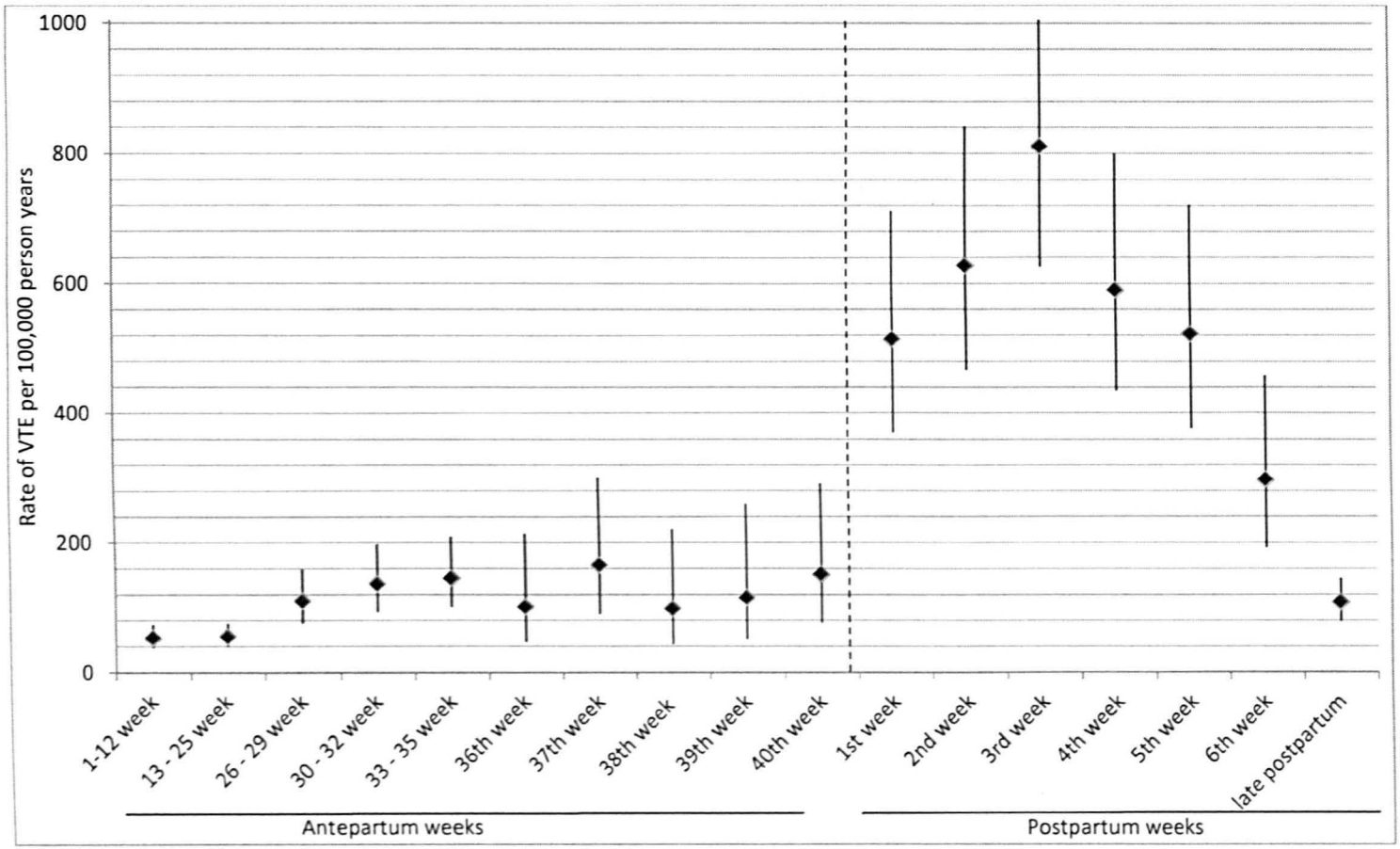
Absolute rates of VTE were roughly similar in the first and second trimester with incidence rates of 53 and 55 per 100,000 person years respectively (Table 2-5). The rate of VTE was higher in the third trimester (133 per 100,000 person-years; 5-fold increase in risk) and peaked in the early postpartum period (561 per 100,000 person years; 20-fold increase in risk compared to time outside pregnancy). The rate of VTE was also slightly high in the late postpartum period with an absolute rate of 108 per 100,000 person-years (3-fold increased risk). Figure 2-4 shows the rate of VTE per 100,000 person-years by weeks of antepartum and postpartum time showing that the rate of VTE is much higher in the first five weeks postpartum compared to the weeks immediately preceding delivery. However, the rate of VTE sharply declined from the fifth week onwards in the postpartum period.

Table 2-5: Rate of VTE per 100,000 person years during different time periods of pregnancy and postpartum (live or stillbirths) compared to time outside pregnancy

Variable	Rate (95%CI)	IRR (95% CI) (unadjusted)	IRR (95% CI) (Adjusted)*
Outside pregnancy	28 (27-29)	1.00	1.00
Antepartum			
First trimester	53 (39-72)	1.86 (1.36-2.53)	2.01 (1.47-2.74)
Second trimester	55 (41-74)	1.94 (1.45-2.59)	2.08 (1.55-2.77)
Third trimester	133 (112-159)	4.65 (3.89-5.56)	4.95 (4.13-5.93)
Postpartum			
Early postpartum	561 (494-636)	19.5 (17.1-22.3)	20.6 (18.0-23.6)
Late postpartum	108 (80-144)	3.76 (2.80-5.06)	3.95 (2.93-5.31)

*Adjusted for age and calendar year
CI: Confidence interval

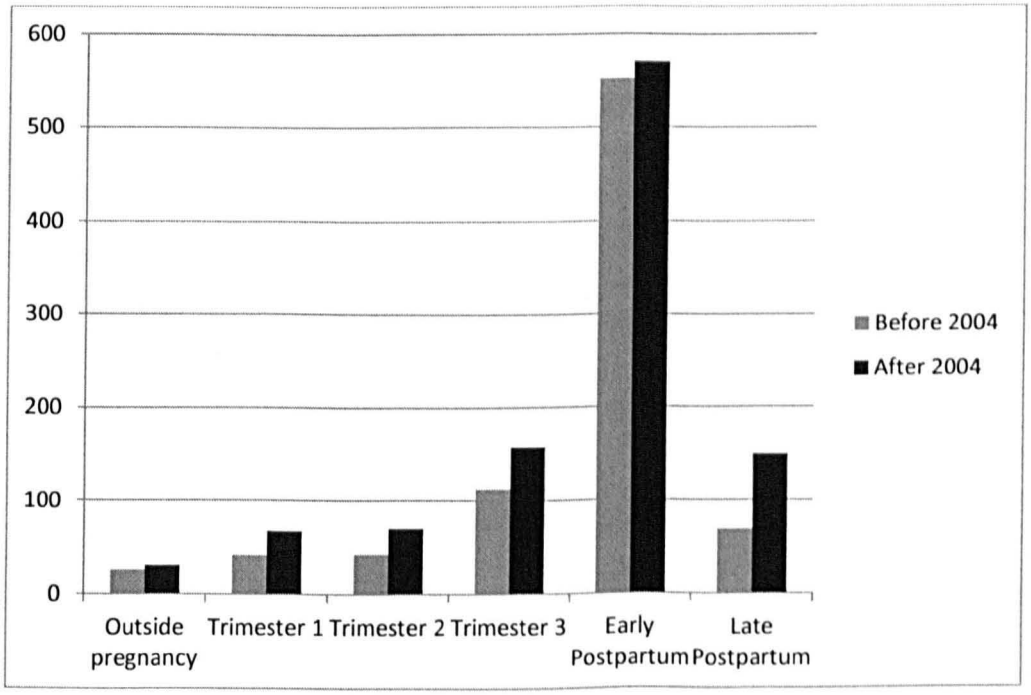
Figure 2-4 Rate of venous thromboembolism per 100,000 person-years in weeks of antepartum and postpartum (live or stillbirths only)



2.3.6 Rate of VTE stratified by calendar year

Figure 2-5 presents the overall rate of VTE at different time periods around pregnancy and outside pregnancy before and after 2004. Overall, the rate of VTE remained roughly similar for outside pregnancy and the three trimesters of antepartum when stratified by calendar year. However the rate of VTE more than doubled in the late postpartum from 69 per 100,000 person years (95%CI 33-99) before 2004 to 149 per 100,000 person years (95% CI 89-190) after 2004. However this difference was not statistically significant.

Figure 2-5: Rate of VTE stratified by calendar year (pregnancies of women resulting in live or stillbirths only)



2.3.7 Sensitivity analysis

2.3.7.1 Rate of VTE using restrictive definition (pregnancies of women resulting in live or stillbirths only)

Around 84% of VTE cases were confirmed based on warfarin or related drugs (Fondaparinux, Lepiradin, Phenidione and Acenocoumarol) prescribed in primary care or a medical code indicating anticoagulant therapy within 90 days of the event occurring or death within 30 days of the event. For those events that occurred in the 1st and 2nd trimester this proportion was far lower (7 of 88= 8%) increasing to 33% in the third trimester and 87% in the postpartum. Therefore my results remained broadly unchanged during time outside pregnancy, third trimester of antepartum and postpartum when using this restricted definition (Table 2-6). However my calculated estimates were much lower in the 1st and 2nd trimesters corresponding to the absolute rates of 5 and 3 per 100,000 person-years respectively.

Table 2-6 Rate and rate ratio of VTE using restrictive definition (pregnancies of women resulting in live or stillbirths only)

Time period	N	Rate (95%CI)	IRR (95%CI)
Time outside pregnancy	1904	25 (24-26)	1.00
Antepartum overall	49	19 (14-25)	0.81 (0.61-1.07)
Trimester 1	4	5 (1-13)	0.22 (0.08-0.59)
Trimester 2	3	3 (1-11)	0.15 (0.04-0.46)
Trimester 3	42	44 (32-59)	1.85 (1.36-2.51)
Postpartum overall	248	293 (259-332)	12.2 (10.6-13.9)
Early postpartum	206	481 (420-552)	20.0 (17.3-23.2)
Week 1	32	445 (314-629)	18.6 (13.1-26.4)
Week 2	37	515 (373-711)	21.5 (15.5-29.8)
Week 3	45	629 (470-843)	26.2 (19.5-35.3)
Week 4	37	520 (366-704)	21.6 (15.6-30.0)
Week 5	36	508 (366-704)	21.1 (15.2-29.4)
Week 6	19	262 (171-422)	11.2 (7.12-17.6)
Late postpartum	42	100 (74-136)	4.18 (1.00-1.18)

2.3.7.2 Incidence rate ratio stratified by calendar year

The rate of VTE slightly increased after 2004 for both antepartum and postpartum periods (Table 2-7). The absolute rate increased from 66 per 100,000 person-years before 2004 to 96 per 100,000 person years after 2004 for antepartum. Similarly, for postpartum, the absolute rate was calculated to be 291 per 100,000 person years and 334 per 100,000 person years for before and after 2004 respectively. However the relative increase in the risk for antepartum and postpartum periods compared to outside pregnancy remained roughly similar when stratified by calendar year as rates outside of pregnancy also increased over this time period.

Table 2-7: Rate and rate ratios stratified by calendar year (pregnancies of women resulting in live or stillbirths only)

Time period	N	Rate (95%CI)	IRR (95%CI)
	Before 2004		
Time outside pregnancy	1085	26 (24-28)	1.00
Antepartum (overall)	100	66 (54-80)	2.73 (2.22-3.36)
Postpartum (overall)	148	291 (248-343)	11.9 (9.99-14.1)
	After 2004		
Time outside pregnancy	1053	31 (29-33)	1.00
Antepartum (overall)	124	96 (81-115)	3.26 (2.27-3.96)
Postpartum (overall)	158	334 (285-390)	11.2 (9.46-13.2)

2.3.7.3 Only restricting analysis to pulmonary embolism

Table 2-8 presents the absolute and relative risk of PE during different time periods of antepartum and postpartum compared to outside pregnancy. Around 36% of VTEs were categorized as PE based on medical codes. Of the 65 PE cases diagnosed during the antepartum period 62% occurred during the third trimester. The absolute rate of PE was lower in the first and second trimester. During the third trimester and early postpartum period the relative risk increased to 4.1 fold (95% CI 3.0-5.7) and 21.4 fold (95%CI 17.2-26.7) respectively compared to time outside pregnancy.

Table 2-8 Absolute rate and incidence rate ratios of PE per 100,000 person-years in different time period of pregnancy and outside pregnancy

Time period	N	Rate (95%CI)	IRR (95%CI)
Time outside pregnancy	789	10 (9-11)	1.00
Antepartum overall	65	25 (19-32)	2.53 (1.96-3.27)
Trimester 1	14	18 (10-30)	1.80 (1.06-3.07)
Trimester 2	11	13 (7-23)	1.28 (0.70-2.33)
Trimester 3	40	42 (30-57)	4.13 (3.00-5.69)
Postpartum overall	104	123 (101-149)	12.0 (9.8-14.8)
Early postpartum	93	217 (177-266)	21.4 (17.2-26.7)
Week 1	14	194 (115-328)	19.2 (11.3-32.7)
Week 2	16	223 (136-364)	22.0 (13.4-36.2)
Week 3	19	265 (196-419)	26.8 (16.9-41.5)
Week 4	21	295 (169-419)	29.2 (18.8-45.0)
Week 5	13	183 (106-316)	18.0 (10.4-31.3)
Week 6	10	141 (7-114)	13.9 (7.47-26.0)
Late postpartum	11	26 (14-47)	2.59 (1.42-4.70)

2.4 Discussion

2.4.1 Main findings

Using data from a large population-based cohort, I found a relatively low rate of first VTE in pregnancy; however, this rate was still much higher than that seen in the time outside pregnancy, with a noticeably raised risk in the first five weeks postpartum. During the antepartum period, women in their third trimester were at a 5 fold increased risk of first VTE compared to their time outside pregnancy whereas in the first and second trimester this rate was only marginally higher. It was also found women aged≥35 years were 41% (absolute risk=0.1%) and 57% (absolute risk 0.5%) more likely to develop VTE compared to those aged 25-24 years during antepartum and postpartum periods respectively. These findings are generalisable to the majority of pregnant women who have not had a prior VTE providing valuable information to accurately assess the risk of VTE and the potential need for prophylaxis.

2.4.2 Strengths and limitations

This study used information from approximately 1.7 million women aged between 15 and 44 to accurately determine the absolute and relative risks of first VTE within specific antepartum and postpartum periods in a contemporary, population-based manner. It used an open cohort approach to the analysis that calculated the rate of VTE in pregnancy taking account of time varying risk periods using person-years as the denominator. This method adjusted for differences in the duration of antepartum and postpartum periods unlike traditional approaches (using number of pregnancies as the denominator) which assume that the time women spend in antepartum and postpartum periods is similar. Furthermore it also enabled me to capture the time period outside pregnancy and make appropriate

unbiased comparisons of these rates with those in the antepartum and postpartum periods.

An important strength of this study is its population-based nature with a large sample size in a nationally representative population which makes the estimates more generalisable and precise. A limitation to this generalisability is the exclusion of pregnancies not resulting in live births or stillbirth from my subsequent trimester analysis due to lack of precise information on length of gestation. However I believe that the effect of those exclusions on estimates is likely to be small as only 30 VTE events were associated with miscarriages/terminations. Our higher rate of VTE in the third trimester contradicts with the CMACE reports that have consistently highlighted higher proportions of deaths in the first trimester of the antepartum. However the case fatality associated with VTE is rare (case fatality of 0.2-3%). It is also important to consider that my study aim was to look at the incidence of VTE which included both fatal and non fatal VTE events as opposed to CMACE reports which are only based on only few fatal VTE events (3 deaths between 2006-2008) resulting in death (mortality rates). In my study population there were only 14 deaths which occurred during the antepartum period of which 4 occurred during the first trimester. Even assuming that all those deaths during the first trimester were due to VTE, the incidence of VTE increased only slightly (57 versus 53 per 100,000 person-years).

Another potential weakness of this study is the use of anonymised patient records with no direct access to individual patients. I was therefore dependent on the physicians for accurate recording of diagnoses. However, a large proportion of practices in THIN also contribute to a similar database, the Clinical Practice Research Datalink, that has been extensively used for

research and the definition of VTE I used has been previously validated in this database.[85]

My comparisons to time outside pregnancy need to be interpreted with the understanding that some of the non-pregnant women will be taking the combined oral contraceptive which is known to increase VTE risk.[88] However, trying to characterise periods of oral contraceptive use within the non-pregnant time was beyond the scope of the present work. Furthermore in the UK, women may get oral contraceptive from other sources other than GPs (e.g. family planning clinics), so exposure maybe misclassified in these data. Finally, the absolute rate of VTE was lower in the present study during the period outside pregnancy than in those from Denmark and the U.S.A.[31, 37] The definition of VTE used in the present study was found to have a positive predictive value of 84% when validated among women of childbearing age in the CPRD. Such validation however does not give an indication of the negative predictive value (or sensitivity), and I cannot ignore the potential for my absolute rates of VTE to be underestimated if some anticoagulant prescriptions emanated from secondary rather than primary care. Regardless of the limitations highlighted above, Huerta et al. reported an age and sex standardised incidence rate of VTE in the general population using the GPRD which was similar to that observed in other Western studies, when using an identical VTE definition to that of the present analysis.[4] Another potential limitation is the lack of cause of death information in my data. Deaths occurring within one month of VTE were automatically assumed to be VTE related which may not be true. However, the impact of this limitation is small as only 1% of total VTE cases were confirmed based on death alone. It is also worth stating that all VTE events occurring within one month of the start of study period were excluded. This was based on the high incidence rate in the first month following registration with the practice. It may be argued whether

a 1 month cut off was sufficient to exclude prevalent cases as women are more likely to join a practice when they are pregnant or planning to be pregnant. However my sensitivity analysis demonstrated that even excluding 6 and 12 month periods following registration did not alter the pattern of my derived estimates.

The ability to identify the use of either heparin or warfarin in primary care allows a greater level of detail than previous studies. When a restricted case definition was applied by including only cases with evidence of therapeutic anticoagulant use (i.e. excluding any potential use of prophylactic heparin) it was found that the absolute rates of VTE were drastically reduced in the 1st and 2nd trimester but not so much in the 3rd trimester or in the postpartum period. Given that heparin is the treatment of choice in pregnancy this is not surprising but means that the estimated rates may actually be too low in the sensitivity analysis as I would have certainly removed VTE cases that were receiving heparin as treatment rather than prophylaxis. Nonetheless the overall interpretation of my results did not alter.

The lack of detailed information on the diagnosis of VTE in primary care data restricted my ability to assess severity of the disease. This could potentially lead to over diagnosis of VTE among pregnant women. Similarly the increased risk in the third trimester could also be the result of frequent GP visits during that time. However my sensitivity analysis showed that despite this rates of VTE have increased in pregnant and postpartum women over time yet the relative increase compared to the time outside pregnancy has remained fairly constant. Furthermore, the relative increase in risk during different time periods of antepartum and postpartum also remained unchanged when I restricted my analysis only to PE where over-diagnosis would seem less likely. It is also important to note that ascertainment bias is not just about the

exposure to health professionals but also about their specific concerns regarding VTE which is not possible to measure in these data. Higher rates of VTE during the postpartum might be mediated by certain complications associated with pregnancy or other co-morbidities. However I did not look at risk factors for VTE as it was beyond the scope of the current study. Secondly, hospitalization increases the risk of VTE[70] which I was not able to take into account in this study.

2.4.3 Comparison to other studies

My absolute rates are slightly higher than those reported previously using the same primary care database up to 2004.[36] This may be due to better case ascertainment over the years. However, the updated incidence rate ratios are broadly similar for both antepartum and postpartum periods to what they were in the earlier analysis. Apart from that, only three previous studies have compared rates of VTE in pregnancy with those outside of pregnancy.[31, 37, 78] Recently, Virkus et al.[37] reported absolute and relative risks of VTE within individual trimesters of antepartum and weeks of early postpartum among Danish women which were similar to those in the present study. However, their rates were higher in the late third trimester suggesting that the risk of VTE in that period is similar to that immediately following childbirth in contrast to our results. This contradictory finding could potentially be due to lack of precise dates of VTE diagnosis. The use of date of admission as the date of diagnosis by Virkus et al. might have shifted the distribution of VTE event to the left so that events which occurred in the 1-2 weeks following delivery were recorded as taking place just before delivery. This could account for why in the current study the incidence of VTE in the weekly intervals immediately following delivery were noticeably higher than the weeks preceding delivery, unlike in the Danish study. My findings were also

broadly similar to those reported in a population-based cohort in Olmsted County in the United States.[31] However, their considerably smaller sample size (50,080 live births and 105 VTE events occurring around pregnancy), meant that there was insufficient power to rigorously compare risks in each trimester or in individual weeks postpartum with time outside pregnancy or by age strata. [89] Finally Pomp et al.[79] in their case-control study reported a 5 and 60-fold increased risk of VTE during the antepartum and postpartum periods respectively compared to non-pregnant. However the lower proportion of controls (1.2% compared with an expected 2.2%) in first three months postpartum in their study may have resulted in the overestimation of odds ratio during the postpartum period. Finally, convenience sampling was used to recruit controls which somewhat limits the generalisability of their study findings.

2.4.4 Conclusion and implications for clinicians

Whilst guidelines issued in 2004 on the prevention of VTE around pregnancy could possibly have contributed to a reduction in the number of maternal deaths from VTE recently reported in the United Kingdom[8], there is still considerable morbidity associated with VTE, which further targeted prophylaxis could effectively reduce. In the current analysis I demonstrated high absolute risks of VTE in the third trimester and first 5 weeks postpartum, whereas during the first two trimesters and late postpartum periods the risks were only marginally higher compared to time outside pregnancy. Furthermore, when comparing women aged 35 and over to the majority of pregnant women I found only a small excess absolute risk of VTE during the antenatal and postnatal periods.

I believe my results have important implications for the way in which thromboprophylaxis is delivered in the health care settings of developed nations and would hope that they will aid the targeting of such prophylaxis in three ways. Firstly, my observation that the highest rates of VTE occur mainly within 5 weeks postpartum suggests that giving thromboprophylaxis in those considered at high risk for this length of time may be appropriate. Secondly, I have found that the risk in the first and second trimester is not greatly increased for those women without previous VTE compared with time outside pregnancy. Therefore, initiation of prophylaxis where it is needed could potentially be delayed until the start of the third trimester thus, avoiding any adverse effects of low molecular weight heparin and prolonged antenatal use in some women. Finally, current clinical guidelines often include age [21], i.e. being ≥35 years old, as an independent risk factor for VTE. My results imply that the absolute excess risk in postpartum women 35 years or older compared to the majority of postpartum women is of the order of 1.8 per 1000 person years. If we assume that thromboprophylaxis is 100% effective at preventing VTE then my results imply that to prevent one excess VTE occurring in this age group we would need to give prophylaxis to approximately 556 women. Overall this study provides new evidence that will aid the ability of clinicians to judge when women are at highest risk of VTE during and immediately after pregnancy. Therefore these findings should influence the development of updated thromboprophylaxis guidelines and impact on the delivery of care to pregnant women across the developed world.

3 Risk factors for first venous thromboembolism around pregnancy: A population based cohort study from the United Kingdom

This chapter sets out to determine how risks of antepartum and postpartum VTE are modified by established and newly identified risk factors. It uses the same computerized primary care data (THIN) and covers both risk factors mentioned in the current RCOG guidelines for thromboprophylaxis during pregnancy along with some additional variables highlighted from previous studies. The following study has been published from this work.[90]

3.1 Introduction

Overall, there is disagreement and inconsistency regarding the characteristics that put women at higher risk of developing a first VTE during pregnancy or postpartum combined with a lack of data about the relative impact of those risk factors with respect to the absolute risk of VTE. For example, existing estimates of the increase in risk of VTE among pregnant women with high BMI (≥30 kg/m^2) compared to those with normal BMI range from 1.5-fold to 5.3-fold higher during antepartum and postpartum periods[7, 12, 41, 55]. Similar inconsistencies surround women's demographic risk factors (e.g. maternal age), comorbidities (such as diabetes) and possible pregnancy complications (e.g. mode of delivery, obstetric haemorrhage and other complications)[7, 10-12, 43, 44, 50, 53, 55] particularly since many studies have inappropriately assumed that these risk factors impact similarly on occurrence of VTE in antepartum and postpartum periods.[7, 12, 50, 55] Of the studies that have separately assessed antepartum and postpartum VTE risks,[10, 41, 43, 44, 53] most have used a case-control design or relied on cross-sectional analysis of hospital discharge records based on risk factor information recorded around the time of delivery. Neither of these enables estimation of absolute risks of VTE based

on recognized risk factors over the entire period of gestation and immediately following childbirth.

3.1.1.1 Justification and aim

The current Royal College of Obstetricians and Gynaecologists (RCOG)[21] and American College of Chest Physicians (ACCP)[64] guidelines on obstetric thromboprophylaxis are based on suboptimal information to distinguish between women who are at low and high risk. Therefore the aim of this study was to determine population level absolute and relative risks of VTE according to women's pre-existing and pregnancy-related factors in both antepartum and postpartum periods, with the primary objective of allowing targeted provision of obstetric thromboprophylaxis. Secondly, I aimed to estimate specific absolute risks of VTE for women categorised as having low, intermediate and high risk pregnancies according to the UK's RCOG guidelines on who should receive prophylaxis.

3.2 Method

3.2.1 Study population

The study population for this study was obtained from THIN. All incident pregnancies ending in live birth or stillbirth for women aged 15-44 years who contributed data to THIN between January 1995 and July 2009 were identified. Pregnancies of women with previous VTE were excluded regardless of whether those events were diagnosed during or outside pregnancy. Therefore, where women developed a VTE in one pregnancy, person-time resulting from subsequent pregnancies was ignored. The pregnancy-related person time for each woman during the study period was divided into antepartum (from the date of conception to the pregnancy outcome) and postpartum (up to 12 weeks following the pregnancy outcome). The database is described in more detail in section 2.2.7.

3.2.2 Defining incident VTE

All first VTE events including deep vein thrombosis (DVT) and pulmonary embolism (PE) experienced by women (excluding superficial VTE) were identified during the study period. VTE cases and person time occurring within one month of the study start date were excluded to ensure only incident cases were retained. VTE cases were defined using methods similar to those previously described in chapter 2 (Section 2.2.8).

3.2.3 Defining risk factors

3.2.3.1 Basic characteristics

Previous studies have found maternal age, smoking status and body mass index to be associated with an increased risk of VTE during pregnancy (Table 1-4). Therefore information on those characteristics was extracted using Read codes. Maternal age was defined as a time varying covariate and was assessed in three equal sized categories (15-24, 25-34 and 35-44 years). BMI and smoking status was defined as follows;

3.2.3.1.1 Body mass index

High BMI is associated with an increased risk of VTE in pregnancy.[10, 12, 43] For this purpose, weight and height information from the additional health information file and medical codes relating to BMI (e.g. Body Mass Index >30 – Obese) were extracted for all pregnant women with live births/stillbirths. BMI was categorized using the World Health Organization categorization: normal (18.5 – 24.9 kg/m^2), underweight (<18.5 Kg/m^2), overweight (25.0 – 29.9 Kg/m^2), and obese (≥30 kg/m^2). Women with no BMI data recorded at any time where they were contributing data were placed in a missing category so that they can be included in the analysis. A BMI value was assigned to each pregnancy using the most recent record before conception. The Read codes used to extract BMI information are presented as Appendix 8

3.2.3.1.2 Smoking status

There is also evidence suggesting that the risk of VTE is affected by cigarette smoking[44, 50] Smoking status for each pregnancy was extracted from additional health data relating to smoking and medical records. Women were categorized as "cigarette smoker" or "non-smoker" (included current and ex-

smokers) using the most recent smoking related code before the pregnancy outcome. Although this categorization of smoking might create some misclassification, current smoking recording in the general practice data is reasonably well recorded.[91] Codes used to extract information on smoking are presented in Appendix 9. Women with no information on smoking before a respective pregnancy were categorized as a non-smoker.

3.2.3.2 Pregnancy related characteristics and complications

Pregnancy related factors considered were mode of delivery, birth outcome (live or stillborn child), length of gestation, multiple gestation and number of previous births. Pregnancy complications (including eclampsia/pre-eclampsia, haemorrhage, diabetes and hypertension) were extracted using Read medical codes if recorded during the pregnancy/postpartum period. The Read codes used to extract obstetric haemorrhage and eclampsia/preeclampsia are summarised in Appendix 10 and Appendix 11

3.2.3.2.1 Gestational diabetes

Women were defined as having gestational diabetes if they had a Read code specifying "gestational diabetes" during pregnancy. Women were also considered as having gestational diabetes if they had a first record of type 1, type 2 or non-specific diabetes recorded during pregnancy with no prior prescriptions for oral hypoglycaemics or insulin.

3.2.3.2.2 Gestational hypertension

Women were defined as having gestational hypertension if they had a Read code specifying gestational hypertension during pregnancy. Women were also considered as having gestational hypertension if they had a first record of

hypertension recorded during pregnancy or had 3 or more readings of high blood pressure (systolic>140 with/or diastolic>90) with no prior prescriptions for oral antihypertensive medication documented before the index pregnancy.

3.2.3.2.3 Acute systemic infection

I also separately investigated two common acute infections: urinary tract infection and acute respiratory tract infection (including pneumonia, acute bronchitis, chest infection and influenza) during pregnancy because of their increased risk associated with VTE.[68, 92] The Read codes used to extract information on acute respiratory tract infection and urinary tract infection are summarised in Appendix 12 and Appendix 13 respectively.

3.2.3.2.4 Mode of delivery

For each pregnancy resulting in live or stillbirth, mode of delivery was assigned. This was categorised as spontaneous vaginal delivery, assisted delivery or caesarean (elective or emergency). For women with no information on mode of delivery were assumed to have undergone spontaneous vaginal delivery.

3.2.3.3 Medical co-morbidities

Information on important co-morbidities was extracted based on previous literature and the current RCOG guideline on thromboprophylaxis.[21] Women were defined as having a relevant medical co-morbidity if they had ever been diagnosed with cancer, systemic lupus erythematosus (SLE), nephrotic syndrome, varicose veins, inflammatory bowel disease (IBD) or cardiac disease (including congestive cardiac disease, coronary artery disease, congenital heart disease, cardiomyopathy, angina or myocardial infarction)

during or prior to pregnancy. Finally pregnant women were defined as having pre-existing diabetes or pre-existing hypertension using combinations of Read and prescription codes (excluding Read codes for gestational hypertension and gestational diabetes) for such conditions if they were recorded before conception. The Read codes used to extract cancer information were similar to those we have used previously for research into VTE among cancer patients,[93] which included 2,548 codes for various cancer types (available on request). The Read codes used to obtain information on IBD, nephrotic syndrome, varicose veins, SLE and cardiac disease are summarised in Appendix 14.

3.2.4 Statistical analyses

3.2.4.1 Risk factor analysis

Absolute rates (AR) of VTE per 100,000 person-years were obtained by dividing the total number of events by the person-years of follow-up. To assess how these risks varied according to the women's risk factors I calculated ARs per 100,000 person-years for each category of variables relating to maternal characteristics (e.g. maternal age category), pregnancy-related characteristics and complications (e.g. each mode of delivery, obstetric haemorrhage etc.), and medical comorbidities (e.g. varicose veins, cardiac disease etc). Values of each risk factor (other than age) were assumed to be fixed for the whole pregnancy regardless of whether it was recorded during or before pregnancy. For factors relating to labour or the puerperium (e.g. mode of delivery) ARs were estimated only for the postpartum period. Incident rate ratios (IRR) of VTE associated with each risk factor were calculated using Poisson regression models and were adjusted for maternal age, body mass index, smoking status and number of previous births (Model 1), which were selected on the basis of previous literature.

Additionally risk factors that were associated with an increased risk of VTE in the initial antepartum and postpartum analyses were included in a separate model (Model 2). As pregnancies are not independent events, a clustering term was fitted in all models to account for women experiencing more than one pregnancy during the study period.

3.2.4.2 Integration of UKs of RCOG guidelines for thromboprophylaxis

Current UK RCOG guidelines for thromboprophylaxis during pregnancy and postpartum use a set of recognised clinical factors to categorise pregnant women as low, intermediate or high risk to guide which women are offered hydration/mobilization and which are offered low molecular weight heparin (LMWH) as thromboprophylaxis[21]. The absolute rates of VTE were calculated using the number of pregnancies as the denominator in this instance. This was done for each factor in isolation where possible. For instance, the value for age≥35 years in block 3 (in Figure 3-1), is the rate per 100,000 pregnancies for women with no other risk factors as these would receive mobilisation and hydration if this risk factor occurred in isolation. Additionally I incorporated factors from my initial analysis that are not currently in the RCOG guideline but were highlighted in either the existing literature or this study (including pre-existing diabetes, stillbirth and preterm birth), which were placed in intermediate or high risk groups based on their AR of VTE in this study. To ensure reasonable precision, I only calculated ARs for pregnancies where ≥5 VTE events occurred among women with the risk factor. For this reason the following medical co-morbidities; SLE, cancer, nephrotic syndrome, cardiac disease and IBD, were grouped together as current guidelines indicate that women with any one of these risk factors should be considered for prophylaxis. Pregnancies complicated by medical co-

morbidities where there were no VTE events (e.g. nephrotic syndrome) during the antepartum and/or postpartum period, were still included in the analysis so as to contribute to the denominator for calculating the incidence rate for VTE, but these were not investigated individually. Also, high BMI (≥30kg/m^2) was separated into obese (BMI≥30 Kg/m^2 & BMI<40Kg/m^2) and class 3 obese (BMI≥40Kg/m^2) whereas acute respiratory tract and urinary tract infections were collectively assessed as stated in the current thromboprophylaxis guideline[21]. All analyses were carried out using Stata SE11.

3.2.4.3 Power calculation

The current study was sufficiently powered such that for a relatively rare risk factor which affects 1% of all pregnancies we had greater than 90% power to detect a 2-fold increase (IRR=2) in risk of VTE in both antenatal and postpartum periods separately.

3.3 Results

3.3.1 Basic characteristics of study population

There were a total of 376,154 pregnancies resulting in live or stillbirths occurring among 280,451 women. Women's basic characteristics for each pregnancy are summarized in Table 3-1. The total person-years associated with the antepartum and postpartum periods were 255,947 and 84,370 respectively. The overall incidence of VTE during antepartum and postpartum period was calculated to be 84 and 337 per 100,000 person-years respectively (as fully described in chapter 2 results).

Table 3-1: Basic characteristics of women for each pregnancy

Variables	Pregnancies (N=376,154 in 280,451 women)	Percentage
Maternal characteristics		
Body mass index		
Normal (18.5-24.9)	164,883	43.8
underweight(<18.5)	12,309	3.3
overweight(25-29.9)	66,068	17.5
obese(≥30)	38,101	10.2
Missing	94,793	25.2
Cigarette smoking	88,617	23.5
Pregnancy related characteristics & complication		
Birth outcome		
Live birth	375,002	99.7
Stillbirth	1,152	0.3
Mode of delivery		
Spontaneous delivery	294,426	78.3
Caesarean	58,109	15.5
Assisted delivery	23,619	6.3
Previous number of births		
None	213,697	56.8
1	116,351	30.9
2	33,819	8.9
3 or more	12,287	3.4
Multiple gestation	6,251	1.7
Preterm delivery (<37 weeks)	26,528	7.1
Eclampsia/pre-eclampsia	1,897	0.5
Obstetric haemorrhage	4,607	1.2
Gestational hypertension	6,294	1.7
Gestational diabetes	2,656	0.7
Acute respiratory tract infection in pregnancy	12,980	2.4
Urinary tract infection in pregnancy	30,765	8.1

Table 3-1: Basic characteristics of women for each pregnancy (continued..)

Variables	Pregnancies (N=376,154 in 280,451 women)	Percentage
Medical co-morbidities		
Pre-existing diabetes	4,022	1.0
Pre-existing hypertension	11,718	3.1
Varicose veins	8,373	2.2
Nephrotic syndrome	214	0.06
Systemic lupus erythematosus	188	0.05
Cancer	5,012	1.3
Inflammatory bowel disease	1,472	0.3
Cardiac disease	354	0.09

3.3.2 Risk factors for VTE during the antepartum period

The relative risk of antepartum VTE was only marginally higher for women aged≥35 years, BMI≥30Kg/m^2, and cigarette smoker corresponding to a 42%, 50% and 15% increased risk compared to their respective baselines (Table 3-2). Of pregnancy related characteristics and complications only urinary tract infection was found to be significantly associated with an increased risk of VTE (88% increase in risk) at the 5% level. However, medical co-morbidities including pre-existing diabetes, recording of varicose veins and IBD (but not pre-existing hypertension or cancer) were all associated with significantly higher rates of VTE, with absolute rates ranging from 216 (varicose veins) to 288 (IBD) per 100,000 person-years. These remained largely unchanged when mutually adjusted for other risk factors associated with an increased risk of antepartum VTE (Model 2).

Table 3-2: Absolute and relative rates of VTE by risk factors in the antepartum period

Variable	Events	Rate[1]	IRR[2] (Model 1)	IRR[3] (Model 2)
		Maternal characteristics		
Maternal age				
15 – 24	45	73 (54-98)	0.87 (0.61-1.24)	0.89 (0.62-1.27)
25 – 34	120	79 (66-95)	1.00	1.00
35 – 44	50	112 (85-148)	1.42 (1.01-1.93)	1.40 (0.99-1.96)
Body mass index				
Underweight (<18.5 kg/m^2)	3	34 (11-1074)	0.48 (0.15-1.54)	0.48 (0.15-1.53)
Normal (18.5-24.9)	86	73 (59-90)	1.00	1.00
Overweight (25-29.9)	49	103 (75-136)	1.41 (0.99-2.00)	1.40 (0.98-2.00)
Obese (≥30)	30	109 (76-156)	1.50 (0.99-2.28)	1.40 (0.90-2.16)
No BMI recorded before conception	47	85 (63-113)	1.18 (0.82-1.71)	1.16 (0.85-1.69)
Cigarette smokers	55	89 (68-116)	1.15 (0.83-1.58)	1.16 (0.84-1.60)

[1] Absolute rate calculated as per 100,000 person-years. [2](Model 1) Adjusted for age, parity, BMI and smoking status when not stratified by them. [3](Model 2) Adjusted for age, parity, BMI, pre-existing diabetes, IBD, varicose veins, acute systemic infection and smoking status when not stratified by them. [4]Incidence rate ratio (IRR) compared to women without risk factor under study.

Table 3-2: Absolute and relative rates of VTE by risk factors in the antepartum period (continued..)

Variable	Events	Rate[1]	IRR[2] (Model 1)	IRR[3] (Model 2)
Pregnancy associated characteristics and complication[4]				
Previous births				
None	127	90 (75-107)	1.00	1.00
1	60	72 (56-93)	0.76 (0.56-1.03)	0.72 (0.53-0.98)
2	19	78 (50-123)	0.79 (0.49-1.28)	0.71 (0.43-1.16)
3 or more	9	103 (53-198)	0.97 (0.48-1.93)	0.89 (0.45-1.78)
Multiple gestation	3	73 (23-227)	0.83 (0.26-2.61)	0.83 (0.26-2.60)
Eclampsia/pre-eclampsia	0	-	-	-
Gestational hypertension	4	95 (35-254)	1.01 (0.37-2.76)	0.99 (0.36-2.72)
Gestational diabetes	3	165 (53-514)	1.71 (0.54-5.41)	*
Acute respiratory tract infection	13	142 (82-245)	1.70 (0.97-2.99)	1.65 (0.94-2.90)
Urinary tract infection	31	145 (102-206)	1.88 (1.28-2.77)	1.80 (1.22-2.67)

[1] Absolute rate calculated as per 100,000 person-years. [2](Model 1) Adjusted for age, parity, BMI and smoking status when not stratified by them. [3](Model 2) Adjusted for age, parity, BMI, pre-existing diabetes, IBD, varicose veins, acute systemic infection and smoking status when not stratified by them. [4]Incidence rate ratio (IRR) compared to women without risk factor under study.

Table 3-2: Absolute and relative rates of VTE by risk factors in the antepartum period (continued..)

Variable	Events	Rate[1]	IRR[2] (Model 1)	IRR[3] (Model 2)
		Medical co-morbidities[4]		
Pre-existing diabetes	8	282 (141-565)	3.08 (1.42-6.39)	3.54 (1.13-11.0)
Pre-existing hypertension	7	82 (39-173)	0.90 (0.42-1.94)	0.74 (0.32-1.71)
Varicose veins	13	216 (125-373)	2.69 (1.53-4.70)	2.21 (1.55-4.76)
Nephrotic syndrome	0	-	-	-
Systemic lupus erythematosus	0	-	-	-
Cancer	6	169 (76-373)	1.97 (0.87-4.44)	1.95 (0.86-4.41)
Inflammatory bowel disease	3	288 (93-895)	3.46 (1.11-10.7)	3.50 (1.12-10.9)
Cardiac disease	0	-	-	-

[1] Absolute rate calculated as per 100,000 person-years. [2](Model 1) Adjusted for age, parity, BMI and smoking status when not stratified by them. [3](Model 2) Adjusted for age, parity, BMI, pre-existing diabetes, IBD, varicose veins, acute systemic infection and smoking status when not stratified by them. [4]Incidence rate ratio (IRR) compared to women without risk factor under study.

3.3.3 Risk factors for VTE during the postpartum period

In the postpartum period, a 4-fold increased risk of VTE in women with BMI≥30Kg/m^2 (Incidence rate ratio (IRR)=3.75 95% CI 2.76-5.07) compared to those with normal BMI (Table 3-3) was observed. However, the rate of VTE was only moderately higher for other maternal characteristics, including age≥35 years and current smoking, when compared with baseline. For pregnancy related characteristics and complications I found a 2-fold or greater increase in the rate of VTE compared to baseline for those with caesarean section delivery, 3 or more previous births, obstetric haemorrhage, and pre-term (<37 weeks) delivery (ARs ranging between 637-963 per 100,000 person-years). Pregnancy ending in stillbirth was associated with a 6-fold increase in the rate of VTE compared with a live birth outcome (AR=2444) with rates associated with medical co-morbidities (including varicose veins, IBD and cardiac disease) ranging from 113 to 2374 VTEs per 100,000 person-years. When all risk factors associated with an increased risk of VTE were fitted together (Model 2) the calculated estimates remained broadly similar.

Table 3-3: Absolute and relative rates of VTE by risk factors in the postpartum period

Variable	Events	Rate[1]	IRR[2] (Model 1)	IRR[3] (Model 2)
Maternal characteristics				
Maternal age (years)				
15 – 24	48	255 (192-339)	0.80 (0.57-1.12)	0.86 (0.62-1.00)
25 – 34	156	316 (270-370)	1.00	1.00
35 – 44	81	497 (399-618)	1.51 (1.15-1.98)	1.37 (1.23-3.01)
Body mass Index				
Underweight (<18.5 kg/m^2)	4	145 (54-386)	0.63 (0.23-1.71)	0.61 (0.22-1.67)
Normal (18.5-24.9)	88	237 (192-292)	1.00	1.00
Overweight (25-29.9)	48	324 (244-429))	1.33 (0.93-1.89)	1.29 (0.90-1.83)
Obese (≥30)	79	926 (742-1554)	3.75 (2.76-5.08)	3.45 (2.54-4.69)
No BMI recorded before conception	66	305 (239-390)	1.40 (1.01-1.92)	1.46 (1.06-2.01)
Current smokers	80	403 (324-504)	1.31 (1.01-1.71)	1.30 (1.00-1.69)

[1] Rate calculated as per 100,000 person-years. [2] (Model 1) Adjusted for age, parity, BMI and smoking status when not stratified by them. . [3] (Model 2) Adjusted for age, parity, BMI, mode of delivery, pregnancy length, obstetric haemorrhage, varicose veins, IBD, cardiac disease and smoking status when not stratified by them. [4]Incidence rate ratio (IRR) compared to women without risk factor under study.

Table 3-3: Absolute and relative rates of VTE by risk factors in the postpartum period (continued..)

Variable	Events	Rate[1]	IRR[2] (Model 1)	IRR[3] (Model 2)
Pregnancy related characteristics and complication[4]				
Mode of delivery				
Spontaneous	186	281 (243-325)	1.00	1.00
Assisted	16	302 (185-494)	1.18 (0.70-1.99)	1.22 (0.73-2.06)
Caesarean	83	637 (513-790)	1.99 (1.52-2.58)	1.88 (1.44-2.45)
No of previous live births				
None	152	318 (271-373)	1.00	1.00
1	75	285 (228-358)	0.81 (0.61-1.08)	0.82 (0.62-1.09)
2	33	432 (307-608)	1.13 (0.77-1.66)	1.08 (0.73-1.60)
3 or more	25	904 (611-608)	2.07 (1.34-3.20)	1.92 (1.22-2.99)
Stillbirth	6	2444 (109-5440)	6.24 (2.77-14.1)	4.07 (1.73-9.56)
Multiple gestation	7	491 (234-1030)	1.39 (0.65-2.93)	0.94 (0.43-2.07)
Pre-term birth	51	854 (649-1124)	2.69 (1.99-3.65)	2.28 (1.66-3.14)
Pre-eclampsia/eclampsia	3	705 (227-2188)	1.84 (0.59-5.78)	1.17 (0.36-3.77)
Obstetric haemorrhage	10	963 (518-1791)	2.89 (1.53-5.43)	2.53 (1.34-4.79)
Gestational diabetes	6	1013 (455-2255)	1.97 (0.87-4.45)	1.68 (0.74-3.82)
Gestational hypertension	10	705 (379-1311)	1.63 (0.85-3.12)	1.49 (0.78-2.84)
Acute respiratory tract infection	18	617 (389-980)	1.65 (1.02-2.66)	1.56 (0.97-2.53)
Urinary tract infection	27	391 (268-571)	1.15 (0.77-1.71)	1.06 (0.71-1.58)

[1] Rate calculated as per 100,000 person-years. [2] (Model 1) Adjusted for age, parity, BMI and smoking status when not stratified by them. . [3] (Model 2) Adjusted for age, parity, BMI, mode of delivery, pregnancy length, obstetric haemorrhage, varicose veins, IBD, cardiac disease and smoking status when not stratified by them. [4]Incidence rate ratio (IRR) compared to women without risk factor under study.

Table 3-3: Absolute and relative rates of VTE by risk factors in the postpartum period (continued..)

Variable	Events	Rate[1]	IRR[2] (Model 1)	IRR[3] (Model 2)
Medical co-morbidities[4]				
Pre-existing diabetes	4	445 (167-1186)	0.88 (0.33-2.38)	0.69 (0.25-1.85)
Pre-existing hypertension	3	113 (36-353)	0.25 (0.81-0.79)	0.22 (0.71-0.68)
Varicose veins	25	1330 (899-1969)	3.83 (2.51-5.82)	3.90 (2.56-5.93)
Nephrotic syndrome	0	-	-	-
Systemic lupus erythematosus	1	2374 (344-16856)	6.69 (0.95-47.0)	5.40 (0.76-38.3)
Cancer	5	446 (185-1073)	1.21 (0.49-2.96)	1.14 (0.46-2.79)
Inflammatory bowel disease	5	1514 (630-3638)	4.56 (1.88-11.0)	4.07 (1.73-9.57)
Cardiac disease	2	2258 (646-10335)	6.58 (1.63-26.5)	5.30 (1.30-21.5)

[1] Rate calculated as per 100,000 person-years. [2] (Model 1) Adjusted for age, parity, BMI and smoking status when not stratified by them. . [3] (Model 2) Adjusted for age, parity, BMI, mode of delivery, pregnancy length, obstetric haemorrhage, varicose veins, IBD, cardiac disease and smoking status when not stratified by them. [4]Incidence rate ratio (IRR) compared to women without risk factor under study.

3.3.4 Risk of VTE per 100,000 pregnancies according to the UK's RCOG guideline

Figure 3-1 and Figure 3-2 contain the risk factors currently listed in the RCOG guideline[21] for antepartum and postpartum thromboprophylaxis with the addition of pre-existing diabetes (antepartum), stillbirth and pre-term birth (both postpartum only). It was found that among women who were classed as being at intermediate risk for antepartum VTE on the basis of a single risk factor the highest risk of VTE was 180/100,000 pregnancies for women with pre-existing diabetes (Figure 3-1). Postpartum, women with a BMI≥40Kg/m^2 had a higher risk of VTE (AR=221/100,000 pregnancies) than those women with any other single intermediate risk factor (pre-term birth, prior medical co-morbidities, caesarean section delivery and haemorrhage) (Figure 3-2). Of factors currently used to classify women as low risk for postpartum VTE if occurring in isolation (i.e. those who are offered non-pharmacological thromboprophylaxis including early mobilization and hydration), high risks of VTE were observed for women with a BMI between 30 and 40 Kg/m^2 (AR=143/100,000 pregnancies) and varicose veins (188/100,000 pregnancies) in the absence of other risk factors. The risk of VTE, however, in the postpartum following stillbirth was calculated to be 0.5% which was higher than any other risk factor.

Figure 3-1: Rate of VTE per 100,000 pregnancies during the antepartum according to the national guideline.[21]

Obstetric thromboprophylaxis risk assessment and management guidelines

Block 1 (High risk factors)
×-Single previous VTE+ Thrombophilia
Unprovoked previous VTE
×-previous recurrent VTE (>1)

→ **Antenatal thromboprophylaxis with LMWH**
No data from current study

Block 2
Intermediate risk factors
×-Single previous VTE with no family history or thrombophilia
x-Thrombophilia + no VTE
√-Medical co-morbidities (SLE, Cancer, IBD, cardiac disease or nephrotic syndrome)
×-Sickle cell
×-Intravenous drug users
×-Surgical procedure
◇-Pre-existing diabetes

→ **Any 1 Factor (may be accompanied by other risk factors in block 3 but not block 2)**
Antenatal thromboprophylaxis with LMWH

Variable	Events	Rate (95% CI)
Medical co-morbidities	9	130 (72-371)
Pre-existing diabetes	7	180 (72-371)
Any 1 risk factor	18	165 (97-260)

Block 3
Low risk factors
√-Age ≥35
√-Obese BMI≥30Kg/m²
√-Previous births≥3
√-Cigarette smokers
√-Eclampsia/preeclampsia
√-Acute systemic infection
√-Varicose veins
×-Any surgical procedure
×-Prolong labour (>24 hours)
×-Mid-cavity rotational operation
×-Immobility
×-Dehydration
√-Multiple pregnancy

→ **≥2 factors with no other risk factors in block 1 and 2**
Antenatal thromboprophylaxis with LMWH

Variable	Events	Rate (95%CI)
Two or more risk factors	47	95 (69-125)

→ **1 factor with no other risk factors in block 2 and 3**
Mobilisation and hydration

Variable	Events	Rate (95%CI)
Age ≥35	23	70 (44-104)
BMI≥30	7	42 (16-85)
Previous births≥3	3	92 (18-268)
Cigarette smokers	24	44 (27-64)
Varicose veins	5	149 (48-346)
Acute systemic infection	13	65 (24-11)
Any one risk factor	75	55 (43-69)
No risk factors	73	41 (32-51)

Key
√Factor is included in the current thromboprophylaxis guideline and in current study analysis
×Factor is included in the current thromboprophylaxis guideline but not included in the current study analysis
◇Factor is included in the study analysis but is not in the current thromboprophylaxis guidelines
LMWH= Low molecular weight heparin

Figure 3-2: Rate of VTE per 100,000 pregnancies during the postpartum according to the national guideline[21]

Obstetric thromboprophylaxis risk assessment and management guidelines

Block 1 (High risk factors)
◇-Still births
×-Previous VTE
×-Antenatal VTE

Factor may be accompanied by other risk factors in block 2 and 3
6 weeks postnatal thromboprophylaxis

Variable	Events	Rate (95%CI)
Stillbirths	6	523 (192-1135)

Block 2
Intermediate risk factors
√-Caesarean section delivery[1]
√-Very obeseBMI≥40Kg/m^2
x-Thrombophilia
◇-Preterm birth
√-Medical co-morbidities (SLE, Cancer, IBD, cardiac disease or nephrotic syndrome)
√-Obstetric Haemorrhage
×-Surgical procedures
×-Intravenous drug users
×-Sickle cell disease
×-Prolonged hospital admission

Any 1 Factor (may be accompanied by other risk factors in block 3 but not block 1 or 2)
7 days postnatal thromboprophylaxis with LMWH

Variable	Events	Rate (95% CI)
Caesarean section	49	101 (75-134)
BMI ≥ 40Kg/m2	6	221 (81-481)
Medical co-morbidities	7	137 (55-282)
Premature birth	22	121 (76-184)
Haemorrhage	5	154 (50-361)

Block 3
Low risk factors
√-Age ≥35
√-Obese (BMI≥30Kg/m^2 & BMI<40Kg/m^2)
√-Previous births≥3
√-Cigarette smokers
√-Eclampsia/preeclampsia
√-Acute systemic infection
√-Varicose veins
×-Any surgical procedure
×-Prolong labour (>24 hours)
×-Mid-cavity rotational operation
×-Immobility

≥2 factors with no other risk factors in block 1 and 2
7 days postnatal thromboprophylaxis with LMWH

Variable	Events	Rate (95%CI)
Two or more risk factors	41	111 (80-151)

1 factor with no other risk factors in block 1, 2 and 3
Hydration and mobilisation

Variable	Events	Rate (95%CI)
Age ≥35	14	44 (24-75)
BMI≥30 & <40Kg/m^2	16	143 (82-233)
Previous births≥3	2	78 (9-284)
Cigarette smokers	17	38 (22-61)
Varicose veins	5	188 (61-440)
Acute systemic infection	5	32 (10-75)
Any one risk factor	61	56 (43-72)
No risk factors	51	36 (26-47)

Key
√Factor is included in the current thromboprophylaxis guideline and in current study analysis
×Factor is included in the current thromboprophylaxis guideline but not included in the current study analysis
◇Factor is included in the study analysis but is not in the current thromboprophylaxis guidelines
[1]Includes elective and emergency caesarean section
LMWH= Low molecular weight heparin

3.4 Discussion

3.4.1 Main finding

In this large nationally-representative cohort of almost 400,000 pregnancies, I have provided population based estimates of the absolute and relative risks of VTE in women during and immediately after pregnancy, combining their socio-demographic, lifestyle and clinical risk factors to better inform targeting of thromboprophylaxis. I have demonstrated that except for pre-existing diabetes, risk factors have a greater impact in the postpartum period in terms of influencing the absolute risk of VTE than the antepartum period. It was also found that women with stillbirths, obstetric haemorrhage, high BMI, preterm birth, prior co-morbidities (IBD and cardiac disease) and caesarean section delivery have higher risk of VTE postpartum. In contrast, cigarette smoking, maternal age ≥35 years, acute infection and number of previous births were only moderately associated with VTE in both antepartum and postpartum periods.

3.4.2 Strength and limitations

The use of nationally representative data not only makes my study findings generalisable to the majority of the pregnant women in the UK, i.e. those who have not had a prior VTE but also provides information on risk factors for VTE in a contemporary and population based manner. Most previous studies have relied on cross-sectional analyses of hospital discharge records collected around the time of delivery,[7, 10, 12] were unable to separate first from subsequent VTE[7, 10, 44] or relied on retrospective recall of risk factor information[11, 53, 55]. In contrast, my open cohort approach to analysis and prospective nature of data recording enabled me to look at the impact of

existing and pregnancy related risk factors on the incidence and relative risk of VTE separately for antepartum and postpartum time periods.

A potential limitation of this study is the lack of validation studies of obstetric complications in the current dataset and the scarcity of national UK or international data estimating the true prevalence of obstetric complications in the general population. Whilst all major medical events in secondary care should be recorded in the general practice notes, minor complications that are well managed in hospital may not be recorded in primary care data. For instance the estimated prevalence of obstetric haemorrhage ranges from 2% to 8% with the prevalence of severe haemorrhage estimated to be between 0.01 and 1.86%.[94-96] I found a prevalence of 1% in the present study which indicates my cases are more likely to represent severe haemorrhage (same may be the case for gestational hypertension and pre-eclampsia).

I also acknowledge that certain risk factors including mild to moderate pre-eclampsia might not always get reported in the hospital discharge summaries which are sent to general practitioners thus underestimating their prevalence[51, 61, 97, 98]. In particular, residual confounding caused by the under ascertainment of pre-eclampsia could have accounted for some of the postpartum effect observed for stillbirths and pre-term births. However around 50% of stillbirths are unexplained[62]. Furthermore the prevalence of caesarean section in the current study (15%) was lower than expected (24%) which may have underestimated my estimates for that risk factor. I was also not able to assess certain parameters including mother's ethnicity and fertility treatments which may often be associated with increased risk of VTE. However, I believe that the following should be considered. Firstly, 91%[99] of the UK population are white which I believe would have limited the impact of confounding by race on our estimates. Additionally, a case-control study from

the UK showed no association between antenatal PE and ethnicity.[11] Secondly, the overall reporting of fertility problems in the UK using primary care data[100] is reported to be 0.5% per annum with an infertility treatment rate of 0.1% per annum. Moreover, the actual number of women conceiving after treatment may be even lower, although I was not able to evaluate this in the current data. This depicts the limited scope of this variable to modify my conclusions from these data. My finding of low absolute and relative rate of VTE observed among cigarette smokers should be interpreted with caution as we did not evaluate the amount of cigarette smoked.

A few other aspects of our data are worthy of note. The current data relied on BMI measured prior to pregnancy in line with most existing research; however, one previous study found that weight gain during pregnancy was a more important predictor of VTE risk[53], something which I was unable to assess. My finding of a high risk of VTE in those with a prior diagnosis of varicose veins should also be interpreted with caution as it may potentially be a consequence of a past unrecorded or concurrent deep vein thrombosis. Finally, I was not able to assess thrombophilia as a potential risk factor in our study. However a diagnosis of thrombophilia cannot be used to predict VTE as an outcome as routine thrombophilia screening is not recommended for pregnant women.

It may be argued that my estimates do not take into account the number of pregnant women already on thromboprophylaxis prior to a VTE event. Although I excluded women with prior history of VTE from our study, It was found that 0.4% of pregnant women without VTE received heparin/LMWH prescribed by a general practitioner during antepartum/postpartum period (which were included in the analysis) which may be due to certain clinical risk factors as suggested in the current RCOG guideline. This however is certainly

an underestimate as I was unable to look at thromboprophylaxis prescriptions emanating from secondary care where prophylaxis around the time of delivery is most likely to occur. I believe though that the impact of this would be small as the first national RCOG guidelines for antenatal thromboprophylaxis were only published in 2004 with an updated version published in 2009.

In the light of this fact I calculated the risk of VTE during pregnancy and postpartum pre- and post-2004 which showed no statistical difference in the postpartum and a 46% (statistically significant) increase in the risk of VTE post 2004 in the antepartum period suggesting minimal impact of the national guidelines on the incidence of VTE. I should also emphasise that assessing the effectiveness of the current national guidelines for obstetric thromboprophylaxis is beyond the scope of this study. One way of assessing this could be calculating the number needed to treat (NNT) and number needed to harm (NNH) from the current data. For instance, if we were to assume that prophylaxis reduces the risk of VTE by 50% as has been reported in trials outside of pregnancy[101], then based on my estimate of the absolute risk, 89 VTE events could be prevented per year in women whose pregnancies end in caesarean mode of delivery (NNT=1980). These values should be interpreted with caution as they are based on speculative data regarding the reduction in risk resulting from LMWH from which there is an absence of RCT data in pregnant women. Also, the absolute risk difference upon which the NNTs are estimated assumes causality which may not also be true.

3.4.3 Comparison to previous studies

My observed relative increases in the risk (more than 2-fold) of VTE in those with preterm birth, obstetric haemorrhage, caesarean section, stillbirth and varicose veins compared to women without those respective risk factors are of roughly similar magnitude to those reported in other studies[7, 10, 12, 44, 53, 55, 56]. I believe that the strong association between VTE events and stillbirths is a finding of real importance which has received only limited attention to date.[56] My finding of low relative increases in the risk of VTE among women over age 35 years, current smokers and those with high BMI during the antepartum period are also in concordance with previous studies.[10, 12, 44]

3.4.4 Conclusion and clinical implications

My overall results may have important implications for the way obstetric thromboprophylaxis is delivered in the health care settings of developed countries and I hope that they will aid the targeting of such prophylaxis in three ways. Firstly, I found an increased risk of VTE among pregnancies of women with preterm birth or stillbirth, factors which have received limited consideration to date and are not currently incorporated into the guidelines for risk assessment of VTE. If they did then thrombotic events associated with those risk factors could potentially be prevented. Secondly, the current data support many of the existing national RCOG guideline recommendations (in terms of high absolute rates), especially that postpartum thromboprophylaxis may be indicated in women with very high BMI (≥40 kg/m^2), those who have prior co-morbidities, obstetric haemorrhage or who have a caesarean section delivery. Thirdly, my results showed a high risk of VTE in women with BMI between 30 and 40 kg/m^2 or varicose veins even if these risk factors occur in isolation which may require careful consideration. The recommendation on whether thromboprophylaxis with LMWH may be effective in pregnant and

postpartum women with specific risk factors will of course be highly dependent on the risk reduction from prophylaxis, for which there is a noticeable void of data from pregnant women. Another important consideration is the costs involved in prophylaxis both financial and also the tolerability surrounding a daily heparin prescription not to mention the well-recognised side effects of allergy and bleeding. For instance, the benefits would need to be weighed against a risk of major haemorrhage which is believed to occur in 1% of pregnant women[64] and for which we showed a 2.5-fold associated risk with VTE. Such a risk-benefit analysis clearly goes beyond the scope of the present work; however, I believe my presentation of population-based risks of VTE based on a number of established risk factors goes some way to help clinicians involved in making decisions in this area. In summary, my analysis provides new and interesting observations on absolute rates of VTE across a range of risk factor categories. It provides valuable information to clinicians for better decision making in terms of identifying high risk pregnant and postpartum women who may require some form of thromboprophylaxis.

4 Defining the incidence of venous thromboembolism in and around pregnancy using linked primary and secondary care data: A population based cohort study and comparative meta-analysis

Using data from primary care (chapter 2 and chapter 3) I was able to look at the incidence of VTE during the antepartum and postpartum and compare it to the time outside pregnancy. I found that the risk of VTE is particularly high during the third trimester of antepartum and early postpartum corresponding to a 5-fold and 21-fold increased risk respectively compared to time outside pregnancy. Furthermore, I also found that the high risk of VTE extends beyond the first week of postpartum. THIN also gave me the opportunity to look at some of the risk factors for VTE both during pregnancy and following childbirth. It was observed that postpartum, the strongest association with VTE was with stillbirth followed by medical co-morbidities (including women with varicose veins, inflammatory bowel disease (IBD) or cardiac disease), BMI≥30kg/m^2, obstetric haemorrhage, preterm delivery, and caesarean section (ARs=637/100,000 person-years or higher). Antepartum, only varicose veins, IBD, acute systemic infection and pre-existing diabetes were associated with a higher risk of VTE. Despite the fact that THIN gave me the opportunity to answer important clinical questions and for the first time provide population level estimates of absolute and relative risk, there are some fundamental issues with only using primary care data which are worth stating. Firstly, the under-ascertainment of some of the risk factors in THIN may have inevitably biased estimates (i.e. differential or non-differential bias resulting from miss-classification of the risk factors). Moreover the strong association observed for stillbirth and preterm birth with postpartum VTE may have been confounded by pre-eclampsia/eclampsia to a certain extent due to

the underestimated prevalence of pre-eclampsia/eclampsia. For instance if we consider HES maternity statistics as the gold standard information on pregnancy in the UK, then the prevalence of pregnancy associated characteristics and complications previously reported in THIN was much lower (Table 4-1). Secondly the incidence of VTE in individual weeks of the postpartum (Figure 2-4) gives the impression that the rate of VTE peaks in the third week and that the high risk of VTE extends well beyond the first four weeks, thus lengthening the duration of time for prophylaxis that may needed to be offered following delivery. However in reality it might be that the recording of VTE from secondary care is delayed and thus this pattern may be incorrect. This also restricted my ability to look at the impact of certain risk factors on the incidence of VTE during the specific postpartum periods. Moreover, this delay in recording from secondary to primary care may also cause misclassification between antepartum and postpartum VTE around the time of delivery leading to low and high absolute rate of VTE for antepartum and postpartum respectively. Lastly, some of the VTE events from the secondary care might not always get recorded in primary care thus leading to underestimation of incidence in all or certain exposure periods. Therefore in the following chapters I report results from a series of studies utilising linked primary and secondary care data to help circumvent some of these limitations. This study has not been accepted for publication and is currently in press.

Table 4-1: Prevalence of risk factors in THIN versus the expected prevalence

Variables	THIN	HES maternity[61]
Mode of delivery		
Spontaneous delivery	78.3	64.9
Caesarean overall	15.5	23.5
Elective caesarean	Not well recorded	√
Emergency caesarean	Not well recorded	√
Assisted delivery	6.3	11.5
Haemorrhage		
Antepartum haemorrhage	0.6	7.6
Postpartum haemorrhage	0.6	8.8
Stillbirth	0.3	0.5
Multiple gestation	1.7	1.4
Preterm delivery (<37 weeks)	7.1	7.7
Eclampsia/pre-eclampsia	0.5	2.4
Gestational hypertension*	1.7	5.0
Gestational diabetes*	0.7	1.1
Hospitalisation	-	√
Duration of hospitalisation	-	√

√Information on risk factor present, -Information not present
*Also depends on the definition selected

4.1 Background

Venous thromboembolism (VTE) is a serious complication of pregnancy, however due to the low incidence of pregnancy related VTEs and uncertainties over risk factors, prospective studies are unlikely to be done because of prohibitive costs. Therefore, to study its occurrence and risk factors, studies using routine data have been used as they provide sufficient power and population coverage to give robust and generalisable estimates.[33, 37] The recent linkage of electronic primary data in the Clinical Practice Research Datalink (CPRD) with the secondary care English Hospital Episode Statistics database (HES) may be useful in providing valuable information on maternal risk factors for VTE including hospitalisation, life style related factors and co-morbidities. However, there have been no studies done using these linked data to quantify the incidence of VTE in and around pregnancy. Furthermore no studies have assessed the disparities between the results from secondary and primary care data in a standalone fashion versus when used together. Additionally, defining VTE may be a concern as currently there have been no studies done to validate VTE in linked primary and secondary data. Whilst VTE has been previously validated in primary care data in non-pregnant women with a positive predictive value (PPV) of 84%,[85] it is important to assess whether secondary care data add any further information on VTE events around pregnancy especially in the United Kingdom where almost all women deliver in hospital. For instance, the previous validation study does not give an indication of the negative predictive value and we cannot ignore the potential for the incidence of VTE recorded in primary care to be underestimated if certain VTE cases are solely recorded in secondary care. Further validation is also required to assess potential false positive diagnoses in the peripartum period.

4.2 Study justification and aim

One way of assessing clinical information captured on VTE during antepartum and postpartum periods is to compare estimates of VTE incidence with previous studies. However to-date, there has not been any formal data synthesis of these previous studies nor an attempt at providing pooled estimates of the incidence of VTE during the antepartum and postpartum periods. The aim of this study was therefore, twofold: to use linked primary and secondary care data to determine an optimum definition for estimating the incidence of first VTE in and around pregnancy; and secondly to conduct a systematic literature review of studies on perinatal VTE incidence with the purpose of comparison with my estimates.

4.3 Method

4.3.1 Data source used

For the purpose of current study and those presented in chapters 5 and 6, following datasets was used;

4.3.1.1 Clinical practice research datalink

The Clinical Practice Research Datalink (CPRD)[102] formerly known as The GPRD is a computerized primary health care database containing demographic, medical, prescription and lifestyle related information from anonymised patients across the United Kingdom. This database is similar to the previously used THIN database in terms of data recording and validation and uses the same Vision software. It contains data from 613 practices with a total of 12.4 million patients. Overall the database is split into ten files each of which can be merged using a unique patient identifier.

4.3.1.1.1 Data quality[103]

CPRD has historically undertaken a set of internal data quality measurements in an effort to ensure high quality data within a subset of UK practices. These are done on both a practice and patient level. The practice level quality check is recognised by the "up to standard" (UTS) date and the patient quality level by the patient acceptability flag. Patients in the CPRD are categorised as "acceptable" for research by a process that allows the exclusion of patients with questionable validity. The UTS date ensures that the data provided by a particular practice is of research quality. It is based on two central concepts. Firstly, the practice mortality rate must be within an acceptable range. This ensures that data provided for patients who have died; death is being recorded and is a marker for irregularities in practice. Secondly, it ensures that there is continuity in the data recording within a practice. CPRD is used

extensively for research and has been validated for several health outcomes.[104, 105] For example a systematic review by Herrett et al. found the overall median accuracy of the diagnosis in CPRD for a wide range of disease group (including circulatory and respiratory diseases) to be 89%.[104]

4.3.1.1.2 Date information in CPRD

A patient file is also accompanied by first registration date, current registration date and transfer out date. The first registration date is the date when a patient is first registered with the practice. If patient only has 'temporary' records then this is the date of their first encounter with the practice. If the patient has 'permanent' records it is the date of the first 'permanent' record (excludes preceding temporary records). The current registration date is the date the patient's current period of registration with the practice began. If there are no 'transferred out periods', then this is the same as the first registration date. If there are 'transferred out periods' then it is the date of the first 'permanent' record after the latest transferred out period. Finally the transfer out date is the date when a patient is transferred out of a practice, if relevant. It is empty for patients who have not transferred out. The work presented in this thesis is restricted to women with permanent records.

4.3.1.2 Hospital episode statistics

The Hospital episode statistics (HES)[106] database contains details of all admissions to NHS hospitals in England. These also include private patients and those resident outside England who were treated at an NHS hospital as well as care delivered by treatment centres funded by the NHS. It contains demographic data along with the information on discharge diagnoses and procedures which are coded using ICD-10 and OPCS-4 respectively. All diagnoses within hospitalisation periods are presented in the form of episodes which are categorised as primary; the main condition treated or investigated, or secondary; not the main condition investigated or treated. Each episode may have multiple diagnoses whereas each hospitalisation period may have multiple episodes. The version of HES used for this study contained admitted patient care data on approximately 2.3 million patients. Broadly the data structure of HES can be categorized as patient, hospitalization, diagnosis, critical care, source and maternity. The key information contained within each file is summarized as Table 4-2. All files can be linked together by a unique patient identifier.

Table 4-2: Overview of data structure of HES

File name	Information contained
Source	Acceptable patients in CPRD which are eligible for HES linkages
Patient	Demographic, registration with HES information
Hospitalization	Hospitalization dates, duration and method of admission
Diagnosis	Medical history and diagnoses by hospitalization and episode[1]
Critical care	Days in critical care and life support
Maternity	Birth outcome, mode of delivery, length of gestation and multiple birth

4.3.1.3 HES maternity

HES maternity contains data on all births which take place in England and aims to include those taking place at home and in non-NHS hospitals as well as the majority of births that take place in NHS hospitals. The vital information contained in HES maternity includes, antenatal and postnatal hospital stay, mode of delivery, place of delivery length of gestation and birth outcome (live or still). Most patients admitted to hospital are categorized as general inpatient; even women admitted to hospitals with the clear intention of birth will be classified as a general admission. However, as soon a women has given birth it becomes a maternity record and is updated in HES maternity. There are two types of maternity records in HES; the delivery record and birth record. The delivery record is the HES record for the mother. It contains the same data as a general record but has a baby tail for information about the baby. The birth record is the HES record for the baby and again has the same format as general record, but it also has a baby tail containing same information recorded in the corresponding tail of the delivery record. Delivery and birth episodes in HES can either be consultant episodes or midwife episodes, depending on who has responsibility for the patient. For the purposes of this study I only looked at the delivery record. As HES maternity data (a subset of HES) is the primary source of maternity statistics in England, more than 90% of its delivery records and 80% of its baby records could be linked to birth registration and NHS Number for Babies (NN4B) dataset.[107] Furthermore, information found in HES maternity data such as birth outcome, baby weight and baby gender is also in good concordance with those data.

4.3.1.4 Linkage

The anonymised patient identifiers from CPRD were linked to HES from 1997 onwards. This was done by a trusted third party using NHS number, date of

birth and gender. As only English hospitals are covered in HES, practices from Northern Island, Wales and Scotland are excluded. At the time of the study 51.3% of the CPRD practices were linked to HES all of which are in England. The CPRD does not use a set sampling approach to for its linkage with secondary care HES data. It is based on practices that have consented to be linked to HES in CPRD. However all patients within a consented practice are included. Additionally, the comparison of CPRD-HES linked data to Office for National Statistics (ONS) data showing the age distribution of the UK population has demonstrated marked similarities between the two data sources.[108]

4.3.2 Study population

The study time period was defined between 1997 and 2010 during which potentially fertile women between the ages of 15 and 44 year registered within the CPRD-HES linked practices were identified. The study start date was defined as the latest date of patient's registration with practice, the first day of April 1997, the date on which the practice became up to standard and the date of woman's 15th birthday. The end date of the study was defined as the earliest date of transfer out date, date of death, first day of October 2010 and the date of the woman's 45th birthday.

4.3.3 Defining pregnancy and birth outcome

In order to identify birth episodes and birth outcomes, HES maternity data were used. Information on birth outcome (including live birth and stillbirth) was identified using the mother's delivery record. For instances where birth outcome was not specified in the HES maternity data, it was identified using ICD-10 codes for live and still births (Appendix 15) from the hospital diagnosis file in HES. HES also has information on pregnancy terminations

and miscarriages for which women had an inpatient hospital stay, however these are not classified in HES maternity data. Since many of these outcomes will not result in hospital stay, miscarriages and terminations are less well captured at population level and were thus not assessed in my study here.

4.3.4 Multiple births

All live or still births were categorized as singleton, twins or triplets or more. However the baby tail coverage is not complete as the rest of HES and there are a number of quality issues, for instance trusts submitting information on a higher number of delivery episodes (mother record) with no information on birth episodes (baby record), can cause concerns when identifying multiple births. In order to minimize the impact of this issue information on multiple births was also extracted from the ICD-10 codes (Appendix 15). A woman was said to have multiple births if there was ICD-10 code indicating multiple births. However if a woman had no ICD-10 code for multiple birth but had valid information on more than one infant in the birth tail (valid birth outcome or valid birth weight), she was still considered to have multiple births. Initially birth outcome for all multiple gestations was defined as live (if all infants were born alive), still birth (if all infants were still born) or live with still birth. However due to a low number of multiple gestations resulting in both live and stillbirth (0.03%), this category was ignored. Therefore in this study I only included pregnancies with multiple births only if all pregnancy outcomes were live births or stillbirths.

4.3.5 Generating the date of delivery

Primarily the date of delivery was extracted from the mother's HES maternity record. Date of delivery was also extracted from the OPCS-4 codes which suggested a valid delivery method (eg. emergency caesarean section), or

method used to facilitate delivery (eg. episiotomy). These are presented in Appendix 16. For women with no date of delivery, the start date of the delivery episode was considered as the date of delivery.

4.3.6 Date of conception

The date of conception was defined by subtracting the length of gestation from the date of delivery. For pregnancies with no information on the length of gestation specified in HES maternity, ICD-10 codes for length of gestation were extracted. Those with an ICD-10 code for "pre-term birth" (ICD-10 code=O60) during the delivery related hospitalisation were assigned gestation length of 36 weeks whereas those with "prolonged pregnancy" codes (ICD-10 code=048) were labelled as having a gestational length of 43 weeks. All remaining pregnancies resulting in live or stillbirth with no information on length of gestation in HES maternity or ICD-10 codes for pregnancy length (33% of pregnancies) were assigned an estimated length of gestation of 40 weeks. This corresponds to that for the median gestation length of pregnant women in the NHS's maternity statistics for England.[109]

4.3.7 Defining Venous thromboembolism

VTE diagnosis codes (including pulmonary embolism and deep vein thrombosis) were extracted from women's primary care data using medical Read codes. From HES, all women with an ICD-10 code of venous thromboembolism including pulmonary embolism (I26.0, I26.9), deep vein thrombosis (I80.1-I80.9) and portal vein thrombosis (I82.0-I82.9) were extracted. ICD-10 codes for VTE specifically related to pregnancy or postpartum (O22.2, O22.3, O87.1, O87.0, O08.2 and O88.2) were also extracted. Information from either or both primary and secondary care data sources was used to define a VTE event and the first VTE diagnosis recorded

in either data source was considered as the incident date. I assessed only the first recorded VTE during the study period and all subsequent VTEs were excluded. I then developed the following three VTE definitions;

Definition A: My most stringent definition included only VTE diagnoses supported by prescription or evidence of anticoagulant therapy (with either warfarin, unfractionated heparin or low molecular weight heparin) within 90 days of the event or death within 30 days of the event. Given the restricted use of oral anticoagulants (e.g. warfarin) during the antepartum period due to its teratogenicity, the majority of cases during the antepartum period were confirmed based on heparin prescriptions.

Definition B: This consisted of cases where signs or symptoms of DVT (e.g. leg pain, calf pain), PE (e.g. chest pain, shortness of breath) or diagnostic tests for VTE (e.g. D-dimer, Ventilation-Perfusion (VQ) scan, Computed Tomography (CT)-scan, venography) had been recorded between 15 days before and 15 days after a first recorded diagnosis of VTE, but there was no evidence of anticoagulant therapy. Cases were also included if they had VTE diagnoses in both primary and secondary care up to 60 days apart, a cut-off based on the initial examination of the recording of VTE in both datasets and prior work others have published on identifying acute medical events in linked data.[110, 111]

Definition C: This included all other diagnoses of VTE that did not fit the criteria for VTE definitions A or B. Specifically, all VTE diagnoses with no accompanying anticoagulant prescription, medical code indicating anticoagulant therapy, death, signs or symptoms of VTE, diagnostic tests for VTE. These cases were only recorded in one data source (HES or CPRD).

4.3.8 Defining exposure period

Women's follow-up time between ages 15-44 years was divided into time associated with pregnancy (defined from the date of any conceptions she had during follow-up until 12 weeks postpartum) and time outside pregnancy (all other available follow-up time, which included all time for women who were never pregnant during the study period; as previously described in Chapter 2).[36] For the purpose of this study I excluded time period associated with miscarriages and termination (from 10 weeks prior to 6 weeks following miscarriage/termination). If the VTE event was recorded during the same hospital admission as the women's delivery (which accounted for 11% of all VTE events), there was thus potential for misclassifying the timing in relation to delivery. As 91% of deliveries occurred on the day women were admitted to hospital for delivery or on the day after and the median duration of hospital stay for delivery was only 2 days, the time associated with pregnancy was divided into the antepartum period (trimesters from the date of conception until 2 days before the date of delivery), time around delivery (1 day before until 2 days after delivery) and the postpartum period (3 days after delivery until 12 weeks postpartum). The postpartum period was subdivided into individual weeks and also into early (first six weeks) and late (second six weeks) postpartum.

4.3.9 Statistical analysis

4.3.9.1 Cohort analysis

The absolute rates (AR) of VTE per 100,000 person-years and 95% confidence interval (CI) were calculated for the antepartum, time around delivery, postpartum and time outside pregnancy separately using VTE definitions A, B and C. This was done by dividing the total number of VTE events by person-years of follow-up. I then restricted the analysis to first

VTEs identified only in primary care data and then VTEs only in secondary care data to compare these with the overall estimates using both sources.

4.3.9.2 Systematic review and meta-analysis of existing VTE incidence studies

For the purpose of comparing my calculated rates to the existing literature, I systematically reviewed previous studies that have estimated VTE incidence among pregnant or postpartum women. I searched MEDLINE and Embase for studies published between January 1960 and January 2013, combining a similar search strategy to that used in a previously published VTE systematic review[29] with an adapted version of the Cochrane Pregnancy Group search strategy to obtain pregnancy studies.[30] The strategy used for MEDLINE and Embase is summarised in Appendix 1 and Appendix 2 respectively. I included studies only if they had estimated the rate of VTE in pregnant and postpartum women in a manner that allowed me to extract the data for the purposes of meta-analysis. Studies' abstracts were independently reviewed for selection by two investigators (AAS and JW) with differences resolved by consensus.

For each study included in my meta-analysis, the natural logarithm of the incidence rate of VTE per 100,000 person-years was obtained along with the standard errors ($1/\sqrt{\text{VTE events}}$). For studies reporting rates of VTE per 100,000 pregnancies I converted this into person-years of antepartum time by multiplying the number of pregnancies by 0.75. For the meta-analysis, I only assessed the first six weeks after childbirth during the postpartum (although this was only the early postpartum period in my cohort study) as this was the definition of postpartum used in the majority of the included publications. These were then pooled separately for antepartum and postpartum periods assuming random effects using the generic inverse

variance method. This method considers the inverse variance of the effect estimates i.e. 1/(standard error)^2 as the weight given to each study, so a study with more VTE events was given greater weight than studies with fewer VTE events. A pooled estimate was also calculated for the third trimester of pregnancy.

Given that diagnosis modalities have improved over the years allowing for better ascertainment of VTE diagnosis in addition to the increasing prevalence of maternal risk factors for VTE (for example obesity), I performed a subgroup analysis by stratifying studies based on calendar year (before and after 2005). This cut-off was based on the initial examination of the forest plot for the incidence of VTE during pregnancy which showed a marked difference in the rates of VTE before and after 2005. I also stratified my analyses based on whether or not VTE cases were subjected to a degree of validation/confirmation, which varied from study to study, however, I accepted methods similar to my own criteria. The methods used to validate/confirm VTE ranged from using a validated algorithm to confirm VTE diagnosis or a registry where VTE cases were previously validated with reasonable accuracy to only include cases where VTE had been objectively confirmed by diagnostic tests. A diagnosis of pulmonary embolism may have been confirmed by pulmonary angiography, CT, Magnetic Resonance Imaging, VQ scan, or pathological confirmation of thrombus. A diagnosis of DVT may have been confirmed by Doppler ultrasound, duplex ultrasonography, venography, or pathological confirmation of thrombus. The heterogeneity was assessed in terms of $I.^2$ All data management and statistical analysis was done using STATA MP11

4.3.10 Ethical statement

This study along with the subsequent studies in chapters 5 and 6 was approved by the Independent Scientific Advisory Committee (ISAC) reference number=10_193R.

4.4 Results

4.4.1 Cohort analysis

Overall there were 1,117,691 women with follow-up data between the ages of 15 and 44 years experiencing 248,953 pregnancies resulting in live or stillbirth (Table 4-3). The median follow-up for each women was 3.2 years (IQR=1.23-6.50).

Defining first VTE using linked primary and secondary care data

There were 3,507 cases of first VTE using both data sources. Around 51% of the VTE cases were categorised under VTE definition A of which 51% of diagnoses were recorded both in primary and secondary care data (Table 4-4). Twenty percent of all VTE cases were categorised under VTE definition B as they had supporting evidence including signs or symptoms or a diagnostic test documented 15 days before or after the date of VTE diagnosis but did not meet my criteria for VTE definition A. A total of 29% of all the VTEs were categorized as VTE definition C, I.e. diagnoses with no supporting evidence, the majority of which were in primary care data. When only using the primary care data to identify first VTE cases, a total of 2,923 cases were identified of which 58%, 19% and 23% where categorised under VTE definition A, B and C respectively (data not shown). Similarly 1,946 potential VTE cases were identified when only using secondary care data to identify first VTE of which 64%, 18% and 18% were categorized as VTE definition A, B and C respectively (data not shown).

Table 4-3: Basic characteristics of study population

Variables	N (%)
Total women in study	1,117,691
Women experiencing at least one pregnancy resulting in live or stillbirth	204,929
Median follow-up (IQR) in years	3.2 (1.23-6.50)
Pregnancy outcome (total pregnancies N=248,953)	
Live births	247,436 (99.3)
Stillbirths	1,517 (0.61)
Study follow-up time in person-years (total study period=4,821,334)	
Time outside pregnancy	4,613,196
Antepartum	156,541
Time around delivery	2,381
Postpartum	49,216

Table 4-4: Percentages of VTE cases categorised under VTE definition A, B and C.

Cases of first VTE	N=3,507 n (%)
VTE definition A[1] Total	**1,805 (51.0)**
Diagnosis of VTE in HES and CPRD	925 (51.2)*
Diagnosis in HES only	168 (9.4)*
Diagnosis in CPRD only	712 (39.4)*
VTE definition B[2] Total	**728 (20.6)**
Diagnosis of VTE in HES and CPRD	161 (22.1)*
Diagnosis of VTE in HES only with supporting evidence	162 (22.2)*
Diagnosis of VTE in CPRD only with supporting evidence	405 (55.6)*
VTE definition C[3] Total	**974 (27.6)**
Only HES with no supporting evidence	316 (32.4)*
Only CPRD with no supporting evidence	658 (67.5)*

[1]Recorded VTE with supporting anticoagulant prescription, or medical code indicating anticoagulant therapy within 90 days of the event or death within 30 days of the event.
[2]Recorded VTE codes with supporting sign or symptom of VTE within 15 days before or after the date of event
[3]Recorded VTE with no evidence of signs and symptoms or anticoagulant therapy.
*Percentages based on different denominators (in bold)

4.4.2 Timing of VTE diagnosis (for cases diagnosed both in primary and secondary care

Of the total 1,086 VTE cases documented in both primary and secondary care, 35% (n=377) had the same date of diagnosis for VTE in both datasets. Of the total cases with a different date of diagnosis, 82% (n=581) were first diagnosed in HES with a median delay of 7 days (IQR=3-13) until it was recorded in patients' primary care records. For VTE cases first diagnosed in primary care (number of cases=128) there was a median of 4 days difference (IQR=1-18) in the recording between primary and secondary care date of VTE. This was broadly the same in the antepartum and postpartum period and time outside pregnancy.

4.4.3 Incidence of VTE in and around pregnancy

The rate of any VTE (VTE definition A, B or C) during the time outside pregnancy using both primary and secondary care data was 61 per 100,000 person-years (Table 4-5). This rate decreased by half when restricting to VTE definition A (32 per 100,000 person-years). When relying solely on primary care recording of first VTE, the rate using VTE definition A during the antepartum period, around delivery and postpartum period was calculated to be 80, 461 and 324 per 100,000 person-years respectively (Table 4-6). Relying solely on secondary care data for the recording of first VTE, the calculated VTE rate during the time around delivery and postpartum period was calculated to be 1799 and 180 per 100,000 person-years respectively.

Table 4-5: Incidence rate of VTE per 100,000 person-years using different definitions of VTEs in and around pregnancy (for pregnancies resulting in live or stillbirths) and outside pregnancy using both primary and secondary care data to identify first VTE events

Time period	VTE definition A[1], B[2] or C[3]		VTE definition A[1] or B[2]		VTE definition A[1]	
	n	Rate* (95%CI)	n	Rate* (95%CI)	n	Rate* (95%CI)
Time outside pregnancy	2,817	61 (58-63)	2040	44 (42-46)	1480	32 (30-33)
Antepartum	377	240 (217-266)	268	171 (151-192)	156	99 (85-116)
Trimester 1	47	95 (71-127)	41	83 (61-113)	23	46 (31-70)
Trimester 2	76	148 (118-186)	49	95 (74-126)	30	58 (41-83)
Trimester 3	254	450 (398-509)	178	315 (272-365)	103	182 (150-221)
Around delivery	76	3192 (423-546)	38	1596 (1161-2193)	34	1428 (1020-1998)
Postpartum	237	481 (423-546)	187	379 (329-438)	135	274 (231-324)
Early postpartum	200	801 (695-920)	157	629 (537-735)	117	468 (391-561)
Late postpartum	37	151 (109-208)	30	122 (95-175)	18	73 (46-116)

*Rate per 100,000 person-years
**With women recorded as having a VTE event if they had a diagnosis in either database.
[1]Recorded VTE with supporting anticoagulant prescription, or medical code indicating anticoagulant therapy within 90 days of the event or death within 30 days of the event.
[2]Recorded VTE codes with supporting sign or symptom of VTE within 15 days before or after the date of event
[3]Recorded VTE with no evidence of signs and symptoms or anticoagulant therapy

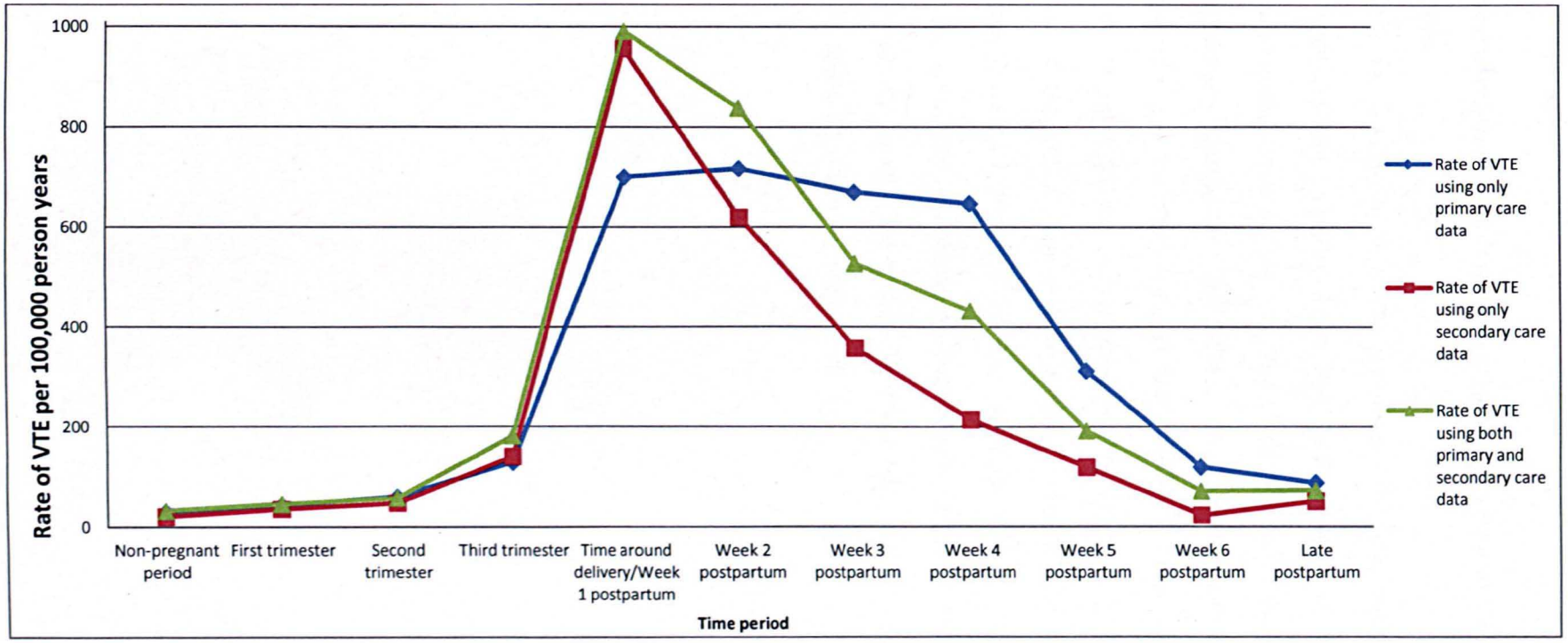
Table 4-6: Incidence rate of VTE per 100,000 person-years in and around pregnancy (for pregnancies resulting in live or stillbirths) by data source

Time period	VTE definition A[1]	
	n	Rate* (95% CI)
Using only primary care data to identify first VTE events		
Time outside pregnancy	1387	30 (28-31)
Antepartum	126	80 (67-95)
Trimester 1	22	44 (29-68)
Trimester 2	31	60 (42-86)
Trimester 3	73	129 (102-162)
Around delivery	11	461 (255-833)
Postpartum	160	324 (278-379)
Early postpartum	138	552 (467-652)
Late postpartum	22	89 (591-136)
Using only secondary care data to identify first VTE events		
Time outside pregnancy	985	21 (19-22)
Antepartum	123	78 (65-93)
Trimester 1	18	36 (23-58)
Trimester 2	25	48 (32-72)
Trimester 3	80	141 (113-176)
Around delivery	43	1799 (1334-2426)
Postpartum	89	180 (146-221)
Early postpartum	76	303 (242-279)
Late postpartum	13	52 (30-91)

*Rate per 100,000 person-years

During the early postpartum, the observed rate of VTE using both primary and secondary care data, peaked around the time of delivery and first week of postpartum (AR=991 per 100,000 person years) after which the rates showed a graded decline throughout the remaining postpartum period (Figure 4-1). Compared to rates from the combined data sources, secondary care data showed a similar rate around delivery but much lower rates postpartum that decreased more rapidly following delivery, whereas primary care data showed lower rates around delivery but higher postpartum rates that remained consistently high until 4 weeks postpartum.

Figure 4-1: Rate of VTE in and around pregnancy and outside pregnancy using data using only established VTEs for pregnancies resulting in live or stillbirths



4.4.4 Systematic review and meta-analysis of perinatal VTE incidence studies

I identified 1,831 articles of which 34 had their full-texts reviewed and 21 were eventually included (Figure 4-2). The characteristics of the included studies are presented in Appendix 17. The overall pooled incidence rates in the antepartum and postpartum periods are shown in Figure 4-3 and Figure 4-4. Antepartum, the incidence rate of VTE during from previous studies ranged from 37 per 100,000 person-years in the UK to 144 per 100,000 person-years in the U.S.A. The pooled incidence rate of VTE was 76 per 100,000 person-years (95% CI 65-90; heterogeneity I^2=97.6%). The incidence rate during the first six weeks postpartum ranged from 126 to 2815 per 100,000 person-years. The pooled incidence rate was 410 per 100,000 person-years (95% CI 302-555) with I^2=99.2%.

Figure 4-2: PRISMA flow diagram for identification of VTE incidence studies during pregnancy and/or postpartum

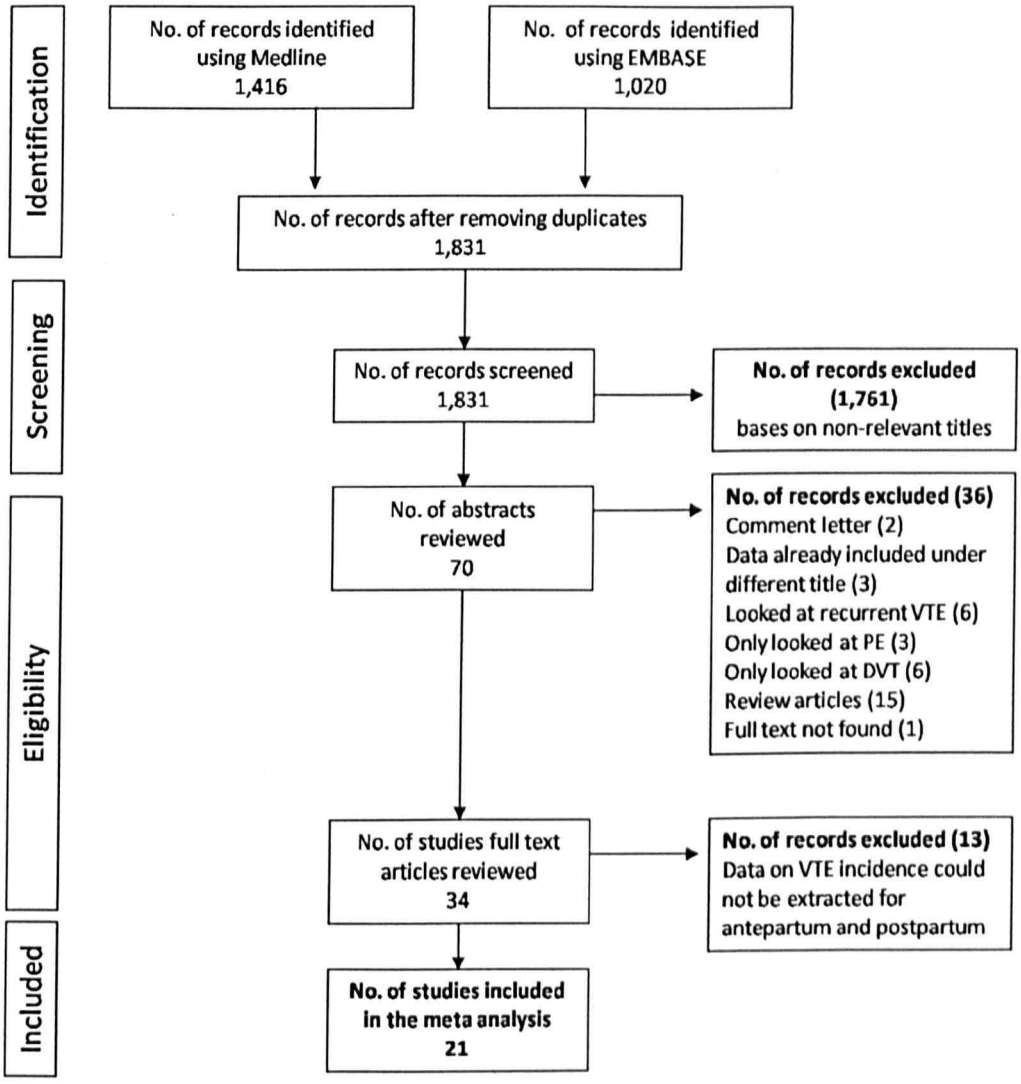


Figure 4-3: Rate of VTE per 100,000 person years during the antepartum period

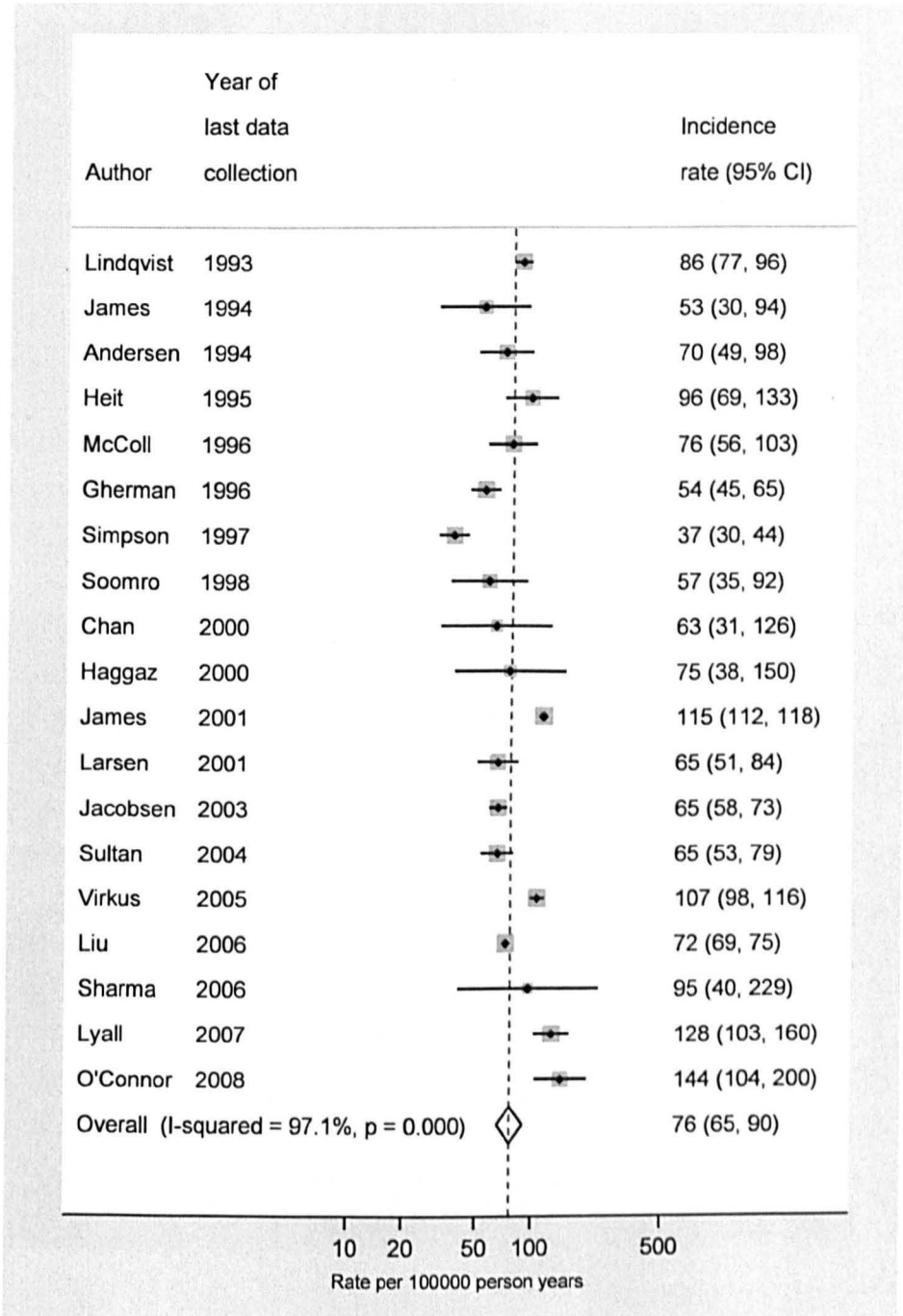
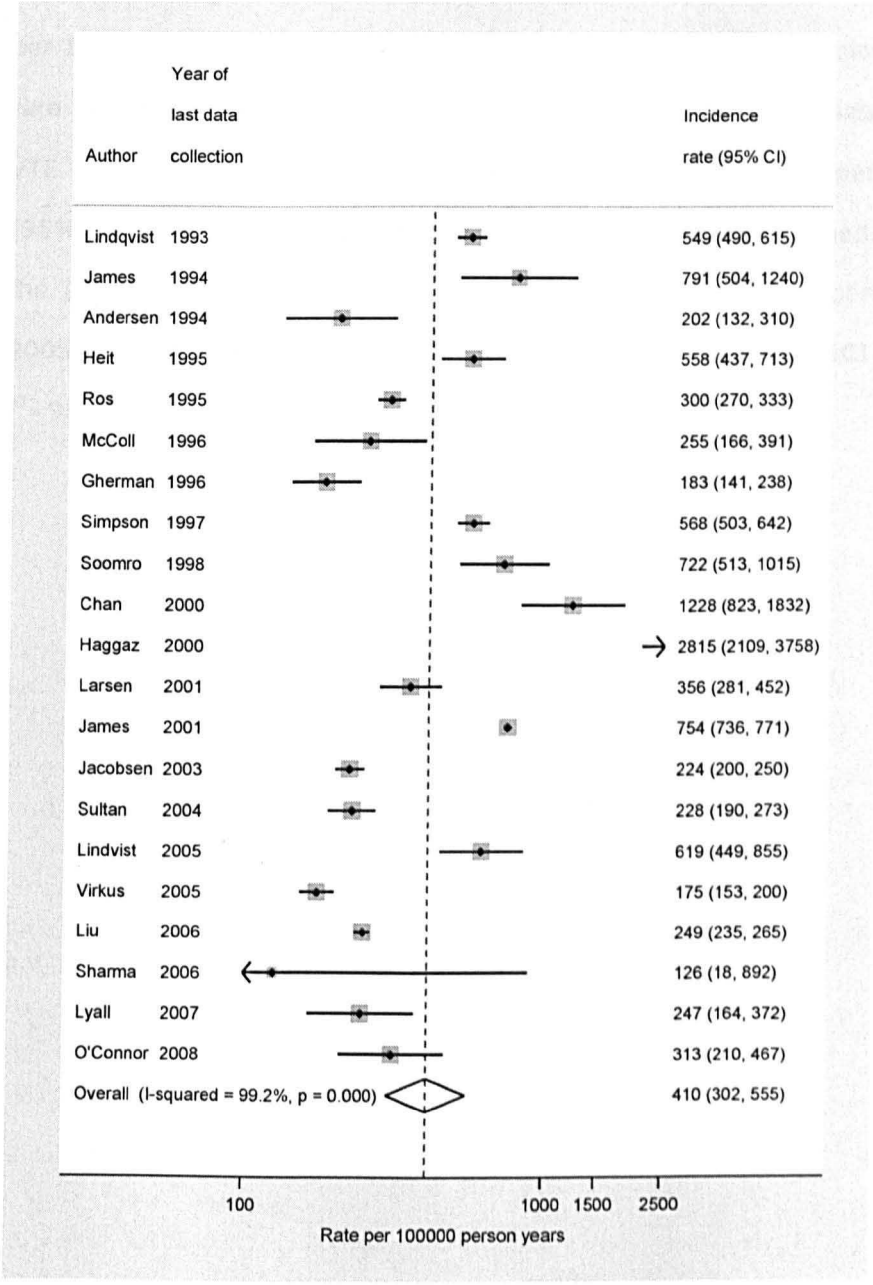


Figure 4-4: Rate of VTE per 100,000 person years during the postpartum period.



When restricting only to studies where VTE cases were validated/confirmed (14 studies), I found higher incidence of VTE after 2005 (AR=118 per 100,000 person-years I^2=40%) compared to the rate before 2005 (AR=64 per 100,000; I^2=0.0%) for the antepartum. (Figure 4-5). The pooled absolute rate of VTE during the third trimester of pregnancy post 2005 (based on 389 VTE cases; Figure 4-7) was calculated to be 142 per 100,000 person-years (95% CI 93-158; I^2=70%) when a similar restriction was applied. Similarly the pooled absolute rate of VTE during the first six week postpartum (post 2005) was calculated to be 424 per 100,000 person-years (95%CI 238-755; I^2=96%; Figure 4-6).

Figure 4-5: Rate of VTE per 100,000 person years during the antepartum period only including studies where some degree of case validation/confirmation was used. The data were stratified by year.

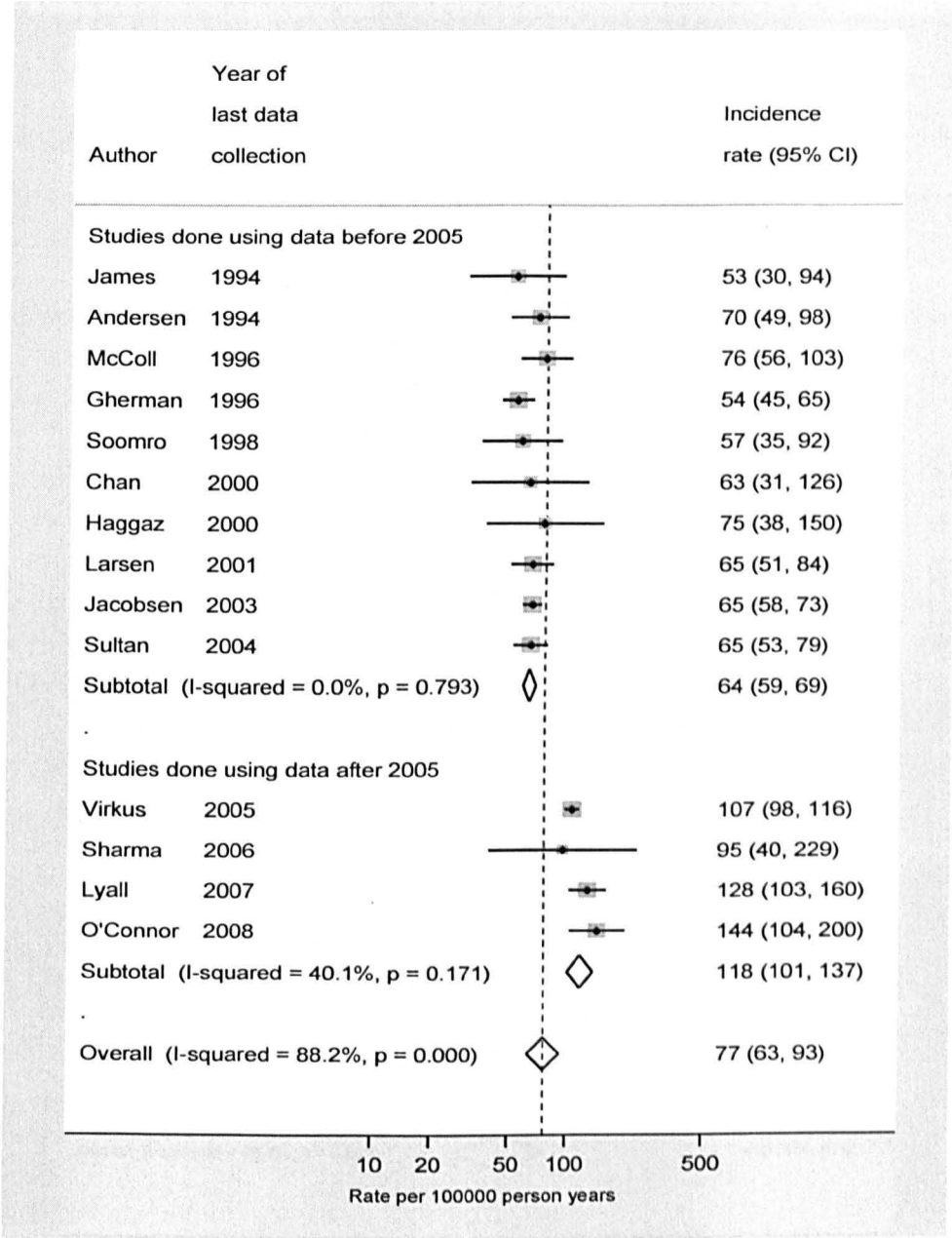


Figure 4-6: Rate of VTE per 100,000 person years during the postpartum (first six week after childbirth) period only including studies where some degree of case validation/confirmation was used. The data were stratified by year.

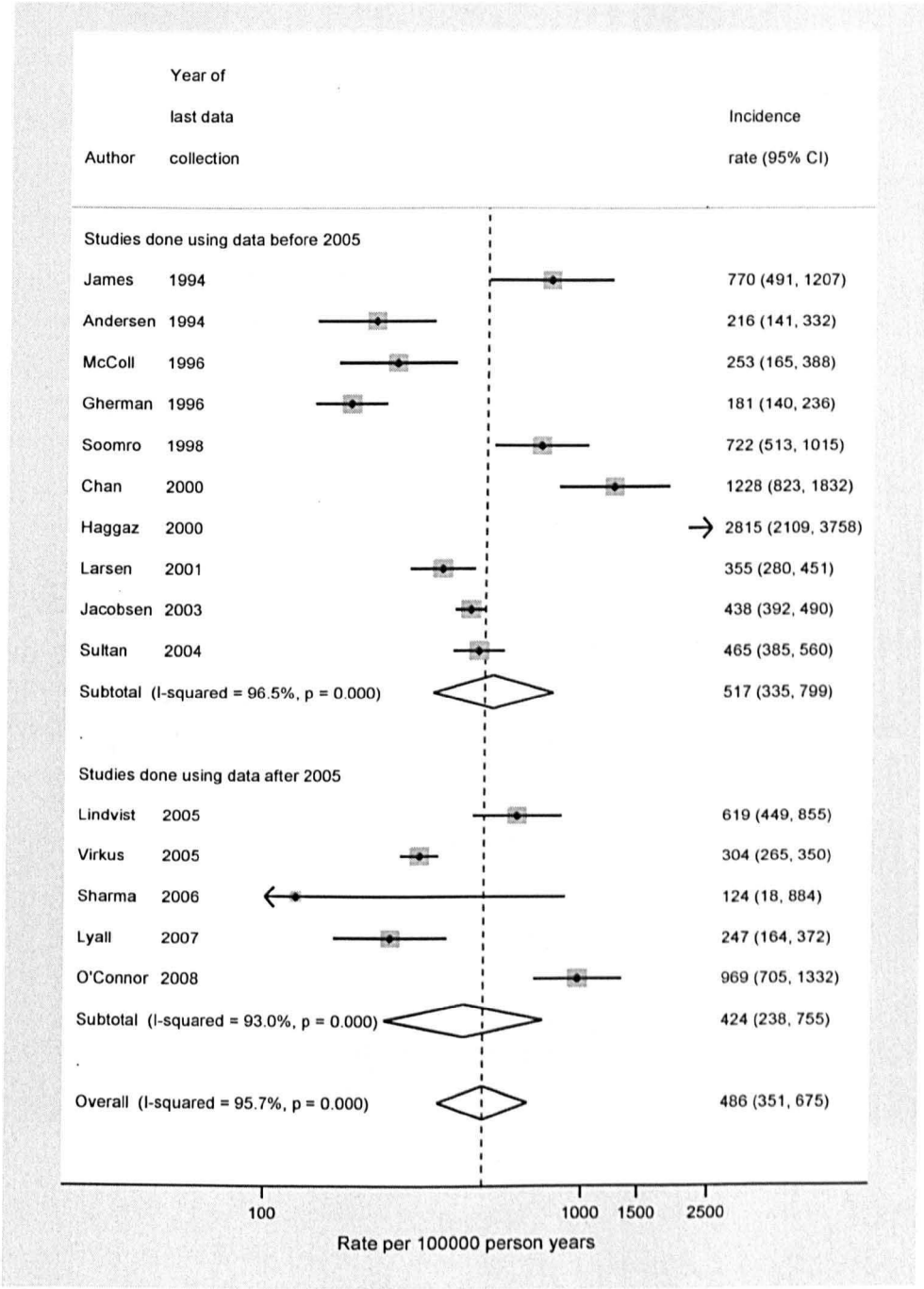
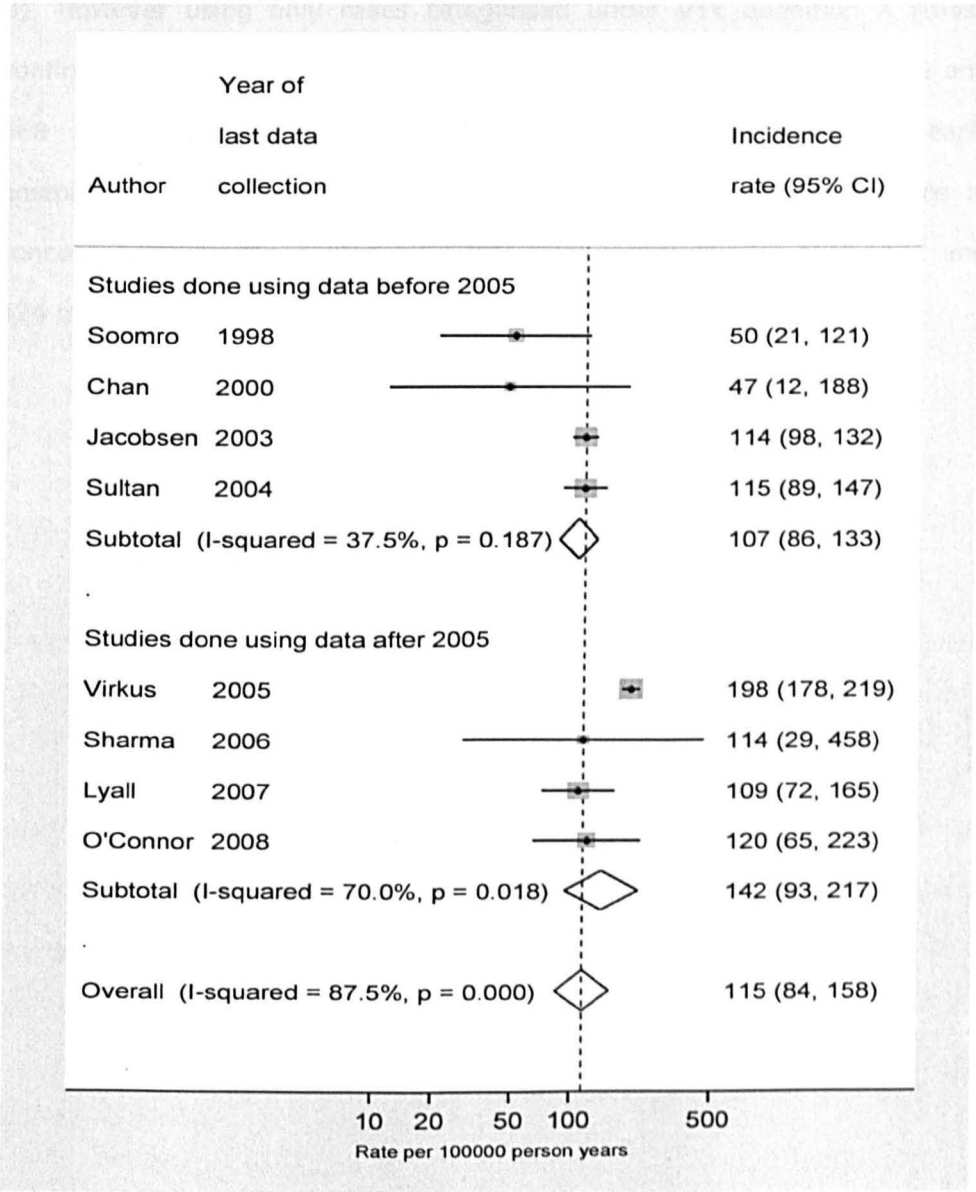


Figure 4-7: Rate of VTE per 100,000 person years during the third trimester of antepartum period only including studies where some degree of case validation/confirmation was used. The data were stratified by year.



4.4.5 Comparison of meta-analysis estimates to the cohort analysis

The estimates from the meta-analysis post-2005 were lower those generated using inclusive VTE definition (VTE definition A, B or C and VTE definition A or B). However using only cases categorised under VTE definition A (those confirmed based on prescriptions or death), the incidence rate of 99, 182 and 468 during the antepartum, third trimester of antepartum and early postpartum (first six week after birth) from my cohort analysis are in concordance with the pooled estimates from recent studies (118, 142 and 424 respectively).

4.5 Discussion

4.5.1 Main findings

In this study, I have shown that a highly specific definition of VTE (VTE definition A) using data from both primary and secondary care health care settings is required to accurately estimate the incidence of VTE in and around pregnancy. The estimates I have derived are comparable with the pooled incidence rates for the antepartum and early postpartum periods from the existing literature. With the use of linked primary and secondary care data I was able to get a far more accurate date of diagnosis for VTE which resulted in more precise estimates of rates close to delivery. Whilst the VTE rate can be accurately estimated in the separate data sources in some circumstance (e.g. trimesters of antepartum), when relying solely on primary care data I found that the rate of VTE was much lower during the time around delivery but higher during the postpartum period compared to solely using secondary care data. This difference is likely because of a delay in hospitalised events being recorded in primary care. However when solely relying on secondary care data the rate of VTE was much lower during the postpartum period and the time outside pregnancy. The best method for defining and quantifying the incidence of VTE in and around pregnancy is therefore to use both primary and secondary care data and applying my VTE definition A to identify cases, as it has previously been validated in non-pregnant population[85] and is externally comparable to other pregnancy studies.

4.5.2 Ascertainment of VTE events

In this study, I was able to analyse 1,117,689 women of childbearing age and over 248,000 pregnancies to determine how the incidence of VTE in and around pregnancy varies based on the VTE definition and the dataset used; such analysis had not been done before. My VTE definition A mimics a

previously validated VTE definition in primary care CPRD[85] data in a non-pregnant population with a reported positive predictive value of 84%. To this algorithm I added secondary care diagnosis data which has an overall accuracy of 91%[112]. One current drawback of UK secondary care data is the lack of information on hospital prescribed heparin and warfarin which may have lead to under ascertainment of cases using VTE definition A. However, I believe that the impact of this limitation should be minimal as pregnant women with a VTE diagnosis are expected to be on anticoagulation therapy throughout their pregnancies and this therapy period extends up to three months for postpartum women.[16] Therefore these prescriptions are likely to be captured in the primary care data.

I must acknowledge that 33% of pregnancies had no information on the length on gestation. When I conducted a sensitivity analysis, however, and calculated the rate of VTE stratified by those with and without information on gestational age this showed no difference in my estimates of VTE within each trimester of pregnancy. It is also worth stating that I excluded pregnancies resulting in miscarriages and terminations from my analysis as I did not extract this information from women's primary care data which was beyond the scope of the present work.

4.5.3 Date of VTE diagnosis

Another strength of linked data is the improvement in estimation of the date of diagnosis of VTE. The majority (84%) of the VTEs diagnosed in both primary and secondary care using the linked data had the diagnosis made in secondary care data first. Therefore if I was completely reliant on primary care data alone there would be a concern with the delay in recording of VTE from secondary to primary care. My study demonstrated a median lag of 7

days in the recording of VTE events from secondary to primary care. This delay can restrict the ability to give precise incidence estimates in narrow windows of time such as around delivery and probably explains my low incidence rate during the time around delivery and prolonged high risk during the early weeks of postpartum when only relying on primary care data for VTE diagnosis. One potential limitation of the secondary care data is the reliance on episode start date as the date of VTE event. This creates problems in separating out antepartum versus postpartum VTE events occurring around the time of delivery. An example of this problem is that reported in a cohort study of women delivering in hospital by Virkus et.al[37] who considered the date of admission to hospital as the date of diagnosis for VTE. They reported a high rate of VTE during the third trimester of the antepartum compared to previous studies in the meta-analysis after 2005. This may be explained by some postpartum VTE events occurring during the maternal admission having been classified as antepartum. A similar, yet not acknowledged, problem may be the case for other studies utilizing hospital discharge data.[7, 10] In the present study HES provides a better option in terms of date of episodes for each diagnosis within each hospital period. I think this rather than the date of hospital admission or discharge will more accurately estimate the true VTE diagnosis date (although not necessarily the actual biological onset of the VTE). Furthermore the division of pregnancy periods as antepartum, around delivery, and postpartum adequately addresses the concern of miss-classification of VTE events around childbirth.

4.5.4 Meta-analysis

My meta-analyses showed high levels of heterogeneity occurring among the individual studies both in the antepartum and postpartum analyses. In descriptive epidemiological studies where a statistic is estimated among a

single group (such as pregnant women in this review), the potential for heterogeneity is far greater than for analytic or comparative studies (i.e., when two groups are compared to calculate a measure of effect such as an odds or risk ratio). This is because incidence rates are very sensitive to the choice of study population, outcome definition and dataset used meaning at least some heterogeneity will be inevitable; other published meta-analyses of this type also report very high levels of heterogeneity.[29, 113, 114] The heterogeneity in my data during the antepartum period was partially explained by calendar year and whether VTE cases were subjected to a certain degree of validation/confirmation or not. For instance, when I restricted my analysis only to studies where VTE cases were validated/confirmed and stratified them by calendar year, my I^2 value was less than 50%. For the postpartum period, incidence rates during the first six weeks post-delivery were largely inconsistent even after restricting to studies with validated/confirmed VTE and stratifying the estimates by calendar year. This wide variation in the reported rates can probably be explained by the various countries' health care systems and their thromboprophylaxis practices after childbirth. The UK Royal College of Obstetricians and Gynaecologists recommendation on VTE risk assessment and thromboprophylaxis post-caesarean section dates back to 1993, which may have been adapted by different countries at different points in time. For instance a study from China[43] reported the rate of VTE to be 1228 per 100,000 person-years where there was no concept of thromboprophylaxis prior to the year 2000 versus studies from Norway[32] and UK[36] with lower reported rates (AR around 400 per 100,000 person-years). This is something I was not able to take account of in my meta-analysis for postpartum VTE. Most of the previous literature on this subject has relied on secondary care data which will inevitably miss many non-fatal VTE events diagnosed and managed exclusively in primary care, particularly during the postpartum period.[33, 34, 37, 40]

Although I did no external validation of my VTE definitions among women included in my cohort study, based on my most inclusive definition (i.e. including events categorised under VTE definition A, B or C) my calculated rates of VTE during the antepartum and postpartum periods were considerably higher than the pooled incidence rate of previous studies. This suggests the inclusion of many false positive events, limiting the validity of such an inclusive VTE definition. The same occurred, although to a lesser extent, when including VTE events classified under VTE definition A or B where I included cases with clinical signs and symptoms of VTE or evidence of diagnostic tests in addition to anticoagulant therapy. This may be due to the fact that leg swelling and calf pain are common in the third trimester of pregnancy in women without DVT which can lead to potential misclassification. Additionally, D-dimer levels increase[17] in pregnancy with gestational hypertension, and in preterm labour leading to false positive events which may add to that misclassification. In contrast the absolute rates of VTE using VTE definition A for antepartum and postpartum periods of 99 and 468 per 100,000 person-years respectively are broadly in concordance with pooled estimates from previous studies using similar methodology where VTE cases were validated/confirmed.

4.5.5 Conclusion and implications

My results have important implications for the way in which VTE is studied in pregnancy using routinely available electronic health care records, data which are crucial for assessing outcomes that are severe and rare and thus rely on evidence from large population-based sources. Firstly, I have quantified the incidence of VTE in and around pregnancy using a variety of VTE definitions. This demonstrated that the absolute rate of VTE greatly varies based on the

VTE definition used, with my VTE definition A providing the most comparable estimates of the absolute rates to previous work. I also demonstrated that there are some important limitations in using solely primary care or secondary care data in terms of the date and ascertainment of VTE diagnosis which needs to be considered when interpreting studies that do this. I have shown in my study that using both primary and secondary care data not only provide better estimation of the date of VTE diagnosis but also enable researchers to comprehensively identify VTE cases diagnosed and recorded both in primary or secondary care. Furthermore, the use of both primary and secondary care data combined may provide better ascertainment of maternal risk factors for VTE, information on hospitalization, primary care prescriptions, information on life style related factors and co-morbidities. This vital information could be used to better understand the occurrence of and risk factors for VTE in and around pregnancy for future research

5 Risk of first Venous thromboembolism in hospitalised pregnant women: A population based cohort study from England

This chapter describes a cohort study conducted to assess the impact of hospitalisation and post-hospitalisation on the incidence of VTE during the antepartum period using the linked primary and secondary care data described in detail in the previous chapter.

5.1 Background

Of all potential risk factors for VTE, hospitalisation must be considered as potentially the most important given that in non-pregnant populations, the risk of VTE during episodes of hospitalisation has been found to be more than 100-fold[70] higher than time outside hospital. In the UK alone hospitalisation is responsible for an estimated 25,000 deaths from VTE annually[3]. However, it is not clear if the same magnitude of risk exists for pregnant women. Also, the risk of VTE post-hospital discharge needs to be determined to assess the need for thromboprophylaxis post hospitalisation.

5.1.1 Justification and aim

The current Royal College of Obstetricians and Gynaecologist (RCOG) guidelines[21] recommends antenatal pharmacological thromboprophylaxis for prolonged hospitalisation (three or more days) if accompanied by two or more VTE risk factors (e.g. BMI≥30Kg/m^2, medical co-morbidities etc). However, estimates of the absolute risks of VTE during and following antepartum hospitalisation, including those in women with no other medical co-morbidities or risk factors are not available. Utilising linked primary and secondary care data sources I have conducted the first study to determine

the risk of first VTE in hospitalised pregnant women while accounting for other maternal and pregnancy associated risk factors and medical co-morbidities.

5.2 Method

5.2.1 Study population

The population for this study came from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) details of which are summarised in Chapter 4. The study time period was defined between 1997 and 2010 during which women between the ages of 15 and 44 years registered within CPRD-HES linked practices with no prior confirmed VTE experiencing at least one delivery resulting in live birth or stillbirth were identified. Pregnancies occurring among women with previous confirmed VTE were excluded regardless of whether those events were diagnosed within or outside pregnancy. Therefore, where women developed a VTE in one pregnancy, person-time resulting from subsequent pregnancies was ignored.

5.2.2 Defining pregnancy and associated time period

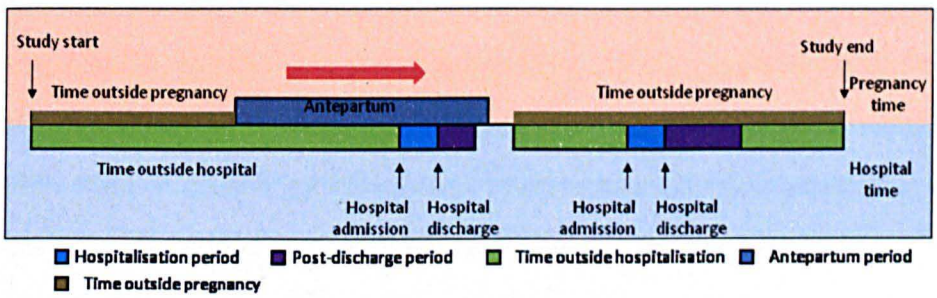
Person-time for each woman with at-least one pregnancy was divided into antepartum (from conception up to two days before childbirth) and "outside pregnancy" (excluding 1 day before childbirth up to 12 weeks afterwards which was time associated with the peripartum and postpartum). Methods used to define pregnancy and exposure periods are presented in Sections 4.3.3 and Section 4.3.8.

5.2.3 Hospitalisation

For each woman, information on all hospitalisations (non-delivery related) where VTE was not the primary recorded reason for admission lasting ≥1 day was obtained (i.e. where there was at least one overnight stay). For all hospital admissions which involved a VTE event, 30 days of electronic primary and secondary data before and after the VTE event were independently

reviewed by two investigators (AAS and JW) to determine whether the VTE event was the cause or consequence of the admission. There was good concordance between the investigators (Kappa =0.81) with all differences resolved by consensus. I considered hospitalisation as a time varying covariate with 3 levels: "hospitalised" (defined as the time between the date of admission and date of discharge); "post-discharge" (defined as the earliest of the date of delivery minus 2 days and the discharge date plus 28 days), which was further divided into weeks; and "time outside hospital" (time not associated with hospitalisation) (Figure 5-1). My choice of 28 days for the post-discharge period for the majority of my analyses was arbitrary but mainly based on recommendations of thromboprophylaxis among patients undergoing knee surgery.[115] As such I also ascertained the risk in the period from 28 days to ten weeks after discharge to assess to what extent the risk of VTE persists longer term. The choice of ten weeks was based on the median follow-up duration from hospital discharge until the date of delivery

Figure 5-1: Division of antepartum person-time into "hospitalised time" and "time outside hospital".



5.2.4 Information on other risk factors

I extracted information on women's demographic factors such as body mass index (most recent recording before conception), smoking status (latest recording before the date of delivery) and age (as described previously) from their medical records using primary care CPRD data using methods similar to that described in section 3.2.3.1. For each woman, I also extracted information on pregnancy associated characteristics (multiple gestations) and pregnancy associated complications (hyperemesis, antepartum haemorrhage, gestational diabetes and hypertension and gestational systemic infection) using data from both primary and secondary care if they were recorded during pregnancy. The Read codes used to extract information on hyperemesis are listed in Appendix 18 whereas ICD-10 codes used extract secondary care information on antepartum haemorrhage, gestational acute systemic infection and hyperemesis are listed in Appendix 19. Information on gestational diabetes, gestational hypertension, and medical co-morbidities including varicose veins, IBD, nephrotic syndrome, cardiac disease, pre-existing hypertension and pre-existing diabetes was extracted using similar methods to those described in section 3.2.3.2.1 and section 3.2.3.2.2 with the addition of relevant ICD-10 codes to identify events recorded in hospital records (Appendix 20).

5.2.5 Venous thromboembolism

VTE was defined as the recording of a medical code relating to the diagnosis of pulmonary embolism or deep vein thrombosis in HES or CPRD where there was evidence of anticoagulation within 90 days of diagnosis or if death occurred within 30 days of diagnosis (VTE definition A as previously highlighted in chapter 4).

5.2.6 Statistical analysis

Absolute rates (AR) of VTE per 100,000 person-years and 95% CIs were calculated by dividing the total number of VTE events by the person-years of follow-up. In order to determine which factors were associated with an increased risk of VTE, incidence rate ratios (IRRs) were calculated for each category of the risk factor for antepartum compared with baseline using a Poisson regression model. Similar methods were used to compare rates of VTE during hospitalisation and the 28 days post-discharge with time outside hospital for antepartum (for comparative purposes this analysis was repeated for "time outside pregnancy"). Initially, I estimated the IRR comparing the rate of VTE during hospitalisation and post-discharge period to time outside hospital adjusted for age and calendar year. The calculated IRRs were also adjusted for additional risk factors found to be associated with increased risk of VTE. Women with missing information on BMI were initially placed in a separate category for purposes of presenting rates of VTE according to body mass index. For the adjusted analyses of VTE rate by hospitalisation, missing values for BMI were replaced using multivariate normal imputation. This involved regressing existing BMI values on age and performing analyses on 10 imputed datasets before results were combined. Imputations were carried out using actual BMI values, after which this variable was categorised (using existing BMI categories) prior to analysis. A sensitivity analysis was also conducted where I categorised missing BMI as a separate category and included it in our regression analysis. I also fitted a clustering term to take account of multiple pregnancies experienced by a woman. The current RCOG guideline suggests pharmacological thromboprophylaxis for pregnant women hospitalised for 3 or more days with the presence of two or more risk factors including obesity (BMI>30kg/m^2) and any significant co-morbidity. Therefore I also calculated the absolute and relative rate for hospitalisation and post

discharge period restricting only to pregnancies in women without those factors.

Subsequent sub-group analyses for antepartum combined the hospitalisation and post-discharge periods due to the relatively small number of VTE events which occurred in either of these periods. These analyses included stratification of results according to maternal age, BMI, trimester of pregnancy, duration of hospital stay and calendar year (before and after 2004 based on the publication of first national guideline for thromboprophylaxis during pregnancy). I also formally tested for interaction between maternal age and hospitalisation by fitting an interaction term between them and conducting a likelihood ratio test at the 5% level of significance. Similarly, I tested for an interaction between hospitalisation and BMI category using the same methods. All statistical analysis was conducted using Stata version 11.2.

5.3 Results

5.3.1 Basic Characteristics

A total of 206,785 women had 245,661 pregnancies resulting in live or stillbirth during the study period. The median follow-up for women in the study was calculated to be 6.1 years (Inter quartile range=2.0-10.2 years). The basic characteristics of women with those pregnancies are summarised in Table 5-1. During the antepartum period, the total person-years associated with hospitalisation and post-discharge was 342 and 2,956 respectively.

Table 5-1: Characteristics of pregnancies occurring among women in linked CPRD-HES data*

Variable	Number of pregnancies 245,661	%
Hospitalisation**		
Not hospitalized	203,405	82.80
Hospitalized once	30,784	12.53
Hospitalized twice	7,470	3.04
Hospitalized thrice or more	4,002	1.63
Demographic characteristics		
Body mass Index		
Normal(18.5-24.9)	107,275	43.67
Underweight(<18.5)	7,733	3.15
Overweight(25-29.9)	45,132	18.37
Obese(>=30)	28,701	11.68
Missing	56,820	23.13
Smoking status		
Non smoker	186,926	76.09
Current smoker	58,735	23.91
Pregnancy associated characteristics and complication		
Diabetes		
Gestational diabetes	3,807	1.57
Pre-existing diabetes	2,739	1.13
Hypertension		
Gestational hypertension	13,039	5.65
Pre-existing hypertension	14,962	6.43
Gestational acute systemic infection	32,668	13.30
Hyperemesis	8,502	3.46
Antepartum haemorrhage	11,614	4.73
Multiple gestation	3,564	1.45
Varicose veins	6,244	2.54
Cardiac disease	2,471	1.01
IBD	1,213	0.49
Nephrotic syndrome	181	0.07

* Pregnancies occurred in 206,785 individual women. Where women had more than one pregnancy, the status of all the above risk factors could potentially differ between pregnancies.
** Hospitalisation during antepartum period

5.3.2 Hospitalisation

Around 17% of women's pregnancies (42,256 pregnancies), had at least one hospitalisation spell with 4.7% hospitalised more than once during an individual pregnancy (Table 5-2). This amounted to a total of 59,537 non-delivery hospitalisation spells that occurred during the antepartum period of which 57%, 22% and 22% concluded within one day, two days and three or more days respectively. The overall rate of antepartum hospitalisation was calculated to be 242/1000 pregnancies. This was much higher in the third trimester (176/1000 pregnancies) compared to first and second trimester (29 and 37/1000 pregnancies respectively). In total 16,137 (27%) antepartum hospitalisation spells occurred among women with pre-existing medical risk factors (including cardiac disease, varicose veins, pre-existing diabetes, hypertension, IBD and nephrotic syndrome during pregnancy or women with a BMI≥30kg/m^2).

Table 5-2: Basic Characteristics of hospitalisation during the antepartum period

Variable	Number 59,772 hospitalisation among 245,661 pregnancies	Percentage
Overall antepartum		
Total hospitalisation	59,573	-
Hospital duration		
1 day	33,560	56.3
2 days	12,883	21.6
3 or more days	13,094	21.9
First trimester		
Total hospitalisation	7,256	-
Hospital duration		
1 day	3,341	46.0
2 days	1,767	24.6
3 or more days	2,148	29.6
Second trimester		
Total hospitalisation	9,100	-
Hospital duration		
1 day	4,747	52.1
2 days	2,013	22.1
3 or more days	2,340	25.7
Third Trimester		
Total hospitalisation	43,181	-
Hospital duration		
1 day	25,472	58.9
2 days	9,103	21.0
3 or more days	8,606	19.9

5.3.3 Venous thromboembolism events

Initially, I identified 100 women who developed venous thromboembolism during or within four weeks after admission (of whom 35 women were pregnant at the time of diagnosis). After the independent reviews, I classed 72 venous thromboembolism events as being a consequence of the admission, of which 46 and 26 occurred during the time outside pregnancy and antepartum period, respectively. There were 176 venous thromboembolism events diagnosed during the antepartum period, of which 15% (n=26) occurred when the woman was an inpatient (occurring during or up to four weeks after admission and when venous thromboembolism was not the reason of admission).

5.3.4 Rate of VTE by maternal risk factors

Overall the rate of VTE during the antepartum period and time "outside pregnancy" was calculated to be 112 and 32/100,000 person-years respectively. I found high rates of antepartum VTE (>2-fold compared with their respective baseline) in women who had gestational diabetes, gestational acute systemic infection, hyperemesis, varicose veins or cardiac disease (Table 5-3). These absolute rates were broadly similar to those presented in chapter 3.

Table 5-3: Absolute rate of VTE per 100,000 person-years and incidence rate ratios during the antepartum period by potential risk factors

Variable	VTE N	Rate[1](95% CI)	IRR (95% CI) (Unadjusted)
Demographic characteristics			
Maternal age			
15 – 24 years	38	101 (74-139)	0.89 (0.61-1.29)
25 - 34 years	103	114 (94-138)	1.00
35 – 44 years	35	118 (85-164)	1.03 (0.70-1.52)
Body mass index			
Normal(18.5-24.9)	61	85 (66-110)	1.00
Underweight(<18.5)	3	59 (19-185)	0.85 (0.64-2.09)*
Overweight(25-29.9)	37	120 (87-166)	1.29 (0.85-1.96)*
Obese(≥30)	35	178 (128-248)	1.76 (1.16-2.67)*
Missing	40	130 (95-177)	**
Smoking status			
Non smoker	128	107 (90-127)	1.00
Current smoker	48	127 (96-169)	1.18 (0.85-1.65)
Antepartum complications[2]			
Hyper emesis	11	222 (123-402)	2.05 (1.16-3.78)
Antepartum haemorrhage	4	181 (67-482)	1.63 (0.60-4.39)
Multiple gestation	5	223 (93-537)	2.02 (0.83-4.92)
Gestational diabetes	9	361 (187-694)	3.30 (1.69-6.46)
Gestational systemic infection	30	269 (188-358)	2.69 (1.81-3.98)
Gestational hypertension	14	170 (100-287)	1.63 (0.94-2.83)
Medical co-morbidities[2]			
Varicose veins	11	253 (140-458)	2.35 (1.27-4.32)
Cardiac disease	5	303 (126-728)	2.75 (1.13-6.70)
Pre-existing hypertension	18	174 (110-277)	1.64 (1.03-2.74)

[1]Rate calculated as per 100,000 person-years
[2]IRR compared to pregnancies without condition under study
Note: No VTE events were observed in pregnancies complicated by IBD, nephrotic syndrome or pre-existing diabetes during the antepartum period
**Missing data were imputed

5.3.5 Rate of VTE by hospitalisation and post-hospitalisation

The risk of antepartum VTE markedly increased during hospitalisation and post-discharge with absolute rates (AR) of 1752 and 676/100,000 person-years respectively (Table 5-4). After adjusting for potential confounding factors (including maternal age and calendar year), there was an 17.5-fold (95%CI=7.69-40.0) and a 6-fold (95%CI=3.74-10.5) increase in risk of VTE during hospitalisation and post-discharge period respectively compared to outside hospital in the antepartum period. When I only considered hospitalisations which occurred among women with no associated pre-existing medical co-morbidity or BMI>30Kg/m2, the magnitude of the increase in relative risk associated with hospitalisation remained similar. When I assessed risk of VTE associated with hospitalisation for time outside pregnancy, I found that hospitalisation and post-discharge corresponded to a 66-fold and a 33-fold increases in risk (after adjusting for age and calendar year) respectively compared to time outside hospitalisation (Table 3). For antepartum, I found the rate of VTE to be altered by the duration of hospital stay. Those with a hospital stay of <3 days had 4-fold higher risk whereas those with ≥3 days of hospital stay had a 12.2-fold increased risk of VTE during hospitalisation/post-discharge period compared to time outside hospital in the antepartum period.

Table 5-4: Rate of VTE during antepartum by hospitalisation and post-hospitalisation

Variable	VTE N	Rate[1] (95%CI)	IRR[2] (95% CI)	IRR[3] (95% CI)
Antepartum overall				
Time outside hospital	150	97 (83-114)	1.00	1.00
Hospitalisation	6	1752 (787-3900)	18.2 (8.04-41.3)	17.5 (7.69-40.0)
Post-discharge	20	676 (436-1048)	7.08 (4.41-11.3)	6.27 (3.74-10.5)
Pregnancies not complicated by BMI>30 or major medical co-morbidity[4]				
Time outside hospital	109	84 (69-101)	1.00	-
Hospitalisation	5	1821 (757-4375)	22.0 (8.97-54.3)	-
Post-discharge	15	623 (375-1034)	7.56 (4.36-13.1)	-
Variation by duration of hospital stay (combining hospitalisation/post-discharge)				
Antepartum overall				
Time outside hospital	150	97 (83-114)	1.00	1.00
Less than 3 days	13	558 (331-943)	5.85 (3.37-10.1)	4.05 (2.23-7.38)
3 or more days	13	1511 (858-2661)	15.7 (8.71-28.5)	12.2 (6.65-22.7)
Time outside pregnancy				
Time outside hospital	326	28 (25-31)	1.00	-
Hospitalisation	11	1890 (1046-3412)	66.2 (36.3-120)	-
Post-discharge	35	911 (654-1269)	32.3 (22.8-45.8)	-

[1]Rate calculated per 100,000 person-years [2]Adjusted for maternal age and calendar year when not stratified by them [3]Adjusted for maternal age, calendaryear, BMI, gestational infection, cardiac disease, varicose vein, gestational diabetes & hyperemesis
[4]Including varicose vein and cardiac disease

5.3.6 Variation of the risk by age, trimester, BMI and calendar year

I also found the collective rate of VTE during hospitalisation and post-discharge to be higher in the third trimester of pregnancy (AR=961/100,000 person-years; Table 5-5). The rate VTE increased with age with highest risk among those age≥35 years (AR=1756/100,000 per-years). Furthermore, I observed a statistically significant interaction between age and hospitalisation (p value=0.01). My results highlighted that the increased risk associated with hospitalisation and post-discharge period remains broadly unaltered by women's BMI as supported by a non-significant test for interaction between BMI category and hospitalisation (p value=0.36). I also observed higher absolute and relative rates of VTE post 2004 during both hospitalisation and the post-discharge period. All my calculated IRRs remained broadly similar when additionally adjusted for other risk factors significantly associated with increased risk of VTE (model 2).

5.3.7 Rate of VTE in the weeks following hospital admission

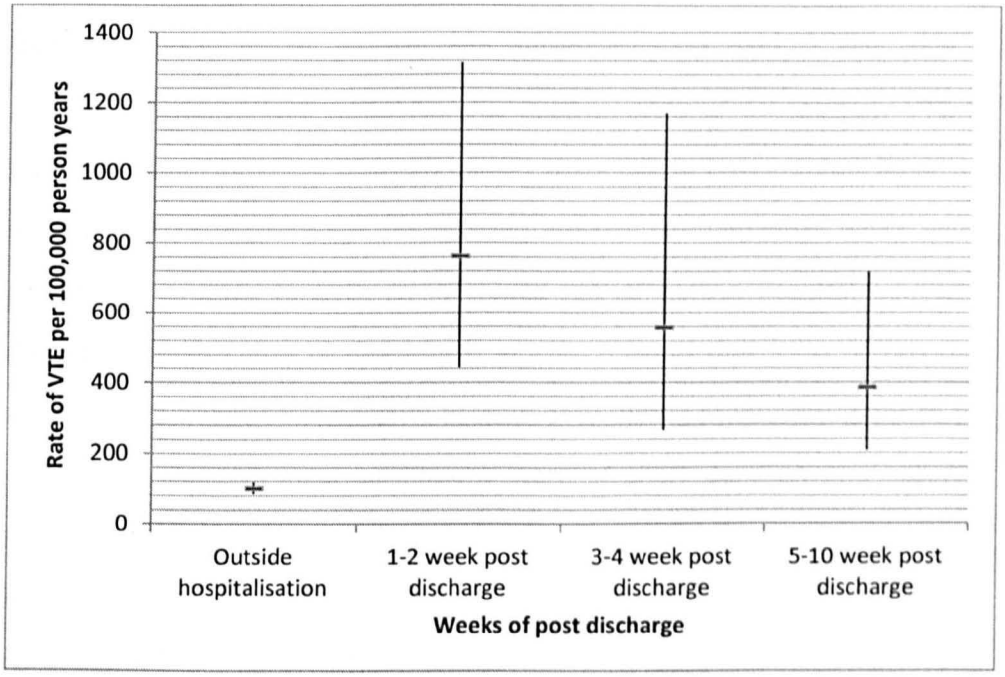
The rate of post-hospitalisation VTE was highest during the first two weeks post discharge (763/100,000 person-years; IRR=7.98 95%CI 4.50-14.1) (Figure 5-2). The risk decreased after 4 weeks with an absolute rate of 387/100,000 person-years (IRR=4.19 95%CI 4.57-11.6) between 5 and 10 weeks post-discharge.

Table 5-5: Rate of antepartum VTE during hospitalisation/post-discharge stratified by trimester, calendar year, age and BMI

Variable	VTE N	Rate[1] (95%CI)	IRR[2] (95% CI)	IRR[3] (95%CI)
Variation by Antepartum trimester				
Trimester 1 and 2				
Time outside hospital	60	60 (46-77)	1.00	1.00
Hospitalisation/post-discharge	5	449 (186-1078)	7.61 (3.03-19.0)	8.43 (3.27-21.7)
Trimester 3				
Time outside hospital	90	162 (134-203)	1.00	1.00
Hospitalisation/post-discharge	21	961 (426-1473)	5.93 (3.64-9.65)	5.57 (3.32-9.34)
Variation by calendar year in hospitalisation/post-discharge				
1997-2003				
Time outside hospital	62	96 (74-123)	1.00	1.00
Hospitalisation/post-discharge	8	550 (275-1100)	5.82 (2.76-12.2)	4.59 (2.08-10.1)
2004-2010				
Time outside hospital	88	98 (79-121)	1.00	1.00
Hospitalisation/post-discharge	18	975 (614-1548)	10.1 (6.03-16.9)	8.51 (4.94-14.6)
Variation by maternal age				
15 – 24 years				
Time outside hospital	34	93 (66-131)	1.00	1.00
Hospitalisation/post-discharge	4	363 (136-967)	3.88 (1.37-10.9)	3.80 (1.25-11.5)
25 – 34 years				
Time outside hospital	90	101 (82-124)	1.00	1.00
Hospitalisation/post-discharge	13	771 (447-1328)	7.61 (4.24-13.6)	6.15 (3.24-11.7)
35 – 44 years				
Time outside hospital	26	89 (60-131)	1.00	1.00
Hospitalisation/post-discharge	9	1756 (913-3376)	19.6 (9.20-42.0)	21.7 (9.62-49.0)
Variation by BMI				
Normal BMI (18.5-24.9 Kg/m^2)				
Time outside hospital	51	72 (55-95)	1.00	1.00
Hospitalisation/post-discharge	10	766 (412-1423)	6.24 (2.41-16.1)	4.72 (1.71-13.0)
Overweight (25-29.9 Kg/m^2)				
Time outside hospital	34	113 (81-158)	1.00	1.00
Hospitalisation/post-discharge	3	474 (153-1472)	10.3 (5.15-20.8)	9.42 (4.38-20.5)
Obese (≥30 Kg/m^2)				
Time outside hospital	30	157 (109-224)	1.00	1.00
Hospitalisation/post-discharge	5	974 (405-2341)	4.30 (1.30-14.1)	4.50 (1.23-16.4)

[1]Rate calculated per 100,000 person-years [2]Adjusted for maternal age and calendar year when not stratified by them [3]Adjusted for maternal age, calendaryear, BMI, gestational infection, cardiac disease, varicose vein, gestational diabetes & hyperemesis

Figure 5-2: Rate of VTE per 100,000 person years by weeks of post discharge during antepartum period



5.4 Discussion

5.4.1 Main finding

Using nationally linked primary and secondary care data, I was able to provide population-level absolute and relative rates of antepartum VTE by hospitalisation (including post-discharge) while taking into account other risk factors for VTE in particular pre-existing medical co-morbidities which would pre-dispose women to both an increased risk of both a hospital admission during pregnancy and of developing a VTE. I found that 17% of pregnant women were admitted to hospital at least once during pregnancy (prior to the delivery admission). Most admissions were of short duration and occurred during the third trimester. Whilst 85% of antepartum VTE events occurred in out of hospital, the risk of VTE per unit of time was 17-fold higher during hospitalisation compared with time "outside hospital". I also found a higher rate of VTE during the first 28 days post-discharge corresponding to 6-fold increased risk compared to baseline. While the rate of VTE whilst hospitalised and following discharge was particularly high for women with 3 or more days of hospital stay, a 4-fold increase in the risk of VTE still existed for those admitted to hospital for less than three days. The rate for hospitalisation/post-discharge period was also high in all three trimesters of antepartum and those aged≥35 years. The strong association between hospitalisation and VTE remained when I restricted our analysis to women without medical co-morbidities including obesity, cardiac disease and varicose veins.

5.4.2 Strength and limitations

This study used an open cohort approach, with prospectively collected data and utilised information from linked primary and secondary care data sources. This not only enabled me to obtain comprehensive information on risk factors

documented in either level of care but gave me the opportunity to follow pregnant women in and outside hospital with accurate dates of admission and discharge. This also permitted me to calculate the absolute and relative rates of antepartum VTE with respect to hospitalisation while taking into account other potential risk factors which has not been assessed previously in the literature. It also makes my study findings nationally generalisable. The completeness of HES data and recording of diagnosis in different centres is always a concern. However, the Department of Health has undertaken studies to assess the completeness of HES coverage which is reported to be high.[116] Moreover a systematic review of discharge coding in HES had found that the accuracy for diagnostic codes is 91%.[112] Utilising data from both primary and secondary care, the prevalence of risk factors in the current study such as diabetes in pregnancy, gestational hypertension and antepartum haemorrhage is similar to the expected prevalence in the UK.[117-119]

A limitation of this study is the relatively small number of VTE events occurring either within or immediately following hospitalisation. This not only gave estimates with wide confidence intervals but restricted my ability to stratify analysis by reason for admission. I also acknowledge that the increased risk of VTE during hospitalisation may be due to other well understood risk factors for VTE (eg. unmeasured co-morbidities) leading to an overestimate in the independent effect of hospitalisation/post-hospitalisation on VTE. However my calculated estimates for hospitalisation and post-discharge periods remained unchanged when excluding pregnant women with other known risk factors for VTE. I also found that the increased rate of VTE decreases in the weeks following hospital discharge which should not have been the case if the effect was solely due to other risk factors. Despite the fact that the risk of VTE was high in the late post-discharge period, the decrease in the risk of VTE from 1800 (during hospitalisation) to 408 per

100,000 person-years (during late post-discharge: 5-10 weeks) demonstrates some longer term effect of hospitalisation on the incidence of VTE. While the cause of the association between hospitalisation and VTE is not clear, immobility is often considered the main culprit.[53] Regardless of the reasons for hospitalisation, pregnant women admitted to hospital for reasons other than delivery represent a group at high risk as evident by a 5-fold increased risk of VTE in those with hospital duration of less than 3 days.

It may be argued that my conclusions, in part, depend upon two authors agreeing on whether VTE was a cause or consequence of the hospital admission. To address this, 30 days of electronic primary and secondary data before and after all VTE events occurring during the antepartum period were carefully and independently reviewed by two of the investigators. Overall, agreement between investigators was very high. When I repeated analyses accepting only cases where antepartum VTE was judged to be the consequence of the hospitalisation by investigators 1 (n=24 VTE events) and 2 (n=27 VTE events) separately, the impact on our effect estimates was only modest and my conclusions were unaltered. Subsequently I also involved, a third investigator who independently agreed with the consensus assessment of investigators 1 and 2 for all cases.

My estimates for hospitalisation and post-discharge VTE risk do not take into account that some pregnant women may already be receiving thromboprophylaxis during those periods. However, I believe that since the first RCOG guidelines for antenatal thromboprophylaxis were only published in 2004 (updated 2009), the use of antenatal thromboprophylaxis with LMWH was rare before 2004 except for those women with previous VTE. I found that both absolute and relative rates of VTE have increased since 2004 which should not be the case if those women were given adequate pharmacological

thromboprophylaxis. This however does not take into account increasing ascertainment of less severe VTEs which would account for an increase in risk of diagnosed VTEs in recent years. Additionally, 67% of all pregnant women diagnosed with antepartum pulmonary embolism (in 2005 and 2006) in the UK did not receive pharmacological thromboprophylaxis according to national guidelines even though they qualified for thromboprophylaxis.[11] This suggests that even with the existence of the RCOG guidelines, widespread prophylaxis of at risk women is not sufficiently taking place.

5.4.3 Comparison to previous studies

To my knowledge this is the first study to assess the impact of antepartum hospitalisation on the incidence of VTE during pregnancy. Therefore I cannot directly compare my finding to any prior research. However a previous study carried out in Rochester, Minnesota has shown an age adjusted 135-fold[70] increased risk of VTE among hospitalised patients compared to non-hospitalized patients in the non-pregnant population (including men), somewhat similar to 67-fold increase observed outside pregnancy in the present study. Whilst my confidence interval surrounding this estimate (95% CI 36 to 120) does not include the effect size observed in the Rochester study, this may not be surprising given that this study was carried out in a much older population (mean age=65 years) who would therefore be more likely to have longer inpatient spells complicated by co-morbidity .

5.4.4 Conclusion and clinical implication

I believe that this study has important implications in the way pharmacological thromboprophylaxis is delivered to pregnant women and hope that it will help targeting prophylaxis in three ways. Firstly I found 6-fold increased risk of VTE in the 28 days following hospital discharge. This

suggests prudent consideration of all pregnant women during that period in terms of VTE risk assessment. Secondly, at present RCOG guidelines advise that prophylaxis should be considered for women at the time of hospital admission provided that she has two or more risk factors including obesity (BMI>30Kg/m^2), significant medical co-morbidity and is expected to be immobile for 3 or more days. This study demonstrated that the risk of VTE during hospitalisation and post-discharge period remained around 21-fold and 8-fold respectively, even in women without such risk factors. Therefore thromboprophylaxis with LMWH may be appropriate during hospitalisation and for the 28 days post-discharge particularly in women with longer hospital duration or aged≥35 years regardless of other risk factors. Finally, the risk of VTE remained increased by 4-fold (during hospitalisation and 28 days post-discharge period) even in women in hospital for less than 3 days (rate equivalent to 0.4% per year). Whether prophylaxis would also be advised for hospital spells anticipated to be of shorter duration would of course depend on the threshold for intervention which would depend both on the costs and tolerability surrounding a daily heparin injection[22] which was beyond the scope of this work. In conclusion I found that hospitalisation exerts a noticeably increased risk of VTE in pregnant women as has been found in other populations. Consideration of which women should receive prophylaxis during an antepartum hospitalisation and for how long is therefore needed.

6 Risk factors for VTE during the postpartum period using linked primary and secondary care data: A population based cohort study from England

This chapter identifies the risk factors for VTE during the postpartum period utilising linked primary and secondary care data. It also evaluates the impact of those risk factors on the timing of VTE around delivery and specific periods of postpartum.

6.1 Introduction

Whilst previous studies have shown the rate of VTE to be highest during the postpartum period,[31, 33, 36] there is limited evidence on specific risk factors for VTE resulting in difficulty when targeting thromboprophylaxis for VTE prevention. The few studies that have specifically assessed risk factors for postpartum VTE indicate that obesity, postpartum haemorrhage, caesarean section delivery, pre-eclampsia, stillbirth and pre-term birth increase a woman's risk.[10, 39, 41, 44, 53] Most of the risk factor estimates are inconsistent across studies with a lack of studies providing information on absolute rates. For instance, increased risks of VTE after caesarean section delivery range from 2.6- fold to 7-fold,[10, 39, 41, 44] with only few studies assessing whether the impact of elective differs from emergency caesarean delivery.[32, 43] In particular, there is a lack of studies which comprehensively assess the relative importance of risk factors occurring before, during and after childbirth while taking into account both their interrelations and also confounding by women's background risk factors such as obesity or pre-existing diabetes. Furthermore, there also is lack of evidence quantifying whether the impact of risk factors on the incidence of VTE differs from early to later postpartum periods, which is important for planning thromboprophylaxis regimens.[120]

6.1.1 Justification

The current Royal College of Obstetricians and Gynaecologist (RCOG)[21] and American College of Chest Physician (ACCP)[64] thromboprophylaxis guidelines are based on limited evidence that does not allow adequate separation of antepartum from postpartum risk factors for VTE. Moreover, the RCOG[21] and ACCP[64] recommendation of seven days and in-hospital (the duration of delivery admission) pharmacological postpartum thromboprophylaxis respectively for women with intermediate risk factors and no previous VTE are based on expert clinical consensus rather than on robust evidence. Using prospectively recorded primary care and secondary care data the current study provides precise estimates of the risks of postpartum VTE associated with pregnancy complications, delivery events and women's co-existing morbidities, and examines the timing of VTE in specific postpartum periods.

6.2 Methods

6.2.1 Study population

I used longitudinal primary care data from the Clinical Practice Research Datalink (CPRD)[102] linked to Hospital Episode Statistics (HES)[106] data containing information on all hospitalisations in England including discharge diagnoses and procedures (details of which are summarised in Chapter 4). Pregnancies ending in live birth or stillbirth between 1997 and 2010 for women age 15-44 years, registered with CPRD-HES linked practices and with no VTE before or during pregnancy were identified from the study population.

6.2.2 Defining venous thromboembolism in postpartum time periods

Information on first VTE events was extracted using Read codes in CPRD and ICD-10 codes in HES. For the purpose of this study VTE was defined as a medical code relating to the diagnosis of pulmonary embolism or deep vein thrombosis in HES or CPRD or both (taking the first date as the date of diagnosis) which was confirmed using the algorithm presented in section 4.3.7 (VTE definition A). For VTE events first recorded in HES, the date of VTE was taken as the date of hospital admission. As 90% of deliveries occurred on the day women were admitted to hospital for delivery or on the day after, the postpartum period was defined from one day before up to 12 weeks post delivery. This was to ensure complete capture of all postpartum VTE events diagnosed during hospital admissions.

6.2.3 Defining potential risk factors

6.2.3.1 Demographics, lifestyle characteristics and pre-existing co-morbidities

For all pregnancies I extracted information on women's demographic and lifestyle characteristics as well as important co-morbidities from both primary and secondary care data. Information on body mass index (BMI) (Kg/m^2), cigarette smoking and age at delivery was obtained from CPRD data, whilst cardiac disease, varicose veins, inflammatory bowel disease (IBD), pre-existing diabetes and hypertension were ascertained using both CPRD and HES using methods similar to previously described.[90] Similarly I also defined women as having pre-existing renal disease if they had a diagnosis of acute or chronic kidney disease, glomerular or renal tubule-interstitial disease before conception in HES or CPRD.

6.2.3.2 Pregnancy characteristics and complications

Information on pre-eclampsia/eclampsia, hyperemesis, multiple birth, gestational diabetes or hypertension (as previously defined[90]) was extracted using both CPRD and HES. I also investigated two common acute systemic infections during pregnancy (urinary and respiratory tract (pneumonia, acute bronchitis, chest infection and influenza)) as these have been associated with VTE in non-pregnant populations.[68, 92]

6.2.3.3 Delivery characteristics and complications

From HES I extracted risk factors occurring around delivery: length of gestation, mode of delivery (spontaneous, assisted (forceps, breech or vacuum), emergency or elective caesarean), stillbirth, and postpartum haemorrhage (including intra-partum haemorrhage). We also investigated

acute systemic infections during the postpartum period, termed puerperal infection. The ICD-10 codes used to extract information on postpartum haemorrhage pre-eclampsia/eclampsia from HES are presented in Appendix 21.

6.2.4 Statistical analysis

I calculated incidence rates of VTE per 100,000 person-years and 95% confidence intervals by dividing the number of VTEs by the postpartum follow-up time, stratified by each demographic and lifestyle characteristic, pre-existing co-morbidity, pregnancy and delivery characteristic and complication. Using Poisson regression I calculated unadjusted incidence rate ratios (IRR) to examine the associations between each risk factor and VTE. Risk factors where the likelihood ratio (LRT) test p-value was <0.1, were included in multivariate models that were constructed using a pre-developed conceptual hierarchical framework (Figure 6-1) that considers the complex causal pathways between variables.[121] For instance, some of the impact of delivery complications (e.g. mode of delivery, postpartum haemorrhage) on postpartum VTE may be confounded by pregnancy characteristics (e.g. pre-eclampsia), pre-existing medical co-morbidities (e.g. cardiac disease) or demographic factors (e.g. maternal age). However each of these factors may also have direct effects on postpartum VTE that are not mediated through delivery complications.

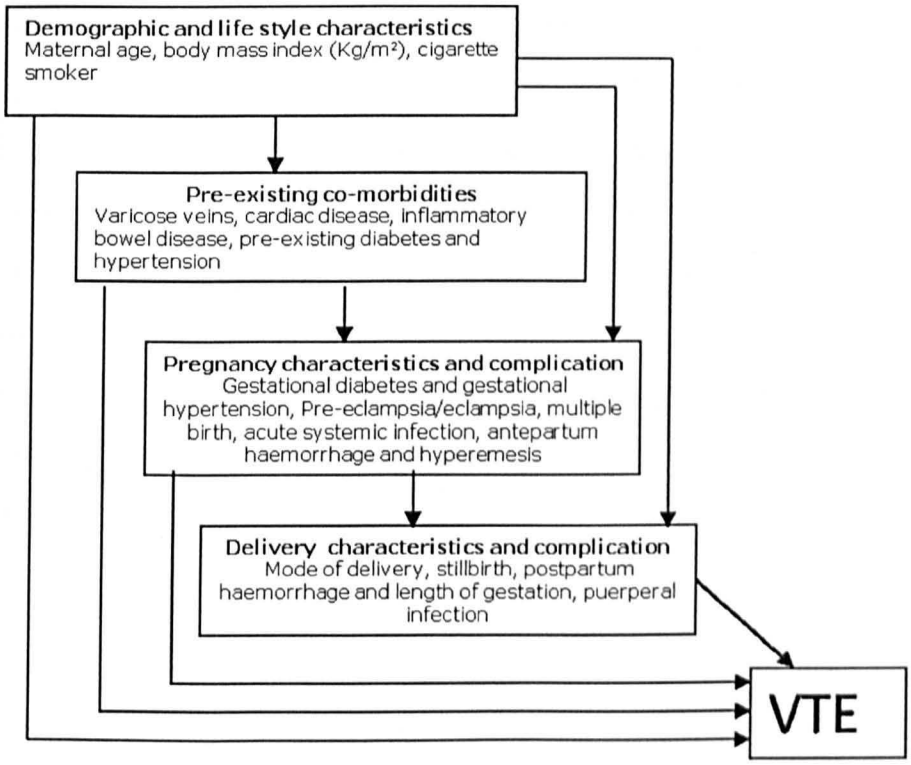
In my hierarchical framework I grouped factors that were considered to have more proximate associations with postpartum VTE (e.g. caesarean section) separately from more distant factors (e.g. pre-pregnancy BMI) that may have direct effects on VTE but may also have indirect effects mediated through

proximate risk factors (e.g. pre-pregnancy BMI is related to one's likelihood of developing pre-eclampsia).[58] Based on this I created three modelling frameworks (MF) to present rate ratio estimates adjusted for different groups of risk factors. In modelling framework 1 I created separate models for each pre-existing co-morbidity, pregnancy and delivery characteristic/complication to estimate their overall effects on postpartum VTE, adjusting only for demographic and lifestyle characteristics (e.g. maternal age, BMI). In MF 2, models from MF 1 were additionally adjusted for any pre-existing medical co-morbidities (e.g. cardiac disease). In MF 3, models were adjusted for demographic and life style related factors, pre-existing medical co-morbidities and pregnancy related characteristics and complications, to estimate each of their effects unmediated by their more proximate risk factors, and also the fully adjusted effects of each delivery characteristic/complication. At that point I re-added statistically non-significant variables previously excluded to assess if they became significant. Because the direction of causal pathways between assisted and caesarean delivery and other delivery complications (e.g. stillbirth) can vary, I carried out a subgroup analysis restricting to women who only underwent spontaneous vaginal or assisted delivery.

For pregnancy and delivery complications showing increased postpartum VTE risks with more than 10 associated VTE events (to ensure reasonable precision), I assessed whether the absolute and relative risks (AR and RR) of VTE differed during the early postpartum (weeks 1-3 and weeks 4-6 post delivery) and late postpartum (weeks 7-12 post delivery). As a sensitivity analysis, I re-ran all models, excluding a small proportion (7%) of VTE events first recorded in HES because they occurred during the same hospital admission as the delivery or another risk factor event (e.g. postpartum haemorrhage) and therefore precise temporality could not be established (i.e. I was not able to determine whether VTE was the cause or consequence of a

caesarean section or postpartum haemorrhage, particularly for those occurring on the same day).

Figure 6-1: Conceptual hierarchical framework for multivariate modelling of risk factors for VTE during the postpartum period



6.3 Results

6.3.1 Basic characteristics

Among 168,077 women there were 222,334 pregnancies ending in live birth or stillbirth. Fifty seven percent of women delivered between the ages of 25 and 34 years, 29% had a pre-pregnancy BMI greater than 25kg/m^2 and 23% were cigarette smokers. Table 6-1 shows absolute rates of postpartum VTE and associations with each of the 21 risk factors assessed, 14 of which were significantly associated with postpartum VTE in bivariate models (LRT $p<0.01$). The highest absolute rates were related to stillbirth, IBD, varicose veins, pre-eclampsia/eclampsia, cardiac disease, preterm gestation and obesity.

Table 6-1: Prevalence, absolute rates of VTE per 100,000 person-years and IRR of potential risk factors in the postpartum period

Variable	Pregnancies N (%)	VTE N	Rate(95%CI)*	IRR (95%CI) Unadjusted
Demographic and lifestyle characteristics				
Maternal age at delivery				
15 – 19 years	12,927 (5.8)	5	170 (70-408)	0.43 (0.17-1.08)
20 – 24 years	36,960 (16.6)	28	330 (228-478)	0.84 (0.53-1.33)
25 - 29 years	58,207 (26.1)	53	390 (298-551)	1.00
30 – 34 years	68,753 (30.9)	37	228 (165-315)	0.58 (0.38-8.9)
35 – 39 years	37,968 (17.0)	44	491 (366-661)	1.25 (0.84-1.87)
40 – 44 years	7,519 (3.3)	11	625 (346-1130)	1.60 (0.83-3.06)
Body mass index (Kg/m^2)				
Normal(18.5-24.9)	98,730 (44.4)	60	259 (201-334)	1.00
Underweight(<18.5)	7,339 (3.30)	3	179 (56-545)	0.67 (0.21-2.16)
Overweight(25-29.9)	39,652 (17.8)	33	353 (252-499)	1.36 (0.89-2.09)
Obese(>=30)	24,141 (10.8)	40	707 (519-964)	2.72 (1.82-4.06)
Cigarette smoker	51,731 (23.27)	51	428 (322-558)	1.33 (0.96-1.84)
Pre-existing co-morbidities				
Varicose veins	5,895 (2.65)	16	1154 (707-1884)	3.59 (2.15-6.01)
Cardiac disease	2,264 (1.0)	5	945 (393-2271)	2.80 (1.15-6.83))
Inflammatory bowel disease	1,105 (0.5)	4	1545 (580-4117)	4.58 (1.69-12.3)
Pre-existing hypertension	13,814 (6.5)	17	524 (326-844)	1.68 (1.01-2.78)
Pre-existing diabetes	2,501 (1.1)	4	685 (257-1826)	2.03 (0.75-5.46)
Pre-existing renal disease	1,493 (0.7)	2	575 (143-2300)	1.68 (0.41-6.78)

*Rate calculated per 100,000 person-years.
IRR: Incidence rate ratio
CI: confidence interval

Table 6-1: Prevalence, absolute rates of VTE per 100,000 person-years and IRR of potential risk factors in the postpartum period (continued..)

Variable	Pregnancies N (%)	VTE N	Rate(95%CI)*	IRR (95%CI) Unadjusted
Pregnancy characteristics and complications				
Antepartum haemorrhage	10,329 (4.6)	10	416 (224-774)	1.22 (0.64-2.31)
Acute systemic infection	26,572 (11.9)	20	323 (208-550)	0.93 (0.58-1.48)
Pre-eclampsia/eclampsia	5,237 (2.3)	14	1148 (679-1938)	3.54 (2.05-6.11)
Multiple birth	3,282 (1.4)	3	390 (125-1211)	1.14 (0.36-3.57)
Gestational hypertension	11,796 (5.6)	18	655 (413-1041)	2.10 (1.28-3.43)
Gestational diabetes	3,518 (1.6)	4	486 (182-1294)	1.44 (0.53-3.88)
Hyperemesis	7,838 (3.53)	9	494 (257-950)	1.46 (0.74-2.86)
Delivery characteristics and complications				
Length of gestation				
Normal gestation	184,744 (83.0)	15	313 (264-370)	1.00
Pre-term gestation	17,112 (7.7)	29	727 (505-1047)	2.31 (1.55-3.46)
Prolonged gestation	20,478 (9.2)	14	293 (173-494)	0.93 (0.53-1.62)
Mode of delivery				
Spontaneous	141,1207 (63.5)	76	230 (184-288)	1.00
Assisted	26,943 (12.1)	19	304 (194-476)	1.31 (0.79-2.18)
Elective caesarean	22,341 (10.0)	33	630 (448-886)	2.73 (1.81-4.11)
Emergency caesarean	31,843 (14.3)	50	674 (511-890)	2.92 (2.04-4.18)
Stillbirth	1,356 (0.61)	8	2595 (1297-5189)	7.86 (3.87-15.9)
Postpartum haemorrhage	20,762 (9.34)	30	629 (440-900)	2.00 (1.35-2.96)
Puerperal infection	7,740 (3.4)	18	1291 (813-2049)	4.07 (2.50-6.63)

*Rate calculated per 100,000 person-years.
IRR: Incidence rate ratio
CI: confidence interval

6.3.2 Multivariate analyses of postpartum VTE risks

When I assessed the direct and mediated effects of each factor using different modelling frameworks (Figure 6-1 and Table 6-2), I found that the risk of VTE increased by only 2% for each year of maternal age and this was not statistically significant. Obesity (BMI ≥30 kg/m^2) was associated with high postpartum VTE risk across all three models indicating that little of the increased risk associated with obesity was mediated through other factors, either pre-existing or pregnancy related. Similarly there were almost 4-fold and 3-fold increased risks for women previously diagnosed with varicose veins and cardiac disease respectively, which did not appear to be strongly mediated by other risk factors.

Table 6-2: Multivariate analysis for VTE risk factors during the postpartum period

Variable	Incidence rate ratios (95%CI)			
	Modelling framework 1	Modelling framework 2	Modelling framework 3	Modelling framework 3 restricted to Spontaneous vaginal/Assisted deliveries
Demographic and lifestyle characteristics				
Maternal age at delivery				
Age (years)	1.03 (1.00-1.06)	1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.02 (0.98-1.07)
Body mass index (Kg/m^2)				
Normal(18.5-24.9)	1.00	1.00	1.00	1.00
Underweight(<18.5)	0.70 (0.21-2.27)	0.69 (0.21-2.23)	0.74 (0.23-2.39)	0.84 (0.19-3.56)
Overweight(25-29.9)	1.35 (0.88-2.07)	0.69 (0.21-2.23)	1.21 (0.77-1.90)	0.67 (0.30-1.46)
Obese(>=30)	2.71 (1.81-4.04)	1.36 (0.89-2.09)	2.40 (1.55-3.72)	3.41 (1.95-5.98)
Cigarette smoker	1.43 (1.03-1.99)	1.44 (1.04-2.01)	1.39 (0.98-1.97)	1.16 (0.71-1.89)
Pre-existing co-morbidities				
Varicose veins	3.44 (2.05-5.78)	3.44 (2.05-5.78)	3.97 (2.36-6.68)	4.88 (2.61-9.11)
Cardiac disease	2.69 (1.10-6.57)	2.60 (1.06-6.37)	2.78 (1.02-7.53)	2.69 (0.66-10.9)
Inflammatory bowel disease	4.57 (1.69-12.3)	4.58 (1.69-12.4)	2.62 (0.64-10.6)	**
Pre-existing hypertension	1.49 (0.89-2.47)	-	-	-
Pregnancy characteristics and complications				
Pre-eclampsia/eclampsia	3.22 (1.84-5.62)	3.28 (1.88-5.72)	4.41 (1.29-15.0)	3.02 (1.20-7.61)[3]
Gestational hypertension	1.89 (1.14-3.12)	1.91 (1.15-3.15)	0.78 (0.26-2.33)	0.14 (0.05-4.15)

Table 6-2: Multivariate analysis for VTE risk factors during the postpartum period (continued...)

Variable	Incidence rate ratios (95%CI)			
	Modelling framework 1	Modelling framework 2	Modelling framework 3	Modelling framework 3 restricted to Spontaneous vaginal/Assisted deliveries
Delivery characteristics and complications				
Pregnancy length				
Normal gestation (37-42 weeks)	1.00	1.00	1.00	1.00
Pre-term gestation (<37 weeks)	2.26 (1.51-3.39)	2.28 (1.52-3.41)	2.90 (1.39-3.13)[1]	1.87 (1.03-3.39)
Pro-longed gestation (>42 weeks)	0.91 (0.52-1.57)	0.91 (0.52-1.57)	0.89 (0.49-1.61)[1]	1.02 (0.49-2.13)
Mode of delivery				
Spontaneous	1.00	1.00	1.00	-
Assisted delivery	1.37 (0.83-2.27)	1.41 (0.85-2.33)	1.28 (0.75-2.19)[2]	-
Elective caesarean delivery	2.43 (1.58-3.74)	2.44 (1.59-3.75)	2.52 (1.63-3.93)[2]	-
Emergency caesarean delivery	2.75 (1.91-3.95)	2.81 (1.95-4.05)	2.25 (1.51-3.36)[2]	-
Stillbirth outcome	7.52 (3.70-15.3)	7.63 (3.75-15.5)	7.34 (3.42-15.7)	12.3 (5.67-26.8)
Postpartum haemorrhage	1.94 (1.31-2.88)	1.93 (1.03-2.87)	1.78 (1.17-2.74)	2.34 (1.32-4.14)
Puerperal infection	3.98 (2.44-6.48)	3.90 (2.39-6.37)	3.55 (2.07-6.06)	3.15 (1.44-6.88)

Modelling framework (MF) 1: Models are built for each risk factor separately, adjusting for demographic and lifestyle characteristics only
Modelling framework 2: As MF 1 and additionally adjusted for pre-existing co-morbidities
Modelling framework 3: As MF 2 and additionally adjusted for pregnancy characteristics and complications
**No VTE events to perform analysis
[1] Additionally adjusted for stillbirths
[2] Additionally adjusted for stillbirths, puerperal infection and postpartum haemorrhage
[3] Gestational hypertension dropped from the model because of its co-linearity with pre-eclampsia/eclampsia

The 3-fold increased risk associated with pre-eclampsia/eclampsia was independent of women's other pregnancy characteristics, pre-existing medical co-morbidities, demographic and lifestyle factors, whereas the risk associated with gestational hypertension was modest. For delivery characteristics and complications I found a 7.3-fold (95%CI 3.42-15.7) increased risk of VTE for those with stillbirth even after adjusting for important background factors. Elective caesarean and emergency caesarean, puerperal infection and pre-term birth were associated with at least 2-fold increased risks compared to spontaneous vaginal deliveries, those with no puerperal infection and normal gestational length respectively. Furthermore, pregnant women with postpartum haemorrhage were 79% (95%CI 1.17-2.74) more likely to develop postpartum VTE. These factors were still important even after adjusting for women's pre-existing co-morbidities and factors occurring prior delivery.

Even among women with spontaneous vaginal deliveries, stillbirth, postpartum haemorrhage, puerperal infection, pre-term birth, pre-eclampsia/eclampsia, varicose veins and BMI $\geq$ 30Kg/m^2 were all still associated with increased risks. No associations changed when I excluded the 7% of VTE events occurring during the same hospital admission as the delivery or risk factor event where I could not establish their relative order. The increased risk of VTE observed with BMI $\geq$30 Kg/m^2 and caesarean section remained consistent when I restricted my analysis to women without any other risk factor (Table 6-3).

Table 6-3: Rate of VTE per 100,000 person-years and incidence rate ratio

Variable	N	Rate (95%CI)	IRR (95%CI)
BMI (≥30Kg/m^2)[1]			
No	14	106 (63-179)	1.00
Yes	13	528 (306-909)	5.29 (3.28-8.65)
Caesarean section[2]			
No	14	100 (59-169)	1.00
Yes	16	464 (284-758)	4.32 (2.80-6.45)

[1] Women without caesarean section and delivering at term or post term and without puerperal infection, stillbirth, postpartum haemorrhage, gestational hypertension, IBD, varicose veins and cardiac disease

[2] Women who are not obese and delivering at term or post term and without puerperal infection, stillbirth, postpartum haemorrhage, gestational hypertension, IBD, varicose veins and cardiac disease

6.3.3 Variation in VTE incidence and incidence rate ratios during postpartum periods

When I ascertained absolute risks of VTE within specific postpartum intervals (Table 6-4), I found that the risk of VTE remained consistently high up to six weeks postpartum (AR > 700/100,000 person-years) for pregnancies among women with obesity or caesarean delivery. The relative risk of VTE was only elevated for three weeks postpartum (>850/100,000 person-years) in those with pre-term birth or postpartum haemorrhage. My absolute rates of VTE for the above stated risk factors were broadly similar when restricted to the first week compared to those over weeks 1-3 postpartum (Table 6-5).

Table 6-4: Incidence rate of VTE per 100,000 person-years and incidence rate ratios during different periods of postpartum and around delivery

Variables	1-3 weeks postpartum			4-6 weeks postpartum			7-12 weeks postpartum		
	n	Rate (95%CI)[2]	IRR (95%CI)[1]	n	Rate(95%CI)[2]	IRR (95%CI)[1]	n	Rate(95%CI)[2]	IRR (95%CI)[1]
BMI≥30Kg/m²									
No	40	598 (438-815)	1.00	9	161 (84-311)	1.00	11	101 (56-182)	1.00
Yes	27	1650 (1131-2406)	2.74 (1.66-4.52)	10	735 (395-1366)	4.18 (1.65-10.5)	3	112 (36-350)	0.97 (0.4-3.88)
Preeclampsia/eclampsia									
No	119	814 (680-974)	1.00	27	221 (151-322)	1.00	18	75 (47-119)	1.00
Yes	8	2263 (1131-4525)	2.54 (1.23-5.26)	4	1360 (510-3623)	5.41 (1.84-15.8)	2	329 (87-1397)	4.76 (1.05-21.6)
Length of gestation									
Normal (36-42 weeks)	98	788 (646-960)	1.00	22	211 (139-321)	1.00	15	73 (44-122)	1.00
Pre-term (<37 weeks)	20	1736 (1120-2691)	2.04 (1.26-3.28)	5	519 (216-1247)	1.92 (0.77-4.78)	4	213 (80-569)	2.81 (0.86-9.16)
Caesarean section									
No	75	662 (528-831)	1.00	9	95 (49-182)	1.00	11	59 (33-107)	1.00
Yes	52	1425 (1086-1870)	1.89 (1.30-2.74)	22	722 (475-1096)	6.99 (3.07-15.9)	9	151 (78-290)	2.22 (0.85-5.79)
Postpartum haemorrhage									
No	103	756 (623-917)	1.00	27	237 (163-346)	1.00	18	81 (51-129)	1.00
Yes	24	1778 (1192-2653)	2.22 (1.42-3.47)	4	347 (130-353)	1.38 (0.47-4.04)	2	88 (22-353)	1.00 (0.22-4.46)
Puerperal infection									
No	114	775 (645-932)	1.00	28	230 (158-333)	1.00	18	76 (48-121)	1.00
Yes	13	4813 (279-828)	5.99 (3.36-10.6)	3	899 (289-2787)	3.56 (1.08-11.7)	2	253 (63-1011)	3.27 (0.73-14.6)

[1]Adjusted for demographic characteristics, pre-existing medical co-morbidities and pregnancy related complication and characteristics when not stratified by them [2]Rate per 100,000 person-years

Table 6-5: Rate per 100,000 person-years of VTE in the first week of postpartum

Variable	N	Rate (95%CI)
BMI (≥30Kg/m^2)		
No	20	678 (437-1051)
Yes	13	1800 (1045-3100)
Caesarean section[2]		
No	42	843 (623-1141)
Yes	26	1620 (1103-2379)
Postpartum haemorrhage		
No	56	933 (718-1212)
Yes	12	2053 (1165-3615)
Pre-eclampsia/eclampsia		
No	64	995 (779-1271)
Yes	4	2567 (963-6840)
Length of gestation		
Normal (36-42 weeks)	54	987 (756-1289))
Pre-term (<37 weeks)	9	1776 (924-3414)
Age>35 years		
No	43	821 (609-1108)
Yes	25	1849 (1249-2736)
Puerperal infection		
No	60	944 (733-1215)
Yes	8	3489 (1745-6977)

6.4 Discussion

6.4.1 Summary of main findings

This study provides precise absolute and relative risks of postpartum VTE for maternal risk factors occurring before, during and after childbirth and quantifies which have the greatest impact on VTE during specific postpartum intervals. The highest risk occurred in women whose pregnancies ended in stillbirth, which was 7-fold higher than women whose pregnancies ended in live birth. Caesarean delivery (elective or emergency), pre-term birth, postpartum haemorrhage, puerperal infection and BMI≥30Kg/m^2 were also associated with approximately 2-fold increased risks of postpartum VTE compared to their respective baselines. These augmented risks were not explained by other pregnancy characteristics and complications, pre-existing co-morbidities, and demographic or lifestyle factors. My results remained consistent when I restricted my analyses to women who underwent spontaneous vaginal/assisted delivery. For women with obesity or those having caesarean deliveries, the rate of VTE remained elevated for 6 weeks postpartum whereas for women with postpartum haemorrhage or pre-term birth the relative rate of VTE was only increased for the first 3 weeks postpartum.

6.5 Strengths and limitations

My study used information on more than 222,000 pregnancies with postpartum follow-up from a nationally representative cohort of pregnant women which makes my study findings generalisable to the majority of pregnant women in England with no prior diagnosis of VTE. By using linked primary and secondary care data I had comprehensive medical information on women's baseline health risks recorded before pregnancy as well as their pregnancy and delivery health records, all of which were prospectively

recorded. This enabled me not only to assess the impact of specific risk factors on postpartum VTE while adequately controlling for confounding factors but also to assess the impact of risk factors on the incidence of VTE during specific postpartum periods.

Another particular strength of this study was the use of a conceptual hierarchical framework to adjust my estimates for potential confounding factors. Most previous studies have used stepwise regression models for their risk factor analysis. This is solely reliant on statistical association rather than any conceptual basis for the interrelationship between factors where all explanatory variables are treated at the same hierarchical level, an assumption which may not be appropriate in all cases. In contrast my categorisation of risk factors and adjusting them in hierarchical order enabled me to evaluate whether the effect of a particular risk factor was direct (e.g. BMI, age) or mediated by other distant risk factors (Preeclampsia/eclampsia).

A limitation of this analysis is my inability to establish temporality between VTE and risk factors that were recorded during the same hospital admission as the VTE event (e.g. postpartum haemorrhage). However this only affected 7% of my cases and my sensitivity analysis demonstrated that removing those women from our analysis did not affect my estimates. I also acknowledge that I was not able to consider certain risk factors such as family history of VTE and thrombophilia. However I believe that the following arguments should be considered. Firstly, whilst family history may be important, it has rarely been looked at in previous population-based studies, possibly for the reason that accurate recall of a family history is problematic. Secondly thrombophilia screening is not routinely recommended for pregnant women therefore pragmatically it cannot be used as a predictor for VTE outcome.

6.5.1 Comparison with previous studies

My relative increased risk observed for those with BMI ≥ 30Kg/m^2, cardiac disease, varicose veins, pre-eclampsia/eclampsia and puerperal infection are in concordance with most previous studies.[7, 10, 41, 44, 53, 56] Additionally my study findings support increased risks of more than 2-fold and 6-fold in women experiencing pre-term delivery and stillbirth respectively, both of which have been previously reported[10, 56, 90] but are not incorporated in the current thromboprophylaxis guidelines. I also found a 2-fold relative increase in the risk of VTE for both elective and emergency caesarean delivery compared to spontaneous vaginal delivery. My finding of an increased risk of VTE associated with elective caesarean section contradicts that of Jacobsen et al[53] who only found an increased VTE risk associated with emergency caesarean section. Jacobsen et al[53], however, obtained VTE cases using a patient registry for the whole population of Norway and controls from a single hospital where they had many more elective caesarean sections (9.2%) compared to the general population (4.8%), which may have biased their estimates towards null. However, I was not able to look at the reasons for caesarean section in more detail, for example the urgency grade of the caesarean section[122] which may have caused misclassification between emergency and elective caesarean section. Conversely, Chan et.al[43] found a more than 11-fold increase risk of VTE for both elective and emergency caesarean delivery which may be due to difference in the study design, population and thromboprophylaxis practices post caesarean section. For instance this study from China[43] reported the overall rate of VTE to be 1228/100,000 person-years during the first six weeks postpartum where there was no concept of thromboprophylaxis up to the year 2000 as opposed

to studies from Norway[32] and UK[36] with lower reported rates (AR approximately 400 /100,000 person-years).

There is a lack of studies evaluating the impact of multiple risk factors on the absolute and relative rates of VTE during specific postpartum periods. Morris et al[56] in a population-based study from Australia showed that a high absolute rate of pulmonary embolism (PE) persists for up to 4 weeks after caesarean delivery. This may have been underestimated as only secondary care data were used to identify only PE cases and hospital admission date was considered as the date of diagnosis. Finally, the higher relative risk of VTE associated with obesity and caesarean delivery in weeks 4-6 following delivery than in the first three weeks may be explained by the fact that those women would have received some form of thromboprophylaxis during the initial postpartum week, as suggested by the current thromboprophylaxis guidelines, which I was not able to quantify.

6.5.2 Clinical implications

I believe that this study will have important implications in deciding how and when thromboprophylaxis is delivered in the obstetric health care setting and hope that it will help targeting of thromboprophylaxis in the following ways; Firstly, women whose pregnancies are complicated by stillbirth, pre-term birth, caesarean section, puerperal infection or postpartum haemorrhage should be considered at high risk of VTE postnatally. These risk factors are not particularly mediated or confounded by factors occurring before delivery. Therefore pregnancies complicated by any one of those factors may require careful consideration in terms of VTE risk assessment during the postpartum. Secondly, the absolute and relative rates of VTE are similar for both elective and emergency caesarean section. Therefore all women undergoing

caesarean section should be considered at high risk regardless of the type of caesarean section. Thirdly, there is a high risk of VTE among those with BMI≥30Kg/m^2 or in those who underwent caesarean mode of delivery for 6 weeks postpartum whereas for postpartum haemorrhage or pre-term birth, the risk of VTE is increased only for up to three weeks postpartum. This suggests that the higher risk of VTE extends beyond the currently suggested 7 days for certain risk factors. However recommendations on whether thromboprophylaxis with LMWH may be effective in pregnant and postpartum women with the above highlighted risk factors will of course be highly dependent on the risk reduction from prophylaxis and any adverse events from its use. Nevertheless throughout the developed world risk stratification models for the purposes of intervening in this regard exist for cancer, hospitalised medical patients and pregnant women. This study provides the most robust, comprehensive, up-to-date, clinically relevant information on risk factors for postpartum VTE that can be of direct use in formulating such guidelines.

7 Conclusion and implications of the work in this thesis

7.1 Summary of the main findings

7.1.1 Incidence of VTE in and around pregnancy utilising general practice primary care data

Using data from a large primary care database (THIN), I reported a low rate of first VTE in pregnancy; however, this rate was still much higher than that seen in the time outside pregnancy when women are 15-44 years of age, with a noticeably raised risk in the postpartum which persisted for five weeks following delivery. During antepartum, women in their third trimester were at a 5-fold increased risk of first VTE compared to their time outside pregnancy whereas in the first and second trimesters this rate was only marginally higher.

7.1.2 Risk factors for VTE in and around pregnancy during the postpartum period using general practice primary care data

Using the same primary care database, I investigated which factors influence the risk of VTE during pregnancy and the postpartum. In this study I provided population based estimates of the absolute and relative risks of VTE in women during and immediately after pregnancy, taking account of their socio-demographic, lifestyle and clinical risk factors. Overall, except for pre-existing diabetes, I found that these risk factors had a greater impact in the postpartum period in terms of influencing the absolute risk of VTE than in the antepartum period. Specifically, I found that women with stillbirth, obstetric haemorrhage, high BMI, preterm birth, prior co-morbidities (specifically IBD and cardiac disease) and caesarean section delivery have a substantially higher risk of VTE postpartum. In contrast, cigarette smoking, maternal age

≥35 years, acute infection and number of previous births were only moderately associated with VTE in both antepartum and postpartum periods.

7.1.3 Defining the incidence of venous thromboembolism in and around pregnancy using linked primary and secondary care data: A population based cohort study and comparative meta-analysis

This was my first study utilising the linked primary and secondary care data. In this study I demonstrated that a highly specific definition of VTE using data from both primary and secondary is required to accurately estimate the incidence of VTE in and around pregnancy and during the time outside pregnancy. These estimates are comparable with respect to the pooled incidence rates for the antepartum and postpartum VTE obtained from existing literature. With the use of linked primary and secondary care data I was able to get a far more accurate date of diagnosis for VTE which resulted in more precise estimates of rates close to and around delivery. Relying solely on primary care data I found that the rate of VTE was much lower during the time around delivery and higher during the postpartum period compared to solely using secondary care data due to a delay in events being recorded in primary care. However when solely relying on secondary care data the rate of VTE was much lower during postpartum period and the time outside pregnancy. Despite this, the relative incidence of VTE in the antepartum and postpartum compared to outside pregnancy were similar across all VTE definitions which supports my finding in section 7.1.1 and 7.1.2.

7.1.4 Impact of hospitalisation on antepartum VTE

Using the linked primary and secondary care data, I was able to conduct the first population-based study to estimate the absolute and relative rates of antepartum VTE by hospitalisation (including the period post-discharge) while taking into account risk factors for VTE which may pre-dispose women to being hospitalised. Whilst 85% of antepartum VTE events occurred in out-patients, the risk of VTE was 17-fold higher during hospitalisation compared with time outside hospital when women were still pregnant. I also found a high rate of VTE during the first 28 days post-discharge corresponding to 6-fold increased risk compared to baseline. While the rate of VTE during hospitalised and post-discharge periods (combined) was particularly high for women with 3 or more days of hospital stay, a 5-fold increase in the risk of VTE still existed for those admitted to hospital for less than three days. The hospitalisation/post-discharge VTE rate compared with baseline was similar for the three trimesters but noticeably raised in women aged≥35 years.

7.1.5 Risk factors for VTE in and around pregnancy during the postpartum period using linked primary and secondary care data

Given some limitations with the primary care data highlighted in chapter 3, it was important to repeat the analyses which ascertained risk factors for postpartum VTE utilising the linked primary and secondary care data. Furthermore, absolute and relative rates of VTE for recognised risk factors were presented separately for specific periods of postpartum. Overall the magnitude of effect size for individual risk factors was similar between CPRD and THIN VTE risk was highest for pregnancies ending in stillbirth compared with live birth pregnancies. Women of older age, having a caesarean delivery, pre-term birth, postpartum haemorrhage or with a BMI≥30Kg/m^2 also had

high VTE risks that were not mediated by other co-existing risk factors. Risk of VTE remained consistently high for six weeks postpartum in women with BMI≥30Kg/m^2 or caesarean delivery, whereas risk was high only up to three weeks postpartum in those with pre-term birth and who experienced acute gestational infection or postpartum haemorrhage.

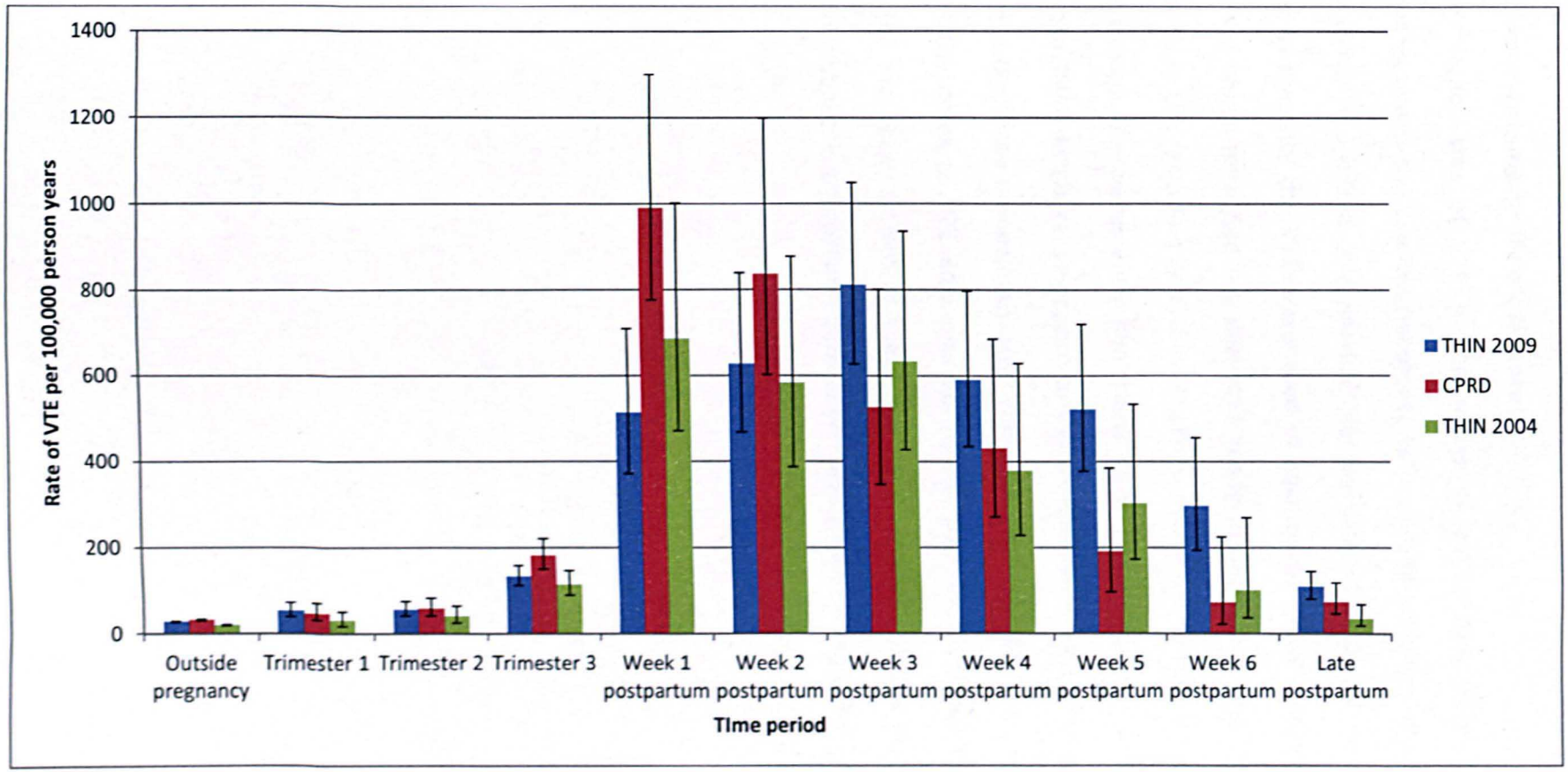
7.2 Comparing databases findings (THIN versus CPRD-HES linked)

The THIN database gave me the opportunity to answer important clinical question and for the first time provide population level estimates of the absolute rate of VTE by risk factors, however there are some fundamental issues when only using primary care data which were addressed using the linked primary and secondary care data. These are presented below:

7.2.1 Ascertainment of VTE

When using the THIN database (chapter 2 and 3) I used a reasonably restrictive method for defining VTE in primary care data[36] which has a positive predictive value of 84%[85], however, this validation study excluded pregnant women from their analysis. As in the United Kingdom (UK) and other countries with similar health care provision almost all women will be in hospital over the time of delivery, there was a possibility of excluding VTE cases recorded solely in secondary care. With the addition of VTE cases identified from HES to the validated algorithm using CPRD-HES linked data I was able to get estimates of the incidence that were more comparable to the pooled estimates of the previous studies done on the subject where VTE outcome was validated. Overall the rate of VTE in and around pregnancy was higher particularly in the third trimester and postpartum periods using CPRD-HES linked data compared to previously published THIN data utilising data up to 2004 (Figure 7-1).This could be due to the better ascertainment of VTE in recent years.

Figure 7-1: Absolute rate of VTE in and around pregnancy in THIN versus CPRD



7.2.2 Ascertainment of risk factors

My calculated rates of VTE in the weeks of postpartum were markedly different between the two data sources. As previously highlighted in chapter 4, the CPRD-HES linked data provide a better estimation of the date of VTE events as majority the VTEs diagnosed in both primary and secondary care using the linked data had the diagnosis made in secondary care data first. The delay in the recording of VTE events from secondary to primary care may partly explain the consistently high rates up till the forth week postpartum using the THIN database as oppose to CPRD-HES linked data where the rate started to decrease immediately after childbirth (Figure 7-1). The uncertainty around the dates of VTE diagnosis during the postpartum using THIN data restricted my ability to look at the impact of risk factors on the incidence of VTE during specific postpartum periods as I was able to using CPRD-HES.

7.2.3 Ascertainment of risk factors

The prevalence of eclampsia/pre-eclampsia in THIN was calculated to be 0.05% compared to the CPRD-HES linked data (2.5%). This would inevitably lead to the failure to detect any important effects this variable would have on the rate of VTE due to both insufficient statistical power and also introduction of non-differential misclassification.

It may also be argued that the residual confounding caused by the under ascertainment of pre-eclampsia/eclampsia could have accounted for some of the postpartum effect I observed for stillbirths and pre-term births using the primary care THIN data. Similarly, the under ascertainment of postpartum haemorrhage in primary care data may have accounted for some of the postpartum effect I observed for caesarean section. However these limitations were addressed to certain extent by using the HES-CPRD linked data. Overall my absolute rates remained fairly consistent across both data sources (Figure 7-2 and Figure 7-3) with the exception of a few risk factors for which hospital data were more useful (acute systemic infection, gestation diabetes and Preeclampsia/eclampsia).

Whilst the use of CPRD-HES linked data supported my findings from the primary care only THIN data, in some instances it provided more detailed information on risk factors (e.g. emergency versus elective delivery, pre-eclampsia, hyperemesis) which was lacking in the previous data source. The hospitalisation information from the CPRD-HES linked data enabled me conduct the first study to look at the risk of first VTE in hospitalised pregnant women for which there was void of data from the existing literature. Better estimation of dates of VTE also enabled me to evaluate the impact of those risk factors on the timing of VTE around delivery and during specific

postpartum periods which is of crucial clinical importance when planning the duration of thromboprophylaxis.

Figure 7-2: Absolute risk of VTE during the antepartum by risk factors in THIN versus CPRD

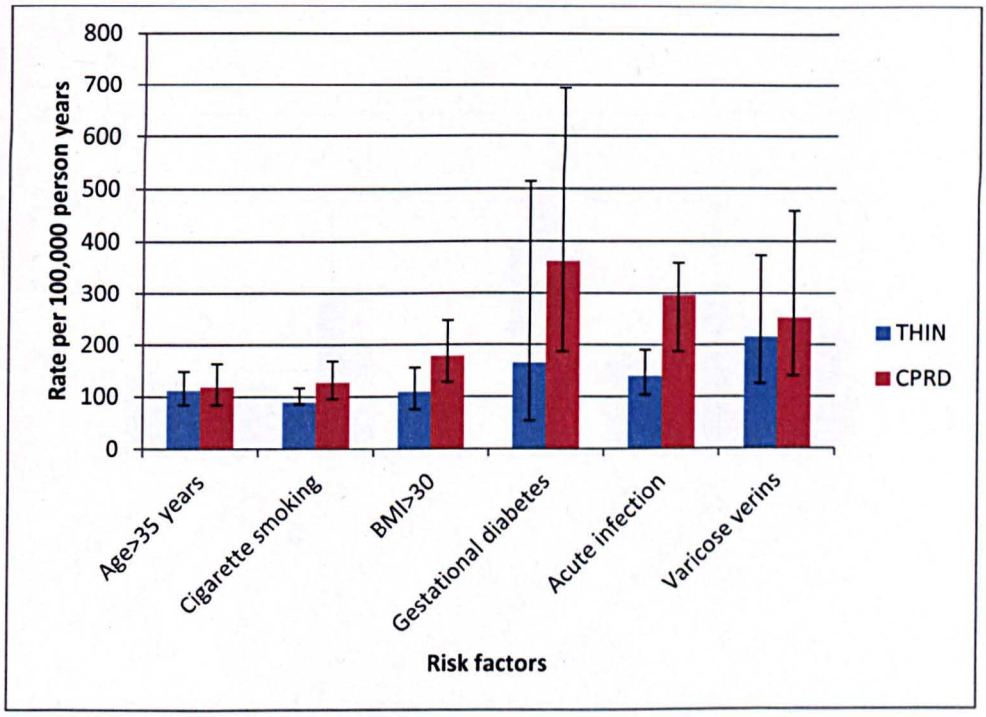
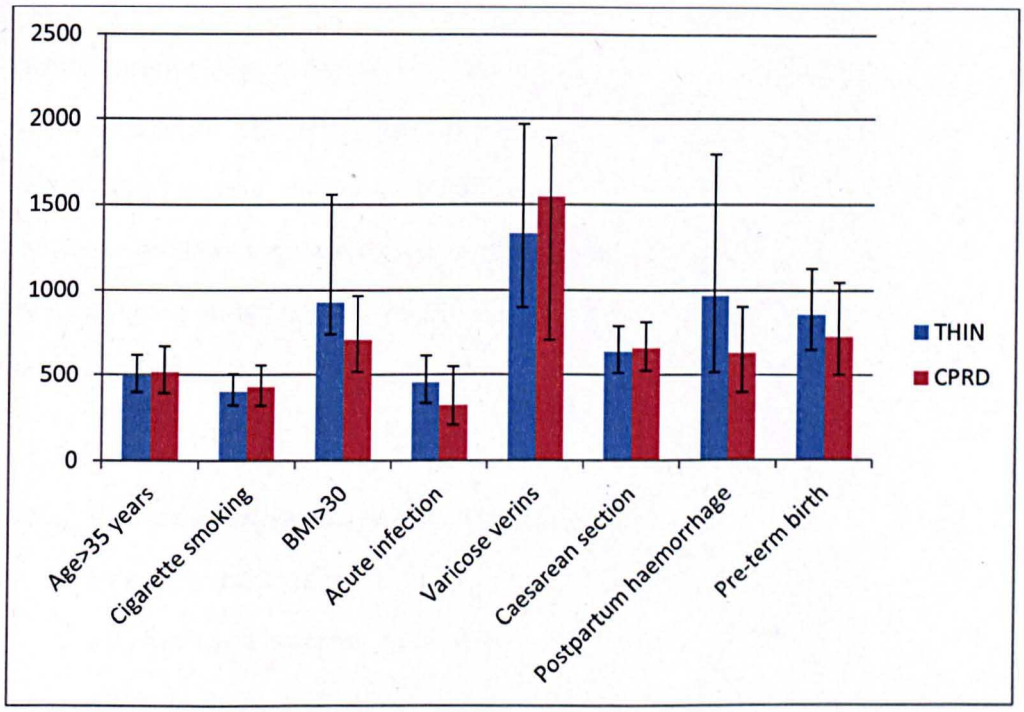


Figure 7-3: Absolute risk of VTE during the postpartum by risk factors in THIN versus CPRD



7.3 Clinical implications

The work done in this thesis has important implications for the way thromboprophylaxis is delivered in the health care setting of countries where advanced health and antenatal care resources are available for almost all women and I hope it will aid in better targeting of such prophylaxis. Based on my thesis findings I have come up with the following recommendations which may be incorporated in the RCOG guideline which are due to be updated soon.

7.3.1 Clinical implication for the antepartum period

- I have found that the overall absolute and relative rate of VTE during the first and second trimester is not greatly increased for women without prior VTE. Therefore thromboprophylaxis among women considered at intermediate risk during the antepartum could potentially be delayed until the start of third trimester.

- The absolute rate of VTE varies modestly by most recognised risk factors during the antepartum period particularly among women with age≥35, parity≥3, cigarette smoking, acute systemic infection, medical co-morbidities or multiple gestations. Therefore the need to offer pharmacological thromboprophylaxis to those women has to be carefully re-evaluated based on their absolute risk. The communication of low absolute risk associated with those factors to physicians and pregnant women will be helpful in placing their risk in perspective.

- I have demonstrated that hospitalisation is the single most important identifiable antepartum risk factor, including a 6-fold increased risk of VTE in the 28 days following hospital discharge. This suggests prudent

consideration of all pregnant women during that period in terms of VTE risk assessment.

- At present RCOG guidelines advise that prophylaxis should be considered for women at the time of hospital admission provided that they have two or more risk factors including obesity (BMI>30Kg/m^2), specific medical co-morbidities and are expected to be immobile for 3 or more days. However based on my results, thromboprophylaxis with LMWH may be appropriate during hospitalisation and 28 days post-discharge period particularly in women with longer hospital duration or age≥35 years regardless of other risk factors. Whether prophylaxis would also be advised for hospitalization anticipated to be of shorter duration would of course depend on the threshold for intervention which would depend both on the costs and tolerability surrounding a daily heparin injection.[22]

7.3.2 Clinical implication for the postpartum period

- My results have demonstrated that the overall rate of VTE is relatively high during the time around delivery and in the first 4 weeks postpartum compared to time outside pregnancy. Therefore the need for thromboprophylaxis to those considered intermediate risk of VTE during the postpartum may extends beyond the 7 days currently recommended by the RCOG guidelines.

- The increased risk of VTE among pregnancies of women with preterm birth or stillbirth factors has received limited consideration to date and is not currently incorporated into the guidelines for risk assessment of

VTE. If they were then this would go some way to ensuring that LMWH was administered to the most at risk women.

- My thesis findings support many of the existing national RCOG guideline recommendations (in terms of high absolute rates), especially that postpartum thromboprophylaxis may be indicated in women with very high BMI (≥40 kg/m^2), those who have prior co-morbidities, obstetric haemorrhage, eclampsia/pre-eclampsia or who have a caesarean section delivery. I have also demonstrated that women with BMI between 30 and 40 kg/m^2 or varicose veins even if these risk factors occur in isolation which may require careful consideration. Additionally, the absolute and relative rate of VTE is similar for both elective and emergency caesarean section. Therefore all women undergoing caesarean section should be considered high risk of VTE regardless of the type caesarean section.

- I also found a high risk of VTE in those with BMI>30Kg/m^2 or who underwent caesarean mode of delivery which persisted for 6 weeks postpartum. Similarly, for pregnancies resulting in postpartum haemorrhage or pre-terms birth, the risk of VTE is high for three weeks postpartum. Therefore consideration should be given to extending the duration of pharmacological thromboprophylaxis up to three and six weeks postpartum in certain groups of women.

- The recommendation on whether thromboprophylaxis with LMWH may be effective in pregnant and postpartum women with specific risk factors will of course be highly dependent on the risk reduction from prophylaxis, for which there is a noticeable void of data from pregnant women. Another important consideration is the costs involved in

prophylaxis both financial and also the tolerability surrounding a daily heparin prescription not to mention the well-recognised side effects of allergy and bleeding. For instance, the benefits would need to be weighed against a risk of major haemorrhage which is believed to occur in 1% of pregnant women[64] and for which we showed a 2.5-fold associated risk with VTE. Such a risk-benefit analysis clearly goes beyond the scope of the present work.

7.4 Suggestions for future research

This thesis using routinely collected primary and secondary care data has answered many research questions regarding the occurrence and risk factors of VTE in and around pregnancy. This hopefully demonstrates the usefulness and potential of the databases for future epidemiological research in maternal medicine. The future direction of research mainly involves the use of the linked primary and secondary care data some of which are presented below;

7.4.1 Validation of VTE algorithm during pregnancy

In this thesis I used a reasonably restrictive method for defining VTE in primary care data[36]. To this algorithm I added cases identified in secondary care. Although, this algorithm has been validated by Lawrenson et al.[85] in primary care data with a positive predicted value of 84%, it excluded pregnant women from their analysis. Additionally it is not known to what extent the addition of a secondary care VTE diagnosis impacts the positive predicted value of our VTE definition. Therefore one important area of research would be to externally validate the modified VTE definition currently used. This would require replicating the study conducted by Lawreson et al. which involved validating VTE cases by requesting additional information from general practitioners (e.g. hospital investigation or death certificate) using the modified VTE validation algorithm (addition of VTE cases from secondary care) and including pregnant women in the analysis.

7.4.2 Risk prediction model for VTE during the antepartum and postpartum periods

Another important area of the research would be to create a VTE risk prediction score for women during antepartum and postpartum periods. Risk prediction models apply an algorithm to a combination of risk factors to

estimate the probability that an individual develops a health outcome during a specific period. This could then be used as a risk assessment tool to identify women for whom thromboprophylaxis would be advised and could be incorporated into future updates of the RCOG guidelines. As the strongest approach to validate a risk prediction model is to use an entirely independent cohort, the risk prediction model developed in one dataset should then be tested using another independent dataset.

7.4.3 Risk of recurrent VTEs in and around pregnancy

Limited and inconsistent data exist on the pregnancy associated VTE risk among women with a history of VTE. For instance the rate of recurrence is reported between 2.4% and 10.9%[71-75] whereas rate of recurrent VTE in women who receive anticoagulation is reported to range between 0 and 2.4%. Currently the RCOG guideline on thromboprophylaxis categorises pregnant women with prior VTE as intermediate or high risk and these women are offered pharmacological thromboprophylaxis throughout the antepartum and up to 7 days postpartum. However there is lack of data to show how pregnancy influences the risk of recurrent VTE during antepartum and postpartum period compared to the non-pregnant population. Additionally only few previous studies have looked at the incidence of recurrent VTE specifically during antepartum and postpartum. Therefore another important area of research would be to look at the recurrence rate of VTE in and around pregnancy.

7.4.4 Effectiveness of pharmacological thromboprophylaxis for preventing VTE

Currently there is void of randomised controlled trails evaluating the effectiveness of pharmacological thromboprophylaxis for preventing VTE

among pregnant/postpartum women. Based on the increased risk of VTE during the initial weeks of postpartum especially among women with certain risk factors (e.g. Caesarean section, preterm birth), another important area of research would be to conduct a clinical trial. This would involve randomising postpartum women with certain risk factors (e.g. caesarean section) to either intervention (pharmacological thromboprophylaxis) or no-intervention (placebo) and prospectively following them up to look at the incidence of VTE during the initial weeks of the postpartum period.

8 References

1. Kumar V, Abbas AK, Aster JC. Robbins basic pathology. 9th ed. Philadelphia: Saunders; 2012.

2. Haines ST. Venous thromboembolism: pathophysiology and clinical presentation. Am. J. Health. Syst. Pharm. 2003; **60**(22 Suppl 7): S1-4.

3. Department of Health. Venous thromboembolism prevention: A patient safety priority. Available from: http://www.kingsthrombosiscentre.org.uk/kings/12.pdf. [Accessed: 19/04/2013]

4. Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA. Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch. Intern. Med. 2007; **167**(9): 935-43.

5. Martineau M, Nelson-Piercy C. Venous thromboembolic disease and pregnancy. Postgrad. Med. J. 2009; **85**(1007): 489-94.

6. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003; **107**(23 Suppl 1): 10-6.

7. James AH, Jamison MG, Brancazio LR, Myers ER, Jamison MG, Brancazio LR, et al. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am. J. Obstet. Gynecol. 2006; **194**(5): 1311-5.

8. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006–2008. BJOG. 2011; **118**: 1-203.

9. Haggaz AARD, Mirghani OA, Adam I. Venous thromboembolism in pregnancy and the puerperium in Sudanese women. Int. J.□Gynaecol. Obstet. 2003; **83**(3): 309-10.

10. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. BJOG. 2001; **108**(1): 56-60.

11. Knight M. Antenatal pulmonary embolism: risk factors, management and outcomes. BJOG. 2008; **115**(4): 453-61.

12. Liu S, Rouleau J, Joseph KS, Sauve R, Liston RM, Young D, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. J Obstet Gynaecol Can. 2009; **31**(7): 611-20.

13. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N. Engl. J. Med. 1996; **335**(2): 108-14.

14. Merhi Z, Awonuga A. Acute abdominal pain as the presenting symptom of isolated iliac vein thrombosis in pregnancy. Obstet. Gynecol. 2006; **107**(2, Part 2): 468-70.

15. Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Ann. Intern. Med. 1998; **128**(8): 663-77.

16. Royal College of Obstetricians and Gynaecologist. The acute management of thrombosis and embolism during pregnancy and puerperium. Green-top guideline No. 37b London: RCOG Press; 2010.

17. Drife J. Thromboembolism. Br. Med. Bull. 2003; **67**: 177-90.

18. Lewis G, editor. The Confidential Enquiry into Maternal and Child Health. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer-2003-2005. London; 2007.

19. Lewis G, Drife J, (eds). Reports on confidential enquiries into maternal deaths. Why mothers dies 2000-02. London: RCOG Press; 2004.

20. Royal College of Obstetricians and Gynaecologists. Thromboprophylaxis during pregnancy, labour and after vaginal delivery No.37. London: RCOG Press; 2004.

21. Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG Press; 2009.

22. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous Thromboembolism, Thrombophilia, Antithrombotic Therapy and Pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidlines (8th Edition). Chest. 2008; **133**(6): 844s-86s.

23. Lindqvist PG, Bremme K, Hellgren M. Efficacy of obstetric thromboprophylaxis and long term risk of recurrence of venous thromboembolism. Acta Obstet. Gynecol. Scand. 2011; **90**(6): 648-53.

24. Sanson B-J, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb. Haemost. 1999; **81**(5): 668-72.

25. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005; **106**(2): 401-7.

26. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N. Engl. J. Med. 1995; **332**(20): 1330-6.

27. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am. J. Obstet. Gynecol. 1993; **168**(4): 1265-70.

28. Douketis JD, Ginsberg JS, Burrows RF, Duku EK, Webber CE, Brill-Edwards P. The effects of long-term heparin therapy during pregnancy on bone density. A prospective matched cohort study. Thromb. Haemost. 1996; **75**(2): 254-7.

29. Horsted F, West J, Grainge MJ. Risk of Venous Thromboembolism in Patients with Cancer: A Systematic Review and Meta-Analysis. PLoS Med. 2012; **9**(7): e1001275.

30. Cochrane Pregnancy and Childbirth Group. Search methods for identifying trial reports for the Cochrane Pregnancy and Childbirth Group's Trials Register,. Available from: http://pregnancy.cochrane.org/. [Accessed: 19/04/2013]

31. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann. Intern. Med. 2005; **143**(10): 697-706.

32. Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium--a register-based case-control study. Am. J. Obstet. Gynecol. 2008; **198**(2): 233.e1-7.

33. Ros SH, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. Epidemiology. 2001; **12**(4): 456-60.

34. Gherman RB, Goodwin TM, Leung B, Byrne JD, Hethumumi R, Montoro M. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet. Gynecol. 1999; **94**(5 Pt 1): 730-4.

35. James AH, Tapson VF, Goldhaber SZ. Thrombosis during pregnancy and the postpartum period. Am. J. Obstet. Gynecol. 2005; **193**(1): 216-9.

36. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. Br. J. Haematol. 2012; **156**(3): 366-73.

37. Virkus RA, Lokkegaard ECL, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard O. Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. Thromb. Haemost. 2011; **106**(2): 304-9.

38. O'Connor DJ, Scher LA, Gargiulo NJ, 3rd, Jang J, Suggs WD, Lipsitz EC. Incidence and characteristics of venous thromboembolic disease during

pregnancy and the postnatal period: a contemporary series. Ann. Vasc. Surg. 2011; **25**(1): 9-14.

39. Lindqvist PG, Torsson J, Almqvist A, Bjorgell O. Postpartum thromboembolism: severe events might be preventable using a new risk score model. Vasc Health Risk Manag. 2008; **4**(5): 1081-7.

40. Sharma S, Monga D. Venous thromboembolism during pregnancy and the post-partum period: incidence and risk factors in a large Victorian health service. Aust. N. Z. J. Obstet. Gynaecol. 2008; **48**(1): 44-9.

41. Larsen TB, Sorensen HT, Gislum M, Johnsen SP. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. Thromb. Res. 2007; **120**(4): 505-9.

42. Soomro RM, Bucur IJ, Noorani S. Cumulative incidence of venous thromboembolism during pregnancy and puerperium: a hospital-based study. Angiology. 2002; **53**(4): 429-34.

43. Chan LY, Tam WH, Lau TK. Venous thromboembolism in pregnant Chinese women. Obstet. Gynecol. 2001; **98**(3): 471-5.

44. Lindqvist P, Dahlblack B, Marsal K. Thrombotic risk during pregnancy: a population study. Obstet. Gynecol. 1999; **94**(4): 595-9.

45. McColl MD, Ramsay JE, Tait RC, Walker ID, McCall F, Conkie JA, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb. Haemost. 1997; **78**(4): 1183-8.

46. Andersen BS, Steffensen FH, Sørensen HT, Nielsen GL, Olsen J. The cumulative incidence of venous thromboembolism during pregnancy and puerperium. Acta Obstet. Gynecol. Scand. 1998; **77**(2): 170-3.

47. Macklon NS, Greer IA. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. Scott. Med. J. 1996; **41**(3): 83-6.

48. James K, Lohr J, Deshmukh R, Cranley J. Venous thrombotic complications of pregnancy. Cardiovasc. Surg. 1996; **4**(6): 777-82.

49. James A. Venous Thromboembolism in Pregnancy. Arterioscler. Thromb. Vasc. Biol. 2009; **29**(3): 326-31.

50. Ros HS, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Pulmonary embolism and stroke in relation to pregnancy: how can high-risk women be identified? Am. J. Obstet. Gynecol. 2002; **186**(2): 198-203.

51. Heslehurst N, Ells L, Simpson H, Batterham A, Wilkinson J, Summerbell C. Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36 821 women over a 15-year period. BJOG. 2007; **114**(2): 187-94.

52. Wiener R, Schwartz L, Woloshin S. Time Trends in Pulmonary Embolism in the United States. Arch. Intern. Med. 2011; **171**(9): 831-7.

53. Jacobsen AF, Skjeldestad FE, Sandset PM. Ante- and postnatal risk factors of venous thrombosis: a hospital-based case-control study. J. Thromb. Haemost. 2008; **6**(6): 905-12.

54. Bates SM. Pregnancy-associated venous thromboembolism: prevention and treatment. Seminars in Hematology; 2011: Elsevier; 2011. p. 271-84.

55. Danilenko-Dixon DR, Heit JA, Silverstein MD, Yawn BP, Petterson TM, Lohse CM, et al. Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum: a population-based, case-control study. Am. J. Obstet. Gynecol. 2001; **184**(2): 104-10.

56. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. J. Thromb. Haemost. 2010; **8**(5): 998-1003.

57. Duhl AJ, Paidas MJ, Ural SH, Branch W, Casele H, Cox-Gill J, et al. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Am. J. Obstet. Gynecol. 2007; **197**(5): 457. e1-. e21.

58. Sebire N, Jolly M, Harris J, Wadsworth J, Joffe M, Beard R, et al. Maternal obesity and pregnancy outcome: a study of 287213 pregnancies in London. Int. J. Obes. 2001; **25**(8): 1175-82.

59. Jay SJ, Kahn SR. Cigarette smoking: risk factor for venous thromboembolic disease? Arch. Intern. Med. 1999; **159**(10): 1144.

60. White RH. The epidemiology of venous thromboembolism. Circulation. 2003; **107**(23 Suppl 1): I4-8.

61. The Information Center. NHS maternity statistics, England: 2005-06. Available from: http://www.ic.nhs.uk/webfiles/publications/maternity0506/NHSMaternityStatsEngland200506_fullpublication%20V3.pdf. [Accessed: 19/04/2013]

62. Royal College of Obstetricians and Gynaecologist. Late intrauterine fetal death and stillbriths No.55. London: RCOG Press; 2010.

63. Preeclampsia foundation. Available from: http://www.preeclampsia.org. [Accessed: 19/04/2013]

64. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; **141**(2 Suppl): e691S-736S.

65. Opara E, Zaidi J. The interpretation and clinical application of the word 'parity': A survey. BJOG. 2007; **114**(10): 1295-7.

66. Kuşcu N, Koyuncu F. Hyperemesis gravidarum: current concepts and management. Postgrad. Med. J. 2002; **78**(916): 76-9.

67. Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur. J. Obstet. Gynecol. Reprod. Biol. 2008; **141**(1): 13.

68. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet. 2006; **367**(9516): 1075-9.

69. All-Part Parliamenatary Thrombosis Group. Available from: http://apptg.org.uk/. [Accessed: 19/04/2013]

70. Heit JA, Melton LJ, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin. Proc. 2001; **76**(11): 1102-10.

71. Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N. Engl. J. Med. 2000; **343**(20): 1439-44.

72. De Stefano V, Martinelli I, Rossi E, Battaglioli T, Za T, Mannuccio Mannucci P, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br. J. Haematol. 2006; **135**(3): 386-91.

73. Pabinger I, Grafenhofer H, Kaider A, Kyrle PA, Quehenberger P, Mannhalter C, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J. Thromb. Haemost. 2005; **3**(5): 949-54.

74. Pabinger I, Grafenhofer H, Kyrle PA, Quehenberger P, Mannhalter C, Lechner K, et al. Temporary increase in the risk for recurrence during pregnancy in women with a history of venous thromboembolism. Blood. 2002; **100**(3): 1060-2.

75. White RH, Chan W-S, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolism. Thromb. Haemost. 2008; **100**(2): 246-52.

76. Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. Health Technol. Assess. 2005; **9**(49): iii-iv.

77. Kent N, Leduc L, Crane J, Farine D, Hodges S, Reid G, et al. Prevention and treatment of venous thromboembolism (VTE) in obstetrics. J SOGC. 2000; **22**(9): 736-49.

78. Salonen Ros H, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. Epidemiology. 2001; **12**(4): 456-60.

79. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJM. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J. Thromb. Haemost. 2008; **6**(4): 632-7.

80. Langley T, Szatkowski L, Wythe S, Lewis S. Can primary care data be used to monitor regional smoking prevalence? An analysis of The Health Improvement Network primary care data. BMC Public Health. 2011; **11**(1): 773.

81. Tata L, Hubbard R, McKeever T, Smith C, Doyle P, Smeeth L, et al. Fertility rates in women with asthma, eczema, and hay fever: a general population-based cohort study. Am. J. Epidemiol. 2007; **165**: 1023-30.

82. Lewis J, Schinnar R, Bilker W, Wang X, Strom B. Validation studies of the health improvement network (THIN) database for pharmacoepidmeiology research. Pharmacoepidemiol Drug Saf. 2007; **16**: 393 - 401.

83. Green LA. Read Codes: a tool for automated medical records. J. Fam. Pract. 1992; **34**(5): 633-4.

84. Szatkowski L, Lewis S, McNeill A, Huang Y, Coleman T. Can data from primary care medical records be used to monitor national smoking prevalence? J. Epidemiol. Community Health. 2012; **66**(9): 791-5.

85. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD. Validation of the diagnosis of venous thromboembolism in general practice database studies. Br. J. Clin. Pharmacol. 2000; **49**(6): 591-6.

86. National Institute for Health and Clinical Excellence. Commissooning outcome framework. Available from: http://www.nice.org.uk/. [Accessed: 28/05/2013]

87. Maynard A, Bloor K. Will financial incentives and penalties improve hospital care? BMJ. 2010; **340**(7741): 297-8.

88. Farmer RD, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. Lancet. 1997; **349**: 83-8.

89. Lee RV. Thromboembolism in pregnancy: a continuing conundrum. Ann. Intern. Med. 2005; **143**(10): 749-50.

90. Abdul Sultan A, Tata LJ, West J, Fiaschi L, Fleming KM, Nelson-Piercy C, et al. Risk factors for first venous thromboembolism around pregnancy: a population based cohort study from the United Kingdom. Blood. 2013; **121**(19): 3953-61.

91. Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. Pharmacoepidemiol Drug Saf. 2004; **13**(7): 437-41.

92. Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sørensen H. Acute infections and venous thromboembolism. J. Intern. Med. 2012; **271**(6): 608-18.

93. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer–A cohort study using linked United Kingdom databases. Eur. J. Cancer. 2012; **49**(6): 1404-13.

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

95. Brace V, Kernaghan D, Penney G. Learning from adverse clinical outcomes: major obstetric haemorrhage in Scotland, 2003–05. BJOG. 2007; **114**(11): 1388-96.

96. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaeco. 2008; **22**(6): 999-1012.

97. Office for National Statistics. Birth statistics 1998-2008 England and Wales.

98. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005; **365**(9461): 785-99.

99. Office for National Statistics. Ethnicity and national identity in England and Wales 2011. Available from: http://www.ons.gov.uk/ons/rel/census/2011-census/key-statistics-for-local-authorities-in-england-and-wales/rpt-ethnicity.html. [Accessed: 19/04/2013]

100. Dhalwani NN, Fiaschi L, West J, Tata LJ. Occurrence of fertility problems presenting to primary care: population-level estimates of clinical burden and socioeconomic inequalities across the UK. Hum. Reprod. 2013; **28**(4): 960-8.

101. Själander A, Jansson JH, Bergqvist D, Eriksson H, Carlberg B, Svensson P. Efficacy and safety of anticoagulant prophylaxis to prevent venous thromboembolism in acutely ill medical inpatients: a meta-analysis. J. Intern. Med. 2008; **263**(1): 52-60.

102. Clinical Practice Research Database. Available from: http://www.cprd.com/intro.asp. [Accessed: 19/04/2013]

103. Williams T, Van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf. 2012; **3**(2): 89-99.

104. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br. J. Clin. Pharmacol. 2010; **69**(1): 4-14.

105. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br. J. Gen. Pract. 2010; **60**(572): e128-e36.

106. Hospital Episode Statistics. Available from: http://www.hesonline.nhs.uk. [Accessed: 19/04/2013]

107. Dattani N, Datta-Nemdharry P, Macfarlane A. Linking maternity data for England 2007: methods and data quality. Health Statistics Quarterly. 2012; **53**.

108. Crooks C. Epidemiology of upper gastrointestinal bleeding studying its causes and outcomes using case control studies and survival analyses. Ph.D. Thesis. The University of Nottingham; 2013.

109. Health and social care information center. NHS Maternity Statistics - England, 2010-2011. Available from: http://www.hscic.gov.uk/pubs/maternity1011. [Accessed: 12/12/2012]

110. Wright FL, Green J, Canoy D, Cairns BJ, Balkwill A, Beral V. Vascular disease in women: comparison of diagnoses in hospital episode statistics and general practice records in England. BMC Med Res Methodol. 2012; **12**(1): 161.

111. Crooks C, Card TR, West J. Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality. BMC Health Serv Res. 2012; **12**(1): 392.

112. Campbell SE, Campbell MK, Grimshaw JM, Walker AE. A systematic review of discharge coding accuracy. J Public Health. 2001; **23**(3): 205-11.

113. Eaden J, Abrams K, Mayberry J. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001; **48**(4): 526-35.

114. Thomas T, Abrams K, Robinson R, Mayberry J. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. Aliment. Pharmacol. Ther. 2007; **25**(6): 657-68.

115. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of Venous Thromboembolism*: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2008; **133**(6_suppl): 381S-453S.

116. Thompson A, Shaw M, Harrison G, Ho D, Gunnell D, Verne J. Patterns of hospital admission for adult psychiatric illness in England: analysis of Hospital Episode Statistics data. Br J Psychiatry. 2004; **185**(4): 334-41.

117. National Institute for Health and Clinical Excellence. Diabtes in pregnancy: Management of diabetes and its complication from pre-conception to postnatal period. London: RCOG Press; 2008.

118. Walker RL, Hemmelgarn B, Quan H. Incidence of gestational hypertension in the Calgary Health Region from 1995 to 2004. Can J Cardiol. 2009; **25**(8): e284-e7.

119. Zhang J, Zeisler J, Hatch MC, Berkowitz G. Epidemiology of pregnancy-induced hypertension. Epidemiol. Rev. 1997; **19**(2): 218.

120. Rodger M. Evidence base for the management of venous thromboembolism in pregnancy. ASH Education Program Book. 2010; **2010**(1): 173-80.

121. Victora CG, Huttly SR, Fuchs SC, Olinto M. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int. J. Epidemiol. 1997; **26**(1): 224-7.

122. Lucas D, Yentis S, Kinsella S, Holdcroft A, May A, Wee M, et al. Urgency of caesarean section: a new classification. JRSM. 2000; **93**(7): 346-50.

123. Lyall H, Myers B. Incidence and management of 82 cases of pregnancy-associated venous thromboembolism occurring at a single centre--comparison with Voke et al. Br. J. Haematol. 2008; **142**(2): 309-11; author reply 11-2.

9 Appendices

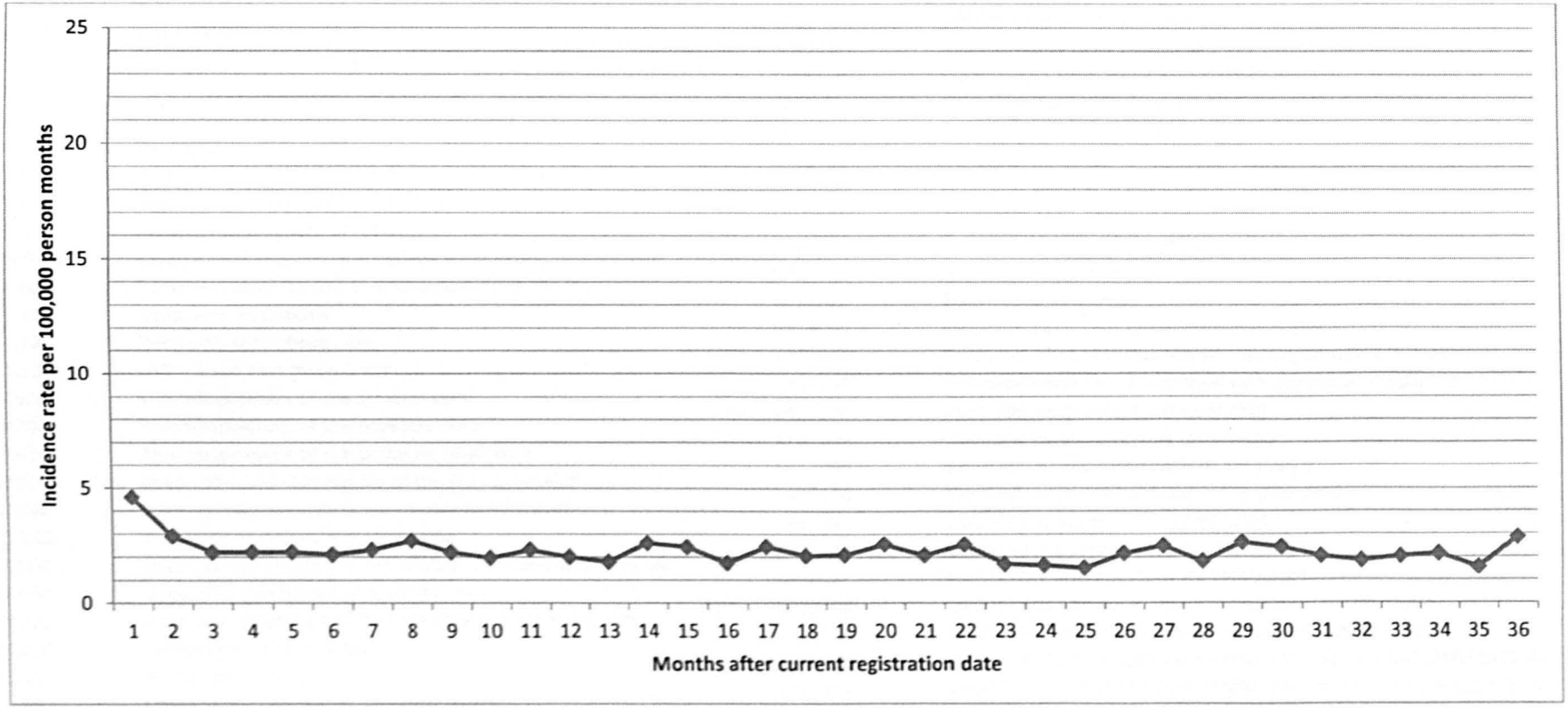
Appendix 1: Search strategy used for Medline database

No.	Terms
1	epidemiologic studies.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2	exp cohort studies/
3	(cohort adj (study or studies)).tw.
4	Epidemiologic Studies/
5	Cohort Studies/
6	(follow up adj (study or studies)).tw.
7	(observational adj (study or studies)).tw.
8	logitudinal.tw.
9	retrospective.tw.
10	Incidence/
11	exp Case-control studies/
12	case control.tw.
13	or/1-12
14	exp Venous thromboembolism/
15	exp Venous Thrombosis/
16	exp Thrombosis/
17	exp Pulmonary Embolism/
18	exp deep vein thrombosis/
19	(dvt$ or (deep adj8 (vein$ or ven$) adj8 thromb$) or embol$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20	14 or 15 or 16 or 17 or 18 or 19
21	exp pregnancy/
22	exp antepartum/
23	exp postpartum/
24	21 or 22 or 23
25	13 and 20 and 24
26	limit 25 to yr="1960 -Current"
27	limit 26 to english language
28	limit 27 to humans

Appendix 2: Search strategy used for Embase database

No.	Terms
1	clinical study/
2	case control study
3	family study/
4	longitudinal study/
5	retrospective study/
6	Prospective study/
7	Randomized controlled trials/
8	6 not 7
9	Cohort analysis/
10	(Cohort adj (study or studies)).mp.
11	(Case control adj (study or studies)).tw.
12	(follow up adj (study or studies)).tw.
13	(observational adj (study or studies)).tw.
14	(epidemiologic$ adj (study or studies)).tw.
15	(cross sectional adj (study or studies)).tw.
16	or/1-5,8-15
17	exp pregnancy/
18	antepartum.mp.
19	antenatal.mp.
20	postpartum.mp.
21	postnatal.mp.
22	17 or 18 or 19 or 20 or 21
23	(dvt$ or (deep adj8 (vein$ or ven$) adj8 thromb$) or embol$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24	exp embolism/ or exp thromboembolism/ or exp thrombosis/ or exp venous thromboembolism/ or exp vein thrombosis/ or exp lung embolism/
25	exp pulmonary embolism/
26	exp deep vein thrombosis/
27	23 or 24 or 25 or 26
28	16 and 22 and 27
29	limit 28 to english language
30	limit 29 to human

Appendix 3: Incidence rate VTE per 100,000 person-months in the months following registration



Appendix 4: VTE Read code list

Readcodes	Description
8HTm.00	Referral to deep vein thrombosis clinic
F053200	Thrombophlebitis lateral venous sinus
F423811	Retinal vein thrombosis
G401.00	PULMONARY EMBOLISM
G401.12	Pulmonary embolus
G401000	Post operative pulmonary embolus
G401100	Recurrent pulmonary embolism
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G801.00	Deep vein phlebitis and thrombophlebitis of the leg
G801.11	Deep vein thrombosis
G801.12	Deep vein thrombosis, leg
G801.13	DVT - Deep vein thrombosis
G801600	Thrombophlebitis of the femoral vein
G801700	Thrombophlebitis of the popliteal vein
G801A00	Thrombophlebitis of the posterior tibial vein
G801B00	Deep vein thrombophlebitis of the leg unspecified
G801C00	Deep vein thrombosis of leg related to air travel
G801D00	Deep vein thrombosis of lower limb
G801E00	Deep vein thrombosis of leg related to intravenous drug use
G801F00	Deep vein thrombosis of peroneal vein
G801z00	Deep vein phlebitis and thrombophlebitis of the leg NOS
G802000	Thrombosis of vein of leg
G81..00	Portal vein thrombosis
G82..00	Other venous embolism and thrombosis
G820.00	Budd - Chiari syndrome (hepatic vein thrombosis)
G820.11	Hepatic vein thrombosis
G822.00	Embolism and thrombosis of the vena cava
G823.00	Embolism and thrombosis of the renal vein
G82z100	Thrombosis of vein NOS
G8y2100	Inferior vena cava syndrome
G8y2200	Superior vena cava syndrome
L096400	PULMONARY EMBOLISM FOLLOWING ABORTIVE PREGNANCY
L413.00	Antenatal deep vein thrombosis
L413.11	DVT - deep venous thrombosis, antenatal
L413000	Antenatal deep vein thrombosis unspecified
L413100	Antenatal deep vein thrombosis - delivered
L413200	Antenatal deep vein thrombosis with antenatal complication
L413z00	Antenatal deep vein thrombosis NOS
L414.00	Postnatal deep vein thrombosis
L414.11	DVT - deep venous thrombosis, postnatal
L414000	Postnatal deep vein thrombosis unspecified
L414100	Postnatal deep vein thrombosis - delivered with p/n comp
L414200	Postnatal deep vein thrombosis with postnatal complication
L414z00	Postnatal deep vein thrombosis NOS
L417.00	Obstetric cerebral venous thrombosis
L417000	Cerebral venous thrombosis in pregnancy
L417100	Cerebral venous thrombosis in the puerperium
L43..00	OBSTETRIC PULMONARY EMBOLISM
L43..11	Obstetric pulmonary embolus
L430.00	OBSTETRIC AIR PULMONARY EMBOLISM
L430000	OBSTETRIC AIR PULMONARY EMBOLISM UNSPECIFIED
L430100	OBSTETRIC AIR PULMONARY EMBOLISM - DELIVERED
L430300	OBSTETRIC AIR PULMONARY EMBOLISM WITH A/N COMPLICATION
L430400	OBSTETRIC AIR PULMONARY EMBOLISM WITH P/N COMPLICATION
L430z00	OBSTETRIC AIR PULMONARY EMBOLISM NOS
L431.00	AMNIOTIC FLUID PULMONARY EMBOLISM
L431000	AMNIOTIC FLUID PULMONARY EMBOLISM UNSPECIFIED
L431100	AMNIOTIC FLUID PULMONARY EMBOLISM - DELIVERED
L431300	AMNIOTIC FLUID PULMONARY EMBOLISM WITH A/N COMPLICATION

L431400	AMNIOTIC FLUID PULMONARY EMBOLISM WITH P/N COMPLICATION
L431z00	AMNIOTIC FLUID PULMONARY EMBOLISM NOS
L432.00	OBSTETRIC BLOOD-CLOT PULMONARY EMBOLISM
L432000	OBSTETRIC BLOOD-CLOT PULMONARY EMBOLISM UNSPECIFIED
L432100	OBSTETRIC BLOOD-CLOT PULMONARY EMBOLISM - DELIVERED
L432300	OBSTETRIC BLOOD-CLOT PULMONARY EMBOLISM + A/N COMPLICATION
L432400	OBSTETRIC BLOOD-CLOT PULMONARY EMBOLISM + P/N COMPLICATION
L432z00	OBSTETRIC BLOOD-CLOT PULMONARY EMBOLISM NOS
L433.00	OBSTETRIC PYAEMIC AND SEPTIC PULMONARY EMBOLISM
L433000	OBSTETRIC PYAEMIC AND SEPTIC PULMONARY EMBOLISM UNSPECIFIED
L433100	OBSTETRIC PYAEMIC AND SEPTIC PULMONARY EMBOLISM - DELIVERED
L433z00	OBSTETRIC PYAEMIC AND SEPTIC PULMONARY EMBOLISM NOS
L43y.00	OTHER OBSTETRIC PULMONARY EMBOLISM
L43y000	OTHER OBSTETRIC PULMONARY EMBOLISM UNSPECIFIED
L43y100	OTHER OBSTETRIC PULMONARY EMBOLISM - DELIVERED
L43y200	OTHER OBSTETRIC PULMONARY EMBOLISM - DELIVERED + P/N COMP
L43y300	OTHER OBSTETRIC PULMONARY EMBOLISM WITH ANTENATAL COMP
L43y400	OTHER OBSTETRIC PULMONARY EMBOLISM WITH POSTNATAL COMP
L43yz00	OTHER OBSTETRIC PULMONARY EMBOLISM NOS
L43z.00	OBSTETRIC PULMONARY EMBOLISM NOS
L43z000	OBSTETRIC PULMONARY EMBOLISM NOS, UNSPECIFIED
L43z100	OBSTETRIC PULMONARY EMBOLISM NOS - DELIVERED
L43z200	OBSTETRIC PULMONARY EMBOLISM NOS - DELIVERED WITH P/N COMP
L43z300	OBSTETRIC PULMONARY EMBOLISM NOS WITH ANTENATAL COMPLICATION
L43z400	OBSTETRIC PULMONARY EMBOLISM NOS WITH POSTNATAL COMPLICATION
L43zz00	OBSTETRIC PULMONARY EMBOLISM NOS
SP12200	Post operative deep vein thrombosis
SP32100	Thromboembolism after infusion

Appendix 5: Anticoagulant prescription codes (multilex)

Miltilex code	generic_name
Unfractionated heparin	
85596998	Heparin calcium inj 12500 iu/0.5ml 10 pre-filled syringe
93267990	HEPARIN SODIUM pf inj 5000 i.u./5ml
85583998	Heparin sodium preservative free inj 5000 i.u./1ml 10 ampoule(s)
93363990	HEPARIN SODIUM pf inj 10000 i.u./10ml
93388996	Heparin sodium inj 10000 iu/ml 10 1ml ampoule(s)
93387998	Heparin sodium inj 25000 i.u./ml 0.2ml ampoule(s) 10
96836992	HEPARIN Ca 12,500iu/0.5mL syr
96246990	HEPARIN SODIUM pf inj 1000 i.u./ml
93387997	Heparin sodium sc inj 25000 i.u./ml 50 0.2ml pre-filled syringe
96246988	HEPARIN SODIUM inj 25000 i.u./ml
93360990	HEPARIN SODIUM pf inj 25000 i.u./5ml
85590998	Heparin sodium inj 5000 i.u./5ml 10 vial(s)
87599998	Heparin sodium preservative free inj 5000 i.u./ml 0.2ml ampoule(s) 10
98265996	HEPARIN SODIUM inj 10000 iu/ml
97531996	HEPARIN SODIUM inj 25000 i.u./ml
97531998	HEPARIN SODIUM inj 1000 i.u./ml
85582998	Heparin sodium preservative free inj 25000 i.u./5ml 10 ampoule(s)
95012990	HEPARIN SODIUM inj 125000 i.u./5ml
93387996	Heparin sodium soln 10 units/ml 10 5ml ampoule(s)
96678992	Heparin sod. 25000u/ml 0.2ml pf inj 0
98265998	HEPARIN SODIUM inj 1000 i.u./ml
93385992	HEPARIN CALCIUM
99420998	HEPARIN SODIUM sc inj 25000 i.u./ml
97530996	HEPARIN SODIUM pf inj 25000 i.u./ml
98826998	HEPARIN CALCIUM inj 25000 i.u./ml
93356990	HEPARIN SODIUM inj 25000 i.u./5ml
85585998	HEPARIN SODIUM PRESERVATIVE FREE
93365990	HEPARIN SODIUM pf inj 1000 i.u./1ml
95013990	HEPARIN SODIUM inj 25000 i.u./5ml
85581998	Heparin sodium preservative free inj 5000 i.u./0.2ml ampoule(s) 10
93266990	HEPARIN SODIUM pf inj 10000 i.u./10ml
93359990	HEPARIN SODIUM pf inj 25000 i.u./1ml
93355990	HEPARIN SODIUM inj 125000 i.u./5ml
95288992	HEPARIN Na 5000iu/0.2mL syrng
95957992	HEPARIN Na 5000iu/0.2mL syrng
93362990	HEPARIN SODIUM pf inj 20000 i.u./20ml
93358990	HEPARIN SODIUM pf inj 5000 i.u./0.2ml
98539990	Heparin sodium inj 25000 i.u./ml 1ml ampoule(s) 5
98264998	HEPARIN SODIUM inj 25000 i.u./ml
85593998	HEPARIN CALCIUM inj 5000 i.u./0.2ml
97759992	HEPARIN Na 5000iu/0.2mL syrng
96339992	HEPARIN Na 5000iu/0.2mL inj
93361990	HEPARIN SODIUM pf inj 5000 i.u./1ml
85584998	HEPARIN SODIUM PRESERVATIVE FREE
93932998	HEPARIN CALCIUM inj 25000 i.u./ml
85597998	Heparin calcium inj 5000 i.u./0.2ml 10 pre-filled syringe
98541990	HEPARIN SODIUM inj 25000 i.u./ml
95091992	HEPARIN SODIUM
98540990	Heparin calcium inj 25000 i.u./ml 0.5ml syringe(s) 15
93354990	HEPARIN CALCIUM inj 5000 i.u./0.2ml
97530998	HEPARIN SODIUM pf inj 1000 i.u./ml
97531997	HEPARIN SODIUM inj 5000 i.u./ml
93388997	Heparin sodium inj 5000 i.u./ml 0.2ml ampoule(s) 10
97573992	Heparin calcium b.p. inj 0
98542990	HEPARIN CALCIUM inj 25000 i.u./ml
93388998	Heparin sodium inj 1000 i.u./ml 5ml vial(s) 10
94950998	HEPARIN CALCIUM inj 25000 i.u./ml
93357990	HEPARIN SODIUM inj 5000 i.u./5ml

85586998 HEPARIN SODIUM PRESERVATIVE FREE
97529998 HEPARIN SODIUM sc inj 25000 i.u./ml
85588998 Heparin sodium inj 125000 i.u./5ml 10 vial(s)
98265997 HEPARIN SODIUM inj 5000 i.u./ml
85589998 Heparin sodium inj 25000 i.u./5ml 10 vial(s)
90388998 Heparin calcium inj 25000 i.u./ml 0.5ml syringe(s) 15
85580998 Heparin sodium preservative free inj 25000 i.u./1ml ampoule(s) 10
93265990 HEPARIN SODIUM pf inj 20000 i.u./20ml
97530997 HEPARIN SODIUM pf inj 5000 i.u./ml
95014990 HEPARIN SODIUM inj 5000 i.u./5ml
94842998 HEPARIN SODIUM sc inj 25000 i.u./ml
97412998 HEPARIN CALCIUM inj 25000 i.u./ml
85587998 HEPARIN SODIUM PRESERVATIVE FREE
87600998 Heparin sodium preservative free inj 1000 i.u./ml 20ml ampoule(s) 10
87598998 HEPARIN SODIUMPRESERVATIVE FREE
96236998 HEPARIN SODIUM inj 1000 i.u./ml
96677992 Heparin sodium b.p. 5000 i/u inj 0
93364990 HEPARIN SODIUM pf inj 5000 i.u./5ml
96246989 HEPARIN SODIUM inj 5000 i.u./ml
85592998 HEPARIN CALCIUM inj 12500 iu/0.5ml

Low Molecular weight heparin

93400998 DALTEPARIN inj soln 10000 iu/4ml
87267998 DALTEPARIN inj soln 10000 iu/0.4ml
87633998 Tinzaparin inj 10000 i.u./0.5ml 6 0.5ml pre-filled syringe
93180997 ENOXAPARIN inj 150mg/ml
92739998 Dalteparin inj soln 5000iu/0.2ml 10 0.2ml syringe
87265998 DALTEPARIN inj soln 15000 iu/0.6ml
87630998 TINZAPARIN inj 40000 i.u./2ml
93398996 HEPARINLOW MOLECULAR WEIGHT
93179998 Enoxaparin inj 100mg/ml 1ml pre-filled syringe (150mg) 10
87631998 Tinzaparin inj 18000 i.u./0.9ml 6 0.9ml pre-filled syringe
87271998 Dalteparin inj soln 12500 iu/0.5ml 5 0.5ml pre-filled syringe
87841998 Bemiparin sodium inj soln 3500 iu 10 pre-filled syringe
87273998 Dalteparin inj soln 7500 iu/0.3ml 10 0.3ml pre-filled syringe
93870996 HEPARINLOW MOLECULAR WEIGHT
98287996 Dalteparin inj soln 2500iu/0.2ml 10 0.2ml syringe
87584998 ENOXAPARIN inj 120mg/0.8ml
90543998 TINZAPARIN sterile soln 5000 i.u./5ml
87842998 Bemiparin sodium inj soln 2500 iu 10 pre-filled syringe
97660996 TINZAPARIN inj 10000 IU/ml
87627998 TINZAPARIN inj 18000 i.u./0.9ml
92739996 Dalteparin inj soln 25000 iu/ml 0.3ml pre-filled syringe 10
98287998 Dalteparin inj soln 10000 iu/4ml 10 ampoule(s)
92647998 TINZAPARIN inj 20000 iu/ml
87264998 DALTEPARIN inj soln 18000 iu/0.72ml
87628998 TINZAPARIN inj 14000 i.u./0.7ml
87591998 Enoxaparin inj 60mg/0.6ml 10 pre-filled syringe
87639998 TINZAPARIN inj 20000 i.u./2ml
93870998 HEPARINLOW MOLECULAR WEIGHT
85809998 Enoxaparin inj 150mg/1ml 10 pre-filled syringe
87586998 ENOXAPARIN inj 60mg/0.6ml
93179997 Enoxaparin inj 150mg/ml pre-filled syringe 10
93865998 DALTEPARIN inj soln 5000iu/0.2ml
84428998 DALTEPARIN inj soln 10000 iu/1ml
92967998 Danaparoid sodium inj 750 iu/0.6ml 10 ampoule(s)
87270998 Dalteparin inj soln 15000 iu/0.6ml 5 0.6ml pre-filled syringe
93180998 ENOXAPARIN inj 100mg/ml
87585998 ENOXAPARIN inj 80mg/0.8ml
87642998 Tinzaparin inj 3500 i.u./0.35ml 10 0.35ml prefilled unit dose syringe
87635998 TINZAPARIN inj 2500 i.u./0.25ml

93865997 DALTEPARIN inj soln 100,000 iu/4ml
93400997 DALTEPARIN inj soln 10000 iu/1ml
87594998 Enoxaparin inj 20mg/0.2ml 10 pre-filled syringe
97666997 TINZAPARIN sterile soln 3500 IU/0.3ml
87592998 Enoxaparin inj 40mg/0.4ml 10 pre-filled syringe
87590998 Enoxaparin inj 80mg/0.8ml 10 pre-filled syringe
92739997 Dalteparin inj soln 100,000 iu/4ml 1 4ml multidose vial
87636998 TINZAPARIN inj 4500 i.u./0.45ml
93865996 DALTEPARIN inj soln 25000 iu/ml
87588998 ENOXAPARIN inj 20mg/0.2ml
87643998 Tinzaparin inj 20000 i.u./2ml 10 2ml vial(s)
90544998 Tinzaparin sterile soln 5000 i.u./5ml 10 5ml ampoule(s)
87589998 Enoxaparin inj 120mg/0.8ml 10 pre-filled syringe
87641998 Tinzaparin inj 4500 i.u./0.45ml 10 0.45ml prefilled unit dose syringe
97627998 HEPARINLOW MOLECULAR WEIGHT
87795998 Bemiparin sodium inj soln 7500 iu 2 pre-filled syringe
98287997 Dalteparin inj soln 10000 iu/1ml 1ml graduated syringe 5
87840998 Bemiparin sodium inj soln 5000 iu 10 pre-filled syringe
87632998 Tinzaparin inj 14000 i.u./0.7ml 6 0.7ml pre-filled syringe
91404998 Tinzaparin inj 20000 iu/ml 0.9ml pre-filled syringe 6
97660998 TINZAPARIN sterile soln 3500 IU/0.3ml
87793998 BEMIPARIN SODIUM inj soln 7500 iu
94154998 ENOXAPARIN inj 150mg/ml
84607998 ENOXAPARIN inj 300mg/3ml
87629998 TINZAPARIN inj 10000 i.u./0.5ml
85807998 ENOXAPARIN inj 150mg/1ml
93398997 HEPARINLOW MOLECULAR WEIGHT
87587998 ENOXAPARIN inj 40mg/0.4ml
87837998 BEMIPARIN SODIUM inj soln 5000 iu
97633996 Tinzaparin sterile soln 2500 iu/0.21ml 5 0.21ml unit dose syringe
87272998 Dalteparin inj soln 10000 iu/0.4ml 5 0.4ml pre-filled syringe
85810998 Enoxaparin inj 100mg/1ml 10 pre-filled syringe
99021997 Tinzaparin inj 10000 iu/ml 0.25ml prefilled unit dose syringe 10
99021998 Tinzaparin sterile soln 4500 iu/0.39ml 5 0.39ml unit dose syringe
84427998 DALTEPARIN inj soln 10000 iu/1ml
97633997 Tinzaparin sterile soln 5000 i.u./0.5ml 10 0.5ml ampoule(s)
87637998 TINZAPARIN inj 3500 i.u./0.35ml
93398998 HEPARINLOW MOLECULAR WEIGHT
97627997 Heparin low molecular weight sterile soln 4500 iu/0.39ml 5 0.39ml unit dose syri
92966998 DANAPAROID SODIUM inj 750 iu/0.6ml
87838998 BEMIPARIN SODIUM inj soln 3500 iu
87634998 Tinzaparin inj 40000 i.u./2ml 1 2ml vial(s)
97666998 TINZAPARIN sterile soln 2500 IU/0.21ml
97633998 Tinzaparin sterile soln 3500 iu/0.3ml 10 0.3ml unit dose syringe
93045992 TINZAPARIN 20,000iu/2mL inj
93870997 HEPARINLOW MOLECULAR WEIGHT
87640998 Tinzaparin inj 2500 i.u./0.25ml 10 0.25ml prefilled unit dose syringe
93400996 DALTEPARIN inj soln 2500iu/0.2ml
87268998 DALTEPARIN inj soln 7500 iu/0.3ml
85808998 ENOXAPARIN inj 100mg/1ml
87266998 DALTEPARIN inj soln 12500 iu/0.5ml
87269998 Dalteparin inj soln 18000 iu/0.72ml 5 0.72ml pre-filled syringe
97666996 TINZAPARIN sterile soln 4500 IU/0.39ml
84608998 Enoxaparin inj 300mg/3ml 1 multi-dose vial(s)
97660997 TINZAPARIN sterile soln 5000 i.u./0.5ml
87839998 BEMIPARIN SODIUM inj soln 2500 iu
87792998 BEMIPARIN SODIUM inj soln 10000 iu
87794998 Bemiparin sodium inj soln 10000 iu 2 pre-filled syringe

Oral anticoagulants

95630990 WARFARIN SODIUM tabs 500 micrograms
96318989 WARFARIN SODIUM tabs 3mg
83976998 WARFARIN SODIUM

95234990	WARFARIN SODIUM tabs 3mg
99331989	WARFARIN SODIUM tabs 3mg
96163990	WARFARIN SODIUM tabs 1mg
83977998	WARFARIN SODIUM
94877990	WARFARIN SODIUM tabs 5mg
97089989	WARFARIN SODIUM tabs 3mg
97941990	WARFARIN SODIUM tabs 1mg
97089988	WARFARIN SODIUM tabs 5mg
97711989	WARFARIN SODIUM tabs 3mg
96161990	WARFARIN SODIUM tabs 5mg
96318988	WARFARIN SODIUM tabs 5mg
95617998	Warfarin sodium tabs 1mg 28 tablet(s)
99331990	WARFARIN SODIUM tabs 1mg
98906998	WARFARIN SODIUM tabs 1mg
98014988	WARFARIN SODIUM tabs 5mg
92245998	WARFARIN SODIUM tabs 500 micrograms
98289996	WARFARIN SODIUM tabs 5mg
95513990	WARFARIN SODIUM tabs 3mg
95512990	WARFARIN SODIUM tabs 5mg
98031989	WARFARIN SODIUM tabs 3mg
97089990	WARFARIN SODIUM tabs 1mg
95514990	WARFARIN SODIUM tabs 1mg
98031988	WARFARIN SODIUM tabs 5mg
86425998	WARFARIN SODIUM
95237990	WARFARIN SODIUM tabs 1mg
96162990	WARFARIN SODIUM tabs 3mg
96308990	WARFARIN SODIUM tabs 1mg
98906997	WARFARIN SODIUM tabs 3mg
88944998	Warfarin sodium tabs 500 micrograms 28 tablet(s)
99035989	WARFARIN SODIUM tabs 5mg
98289997	WARFARIN SODIUM tabs 3mg
97941989	WARFARIN SODIUM tabs 3mg
96308988	WARFARIN SODIUM tabs 5mg
99034990	WARFARIN SODIUM tabs 1mg
98289998	WARFARIN SODIUM tabs 1mg
98031990	WARFARIN SODIUM tabs 1mg
98906996	WARFARIN SODIUM tabs 5mg
93532990	WARFARIN SODIUM tabs 500 micrograms
99034989	WARFARIN SODIUM tabs 3mg
98014989	WARFARIN SODIUM tabs 3mg
93227990	WARFARIN SODIUM tabs 500 micrograms
93575990	WARFARIN SODIUM tabs 5mg
95232990	WARFARIN SODIUM tabs 5mg
84565998	WARFARIN SODIUM
99035990	WARFARIN SODIUM tabs 1mg
94878990	WARFARIN SODIUM tabs 3mg
95741992	WARFARIN
98014990	WARFARIN SODIUM tabs 1mg
93576990	WARFARIN SODIUM tabs 3mg
95243992	WARFARIN SODIUM
94879990	WARFARIN SODIUM tabs 1mg
93577990	WARFARIN SODIUM tabs 1mg
94106990	WARFARIN SODIUM tabs 5mg
95617997	Warfarin sodium tabs 3mg 28 tablet(s)
94108990	WARFARIN SODIUM tabs 1mg
96308989	WARFARIN SODIUM tabs 3mg
99331988	WARFARIN SODIUM tabs 5mg
95617996	Warfarin sodium tabs 5mg 28 tablet(s)
97711990	WARFARIN SODIUM tabs 1mg
97941988	WARFARIN SODIUM tabs 5mg
94107990	WARFARIN SODIUM tabs 3mg
97711988	WARFARIN SODIUM tabs 5mg

99034988	WARFARIN SODIUM tabs 5mg
96318990	WARFARIN SODIUM tabs 1mg
95556997	Phenindione tabs 25mg tablet(s) 28
99138998	ACENOCOUMAROL tabs 1mg
96447989	PHENINDIONE tabs 25mg
91984998	Fondaparinux sodium inj 2.5mg/0.5ml 10 0.5ml pre-filled syringe (2.5mg)
88070998	LEPIRUDIN inj 50mg
86850998	FONDAPARINUX SODIUM inj 7.5mg/0.6ml
96749997	Acenocoumarol tabs 4mg 100 tablet(s)
86853998	Fondaparinux sodium inj 7.5mg/0.6ml 10 0.6ml pre-filled syringe
84390998	FONDAPARINUX SODIUM inj 1.5mg/0.3ml
99138997	ACENOCOUMAROL tabs 4mg
86849998	FONDAPARINUX SODIUM inj 10mg/0.8ml
95556996	Phenindione tabs 50mg tablet(s) 28
98293998	PHENINDIONE tabs 10mg
84391998	Fondaparinux sodium inj 1.5mg/0.3ml
88073998	Lepirudin inj 50mg 1 vial(s)
96749998	Acenocoumarol tabs 1mg 100 tablet(s)
86854998	Fondaparinux sodium inj 5mg/0.4ml 10 0.4ml pre-filled syringe
98293997	PHENINDIONE tabs 25mg
95556998	Phenindione tabs 10mg tablet(s) 28
96447988	PHENINDIONE tabs 50mg
96447990	PHENINDIONE tabs 10mg
88974998	FONDAPARINUX SODIUM inj 2.5mg/0.5ml
86851998	FONDAPARINUX SODIUM inj 5mg/0.4ml
98293996	PHENINDIONE tabs 50mg
86852998	Fondaparinux sodium inj 10mg/0.8ml 10 0.8ml pre-filled syringe

Appendix 6: Medical codes indicating anticoagulant therapy

Readcode	Description
14LP.00	H/O: warfarin allergy
14P1.00	H/O: anticoagulant therapy
42P8.00	Heparin induced thrombocytopenia screening test
42Q7.00	Heparin assay
66Q..00	Warfarin monitoring
66Q..11	Anticoagulant monitoring
66Q1.00	Initial warfarin assessment
66Q2.00	Follow-up warfarin assessment
66Q3.00	Warfarin side effects
66Q4.00	Warfarin dose changed
66Q5.00	Warfarin therapy stopped
66Q6.00	Warfarin therapy started
66Q9.00	Warfarin dose unchanged
66QA.00	Warfarin treatment plan
66QB.00	Annual warfarin assessment
66QZ.00	Warfarin monitoring NOS
66c1.00	Anticoagulant therapy stopped
7L10400	Continuous infusion of heparin
7L10400	Continuous infusion of heparin
7L19B00	Subcutaneous injection of heparin
7L19B00	Subcutaneous injection of heparin
88A5.00	Anticoagulant therapy
8B2K.00	Anticoagulant prescribed by third party
8B61.00	Anticoagulant prophylaxis
8B6X.00	Low dose heparin prophylaxis
8BG7.00	Warfarin indicated
8BP7.00	Duration of anticoagulant therapy
8CAu.00	Patient advised of anticoagulant dose
8HHW.00	Referral for warfarin monitoring
8I25.00	Warfarin contraindicated
8I3E.00	Warfarin declined
8I65.00	Warfarin not indicated
8I71.00	Warfarin not tolerated
9NiJ.00	Did not attend general practitioner anticoagulant clinic
9k23.00	Pt held anticoagulant therapy record updatd - enh serv admin
9k23.11	Patient held anticoagulant therapy record updated
9k24.11	Date of next anticoagulant clinic appointment
D305.00	Haemorrhagic disorder due to circulating anticoagulants
D305100	Haemorrhagic disorder due to hyperheparinaemia
D305z00	Heamorrhagic disorder due to circulating anticoagulants NOS
PK82.00	Dysmorphism due to warfarin
SL42.00	Anticoagulant poisoning
SL42100	Heparin poisoning
SL42300	Warfarin sodium poisoning
SL42400	Warfarin poisoning
SL42z00	Anticoagulant poisoning NOS
SL45.00	Anticoagulant agonist poisoning
SL45z00	Anticoagulant agonist poisoning NOS
T937300	Accidental poisoning by warfarin
TJ42.00	Adverse reaction to anticoagulants
TJ42000	Adverse reaction to heparin
TJ42000	Adverse reaction to heparin
TJ42100	Adverse reaction to warfarin sodium
TJ42z00	Adverse reaction to anticoagulants NOS
U604200	[X]Anticoagulant causing adverse effects in therapeutic use
U604211	[X] Adverse reaction to anticoagulants
U604212	[X] Adverse reaction to heparin
U604213	[X] Adverse reaction to warfarin sodium

U604216	[X] Adverse reaction to anticoagulants NOS
U604314	[X] Adverse reaction to anticoagulant antagonists
U604318	[X] Adverse reaction to anticoagulant antagonist NOS
Z1Q2C00	Giving anticoagulant therapy

Appendix 7: Derivation of date of death

Although deaths recorded in the primary care data are accurate, it is important to know how these data are recorded in the Vision practice management software by General Practitioner (GP). When a patient dies, a GP should record a Read code for death known as the Statement of Death in the medical record. However there is often a delay between the actual date of the patient's death and the recorded transfer out date indicating transfer out reason as death (the median delay is 19 days). Whilst THIN provides data on date of death which is the last date associated with death administration or medical codes indicating death, there are inconsistencies in the recorded codes for deaths and transfer out dates. Furthermore, there may be instances where a practice might not update the registration status of patients, in which case patients who have died will appear to be alive in the dataset. Mortalities and dates of death were also identified using combinations of medical and death administration codes (presented below). The following steps were taken to ensure that the date of death recorded is accurate and consistent with the transfer out date and that there are no immortal persons in the data in addition to the information on deaths provided by THIN.

Step 1:

A patient was considered to be dead, if she had medical or death administration codes which indicated unequivocally that the patient has died. The date of the medical/death administration code was used as date of death if it preceded the transfer out date by 95 days. In cases where there was no date of death, a medical code indicating death or death administration record, the transfer out date was used as date of death if patient registration status indicated that the patient has died.

Step 2

For medical codes or death administration codes recorded after the transfer out date, the latter date was used as the date of death. For patients with medical codes or death administration record which preceded the transfer out date by more than 95 days, prescription records were explored. A patient was only considered dead, it she had no prescription record for two years after the code for death. Date of medical/dead administration codes was used as the date of death. The same was done for those with medical codes indicating death but no transfer out date. For patients with no transfer out date but with medical/death administration code, these were only considered dead if they had no prescription records two years after the date of death. In this instance date of medical/death administration code was used as date of death.

Appendix 8: Body mass index codes

Medcode	Description
22K1.00	Body Mass Index normal K/M2
22K2.00	Body Mass Index high K/M2
22K3.00	Body Mass Index low K/M2
22K4.00	Body mass index index 25-29 - overweight
22K5.00	Body mass index 30+ - obesity
22K6.00	Body mass index less than 20
22K7.00	Body mass index 40+ - severely obese
22K8.00	Body mass index 20-24 - normal

Ahdcode	Description
1005010200	Weight

Appendix 9: Smoking codes

Medcode	Description
137..11	Smoker - amount smoked
1371.00	Never smoked tobacco
1371.11	Non-smoker
1372.00	Trivial smoker - < 1 cig/day
1372.11	Occasional smoker
1373.00	Light smoker - 1-9 cigs/day
1374.00	Moderate smoker - 10-19 cigs/d
1375.00	Heavy smoker - 20-39 cigs/day
1376.00	Very heavy smoker - 40+cigs/d
1377.00	Ex-trivial smoker (<1/day)
1378.00	Ex-light smoker (1-9/day)
1379.00	Ex-moderate smoker (10-19/day)
137A.00	Ex-heavy smoker (20-39/day)
137B.00	Ex-very heavy smoker (40+/day)
137C.00	Keeps trying to stop smoking
137F.00	Ex-smoker - amount unknown
137G.00	Trying to give up smoking
137H.00	Pipe smoker
137J.00	Cigar smoker
137K.00	Stopped smoking
137K000	Recently stopped smoking
137L.00	Current non-smoker
137M.00	Rolls own cigarettes
137N.00	Ex pipe smoker
137O.00	Ex cigar smoker
137P.00	Cigarette smoker
137P.11	Smoker
137Q.00	Smoking started
137Q.11	Smoking restarted
137R.00	Current smoker
137S.00	Ex smoker
137T.00	Date ceased smoking
137V.00	Smoking reduced
137X.00	Cigarette consumption
137Y.00	Cigar consumption
137b.00	Ready to stop smoking
137c.00	Thinking about stopping smoking
137d.00	Not interested in stopping smoking
137e.00	Smoking restarted
137f.00	Reason for restarting smoking
137g.00	Cigarette pack-years
137h.00	Minutes from waking to first tobacco consumption
137j.00	Ex-cigarette smoker
137l.00	Ex roll-up cigarette smoker
13p0.00	Negotiated date for cessation of smoking
13p4.00	Smoking free weeks
13p5.00	Smoking cessation programme start date
1V08.00	Smokes drugs in cigarette form
1V09.00	Smokes drugs through a pipe
6791.00	Health ed. - smoking
67A3.00	Pregnancy smoking advice
67H1.00	Lifestyle advice regarding smoking
67H6.00	Brief intervention for smoking cessation
745H.00	Smoking cessation therapy
745H000	Nicotine replacement therapy using nicotine patches
745H100	Nicotine replacement therapy using nicotine gum
745H200	Nicotine replacement therapy using nicotine inhalator
745H300	Nicotine replacement therapy using nicotine lozenges
745H400	Smoking cessation drug therapy

745Hy00	Other specified smoking cessation therapy
745Hz00	Smoking cessation therapy NOS
8B2B.00	Nicotine replacement therapy
8B3Y.00	Over the counter nicotine replacement therapy
8B3f.00	Nicotine replacement therapy provided free
8BP3.00	Nicotine replacement therapy provided by community pharmacis
8CAL.00	Smoking cessation advice
8CAg.00	Smoking cessation advice provided by community pharmacist
8H7i.00	Referral to smoking cessation advisor
8HTK.00	Referral to stop-smoking clinic
8HkQ.00	Referral to NHS stop smoking service
8I2I.00	Nicotine replacement therapy contraindicated
8I39.00	Nicotine replacement therapy refused
8IAj.00	Smoking cessation advice declined
9N2k.00	Seen by smoking cessation advisor
9N4M.00	DNA - Did not attend smoking cessation clinic
9OO1.00	Attends stop smoking monitor.
9OO2.00	Refuses stop smoking monitor
9OO3.00	Stop smoking monitor default
9OO7.00	Stop smoking monitor verb.inv.
9OO8.00	Stop smoking monitor phone inv
9km..00	Ex-smoker annual review - enhanced services administration
9km..11	Ex-smoker annual review
9kn..00	Non-smoker annual review - enhanced services administration
9kn..11	Non-smoker annual review
9ko..00	Current smoker annual review - enhanced services admin
9ko..11	Current smoker annual review
E251.00	Tobacco dependence
E251100	Tobacco dependence, continuous
E251300	Tobacco dependence in remission
E251z00	Tobacco dependence NOS

H310100	Smokers' cough
ZG23300	Advice on smoking
ZRBm200	Fagerstrom test for nicotine dependence
ZRBm211	FTND - Fagerstrom test for nicotine dependence
ZRaM.00	Motives for smoking scale
ZRaM.11	MFS - Motives for smoking scale
ZRao.00	Occasions for smoking scale
ZRao.11	OFS - Occasions for smoking scale
ZRh4.00	Reasons for smoking scale
ZRh4.11	RFS - Reasons for smoking scale
ZV6D800	[V]Tobacco abuse counselling

Ahdcode	**Description**
1003040000	Smoking

Appendix 10: Obstetric haemorrhage Read codes

Read code	description
7F22700	Pack to control postnatal vaginal bleeding
7F22711	Pack to control postnatal vaginal bleeding
7F22712	Pack to control postnatal haemorrhage
7F22713	Pack to control postpartum haemorrhage
7F24100	Obstetric uterine tamponade
851..00	Haemorrhage control by packing
851Z.00	Haemorr. control by pack NOS
G8y0.00	Haemorrhage NOS
K55y300	Haemorrhage of cervix
K56y100	Haemorrhage of vagina
K59yx00	Dysfunctional uterine haemorrhage NOS
K59yy00	Functional uterine haemorrhage NOS
L040100	Unspec spontaneous abortion + delayed/excessive haemorrhage
L041100	Incomp spontaneous abortion + delayed/excessive haemorrhage
L042100	Complete spontaneous abortion +delayed/excessive haemorrhage
L043111	Unsp inevitable mis comp by delayed or excessive haemorrhage
L044111	Incomplete inev mis comp by delayed or excessive haemorrhage
L050100	Unspecified legal abortion + delayed/excessive haemorrhage
L051100	Incomplete legal abortion + delayed or excessive haemorrhage
L052100	Complete legal abortion with delayed/excessive haemorrhage
L060100	Unspec illegal abortion + delayed or excessive haemorrhage
L061100	Incomplete illegal abortion + delayed/excessive haemorrhage
L062100	Complete illegal abortion + delayed or excessive haemorrhage
L070100	Unspecified abortion with delayed or excessive haemorrhage
L071100	Unspecified incomplete abortion + delayed/excess haemorrhage
L072100	Unspecified complete abortion +delayed/excessive haemorrhage
L081.00	Failed attempted abortion + delayed or excessive haemorrhage
L091.00	Delayed/excessive haemorrhage following abortive pregnancy
L091z00	Delayed/excess haemorrhage NOS following abortive pregnancy
L10..00	Haemorrhage in early pregnancy
L10y.00	Other haemorrhage in early pregnancy
L10y000	Other haemorrhage in early pregnancy unspecified
L10y100	Other haemorrhage in early pregnancy - delivered
L10y200	Other haemorrhage in early pregnancy - not delivered
L10yz00	Other haemorrhage in early pregnancy NOS
L10z.00	Early pregnancy haemorrhage NOS
L10z000	Early pregnancy haemorrhage NOS unspecified
L10z100	Early pregnancy haemorrhage NOS - delivered
L10z200	Early pregnancy haemorrhage NOS - not delivered
L10zz00	Early pregnancy haemorrhage NOS
L11..00	Antepartum haemorrhage, abruptio placentae, placenta praevia
L11..11	Antepartum haemorrhage
L111.00	Placenta praevia with haemorrhage
L111000	Placenta praevia with haemorrhage unspecified
L111100	Placenta praevia with haemorrhage - delivered
L111200	Placenta praevia with haemorrhage - not delivered
L111z00	Placenta praevia with haemorrhage NOS
L112.12	Couvelaire uterus
L113.00	Antepartum haemorrhage with coagulation defect
L113.11	Antepartum haemorrhage with afibrinogenaemia
L113.12	Antepartum haemorrhage with hyperfibrinolysis
L113.13	Antepartum haemorrhage with hypofibrinogenaemia
L113000	Antepartum haemorrhage with coagulation defect unspecified
L113100	Antepartum haemorrhage with coagulation defect - delivered
L113200	Antepartum haemorrhage with coagulation defect - not deliv
L113z00	Antepartum haemorrhage with coagulation defect NOS

L114.00	Antepartum haemorrhage with trauma
L114000	Antepartum haemorrhage with trauma unspecified
L114100	Antepartum haemorrhage with trauma - delivered
L114200	Antepartum haemorrhage with trauma - not delivered
L114z00	Antepartum haemorrhage with trauma NOS
L115.00	Antepartum haemorrhage with uterine leiomyoma
L115.11	Antepartum haemorrhage with fibroid
L115.12	Antepartum haemorrhage with uterine fibroid
L115000	Antepartum haemorrhage with uterine leiomyoma unspecified
L115100	Antepartum haemorrhage with uterine leiomyoma - delivered
L115200	Antepartum haemorrhage with uterine leiomyoma - not deliv
L115z00	Antepartum haemorrhage with uterine leiomyoma NOS
L11y.00	Other antepartum haemorrhage
L11y000	Other antepartum haemorrhage unspecified
L11y100	Other antepartum haemorrhage - delivered
L11y200	Other antepartum haemorrhage - not delivered
L11yz00	Other antepartum haemorrhage NOS
L11z.00	Antepartum haemorrhage NOS
L11z000	Antepartum haemorrhage NOS, unspecified
L11z100	Antepartum haemorrhage NOS - delivered
L11z200	Antepartum haemorrhage NOS - not deliv
L11zz00	Antepartum haemorrhage NOS
L260.00	Fetal-maternal haemorrhage
L260000	Fetal-maternal haemorrhage unspecified
L260100	Fetal-maternal haemorrhage - delivered
L260200	Fetal-maternal haemorrhage with antenatal problem
L260z00	Fetal-maternal haemorrhage NOS
L36..00	Postpartum haemorrhage (PPH)
L360.00	Third-stage postpartum haemorrhage
L360000	Third-stage postpartum haemorrhage unspecified
L360100	Third-stage postpartum haemorrhage - deliv with p/n problem
L360200	Third-stage postpartum haemorrhage with postnatal problem
L360z00	Third-stage postpartum haemorrhage NOS
L361.00	Other immediate postpartum haemorrhage
L361000	Other immediate postpartum haemorrhage unspecified
L361100	Other immediate postpartum haemorrhage - deliv with p/n prob
L361200	Other immediate postpartum haemorrhage with postnatal prob
L361z00	Other immediate postpartum haemorrhage NOS
L362.00	Secondary and delayed postpartum haemorrhage
L362000	Secondary postpartum haemorrhage unspecified
L362100	Secondary postpartum haemorrhage - deliv with postnatal prob
L362200	Secondary postpartum haemorrhage with postnatal problem
L362z00	Secondary and delayed postpartum haemorrhage NOS
L363100	Postpartum coagulation defects - delivered with p/n problem
L36z.00	Postpartum haemorrhage NOS
L37..00	Retained placenta or membranes with no haemorrhage
L37..11	Retained membrane without haemorrhage
L37..12	Retained placenta without haemorrhage
L370.00	Retained placenta with no haemorrhage
L370.11	Placenta accreta without haemorrhage
L370000	Retained placenta with no haemorrhage unspecified
L370100	Retained placenta with no haemorrhage - deliv with p/n prob
L370200	Retained placenta with no haemorrhage with postnatal problem
L370z00	Retained placenta with no haemorrhage NOS
L370z11	Retained placenta without haemorrhage
L371.00	Retained portion of placenta or membranes - no haemorrhage
L371000	Retained products with no haemorrhage unspecified
L371100	Retained products with no haemorrhage - deliv with p/n prob
L371200	Retained products with no haemorrhage with postnatal problem
L371z00	Retained products with no haemorrhage NOS
L37z.00	Retained placenta or membranes with no haemorrhage NOS
L3A..00	Intrapartum haemorrhage with coagulation defect

L3X..00	Intrapartum haemorrhage, unspecified
Lyu2000	[X]Other haemorrhage in early pregnancy
Lyu3E00	[X]Other antepartum haemorrhage
Lyu4700	[X]Other intrapartum haemorrhage
Lyu4D00	[X]Other immediate postpartum haemorrhage
Lyu4M00	[X]Intrapartum haemorrhage, unspecified
Q021.00	Fetus/neonate affect other placental separation/haemorrhage
Q021000	Fetus/neonate affected by antepartum haemorrhage unspecified
Q021011	Fetus affected by APH - antepartum haemorrhage
Q021y00	Fetus/neonate affected placental separation/haemorrhage OS
Q021z00	Fetus/neonate affected placental separation/haemorrhage NOS
Q413.00	Umbilical haemorrhage after birth
Q413000	Umbilical haemorrhage after birth, unspecified
Q413y00	Other specified umbilical haemorrhage after birth
Q413z00	Umbilical haemorrhage after birth NOS
Ryu7300	[X]Haemorrhage, not elsewhere classified
SK02.00	Secondary and recurrent haemorrhage
SK02.11	Secondary and recurrent haemorrhage
SK02.12	Secondary and recurrent haemorrhage
SP21.00	Peri-operative haemorrhage or haematoma
SP21.12	Haemorrhage - postoperative
SP21000	Intra-operative haemorrhage
SP21100	Post-operative haemorrhage
TA0..11	Accidental haemorrhage during medical care

Appendix 11: Eclampsia and preeclampsia Read codes

Readcode	description
L124.00	Mild or unspecified pre-eclampsia
L124.11	Mild pre-eclampsia
L124000	Mild or unspecified pre-eclampsia unspecified
L124100	Mild or unspecified pre-eclampsia - delivered
L124200	Mild or unspecified pre-eclampsia - delivered with p/n comp
L124300	Mild or unspecified pre-eclampsia - not delivered
L124400	Mild or unspecified pre-eclampsia with p/n complication
L124500	Mild pre-eclampsia
L124600	Pre-eclampsia, unspecified
L124z00	Mild or unspecified pre-eclampsia NOS
L125.00	Severe pre-eclampsia
L125000	Severe pre-eclampsia unspecified
L125100	Severe pre-eclampsia - delivered
L125200	Severe pre-eclampsia - delivered with postnatal complication
L125300	Severe pre-eclampsia - not delivered
L125400	Severe pre-eclampsia with postnatal complication
L125z00	Severe pre-eclampsia NOS
L126.00	Eclampsia
L126000	Eclampsia unspecified
L126100	Eclampsia - delivered
L126200	Eclampsia - delivered with postnatal complication
L126300	Eclampsia - not delivered
L126400	Eclampsia with postnatal complication
L126500	Eclampsia in pregnancy
L126600	Eclampsia in labour
L126z00	Eclampsia NOS
L127.00	Pre-eclampsia or eclampsia with pre-existing hypertension
L127000	Pre-eclampsia or eclampsia with hypertension unspecified
L127100	Pre-eclampsia or eclampsia with hypertension - delivered
L127200	Pre-eclampsia or eclampsia with hypertension - del+p/n comp
L127300	Pre-eclampsia or eclampsia with hypertension - not delivered
L127400	Pre-eclampsia or eclampsia with hypertension + p/n comp
L127z00	Pre-eclampsia or eclampsia + pre-existing hypertension NOS
L129.00	Moderate pre-eclampsia

Appendix 12: Read codes for acute respiratory tract infection

Readcode	description
43eG.00	Chlamydia pneumoniae IgG level
43eH.00	Chlamydia pneumoniae IgM level
43jQ.00	Avian influenza virus nucleic acid detection
43jx.00	Parainfluenza type 1 nucleic acid detection
43jy.00	Parainfluenza type 2 nucleic acid detection
43jz.00	Parainfluenza type 3 nucleic acid detection
43n1.00	Mycoplasma pneumoniae antibody level
43n7.00	Chlamydia pneumoniae IgA level
4JU0.00	Influenza H1 virus detected
4JU1.00	Influenza H2 virus detected
4JU2.00	Influenza H3 virus detected
4JU3.00	Influenza H5 virus detected
4JU4.00	Influenza A virus, other or untyped strain detected
4JU5.00	Influenza B virus detected
4JUF.00	Human parainfluenza virus detected
4JUK.00	Mycoplasma pneumoniae detected
A022200	Salmonella pneumonia
A116.00	Tuberculous pneumonia
A380300	Septicaemia due to streptococcus pneumoniae
A3B5.00	Haemophilus influenzae infection
A3BXA00	Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr
A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapters
A3BXD00	H influenzae as cause/diseases classified/other chapters
A3By400	Pleuropneumonia-like organism (PPLO) infection
A54x400	Herpes simplex pneumonia
A551.00	Postmeasles pneumonia
A730.00	Ornithosis with pneumonia
A789300	HIV disease resulting in Pneumocystis carinii pneumonia
AB24.11	Pneumonia - candidal
AB40500	Histoplasma capsulatum with pneumonia
AB41500	Histoplasma duboisii with pneumonia
AB4z500	Histoplasmosis with pneumonia
Ayu3U00	[X]Haemophilus influenzae infection, unspecified
AyuK900	[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth chaptr
AyuKA00	[X]Klebsiella pneumoniae/cause/disease classifd/oth chapters
AyuKC00	[X]H influenzae as cause/diseases classified/other chapters
F00y400	Meningitis due to klebsiella pneumoniae
F030800	Encephalitis due to influenza-specific virus not identified
F030A00	Encephalitis due to influenza-virus identified
G520300	Acute myocarditis - influenzal
H040400	Acute haemophilus influenzae laryngitis
H06..00	Acute bronchitis and bronchiolitis
H060.00	Acute bronchitis
H060.11	Acute wheezy bronchitis
H060000	Acute fibrinous bronchitis
H060100	Acute membranous bronchitis
H060200	Acute pseudomembranous bronchitis
H060300	Acute purulent bronchitis
H060400	Acute croupous bronchitis
H060500	Acute tracheobronchitis
H060600	Acute pneumococcal bronchitis
H060700	Acute streptococcal bronchitis
H060800	Acute haemophilus influenzae bronchitis
H060900	Acute neisseria catarrhalis bronchitis
H060A00	Acute bronchitis due to mycoplasma pneumoniae
H060B00	Acute bronchitis due to coxsackievirus
H060C00	Acute bronchitis due to parainfluenza virus

H060D00	Acute bronchitis due to respiratory syncytial virus
H060E00	Acute bronchitis due to rhinovirus
H060F00	Acute bronchitis due to echovirus
H060v00	Subacute bronchitis unspecified
H060w00	Acute viral bronchitis unspecified
H060x00	Acute bacterial bronchitis unspecified
H060z00	Acute bronchitis NOS
H06z.00	Acute bronchitis or bronchiolitis NOS
H06z000	Chest infection NOS
H06z011	Chest infection
H06z200	Recurrent chest infection
H2...00	Pneumonia and influenza
H20..00	Viral pneumonia
H20..11	Chest infection - viral pneumonia
H200.00	Pneumonia due to adenovirus
H201.00	Pneumonia due to respiratory syncytial virus
H202.00	Pneumonia due to parainfluenza virus
H20y.00	Viral pneumonia NEC
H20z.00	Viral pneumonia NOS
H21..00	Lobar (pneumococcal) pneumonia
H21..11	Chest infection - pneumococcal pneumonia
H22..00	Other bacterial pneumonia
H22..11	Chest infection - other bacterial pneumonia
H220.00	Pneumonia due to klebsiella pneumoniae
H221.00	Pneumonia due to pseudomonas
H222.00	Pneumonia due to haemophilus influenzae
H222.11	Pneumonia due to haemophilus influenzae
H223.00	Pneumonia due to streptococcus
H223000	Pneumonia due to streptococcus, group B
H224.00	Pneumonia due to staphylococcus
H22y.00	Pneumonia due to other specified bacteria
H22y000	Pneumonia due to escherichia coli
H22y011	E.coli pneumonia
H22y100	Pneumonia due to proteus
H22y200	Pneumonia - Legionella
H22yX00	Pneumonia due to other aerobic gram-negative bacteria
H22yz00	Pneumonia due to bacteria NOS
H22z.00	Bacterial pneumonia NOS
H23..00	Pneumonia due to other specified organisms
H23..11	Chest infection - pneumonia organism OS
H230.00	Pneumonia due to Eaton's agent
H231.00	Pneumonia due to mycoplasma pneumoniae
H232.00	Pneumonia due to pleuropneumonia like organisms
H233.00	Chlamydial pneumonia
H23z.00	Pneumonia due to specified organism NOS
H24..00	Pneumonia with infectious diseases EC
H24..11	Chest infection with infectious disease EC
H240.00	Pneumonia with measles
H241.00	Pneumonia with cytomegalic inclusion disease
H242.00	Pneumonia with ornithosis
H243.00	Pneumonia with whooping cough
H243.11	Pneumonia with pertussis
H244.00	Pneumonia with tularaemia
H245.00	Pneumonia with anthrax
H246.00	Pneumonia with aspergillosis
H247.00	Pneumonia with other systemic mycoses
H247000	Pneumonia with candidiasis
H247100	Pneumonia with coccidioidomycosis
H247200	Pneumonia with histoplasmosis
H247z00	Pneumonia with systemic mycosis NOS
H24y.00	Pneumonia with other infectious diseases EC
H24y000	Pneumonia with actinomycosis

H24y100	Pneumonia with nocardiasis
H24y200	Pneumonia with pneumocystis carinii
H24y300	Pneumonia with Q-fever
H24y400	Pneumonia with salmonellosis
H24y500	Pneumonia with toxoplasmosis
H24y600	Pneumonia with typhoid fever
H24y700	Pneumonia with varicella
H24yz00	Pneumonia with other infectious diseases EC NOS
H24z.00	Pneumonia with infectious diseases EC NOS
H25..00	Bronchopneumonia due to unspecified organism
H25..11	Chest infection - unspecified bronchopneumonia
H26..00	Pneumonia due to unspecified organism
H26..11	Chest infection - pnemonia due to unspecified organism
H260.00	Lobar pneumonia due to unspecified organism
H261.00	Basal pneumonia due to unspecified organism
H262.00	Postoperative pneumonia
H27..00	Influenza
H270.00	Influenza with pneumonia
H270.11	Chest infection - influenza with pneumonia
H270000	Influenza with bronchopneumonia
H270100	Influenza with pneumonia, influenza virus identified
H270z00	Influenza with pneumonia NOS
H271.00	Influenza with other respiratory manifestation
H271000	Influenza with laryngitis
H271100	Influenza with pharyngitis
H271z00	Influenza with respiratory manifestations NOS
H27y.00	Influenza with other manifestations
H27y000	Influenza with encephalopathy
H27y100	Influenza with gastrointestinal tract involvement
H27yz00	Influenza with other manifestations NOS
H27z.00	Influenza NOS
H28..00	Atypical pneumonia
H29..00	Avian influenza
H2y..00	Other specified pneumonia or influenza
H2z..00	Pneumonia or influenza NOS
H30..00	Bronchitis unspecified
H30..11	Chest infection - unspecified bronchitis
H30..12	Recurrent wheezy bronchitis
H300.00	Tracheobronchitis NOS
H301.00	Laryngotracheobronchitis
H302.00	Wheezy bronchitis
H30z.00	Bronchitis NOS
H470312	Aspiration pneumonia due to vomit
H471000	Lipoid pneumonia (exogenous)
H530200	Gangrenous pneumonia
H530300	Abscess of lung with pneumonia
H540000	Hypostatic pneumonia
H540100	Hypostatic bronchopneumonia
H564.00	Bronchiolitis obliterans organising pneumonia
H56y000	Endogenous lipoid pneumonia
H56y100	Interstitial pneumonia
H571.00	Rheumatic pneumonia
Hyu0500	[X]Influenza+other manifestations,influenza virus identified
Hyu0700	[X]Influenza+other manifestations, virus not identified
Hyu0800	[X]Other viral pneumonia
Hyu0900	[X]Pneumonia due to other aerobic gram-negative bacteria
Hyu0A00	[X]Other bacterial pneumonia
Hyu0B00	[X]Pneumonia due to other specified infectious organisms
Hyu0C00	[X]Pneumonia in bacterial diseases classified elsewhere
Hyu0D00	[X]Pneumonia in viral diseases classified elsewhere
Hyu0E00	[X]Pneumonia in mycoses classified elsewhere
Hyu0F00	[X]Pneumonia in parasitic diseases classified elsewhere

Hyu0G00	[X]Pneumonia in other diseases classified elsewhere
Hyu0H00	[X]Other pneumonia, organism unspecified
SP13200	Post operative chest infection
U60K400	[X]Influenza vaccine causing adverse effects therapeutic use
ZV04800	[V]Influenza vaccination
ZV04811	[V]Flu - influenza vaccination

Appendix 13: Read codes for urinary tract infection

Readcode	description
1AG..00	Recurrent urinary tract infections
K101.00	Acute pyelonephritis
K101000	Acute pyelonephritis without medullary necrosis
K101100	Acute pyelonephritis with medullary necrosis
K101z00	Acute pyelonephritis NOS
K15..00	Cystitis
K150.00	Acute cystitis
K151.00	Chronic interstitial cystitis
K151200	Submucous cystitis
K151z00	Chronic interstitial cystitis NOS
K152.00	Other chronic cystitis
K152000	Subacute cystitis
K152y00	Chronic cystitis unspecified
K152z00	Other chronic cystitis NOS
K153.11	Follicular cystitis
K154.00	Cystitis in diseases EC
K154000	Cystitis in actinomycosis
K154100	Cystitis in amoebiasis
K154200	Cystitis in bilharziasis
K154300	Cystitis in echinococcus infestation
K154400	Cystitis in diphtheria
K154500	Cystitis in gonorrhoea
K154600	Cystitis in moniliasis
K154700	Cystitis in trichomoniasis
K154800	Cystitis in tuberculosis
K154z00	Cystitis in diseases EC NOS
K155.00	Recurrent cystitis
K15y.00	Other specified cystitis
K15y000	Cystitis cystica
K15y100	Irradiation cystitis
K15yz00	Other cystitis NOS
K15z.00	Cystitis NOS
K190.00	Urinary tract infection, site not specified
K190.11	Recurrent urinary tract infection
K190200	Post operative urinary tract infection
K190300	Recurrent urinary tract infection
K190500	Urinary tract infection
K190z00	Urinary tract infection, site not specified NOS
Kyu5100	[X]Other cystitis
L09y400	Urinary tract infection following abortive pregnancy
L166.00	Genitourinary tract infections in pregnancy
L166.11	Cystitis of pregnancy
L166000	Genitourinary tract infection in pregnancy unspecified
L166100	Genitourinary tract infection in pregnancy - delivered
L166200	Genitourinary tract infection in pregnancy - deliv +p/n comp
L166300	Genitourinary tract infection in pregnancy - not delivered
L166400	Genitourinary tract infection in pregnancy with p/n comp
L166600	Urinary tract infection following delivery
L166800	Urinary tract infection complicating pregnancy
L166z00	Genitourinary tract infection in pregnancy NOS
L166z11	UTI - urinary tract infection in pregnancy
Lyu2400	[X]Other+unspcf genitourinary tract infection in pregnancy
Lyu6100	[X]Other genitourinary tract infections following delivery
ZG44100	Advice on avoiding recurrent urinary tract infection

Appendix 14: Read codes for medical co-morbidities

Inflammatory bowel disease

medcode	description
J08z900	Orofacial Crohn's disease
J40..00	Regional enteritis - Crohn's disease
J40..11	Crohn's disease
J400.00	Regional enteritis of the small bowel
J400000	Regional enteritis of the duodenum
J400100	Regional enteritis of the jejunum
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation of Crohn's disease of small intestine
J400z00	Crohn's disease of the small bowel NOS
J401.00	Regional enteritis of the large bowel
J401000	Regional enteritis of the colon
J401100	Regional enteritis of the rectum
J401200	Exacerbation of Crohn's disease of large intestine
J401z00	Crohn's disease of the large bowel NOS
J401z11	Crohn's colitis
J40z.00	Regional enteritis NOS
J40z.11	Crohn's disease NOS
Jyu4000	[X]Other Crohn's disease
N031100	Arthropathy in Crohn's disease
N045300	Juvenile arthritis in Crohn's disease
ZR3S.00	Crohn's disease activity index
ZR3S.11	CDAI - Crohn's disease activity index
14C4.11	H/O: ulcerative colitis
J41..12	Ulcerative colitis and/or proctitis
J410.00	Ulcerative proctocolitis
J410100	Ulcerative colitis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
Jyu4100	[X]Other ulcerative colitis
N031000	Arthropathy in ulcerative colitis
N045400	Juvenile arthritis in ulcerative colitis
J4...12	Inflammatory bowel disease
J41..00	Idiopathic proctocolitis
J41y.00	Other idiopathic proctocolitis
J41yz00	Other idiopathic proctocolitis NOS
J41z.00	Idiopathic proctocolitis NOS

Nephrotic syndrome

medcode	description
K0...00	Nephritis, nephrosis and nephrotic syndrome
K01..00	Nephrotic syndrome
K010.00	Nephrotic syndrome with proliferative glomerulonephritis
K011.00	Nephrotic syndrome with membranous glomerulonephritis
K012.00	Nephrotic syndrome+membranoproliferative glomerulonephritis
K013.00	Nephrotic syndrome with minimal change glomerulonephritis
K013.12	Steroid sensitive nephrotic syndrome
K014.00	Nephrotic syndrome, minor glomerular abnormality
K015.00	Nephrotic syndrome, focal and segmental glomerular lesions
K016.00	Nephrotic syndrome, diffuse membranous glomerulonephritis
K01A.00	Nephrotic syndrome, dense deposit disease
K01B.00	Nephrotic syndrome, diffuse crescentic glomerulonephritis
K01w.00	Congenital nephrotic syndrome
K01w011	Microcystic type congenital nephrotic syndrome
K01wz00	Congenital nephrotic syndrome NOS
K01x.00	Nephrotic syndrome in diseases EC
K01x000	Nephrotic syndrome in amyloidosis
K01x100	Nephrotic syndrome in diabetes mellitus
K01x200	Nephrotic syndrome in malaria
K01x300	Nephrotic syndrome in polyarteritis nodosa
K01x400	Nephrotic syndrome in systemic lupus erythematosus
K01xz00	Nephrotic syndrome in diseases EC NOS
K01y.00	Nephrotic syndrome with other pathological kidney lesions
K01z.00	Nephrotic syndrome NOS
K0y..00	Other specified nephritis, nephrosis or nephrotic syndrome
K0z..00	Nephritis, nephrosis and nephrotic syndrome NOS

Systemic lupus erythematosus

medcode	description
H57y400	Lung disease with systemic lupus erythematosus
K01x400	Nephrotic syndrome in systemic lupus erythematosus
N000.00	Systemic lupus erythematosus
N000200	Drug-induced systemic lupus erythematosus
N000300	Systemic lupus erythematosus with organ or sys involv
N000400	Systemic lupus erythematosus with pericarditis
N000z00	Systemic lupus erythematosus NOS
Nyu4300	[X]Other forms of systemic lupus erythematosus
ZRq9.00	Systemic lupus erythematosus disease activity index

Cardiac disease

Readcode	description
P54..00	Ventricular septal defect
P6z..00	Congenital heart anomaly NOS
G580.00	Congestive heart failure
G577.00	Sinus arrhythmia
G581.00	Left ventricular failure
G58..11	Cardiac failure
G573200	Paroxysmal atrial fibrillation
G570000	Paroxysmal atrial tachycardia
G340.12	Coronary artery disease
G572z00	Paroxysmal tachycardia NOS
G33z300	Angina on effort
G33..00	Angina pectoris
G311.13	Unstable angina
G57z.00	Cardiac dysrhythmia NOS
G57y900	Supraventricular tachycardia NOS
7L1H100	External cardioversion NEC
G573000	Atrial fibrillation
G573100	Atrial flutter
P511.00	Double outlet right ventricle
G58..00	Heart failure
G573.00	Atrial fibrillation and flutter
P735.00	Stenosis of pulmonary artery
P70..00	Patent ductus arteriosus
7A01z00	Open correction of patent ductus arteriosus NOS
P51..00	Transposition of great vessels
7936000	Implantation of intravenous cardiac pacemaker system
G580.11	Congestive cardiac failure
G55..00	Cardiomyopathy
7L1H000	Direct current cardioversion
P550.00	Atrial septal defect NOS
P641.00	Bicuspid aortic valve
P71..00	Coarctation of aorta
G571.00	Paroxysmal ventricular tachycardia
G554300	Hypertrophic non-obstructive cardiomyopathy
3272.00	ECG: atrial fibrillation
P6y6000	Dextrocardia
G57y000	Persistent sinus bradycardia
P601.00	Congenital atresia of the pulmonary valve
P6z3.00	Cyanotic congenital heart disease NOS
7908z00	Closure of defect of interventricular septum NOS
G58z.00	Heart failure NOS
G57..00	Cardiac dysrhythmias
G574.00	Ventricular fibrillation and flutter
G57y.14	Heart beats irregular
G311.11	Crescendo angina
G574000	Ventricular fibrillation
P52..00	Tetralogy of Fallot
G555.00	Alcoholic cardiomyopathy
3282.00	ECG: ventricular tachycardia
G570.00	Paroxysmal supraventricular tachycardia
P50..00	Common aorto-pulmonary trunk
AA1..00	Vincent's angina
G554000	Congestive cardiomyopathy
G581000	Acute left ventricular failure
7902.00	Correction of tetralogy of Fallot
G574100	Ventricular flutter
G57y300	Sick sinus syndrome
P6...00	Other congenital heart anomalies
7936.00	Introduction of cardiac pacemaker system via vein
G581.13	Impaired left ventricular function

14A5.00	H/O: angina pectoris
14AN.00	H/O: atrial fibrillation
G57..11	Cardiac arrhythmias
14S4.00	H/O: heart valve recipient
3273.00	ECG: atrial flutter
P64z.00	Congenital aortic valve insufficiency NOS
P63..00	Congenital aortic valve stenosis
7903.00	Atrial inversion ops for transposition of great vessels
7L1H.11	Cardioversion and stimulation
P6z3.11	Blue baby
G343.00	Ischaemic cardiomyopathy
7A01.11	Open correction of patent ductus arteriosus (PDA)
G311100	Unstable angina
7L1H200	Internal electrode cardioversion
G57y400	Sinoatrial node dysfunction NOS
P55..00	Ostium secundum atrial septal defect
G554400	Primary dilated cardiomyopathy
G575300	Electromechanical dissociation
G571.11	Ventricular tachycardia
G57y.00	Other cardiac dysrhythmias
F256000	Hypsarrhythmia
G551.00	Hypertrophic obstructive cardiomyopathy
P6z..11	Chiari's malformation
7936600	Implantation of permanent intravenous cardiac pacemaker
P64..00	Congenital aortic valve insufficiency
G57y600	Nodal rhythm disorder
P543.00	Eisenmenger's complex
P6yy.12	Hypoplasia of heart NOS
P59..00	Isomerism of atrial appendages
P6y2.00	Pulmonary infundibular stenosis
G55y.11	Secondary dilated cardiomyopathy
7936A00	Implant intravenous pacemaker for atrial fibrillation
G580.14	Biventricular failure
G33z500	Post infarct angina
7A01100	Ligation of patent ductus arteriosus
A740.00	Herpangina
1O1..00	Heart failure confirmed
P736.12	Pulmonary arterio-venous malformation
G580.12	Right heart failure
G580.13	Right ventricular failure
662D.11	Digitalised
G331.11	Variant angina pectoris
7936.11	Introduction of intravenous cardiac pacemaker system
P73..00	Pulmonary artery anomalies
P72z111	Congenital dilatation of aorta
G580300	Compensated cardiac failure
P72zz00	Other anomaly of aorta NOS
P6zz.00	Congenital heart anomaly NOS
662T.00	Congestive heart failure monitoring
14AQ.00	History of supraventricular tachycardia
G58z.11	Weak heart
9N0k.00	Seen in heart failure clinic
P61..00	Congenital tricuspid atresia and stenosis
G33z700	Stable angina
7A02000	Percut transluminal prosth occlusion patent ductus arterios
G331.00	Prinzmetal's angina
662K.00	Angina control
662g.00	New York Heart Association classification - class II
662J000	Digoxin monitoring
329..00	ECG: heart block
662K200	Angina control - improving
14A6.00	H/O: heart failure

662Kz00	Angina control NOS
662K100	Angina control - poor
7907z00	Closure of defect of interatrial septum NOS
7902000	Correct Fallot tetralogy- valved right ventr outflow conduit
P6y0.00	Subaortic stenosis
P713.11	Stenosis of aortic arch
14H1.11	H/O: heart anomaly
G58z.12	Cardiac failure NOS
G311200	Angina at rest
J421.11	Angina - abdominal
327..00	ECG: supraventricular arrhythmia
8HBE.00	Heart failure follow-up
7936.00	Implantation of intravenous dual chamber permanent pacemaker
G311400	Worsening angina
G330000	Nocturnal angina
G57y100	Severe sinus bradycardia
3274.00	ECG: paroxysmal atrial tachy.
P55y.11	Other specified atrial septal defect
662S.00	Atrial fibrillation monitoring
P5...13	Heart septal defects
14H1.00	H/O: cardiac anomaly
P733.00	Coarctation of the pulmonary artery
9N2p.00	Seen by community heart failure nurse
662h.00	New York Heart Association classification - class III
7A02011	Percut translum prosth occlus patent ductus arteriosus (PDA)
9Or0.00	Heart failure review completed
662K000	Angina control - good
G311.14	Angina at rest
328..00	ECG: ventricular arrhythmia
7902z00	Correction of tetralogy of Fallot NOS
P53..00	Common ventricle
G330.00	Angina decubitus
P545.00	Roger's disease
G3...12	Atherosclerotic heart disease
P6y6.11	Ectopic heart
P67..00	Hypoplastic left heart syndrome
7A01.00	Open correction of patent ductus arteriosus
1J60.00	Suspected heart failure
P610.00	Congenital tricuspid atresia
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
P603.00	Right hypoplastic heart syndrome
P5...11	Cardiac septal defects
G1yz100	Rheumatic left ventricular failure
P602.00	Congenital pulmonary stenosis
14AD.00	H/O ventricular fibrillation
G55z.00	Cardiomyopathy NOS
G573z00	Atrial fibrillation and flutter NOS
G570100	Paroxysmal atrioventricular tachycardia
P520.11	Ventricular septal defect in Fallot's tetralogy
G580000	Acute congestive heart failure
P62..00	Ebstein's anomaly
P6yy900	Congenital epicardial cyst
P5...12	Congenital heart disease, septal and bulbar anomalies
P511100	Dextratransposition of aorta
A340000	Streptococcal angina
8B29.00	Cardiac failure therapy
P6y5.00	Congenital heart block
P6yyz00	Other specified heart anomalies NOS
P6y..00	Other specified heart anomalies
P6yy.00	Other specified heart anomalies
G572.00	Paroxysmal tachycardia unspecified
P6y4.00	Coronary artery anomaly

G574011	Cardiac arrest-ventricular fibrillation
G33z.00	Angina pectoris NOS
8HHb.00	Referral to heart failure nurse
ZRad.00	New York Heart Assoc classification heart failure symptoms
P6z0.00	Unspecified anomaly of heart valve
G33z600	New onset angina
329Z.00	ECG: heart block NOS
G558100	Cardiomyopathy in myotonic dystrophy
G580200	Decompensated cardiac failure
G582.00	Acute heart failure
7909300	Primary closure of defect of septum of heart NEC
P550.12	Interatrial septal defect NEC
7904.00	Other correction of transposition of great vessels
7907300	Primary closure of defect of interatrial septum NEC
G33zz00	Angina pectoris NOS
P6y4411	Congenital coronary arterio-venous fistula
7905.00	Correction of total anomalous pulmonary venous connection
212R.00	Atrial fibrillation resolved
9hF0.00	Except from atr fib quality indicators: Patient unsuitable
7936400	Removal of intravenous cardiac pacemaker system
662K300	Angina control - worsening
328Z.00	ECG: ventricular arrhythmia NOS
G570300	Paroxysmal nodal tachycardia
G330z00	Angina decubitus NOS
7909.00	Closure of defect of unspecified septum of heart
14AP.00	History of ventricular tachycardia
P721.00	Aortic arch anomalies
9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl
662W.00	Heart failure annual review
P721100	Dextraposition of aorta
7L1H.13	Defibrillation
7903.11	Mustard interatrial tr venous return
7907000	Closure defect of interatrial septum using prosthetic patch
P732.00	Pulmonary artery atresia
G57yz00	Other cardiac dysrhythmia NOS
3283.00	ECG: ventricular fibrillation
P6y4400	Anomalous coronary artery communication
J083300	Ludwig's angina
P5...00	Bulbus cordis and cardiac septal closure anomalies
G57yA00	Re-entry ventricular arrhythmia
7906.00	Closure of defect of atrioventricular septum
P738.00	Atresia of pulmonary artery with septal defect
G580100	Chronic congestive heart failure
P6y3000	Uhl's disease
8H2S.00	Admit heart failure emergency
9Or..00	Heart failure monitoring administration
8CL3.00	Heart failure care plan discussed with patient
7936500	Implantation of emergency intravenous cardiac pacemaker
7904000	Repositioning of transposed great vessels
P602z00	Congenital pulmonary stenosis NOS
P6yy200	Congenital cardiomegaly
P54z.00	Ventricular septal defect NOS
P721z00	Aortic arch anomalies NOS
G311300	Refractory angina
P6y1.00	Cor triatriatum
7907.00	Closure of defect of interatrial septum
G570z00	Paroxysmal supraventricular tachycardia NOS
G573300	Non-rheumatic atrial fibrillation
3293.00	ECG:complete sinu-atrial block
P737.11	Dilatation of pulmonary artery
7908.00	Closure of defect of interventricular septum
P74z600	Scimitar syndrome

7A01200	Closure of patent ductus arteriosus NEC
P713.00	Interruption of aortic arch
P50..11	Aortic septal defect
P6yy700	Atresia of heart valve NEC
P722200	Hypoplasia of aorta
7L1H111	External electrode cardioversion
7936F00	Renewal of intravenous cardiac pacemaker system
P552.00	Persistent ostium secundum
7936300	Maintenance of intravenous cardiac pacemaker system NEC
7903.12	Senning correction for transposition of great vessels
7936B00	Implantation simple one wire intravenous cardiac pacemaker
7936700	Implantation of intravenous fixed-rate cardiac pacemaker
7904z00	Other correction of transposition of great vessels NOS
7906z00	Closure of defect of atrioventricular septum NOS
7L1H300	Electrical sinus rhythm conversion
P721211	Vascular ring
7909y00	Other specified closure of defect unspecified heart septum
P520.00	Tetralogy of Fallot, unspecified
P6z2.00	Acyanotic congenital heart disease NOS
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
Gyu3000	[X]Other forms of angina pectoris
3889.00	Euroscore for angina
7908000	Close defect interventricular septum using prosthetic patch
7906100	Close defect atrioventric septum using prosthetic patch NEC
7906500	Revision of closure of defect of atrioventricular septum
P60..00	Pulmonary valve anomalies
P511300	Taussig-Bing syndrome
P72..11	Anomalies of the aorta excluding coarction
L186500	Cardiomyopathy in the puerperium
3295.00	ECG: partial A-V block - 2:1
3298.00	ECG: complete A-V block
P550.11	Auricular septal defect NOS
G554z00	Other primary cardiomyopathy NOS
P74z300	Stenosis of superior vena cava
P502.11	Truncus arteriosus
G554100	Constrictive cardiomyopathy
7936511	Implantation of temporary intravenous cardiac pacemaker
G574z00	Ventricular fibrillation and flutter NOS
G55y.00	Secondary cardiomyopathy NOS
7909000	Closure of defect of heart septum using prosthetic patch NEC
P73z.00	Pulmonary artery anomaly NOS
P540.00	Ventricular septal defect, unspecified
7936y00	Other specified cardiac pacemaker system introduced via vein
7906300	Closure of persistent ostium primum
7L1H.12	Direct current cardiac shock
7936z00	Cardiac pacemaker system introduced via vein NOS
P74..00	Anomalies of great veins
P56z100	Common atrioventricular canal
7936900	Implantation of intravenous atrial overdrive pacemaker
7907100	Closure defect of interatrial septum using pericardial patch
F391B00	Cardiomyopathy in Duchenne muscular dystrophy
P721500	Persistent right aortic arch
P60z.00	Other pulmonary valve anomalies
P6yy.11	Hypoplastic aortic orifice or valve
P72z.00	Other anomalies of aorta NOS
P56z200	Common atrioventricular-type ventricular septal defect
P500.12	Truncus arteriosus
P740.00	Anomaly of great veins, unspecified
7908300	Primary closure of defect of interventricular septum NEC
P602100	Congenital fusion of pulmonary valve segment
P501.00	Aortic septal defect
6A9..00	Atrial fibrillation annual review

8B27.00	Antianginal therapy
P58..00	Double outlet left ventricle
P742.00	Partial anomalous pulmonary venous return
P721200	Double aortic arch
68B6.00	Heart failure screen
388D.00	New York Heart Assoc classification heart failure symptoms
P6W..00	Congenital malformation of aortic and mitral valves unsp
14AM.00	H/O: Heart failure in last year
P736.11	Pulmonary arterio-venous fistula
P5X..00	Congenital malforms of cardiac chambers+connections unsp
7906400	Primary closure of defect of atrioventricular septum NEC
8HTL.00	Referral to heart failure clinic
P6yy300	Congenital left ventricular diverticulum
P712.13	Postductal aortic stenosis
P72z000	Aneurysm of sinus of Valsalva
P56z.00	Endocardial cushion defects NOS
P721300	Kommerell's diverticulum
P6y4500	Congenital coronary aneurysm
7A01000	Division of patent ductus arteriosus
P72..00	Other anomalies of aorta
1I10.00	Heart failure excluded
P6y6300	Ectopia cordis
7909z00	Closure of defect of unspecified septum of heart NOS
P6yy400	Congenital pericardial defect
P6X..00	Congenital malformation of tricuspid valve, unspecified
7908100	Close defect interventricular septum using pericardial patch
P740100	Anomaly of the vena cava, unspecified
ZRBN.00	Duke's coronary artery disease score
P561.00	Ostium primum defect
G575200	Electromechanical dissociation with successful resuscitation
662i.00	New York Heart Association classification - class IV
P501.11	Aortopulmonary window
7936200	Maintenance of battery of intravenous cardiac pacemaker syst
P521.00	Pentalogy of Fallot
P74z200	Stenosis of inferior vena cava
G570200	Paroxysmal junctional tachycardia
P544.00	Gerbode's defect
P74z800	Atresia of pulmonary vein
P741.00	Total anomalous pulmonary venous return - TAPVR
G211100	Benign hypertensive heart disease with CCF
7907200	Closure defect of interatrial septum using tissue graft NEC
P6y5100	Congenital complete atrio-ventricular heart block
7936100	Resiting of lead of intravenous pacemaker system
P73y.00	Other specified anomaly of pulmonary artery
P60z100	Fallot's trilogy
P6y7.00	Myocardial bridge of coronary artery
388E.00	Canadian Cardiovascular Society classification of angina
327Z.00	ECG: supraventric. arryth. NOS
7936800	Implantation of intravenous triggered cardiac pacemaker
P55y.00	Other specified ostium secundum atrial septal defect
P6y4z00	Coronary artery anomaly NOS
Gyu5a00	[X]Other specified cardiac arrhythmias
P722400	Supra-valvular aortic stenosis
P5z..00	Heart bulb or septal closure defects NOS
P55z.00	Ostium secundum atrial septal defect NOS
P734.00	Hypoplasia of the pulmonary artery
P601000	Hypoplasia of pulmonary valve
P54y.00	Other specified ventricular septal defect
P56z000	Common atrium
ZR3P.00	CLASP angina score
G558.00	Cardiomyopathy in disease EC
7A00000	Correction of persistent truncus arteriosus

P72z100	Congenital aneurysm of aorta
P541.00	Interventricular septal defect
7905100	Correct total anomal pulm venous connect to coronary sinus
14AJ.00	H/O: Angina in last year
P65..00	Congenital mitral stenosis
7906000	Close defect atrioventric septum using dual prosthetic patch
7906y00	Other specified closure of defect of atrioventricular septum
7908y00	Other specified closure of defect of interventricular septum
9Os..00	Atrial fibrillation monitoring administration
ZR3P.11	CLASP angina score
P710.00	Hypoplasia of aortic arch, unspecified
388F.00	Cardiovascular Limitations and Symptoms Profile angina score
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
P722z00	Atresia or stenosis of aorta NOS
P722411	Congenital stenosis of ascending aorta
P640.00	Congenital aortic valve insufficiency, unspecified
7903z00	Atrial inversion op for transposition of great vessels NOS
G55y000	Cardiomyopathy due to drugs and other external agents
7909100	Closure defect of heart septum using pericardial patch NEC
P553.00	Lutembacher's syndrome
P722100	Aplasia of aorta
ZR37.00	Canadian Cardiovascular Society classification of angina
P71z.00	Coarctation of aorta NOS
G572000	Essential paroxysmal tachycardia
67D4.00	Heart failure information given to patient
P51y.11	Transposition of aorta
P66..00	Congenital mitral insufficiency
P56z011	Cor triloculare biventriculare
7A00300	Closure of aortopulmonary window
P500.11	Persistent truncus arteriosus
7A00200	Repair of hemitruncus arteriosus
P6y4100	Single coronary artery
P51y.00	Other specified transposition of great vessels
P720.00	Anomaly of aorta, unspecified
7A02.00	Transluminal operations on abnormality of great vessel
P722500	Atresia of aorta
7903000	Atrium reconstruction atrial patch for transpos great vessel
G21z100	Hypertensive heart disease NOS with CCF
7A00y00	Open operation for combined abnormality of great vessels OS
P52z.00	Tetralogy of Fallot NOS
P652.00	Parachute deformity of the mitral valve
7A01300	Revision of correction of patent ductus arteriosus
P730.00	Pulmonary artery anomaly, unspecified
9RD0.00	Transfer of care from paediatric congenital heart service
P56..00	Endocardial cushion defects
9hF..00	Exception reporting: atrial fibrillation quality indicators
P512.00	Corrected great vessel transposition
P742.11	Anomalous termination of right pulmonary vein
P722300	Stricture of aorta
7936D00	Implantation complex two wire intravenous cardiac pacemaker
9hH1.00	Excepted heart failure quality indicators: Informed dissent
7904y00	Other correction of transposition of great vessels OS
G557z00	Nutritional and metabolic cardiomyopathy NOS
P6z1100	Anomalous ventricular bands
G558200	Dystrophic cardiomyopathy
P712.12	Postductal interruption of aorta
P737.00	Pulmonary artery aneurysm
7A02y00	Transluminal operation on abnormality of great vessel OS
P511z00	Double outlet right ventricle NOS
P501.12	Aorticopulmonary septal defect
7902y00	Other specified correction of tetralogy of Fallot
P502.00	Persistent truncus arteriosus

SP11111	Heart failure as a complication of care
P5y..00	Other heart bulb and septal closure defect
P721000	Anomalous origin of the aortic arch
7907y00	Other specified closure of defect of interatrial septum
7908200	Close defect interventricular septum using tissue graft NEC
P542.00	Left ventricle to right atrial communication
P731.00	Pulmonary artery agenesis
P6yy100	Hypoplasia of cardiac vein
P6y5000	Congenital heart block, unspecified
P722.00	Atresia and stenosis of aorta
SP11100	Cardiac insufficiency as a complication of care
G552.00	Obscure African cardiomyopathy
G554011	Congestive obstructive cardiomyopathy
P741z00	Total anomalous pulmonary venous return NOS
P65..11	Duroziez's disease
P6yy500	Congenital anomaly of myocardium
P603.11	Pseudotruncus arteriosus
7903100	Atrium reconstruction atrial wall for transpos great vessels
9N6T.00	Referred by heart failure nurse specialist
P611.00	Congenital tricuspid stenosis
7903y00	Atrial inversion op for transposition of great vessels OS
P6y6111	Laevocardia
P721111	Overriding aorta
P510.00	Total great vessel transposition
P600.00	Pulmonary valve anomaly, unspecified
G572100	Bouveret-Hoffmann syndrome
7907400	Revision of closure of defect of interatrial septum
8HHz.00	Referral to heart failure exercise programme
Gyu5M00	[X]Other hypertrophic cardiomyopathy
P721700	Overriding aorta
P712.00	Postductal coarctation of aorta
G558000	Cardiomyopathy in Friedreich's ataxia
7902300	Revision of correction of tetralogy of Fallot
P60zz00	Other pulmonary valve anomaly NOS
P6y5z00	Congenital heart block NOS
8Hk0.00	Referred to heart failure education group
P520.12	Dextraposition of aorta in Fallot's tetralogy
P6y6.00	Heart and cardiac apex malposition
P74z700	Transposition of pulmonary veins
P6y4000	Congenital absence of coronary artery
AA1z.00	Vincent's angina NOS
P6y6100	Levocardia
P711.00	Preductal coarctation of aorta
9Or4.00	Heart failure monitoring second letter
P6y6200	Mesocardia
7936C00	Implantation of complex 1 wire intravenous cardiac pacemaker
66g..00	Congenital heart condition monitoring
P550.13	Interauricular septal defect
P500.00	Absent septum between aorta and pulmonary artery
P74z100	Absence of superior vena cava
G210100	Malignant hypertensive heart disease with CCF
9Or3.00	Heart failure monitoring first letter
7902100	Correct Fallot tetralogy- right ventric outflow conduit NEC
P51z.00	Great vessel transposition NOS
P74zz00	Other great vein anomaly NOS
P651.00	Fused commissure of the mitral valve
P74z.00	Other great vein anomalies
P56zz00	Endocardial cushion defects NOS
7906200	Closure defect atrioventricular septum using tissue graft
7905z00	Correction total anomalous pulmonary venous connection NOS
P740000	Anomaly of the pulmonary veins, unspecified
7936J00	Implantat intravenous biventricular cardiac pacemaker system

9N4w.00	Did not attend heart failure clinic
662p.00	Heart failure 6 month review
7936H00	Implantat intravenous dual chamber cardiac pacemaker system
7936G00	Implantat intraven single chamber cardiac pacemaker system
P68..00	Congenital heart disease
9Or5.00	Heart failure monitoring third letter
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
9Or2.00	Heart failure monitoring verbal invite
9Or1.00	Heart failure monitoring telephone invite
P721600	Vascular ring, aorta
P650.00	Congenital mitral stenosis, unspecified
3281.00	ECG: no ventricular arrhythmia
9hH..00	Exception reporting: heart failure quality indicators
8Hg8.00	Discharge from practice nurse heart failure clinic
7A00.00	Open operations for combined abnormality of great vessels
Gyu5N00	[X]Other restrictive cardiomyopathy
P6y6z00	Heart or cardiac apex malposition NOS
P6yy000	Atresia of cardiac vein
P561.11	Persistent ostium primum
3296.00	ECG: partial A-V block - 3:1
14AR.00	History of atrial flutter
P601z00	Congenital atresia of pulmonary valve NOS
P70..11	Botalli's patent ductus
P50z.00	Common aorto-pulmonary trunk NOS
7905000	Correct total anomal pulm venous connect to supracard vessel
G580400	Congestive heart failure due to valvular disease
9N4s.00	Did not attend practice nurse heart failure clinic
P6yyA00	Hemicardia
679X.00	Heart failure education
G57y200	Brugada syndrome
G573500	Persistent atrial fibrillation
P736.00	Pulmonary arterio-venous aneurysm
G573400	Permanent atrial fibrillation
7L1H800	Chemical cardioversion
G5y4z00	Post cardiac operation heart failure NOS
7936K00	Implantation of intravenous cardiac pacemaker system NEC
7A00z00	Open operation for combined abnormality of great vessels NOS
G559.00	Arrhythmogenic right ventricular cardiomyopathy
P6y3z00	Obstructive heart anomaly NEC NOS
G558z00	Cardiomyopathy in diseases EC, NOS
P6y8.00	Congenital dextroposition of heart
ZRB1.00	Euroscore for angina
P6yyC00	Fusion of mitral valve cusps
Gyu5R00	[X]Cardiomyopathy in metabolic diseases CE
P50..12	Common truncus
7A02z00	Transluminal operation on abnormality of great vessel NOS
P6y3.00	Obstructive heart anomaly NEC
7902200	Correct Fallot tetralogy- right ventricular outflow patch
7L1H700	External ventricular defibrillation
P744.00	Portal vein - hepatic artery fistula
P61z.00	Congenital tricuspid atresia or stenosis NOS
P65z.00	Congenital mitral stenosis NOS
P51z.11	Transposition of arterial trunk NEC
P74z.11	Persistent left posterior cardinal vein
P743.00	Anomalous portal vein termination
Pyu2100	[X]Other congenital malformations of cardiac septa
P56y.00	Other specified endocardial cushion defects
P74z000	Absence of inferior vena cava

Varicose veins

medcode	description
2482.00	O/E - varicose veins
7A66112	Subfascial ligation of varicose veins
7A69311	Babcock subcutaneous enucleation of varicose veins
G83..00	Varicose veins of the legs
G830.00	Varicose veins of the leg with ulcer
G831.00	Varicose veins of the leg with eczema
G832.00	Varicose veins of the leg with ulcer and eczema
G833.00	Varicose veins of the leg with rupture
G834.00	Varicose veins of leg without mention of complications
G834000	Varicose veins of leg with long saphenous vein distribution
G834100	Varicose veins of leg with short saphenous vein distribution
G83z.00	Varicose veins of the leg NOS
G85..00	Other varicose veins
G85y.00	Other specified varicose veins
G85z.00	Other varicose veins NOS
Gyu8600	[X]Varicose veins of other specified sites
L41..11	Varicose veins - obstetric
L410.00	Varicose veins of legs in pregnancy and the puerperium
L410000	Varicose veins of legs in pregnancy/puerperium unspecified
L410100	Varicose veins of legs in pregnancy/puerperium - delivered
L410200	Varicose veins of legs in pregnancy/puerperium -del+p/n comp
L410300	Varicose veins of legs in pregnancy/puerperium + a/n comp
L410400	Varicose veins of legs in pregnancy/puerperium + p/n comp
L410500	Varicose veins of legs in pregnancy
L410600	Varicose veins of legs in the puerperium
L410z00	Varicose veins of legs in pregnancy and puerperium NOS
L411.11	Perineal obstetric varicose veins
L411.12	Vulval obstetric varicose veins
L411z00	Varicose veins of perineum/vulva in pregnancy/puerperium NOS

Appendix 15: ICD-10 codes for birth outcomes and multiple gestations

Live and stillbirths birth outcomes

ICD-10	Description
P95X	Fetal death of unspecified cause
Z370	Single live birth
Z371	Single stillbirth
Z372	Twins, both liveborn
Z373	Twins, one liveborn and one stillborn
Z374	Twins, both stillborn
Z375	Other multiple births, all liveborn
Z376	Other multiple births, some liveborn
Z377	Other multiple births, all stillborn
Z380	Singleton, born in hospital
Z381	Singleton, born outside hospital
Z382	Singleton, unspecified as to place of birth
Z383	Twin, born in hospital
Z384	Twin, born outside hospital
Z385	Twin, unspecified as to place of birth
Z386	Other multiple, born in hospital
Z387	Other multiple, born outside hospital
P95	Fetal death of unspecified cause

Miscarriages and terminations

ICD-10	Description
O00	Ectopic pregnancy
O000	Abdominal pregnancy
O001	Tubal pregnancy
O002	Ovarian pregnancy
O008	Other ectopic pregnancy
O009	Ectopic pregnancy, unspecified
O01	Hydatidiform mole
O010	Classical hydatidiform mole
O011	Incomplete and partial hydatidiform mole
O019	Hydatidiform mole, unspecified
O02	Other abnormal products of conception
O020	Blighted ovum and nonhydatidiform mole
O028	Other specified abnormal products of conception
O029	Abnormal product of conception, unspecified
O03	Spontaneous abortion
O030	Spontaneous abortion
O031	Spontaneous abortion
O032	Spontaneous abortion
O033	Spontaneous abortion
O034	Spontaneous abortion
O035	Spontaneous abortion
O036	Spontaneous abortion
O037	Spontaneous abortion
O038	Spontaneous abortion
O039	Spontaneous abortion
O04	Medical abortion
O040	Medical abortion
O041	Medical abortion
O042	Medical abortion
O043	Medical abortion
O044	Medical abortion
O045	Medical abortion
O046	Medical abortion
O047	Medical abortion
O048	Medical abortion
O049	Medical abortion
O05	Other abortion
O050	Other abortion
O051	Other abortion
O052	Other abortion
O053	Other abortion
O054	Other abortion
O055	Other abortion
O056	Other abortion
O057	Other abortion
O058	Other abortion
O059	Other abortion
O06	Unspecified abortion
O060	Unspecified abortion
O061	Unspecified abortion
O062	Unspecified abortion
O063	Unspecified abortion
O064	Unspecified abortion
O065	Unspecified abortion
O066	Unspecified abortion
O067	Unspecified abortion
O068	Unspecified abortion
O069	Unspecified abortion

Appendix 16: Codes used to extract mode of delivery

OPCS 4	Description
R171	Elective upper uterine segment caesarean delivery
R172	Elective lower uterine segment caesarean delivery
R178	Other specified elective caesarean delivery
R179	Unspecified elective caesarean delivery
R181	Upper uterine segment caesarean delivery NEC
R182	Lower uterine segment caesarean delivery NEC
R188	Other specified other caesarean delivery
R189	Unspecified other caesarean delivery
R191	Breech extraction delivery with version
R198	Other specified breech extraction delivery
R199	Unspecified breech extraction delivery
R201	Spontaneous breech delivery
R202	Assisted breech delivery
R208	Other specified other breech delivery
R209	Unspecified other breech delivery
R211	High forceps cephalic delivery with rotation
R212	High forceps cephalic delivery NEC
R213	Mid forceps cephalic delivery with rotation
R214	Mid forceps cephalic delivery NEC
R215	Low forceps cephalic delivery
R218	Other specified forceps cephalic delivery
R219	Unspecified forceps cephalic delivery
R221	High vacuum delivery
R222	Low vacuum delivery
R223	Vacuum delivery before full dilation of cervix
R228	Other specified vacuum delivery
R229	Unspecified vacuum delivery
R231	Manipulative cephalic vaginal delivery with abnormal presentation of head at delivery without instrument
R232	Non-manipulative cephalic vaginal delivery with abnormal presentation of head at delivery without instrument
R238	Other specified cephalic vaginal delivery with abnormal presentation of head at delivery without instrument
R239	Unspecified cephalic vaginal delivery with abnormal presentation of head at delivery without instrument
R249	All normal delivery
R251	Caesarean hysterectomy
R252	Destructive operation to facilitate delivery
R258	Other specified other methods of delivery
R259	Unspecified other methods of delivery

OPCS codes used to facilitate delivery

OPCS	Description
R271	OTHER OPERATIONS TO FACILITATE DELIVERY
R278	OTHER OPERATIONS TO FACILITATE DELIVERY
R279	OTHER OPERATIONS TO FACILITATE DELIVERY
R281	INSTRUMENTAL REMOVAL/PRODUCTS/CONCEPTION FROM DEL.UTERU
R288	INSTRUMENTAL REMOVAL/PRODUCTS/CONCEPTION FROM DEL.UTERU
R289	INSTRUMENTAL REMOVAL/PRODUCTS/CONCEPTION FROM DEL.UTERU
R291	MANUAL REMOVAL/PRODUCTS/CONCEPTION FROM DELIVERED UTERU
R298	MANUAL REMOVAL/PRODUCTS/CONCEPTION FROM DELIVERED UTERU
R299	MANUAL REMOVAL/PRODUCTS/CONCEPTION FROM DELIVERED UTERU
R301	OTHER OPERATIONS ON DELIVERED UTERUS
R302	OTHER OPERATIONS ON DELIVERED UTERUS
R303	OTHER OPERATIONS ON DELIVERED UTERUS
R304	OTHER OPERATIONS ON DELIVERED UTERUS
R308	OTHER OPERATIONS ON DELIVERED UTERUS
R309	OTHER OPERATIONS ON DELIVERED UTERUS
R321	REPAIR OF OBSTETRIC LACERATION
R322	REPAIR OF OBSTETRIC LACERATION
R323	REPAIR OF OBSTETRIC LACERATION
R324	REPAIR OF OBSTETRIC LACERATION
R325	REPAIR OF OBSTETRIC LACERATION
R328	REPAIR OF OBSTETRIC LACERATION
R329	REPAIR OF OBSTETRIC LACERATION
R348	OTHER OBSTETRIC OPERATIONS
R349	OTHER OBSTETRIC OPERATIONS

Appendix 17: Characteristics of the studies included in the systematic review and meta-analysis

Author	Country	Study period	Study design and methodology	Measures taken to confirm VTE
Sultan[36]	United Kingdom	1987-2004	Population based retrospective cohort. Cases were identified using primary care data which were validated	VTE cases were confirmed based on anticoagulant therapy
Vikrus[37]	Denmark	1995-2005	Population based retrospective cohort. Cases were identified from national registry using ICD-10 codes.	Registry was validated for VTE during pregnancy with PPV of more than 80%
O'Cornnor[38]	United States	2003-2008	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively confirmed based on diagnostic tests[1]
Liu[12]	Canada	1991-2006	Cross sectional study. Cases were identified using hospital discharge database using ICD-10 codes.	No measures taken to confirm VTE
Jacobsen[32]	Norway	1990-2003	Cross sectional study. Cases were identified from patient and birth register.	VTE cases were validated for the subset of the data
Lindqvist[39]	Sweden	1990-2005	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively confirmed based on diagnostic tests[1]
Sharma[40]	Australia	1999-2006	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively confirmed based on diagnostic tests[1]
Larsen[41]	Denmark	1980-2001	Cross sectional study. Cases were identified from a single county.	VTE cases were objectively confirmed based on diagnostic tests[1]
James[7]	United States	2000-2001	Cross-sectional study. Cases were identified from national inpatient sample which covers around 100 hospitals using ICD-10 codes.	VTE cases were objectively confirmed[1]. Included some probable and possible VTEs
Heit[31]	United States	1966-1995	Population based cohort. Potentially fertile women were prospectively followed in a single county.	VTE cases were objectively confirmed[1]. Included some probable and possible VTEs
Haggaz[9]	Sudan	1999-2000	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively

Author	Country	Study period	Study design and methodology	Measures taken to confirm VTE
				confirmed based on diagnostic tests[1]
Soomro[42]	Saudi Arabia	1986-1998	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively confirmed based on diagnostic tests[1]
Chan[43]	Japan	1998-2000	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively confirmed based on diagnostic tests[1]
Ros[33]	Sweden	1987-1995	Population based retrospective cohort. Cases were identified using inpatient registry using ICD-9 codes	No measures taken to confirm VTE
Simpon[10]	United Kingdom	1988-1997	Cross sectional study in which cases were identified using ICD codes from hospital database	No measures taken to confirm VTE
Gherman[34]	United States	1978-1996	Cross sectional study. Cases were identified from a single hospital.	VTE cases were objectively confirmed based on diagnostic tests[1]
Lindqvist[44]	Sweden	190-1993	Cross sectional study. Cases were identified from Swedish birth and patient registry	No measures taken to confirm VTE
McColl[45]	United Kingdom	1985-1996	Cross sectional study. Cases were identified using national health service data.	VTE cases were objectively confirmed based on diagnostic tests[1]
Anderson[6]	Denmark	1984-1994	Cross sectional study. Cases were identified using inpatient registry.	VTE cases were objectively confirmed based on diagnostic tests[1]
James[48]	United States	1989-1994	Cross sectional study where cases were identified from medical records at a single hospital.	No measures taken to confirm VTE
Lyall[123]	United Kingdom	1999-2007	Cross sectional study. Cases were identified from a single unit	VTE cases were objectively confirmed based on diagnostic tests[1]

[1]A diagnosis of pulmonary embolism may be confirmed by pulmonary angiography, CT, MRI, ventilation-perfusion scan, pathological confirmation of thrombus etc. whereas the diagnosis of DVT may be confirmed by Doppler ultrasound, duplex ultrasconography, venography, pathological confirmation of thrombus etc. each of which may vary from study to study.

Appendix 18: Read codes for hyperemesis

readcode	description
L13..11	Hyperemesis gravidarum
L130.00	Mild hyperemesis gravidarum
L130000	Mild hyperemesis unspecified
L13..12	Hyperemesis of pregnancy
L131.00	Hyperemesis gravidarum with metabolic disturbance
L130z00	Mild hyperemesis gravidarum NOS
L130200	Mild hyperemesis-not delivered
L131z00	Hyperemesis gravidarum with metabolic disturbance NOS
L131000	Hyperemesis gravidarum with metabolic disturbance unsp
L131200	Hyperemesis gravidarum with metabolic disturbance - not del
L130100	Mild hyperemesis-delivered

Appendix 19: ICD-10 codes for hyperemesis, acute systemic infection and antepartum haemorrhage

Antepartum haemorrhage ICD-10 codes

ICD-10	Description
O460	Antepartum haemorrhage with coagulation defect
O468	Other antepartum haemorrhage
O469	Antepartum haemorrhage, unspecified
O200	Threatened abortion
O208	Other haemorrhage in early pregnancy
O209	Haemorrhage in early pregnancy, unspecified

Hyperemesis ICD-10 codes

ICD-10	Description
O210	Mild hyperemesis gravidarum
O211	Hyperemesis gravidarum with metabolic disturbance

Acute systemic infection ICD-10 codes

ICD-10	Description
J100	Influenza with pneumonia, influenza virus identified
J101	Influenza with oth resp manifest influenza virus identified
J108	Influenza with other manifest influenza virus identified
J110	Influenza with pneumonia, virus not identified
J111	Influenza with oth resp manifestation virus not identified
J118	Influenza with other manifestations, virus not identified
J120	Adenoviral pneumonia
J121	Respiratory syncytial virus pneumonia
J122	Parainfluenza virus pneumonia
J128	Other viral pneumonia
J129	Viral pneumonia, unspecified
J13X	Pneumonia due to Streptococcus pneumoniae
J14X	Pneumonia due to Haemophilus influenzae
J150	Pneumonia due to Klebsiella pneumoniae
J151	Pneumonia due to Pseudomonas
J152	Pneumonia due to staphylococcus
J153	Pneumonia due to streptococcus, group B
J154	Pneumonia due to other streptococci
J155	Pneumonia due to Escherichia coli
J156	Pneumonia due to other aerobic Gram-negative bacteria
J157	Pneumonia due to Mycoplasma pneumoniae
J158	Other bacterial pneumonia
J159	Bacterial pneumonia, unspecified
J160	Chlamydial pneumonia
J168	Pneumonia due to other specified infectious organisms
J170	Pneumonia in bacterial diseases classified elsewhere
J171	Pneumonia in viral diseases classified elsewhere
J172	Pneumonia in mycoses
J173	Pneumonia in parasitic diseases
J178	Pneumonia in other diseases classified elsewhere
J180	Bronchopneumonia, unspecified

J181	Lobar pneumonia, unspecified
J182	Hypostatic pneumonia, unspecified
J188	Other pneumonia, organism unspecified
J189	Pneumonia, unspecified
J200	Acute bronchitis due to Mycoplasma pneumoniae
J201	Acute bronchitis due to Haemophilus influenzae
J202	Acute bronchitis due to streptococcus
J203	Acute bronchitis due to coxsackievirus
J204	Acute bronchitis due to parainfluenza virus
J205	Acute bronchitis due to respiratory syncytial virus
J206	Acute bronchitis due to rhinovirus
J207	Acute bronchitis due to echovirus
J208	Acute bronchitis due to other specified organisms
J209	Acute bronchitis, unspecified
J210	Acute bronchiolitis due to respiratory syncytial virus
J218	Acute bronchiolitis due to other specified organisms
J219	Acute bronchiolitis, unspecified
J22X	Unspecified acute lower respiratory infection
O861	Other infection of genital tract following delivery
O862	Urinary tract infection following delivery
O863	Other genitourinary tract infections following delivery
O230	Infections of kidney in pregnancy
O231	Infections of bladder in pregnancy
O232	Infections of urethra in pregnancy
O233	Infections of other parts of urinary tract in pregnancy
O234	Unspecified infection of urinary tract in pregnancy
O235	Infections of the genital tract in pregnancy
O239	Other and unspec genitourinary tract infection in pregnancy
N390	Urinary tract infection, site not specified
N300	Acute cystitis
N301	Interstitial cystitis (chronic)
N302	Other chronic cystitis
N303	Trigonitis
N304	Irradiation cystitis
N308	Other cystitis
N309	Cystitis, unspecified
N10X	Acute tubulo-interstitial nephritis
N110	Nonobstructive reflux-associated chronic pyelonephritis
N111	Chronic obstructive pyelonephritis
N118	Other chronic tubulo-interstitial nephritis
N119	Chronic tubulo-interstitial nephritis, unspecified
N12X	Tubulo-interstitial nephritis not spec as acute or chronic
N340	Urethral abscess
N341	Nonspecific urethritis
N342	Other urethritis

Appendix 20: ICD-10 codes for medical co-morbidities

ICD-10 codes for diabetes

ICD-10	Description
E100	Insulin-dependent diabetes mellitus with coma
E101	Insulin-dependent diabetes mellitus with ketoacidosis
E102	Insulin-dependent diabetes mellitus with renal complications
E103	Insulin-dependent diabetes mellitus with ophthalmic comps
E104	Insulin-dependent diabetes mellitus with neurological comps
E105	Insulin-dependent diabetes mellitus with periph circ comps
E106	Insulin-dependent diabetes mellitus with other spec comps
E107	Insulin-dependent diabetes mellitus with multiple comps
E108	Insulin-dependent diabetes mellitus with unspec comps
E109	Insulin-dependent diabetes mellitus without complications
E110	Non-insulin-dependent diabetes mellitus with coma
E111	Non-insulin-dependent diabetes mellitus with ketoacidosis
E112	Non-insulin-dependent diabetes mellitus with renal comps
E113	Non-insulin-dependent diabetes mellitus with ophthalm comps
E114	Non-insulin-dependent diabetes mellitus with neuro comps
E115	Non-insulin-depend diabetes mellitus with periph circ comp
E116	Non-insulin-depend diabetes mellitus with other spec comp
E117	Non-insulin-dependent diabetes mellitus with multiple comps
E118	Non-insulin-dependent diabetes mellitus with unspec comps
E119	Non-insulin-depend diabetes mellitus without complication
E120	Malnutrition-related diabetes mellitus with coma
E121	Malnutrition-related diabetes mellitus with ketoacidosis
E122	Malnutrition-related diabetes mellitus with renal comps
E123	Malnutrition-related diabetes mellitus with ophthalmic comps
E124	Malnutrition-related diabetes mellitus with neuro comps
E125	Malnutrition-relat diabetes mellitus with periph circ comp
E126	Malnutrition-relat diabetes mellitus with other spec comps
E127	Malnutrition-related diabetes mellitus with multiple comps
E128	Malnutrition-related diabetes mellitus with unspec comps
E129	Malnutrition-related diabetes mellitus without complications
E130	Other specified diabetes mellitus with coma
E131	Other specified diabetes mellitus with ketoacidosis
E132	Other specified diabetes mellitus with renal complications
E133	Other specified diabetes mellitus with ophthalmic comps
E134	Other specified diabetes mellitus with neurological comps
E135	Other specified diabetes mellitus with periph circ comps
E136	Other specified diabetes mellitus with other spec comps
E137	Other specified diabetes mellitus with multiple comps
E138	Other specified diabetes mellitus with unspecified comps
E139	Other specified diabetes mellitus without complications
E140	Unspecified diabetes mellitus with coma
E141	Unspecified diabetes mellitus with ketoacidosis
E142	Unspecified diabetes mellitus with renal complications
E143	Unspecified diabetes mellitus with ophthalmic complications
E144	Unspecified diabetes mellitus with neurological comps
E145	Unspecified diabetes mellitus with periph circulatory comps
E146	Unspecified diabetes mellitus with other specified comps
E147	Unspecified diabetes mellitus with multiple complications
E148	Unspecified diabetes mellitus with unspecified complications
E149	Unspecified diabetes mellitus without complications
O240	Pre-existing diabetes mellitus, insulin-dependent
O241	Pre-existing diabetes mellitus, non-insulin-dependent
O242	Pre-existing malnutrition-related diabetes mellitus
O243	Pre-existing diabetes mellitus, unspecified
O244	Diabetes mellitus arising in pregnancy
O249	Diabetes mellitus in pregnancy, unspecified
O244	Gestational diabetes mellitus NOS

ICD-10 codes for cardiac disease

ICD-10	Description
I420	Dilated cardiomyopathy
I421	Obstructive hypertrophic cardiomyopathy
I422	Other hypertrophic cardiomyopathy
I423	Endomyocardial (eosinophilic) disease
I424	Endocardial fibroelastosis
I425	Other restrictive cardiomyopathy
I426	Alcoholic cardiomyopathy
I427	Cardiomyopathy due to drugs and other external agents
I428	Other cardiomyopathies
I429	Cardiomyopathy, unspecified
I430	Cardiomyopathy in infectious & parasitic diseases CE
I431	Cardiomyopathy in metabolic diseases
I432	Cardiomyopathy in nutritional diseases
I438	Cardiomyopathy in other diseases classified elsewhere
I500	Congestive heart failure
I501	Left ventricular failure
I509	Heart failure, unspecified
I200	Unstable angina
I201	Angina pectoris with documented spasm
I208	Other forms of angina pectoris
I209	Angina pectoris, unspecified
I210	Acute transmural myocardial infarction of anterior wall
I211	Acute transmural myocardial infarction of inferior wall
I212	Acute transmural myocardial infarction of other sites
I213	Acute transmural myocardial infarction of unspecified site
I214	Acute subendocardial myocardial infarction
I219	Acute myocardial infarction, unspecified
I220	Subsequent myocardial infarction of anterior wall
I221	Subsequent myocardial infarction of inferior wall
I228	Subsequent myocardial infarction of other sites
I229	Subsequent myocardial infarction of unspecified site
I230	Haemopericardium as curr comp folow acut myocard infarct
I231	Atral sept defect as curr comp folow acut myocardal infarct
I232	Ventric sep defect as curr comp fol acut myocardal infarc
I233	Rup cardac wal withou haemopercard as cur comp fol ac MI
I234	Rup chordae tendinae as curr comp fol acut myocard infarct
I235	Rup papilary muscle as curr comp fol acute myocard infarct
I236	Thromb atrium/auric append/vent as curr comp foll acute MI
I238	Oth current comp following acute myocardial infarction
I240	Coronary thrombosis not resulting in myocardial infarction
I241	Dressler's syndrome
I248	Other forms of acute ischaemic heart disease
I249	Acute ischaemic heart disease, unspecified
I250	Atherosclerotic cardiovascular disease, so described
I251	Atherosclerotic heart disease
I252	Old myocardial infarction
I253	Aneurysm of heart
I254	Coronary artery aneurysm
I255	Ischaemic cardiomyopathy
I256	Silent myocardial ischaemia
I258	Other forms of chronic ischaemic heart disease
I259	Chronic ischaemic heart disease, unspecified
Q200	Common arterial trunk
Q201	Double outlet right ventricle
Q202	Double outlet left ventricle
Q203	Discordant ventriculoarterial connection
Q204	Double inlet ventricle
Q205	Discordant atrioventricular connection
Q206	Isomerism of atrial appendages

Q208	Other cong malforms of cardiac chambers and connections
Q209	Cong malforms of cardiac chambers and connections unspec
Q210	Ventricular septal defect
Q211	Atrial septal defect
Q212	Atrioventricular septal defect
Q213	Tetralogy of Fallot
Q214	Aortopulmonary septal defect
Q218	Other congenital malformations of cardiac septa
Q219	Congenital malformation of cardiac septum, unspecified
Q220	Pulmonary valve atresia
Q221	Congenital pulmonary valve stenosis
Q222	Congenital pulmonary valve insufficiency
Q223	Other congenital malformations of pulmonary valve
Q224	Congenital tricuspid stenosis
Q225	Ebstein's anomaly
Q226	Hypoplastic right heart syndrome
Q228	Other congenital malformations of tricuspid valve
Q229	Congenital malformation of tricuspid valve, unspecified
Q230	Congenital stenosis of aortic valve
Q231	Congenital insufficiency of aortic valve
Q232	Congenital mitral stenosis
Q233	Congenital mitral insufficiency
Q234	Hypoplastic left heart syndrome
Q238	Other congenital malformations of aortic and mitral valves
Q239	Congenital malformation of aortic and mitral valves unspec
Q240	Dextrocardia
Q241	Laevocardia
Q242	Cor triatriatum
Q243	Pulmonary infundibular stenosis
Q244	Congenital subaortic stenosis
Q245	Malformation of coronary vessels
Q246	Congenital heart block
Q248	Other specified congenital malformations of heart
Q249	Congenital malformation of heart, unspecified
Q250	Patent ductus arteriosus
Q251	Coarctation of aorta
Q252	Atresia of aorta
Q253	Stenosis of aorta
Q254	Other congenital malformations of aorta
Q255	Atresia of pulmonary artery
Q256	Stenosis of pulmonary artery
Q257	Other congenital malformations of pulmonary artery
Q258	Other congenital malformations of great arteries
Q259	Congenital malformation of great arteries, unspecified
Q260	Congenital stenosis of vena cava
Q261	Persistent left superior vena cava
Q262	Total anomalous pulmonary venous connection
Q263	Partial anomalous pulmonary venous connection
Q264	Anomalous pulmonary venous connection, unspecified
Q265	Anomalous portal venous connection
Q266	Portal vein-hepatic artery fistula
Q268	Other congenital malformations of great veins
Q269	Congenital malformation of great vein, unspecified
I48X	Atrial fibrillation and flutter
I490	Ventricular fibrillation and flutter
I491	Atrial premature depolarization
I492	Junctional premature depolarization
I493	Ventricular premature depolarization
I494	Other and unspecified premature depolarization
I495	Sick sinus syndrome
I498	Other specified cardiac arrhythmias
I499	Cardiac arrhythmia, unspecified

ICD-10 codes for hypertension

ICD-10	Description
I110	Hypertensive heart disease with (congestive) heart failure
I119	Hypertensive heart disease without (conges) heart failure
I120	Hypertensive renal disease with renal failure
I129	Hypertensive renal disease without renal failure
I130	Hypertens heart and renal dis with (conges) heart failure
I131	Hypertensive heart and renal disease with renal failure
I132	Hyper heart and renal dis both (cong) heart and renal fail
I139	Hypertensive heart and renal disease, unspecified
I150	Renovascular hypertension
I151	Hypertension secondary to other renal disorders
I152	Hypertension secondary to endocrine disorders
I158	Other secondary hypertension
I159	Secondary hypertension, unspecified
O100	Pre-exist essen hypertens comp preg childbirth and puerp
O101	Pre-exist hyperten heart dis comp preg childbth and puerp
O102	Pre-exist hyperten renal dis comp preg childbth and puerp
O103	Pre-exist hyperten heart renal dis comp preg chdbth/puerp
O104	Pre-exist sec hypertens comp preg childbth and puerprum
O109	Unspec pre-exist hypertens compl pregn childbth puerprum
O11X	Pre-exist hypertens disorder with superimposed proteinuria
O13	Gest [pregnancy-induced] hypertens without sig proteinuria
O140	Moderate pre-eclampsia
O141	Severe pre-eclampsia
O142	HELLP syndrome
O149	Pre-eclampsia, unspecified

ICD-10 codes for IBD

ICD-10	Description
K500	Crohn's disease of small intestine
K501	Crohn's disease of large intestine
K508	Other Crohn's disease
K509	Crohn's disease, unspecified
K510	Ulcerative (chronic) enterocolitis
K511	Ulcerative (chronic) ileocolitis
K512	Ulcerative (chronic) proctitis
K513	Ulcerative (chronic) rectosigmoiditis
K514	Pseudopolyposis of colon
K515	Mucosal proctocolitis
K518	Other ulcerative colitis
K519	Ulcerative colitis, unspecified

ICD-10 codes for varicose veins

ICD-10	Description
I830	Varicose veins of lower extremities with ulcer
I831	Varicose veins of lower extremities with inflammation
I832	Varicose veins low extremities with both ulcer and inflamm
I839	Varicose veins lower extremities without ulcer or inflamm
O220	Varicose veins of lower extremity in pregnancy

Appendix 21: ICD-10 codes for delivery related complications

Postpartum and intra-partum haemorrhage

ICD-10	Description
O720	Third-stage haemorrhage
O721	Other immediate postpartum haemorrhage
O722	Delayed and secondary postpartum haemorrhage
O723	Postpartum coagulation defects
O670	Intrapartum haemorrhage with coagulation defect
O678	Other intrapartum haemorrhage
O679	Intrapartum haemorrhage, unspecified

Eclampsia/pre-eclampsia

ICD-10	Description
O150	Eclampsia in pregnancy
O151	Eclampsia in labour
O152	Eclampsia in the puerperium
O159	Eclampsia, unspecified as to time period
O11	Pre-exist hypertens disorder with superimposed proteinuria
O140	Moderate pre-eclampsia
O141	Severe pre-eclampsia
O149	Pre-eclampsia, unspecified