

Background incidence rates of maternal adverse events and adverse events of special interest during pregnancy: a cohort study from four European countries

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Background

Surveillance of adverse events of special interest (AESI) is essential for the safety monitoring of vaccines and medicines, with observational studies playing a key role in this work.^{1,2} Existing studies typically estimate background rates in the general population stratified by age and sex, and often across multiple healthcare data sources, to account for biological and healthcare-system differences.² However, pregnant individuals remain underrepresented in such analyses, despite physiological changes during pregnancy potentially modifying baseline risk of AESI compared with non-pregnant individuals of reproductive age. A recent French study provided background incidence rates of AESI during pregnancy; however, further evidence across diverse healthcare systems and populations is still needed.³ In addition, pregnancy is associated with maternal adverse events (MAE) unique to the pregnancy state.

The aim of this study was to leverage European healthcare data mapped to the OMOP Common Data Model to estimate incidence rates of MAE and AESI during pregnancy.

Methods

The protocol for the study was registered in the European Medicines Agency (EMA) Real World Data (RWD) Catalogue (number: EUPAS1000000712).

We conducted a multinational cohort study using nationwide registry data from Sweden (SCIFI-PEARL project) and Norway (NLHR), primary care linked to hospital discharge data from Catalonia, Spain (SIDIAP), and the United Kingdom (UK) primary care data (CPRD GOLD). All four data sources were standardised to the OMOP Common Data Model and included pregnancy data mapped to the OMOP pregnancy extension table.⁴

Women aged 12–55 years with pregnancies starting between January 1, 2018, and with nine months of data visibility before the end of pregnancy were included. The cut-off for pregnancy data was August 2024 for SCIFI-PEARL, December 2023 for NLHR, and December 2024 for SIDIAP and CPRD GOLD.

A total of 13 MAE and 15 AESI were phenotyped following the DARWIN EU[®] framework.⁵ ASL, APU, and

DPA led the development and review of the resulting phenotypes, with a clinical expert in obstetrics (YM) involved in the final approval of diagnostics.

Incidence rates per 100,000 person-years were estimated for each outcome separately, stratified by gestational trimester (Trimester 1: day 0 to 90, Trimester 2: day 91 to 180, and Trimester 3: after 181 days) and maternal age (12 to 17, 18 to 34, and 35 to 55 years).

MAE included foetal loss outcomes, hypertensive and non-hypertensive pregnancy complications, labour and postpartum complications, and maternal death. AESI included thromboembolic, neurological, cardiovascular, haematological, and hypersensitivity outcomes. The study code is publicly available on GitHub: <https://github.com/oxford-pharmacoepi/PregnancyAdverseEvents>

Results

A total of 1,179,636 pregnancies (909,597 subjects) were included. Median maternal age ranged from 30 to 32 years across data sources. Miscarriage (28,619–50,905 per 100,000 person-years) and dysfunctional labour (31,904–71,172) were the most frequent MAE, followed by gestational diabetes mellitus (GDM, 7,279–12,100), preterm delivery (13,090–23,510), pre-eclampsia (832–6,756), and antepartum haemorrhage (APH, 943–6,576). Severe outcomes such as eclampsia, HELLP syndrome, and maternal death were less frequent (incidence rates below 250 per 100,000 person-years). Figure 1 presents incidence rates stratified by gestational trimester, showing that miscarriage and ectopic pregnancy occurred predominantly during the first trimester, whereas GDM, APH, and hypertensive disorders peaked during the third trimester. Figure 2 presents maternal age-stratified incidence rates, where clear age patterns were observed for some outcomes: GDM incidence increased with maternal age, while miscarriage and preterm delivery showed U-shaped incidence distributions by maternal age .

Figure 1. Incidence rates per 100,000 person-years for Maternal Adverse Events across data sources, stratified by gestational trimester.

The study enrolled pregnancies starting between January 2018 and 9 months before the pregnancy data cut-off. The enrolment period ended (9-month before data cut-off) in December 2023 for SCIFI-PEARL (Sweden), March 2023 for NLHR (Norway), and March 2024 for CPRD GOLD (the UK) and SIDIAP (Spain). Points represent the estimated incidence rate (per 100,000 person-years). Error bars indicate 95% Confidence Intervals (exact Poisson method); arrows denote intervals extending beyond the displayed axis limits. Missing points indicate that either the outcome was not assessed in that trimester (third trimester for miscarriage, and first trimester for stillbirth, antepartum haemorrhage, preterm delivery and dysfunctional labour) or event counts were less than 5.

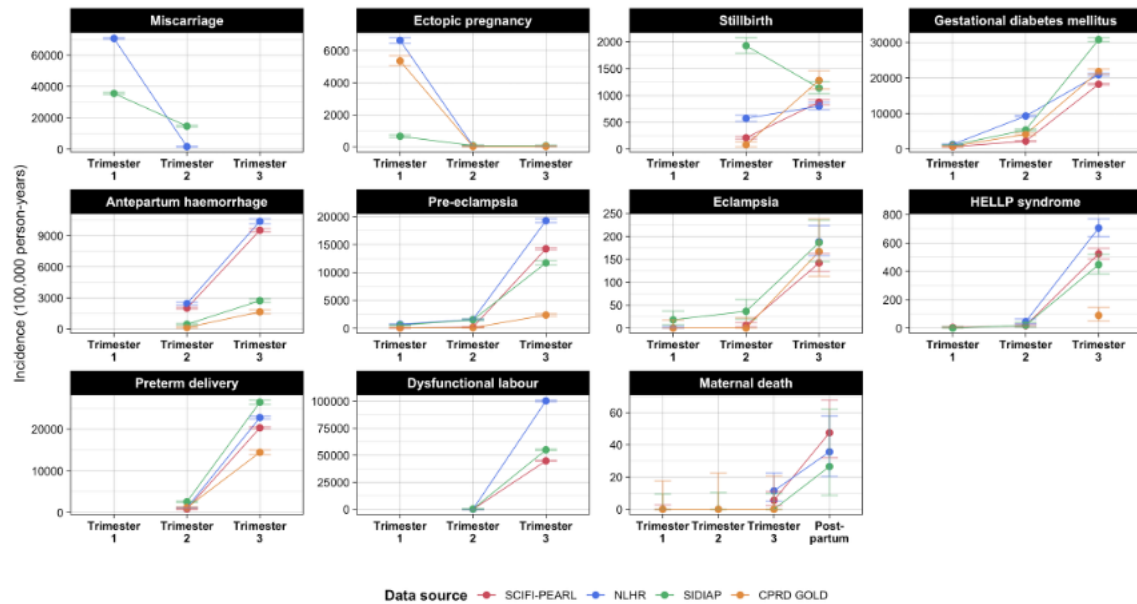
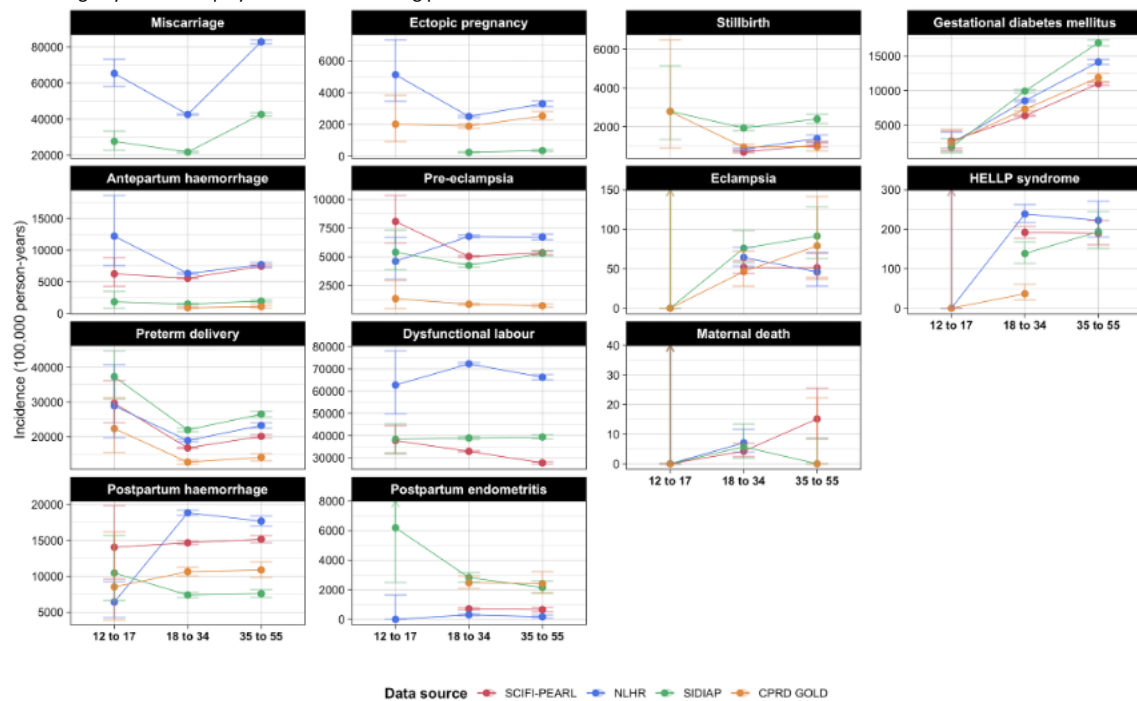


Figure 2. Incidence rates per 100,000 person-years for Maternal Adverse Events across data sources for the overall study period, stratified by maternal age.

The study enrolled pregnancies starting between January 2018 and 9 months before the pregnancy data cut-off. The enrolment period ended (9-month before data cut-off) in December 2023 for SCIFI-PEARL, March 2023 for NLHR, and March 2024 for CPRD GOLD and SIDIAP. Points represent the estimated incidence rate (per 100,000 person-years). Error bars indicate 95% Confidence Intervals (exact Poisson method); arrows denote intervals extending beyond the displayed axis limits. Missing points indicate that event counts were less than 5.

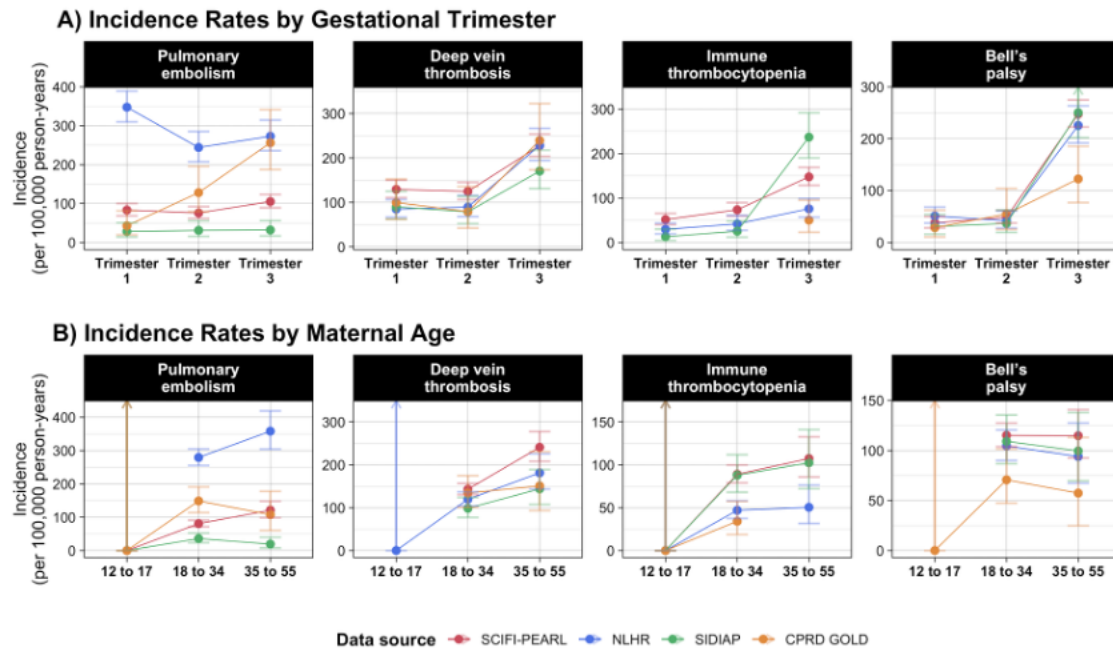


The most common AESI during pregnancy were deep vein thrombosis (DVT), pulmonary embolism (PE),

immune thrombocytopenia (ITP), and Bell's palsy, with incidence rates ranging from 27 to 294 per 100,000 person-years. These were followed by anaphylaxis, myocarditis or pericarditis, and ischaemic stroke (12–48 per 100,000 person-years). All other AESI had rates below 10 per 100,000 person-years. Figure 3 presents the four most common AESI stratified by gestational trimester and maternal age. DVT, ITP, and Bell's palsy peaked during the third trimester, whereas PE showed a first-trimester peak in Norwegian data. By maternal age, DVT incidence was higher among women aged 35–55 years than among those aged 18–34 years; however, no consistent age patterns were observed for the remaining AESI, and event counts were too low to meaningfully assess the youngest age group.

Figure 3. Incidence rates (per 100,000 person-years) for the four most frequent Adverse Events of Special Interest during pregnancy across data sources for the overall study period. Estimates are stratified by gestational trimester and maternal age.

The study enrolled pregnancies starting between January 2018 and 9 months before the pregnancy data cut-off. The enrolment period ended (9-month before data cut-off) in December 2023 for SCIFI-PEARL (Sweden), March 2023 for NLHR (Norway), and March 2024 for CPRD GOLD (the UK) and SIDIAP (Spain). Points represent the estimated incidence rate (per 100,000 person-years). Error bars indicate 95% Confidence Intervals (exact Poisson method); arrows denote intervals extending beyond the displayed axis limits. Missing points indicate that event counts were less than 5.



Results from this study have been published as a preprint in the SSRN open-access platform:

<http://dx.doi.org/10.2139/ssrn.6747563>

Conclusions

Harmonised, multi-country background rates provide an important benchmark for interpreting drug and vaccine safety signals in pregnant populations. Incidence rates of both MAE and AESI varied by gestational

trimester, maternal age, and data source. Despite harmonised analytics, substantial heterogeneity across data sources remained, likely reflecting differences in healthcare systems, data provenance, and coding practices, in addition to underlying population characteristics. Observed-to-expected analyses during pregnancy should therefore account for gestational timing and maternal age, while prioritising within-data-source comparisons. Our data compared to previous reports suggest that some AESI (notably DVT, PE, and ITP) are more common in pregnant women than equivalent background rates in women of reproductive age.⁶

References

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