Statistical analysis plan

Algorithms for characterizing migraine in healthcare databases for use in perinatal studies: A European multi-database study

Drafted by

Socheat Cheng, UOSLO

Hedvig Nordeng, UOSLO

Final editing by Angela Lupattelli, UOSLO

Version 17.01.2022

Contents

Main Author(s) of the SAP

Name	*Institution*	*Role*	*Date*
Hedvig Nordeng	UIO	Author v0.1, v0.2	14.11.2021, 15.01.2022
Socheat Cheng	UIO	Author v0.1	14.11.2021
Angela Lupattelli	UIO	Author v0.2	17.01.2022

Overview of SAP Amendments and Updates

Number	Date (DDMMMYY)	Amendment or update
V0.1	14.11.2021	First version
V0.2	17.01.2022	Clarifications made based on reviewer comments. Update of team members

Reviewers of the document

Name	Name
Marte-Helene Bjørk, UiB	Maarit Leinonen, THL
Joan Morris, SGUL	Christine Damase-Michel, UTOUL
Ditte Mølgaard-Nielsen, NovoNordisk	Sue Jordan, USWANSEA
Miriam Sturkenboom, UMCU	Clara Cavero and Laia Barrachina Bonet, FISABIO
Marianne Cunnington, GSK	Giulia Hyeraci, Rosa Gini on behalf of ARS

Study team members

Name	Role
Hedvig Nordeng (UOSL)	PI. Conceptualization. Task lead PP.
Angela Lupattelli (UOSL)	SAP author, data analytics
Sandra Lopez (Novartis)	Task lead IP (as of 15.01.2022)
Ditte Mølgaard-Nielsen (Novo Nordisk)	Task supervision IP
Joan Morris (SGUL)	Statistical expert
Marte-Helene Bjørk (UiB)	Clinical expert
Vjola Hoxhaj (UMCU)	Coding of SAP and analytics
DAPs	Data analytics

1. Introduction

The focus of the demonstration project 4 (DP4) of work package 1 is to present solutions for studying intermittent medication exposures in diseases with episodic manifestations during pregnancy, using medication for migraine as a motivating example. The project includes both drug utilization and safety studies using large-scale data from multiple healthcare databases. Thus, to ensure accurate and complete capture of migraine disease across the data sources used in DP4, and to distinguish migraine from other headache types, it is essential to develop algorithms for characterizing migraine events.

1.1 Perinatal migraine

Migraine is a complex neurovascular condition, characterized by a moderate-severe unilateral pulsating headache, which occasionally is accompanied by aura (reversible visual, sensory and language disturbances) (1, 2). Migraine is the major contribution to disability globally. The prevalence among women of reproductive age ranges from 20% to 40% (3,4).

Most women experience a marked improvement over the course of pregnancy, partly due to the increase in estrogen levels, which inhibits releasing of neuropeptide known to trigger migraine attacks, such as calcitonin gene-related peptide (CGRP) and neurokinin A (5, 6). The improvement differs depending on migraine types. Migraine with aura is less likely than migraine without aura to improve throughout pregnancy, remission rates (43.6% versus 76.8%) (5). Maternal characteristics (e.g. age) may play some roles in predisposing or triggering migraine attacks during pregnancy. Migraine during pregnancy is associated with several adverse maternal and pregnancy outcomes; a recent meta-analysis shows that pregnant women with migraine have higher odds of having pre-eclampsia (OR=2.1, 95% CI: 1.5 to 2.9), and low birth weight in offspring (OR=1.2, 95%CI: 1.0 to 1.3) compared to those without migraine (7).

Adequate estimation of the risk of medication use in pregnancy versus risks of the underlying maternal illness require adequate identification of migraine types (with/without aura, severity), differentiation from other headache diseases with high precision and accuracy. Data sources differ in what kind of information they contain: some lack diagnostic codes (Dx) while others lack information on medication use (Rx). The implications of having either of these sources, i.e. how well they overlap in case identification and the related consequences for migraine drug safety studies in pregnancy, are poorly characterized. To summarize, it is unknown whether migraine algorithms based on Rx codes alone can adequately capture migraine disease.

1.2 Mapping disease events across healthcare databases

In healthcare databases, data are normally recorded using standardized coding systems, indicating the types of diagnoses, procedures, prescription/reimbursement claims. Some examples of widely used coding systems are International Statistical Classification of Diseases and Related Health Problems (ICD) (8), International Classification of Primary Care (ICPC) (9), Anatomical Therapeutic Chemical classification system (ATC) (10), and Read Codes (11).

Diagnostic codes alone and/or pairing with procedure and medication codes can be used to trace clinical events in databases (12). The work by Thurin et al. (13) shows the terminology used by each database within ConcePTION.

Within the ConcePTION project, Codemapping using the VACEU Codemapper is used to bridge between different diagnosis terminologies based on the Unified Medical Language System, and event-finding algorithms that can deploy different types of components (diagnoses, procedures, medicines) will be employed to characterize variability in migraine disease events rates within and between data sources, and factors related to such variability described (e.g. maternal age, year).

2. Aims of the study

The overall aim of the study is to identify the best algorithms to inform the Migraine DP.
This includes an illustration of how three groups of migraine algorithms work:

- Migraine event-finding (Mig_A)
- Migraine types (Mig_T)
- Migraine severity (Mig_S)

The specific aims are, within each database in DP4:

1. To assess how different migraine algorithms impact the prevalence of migraine events, type and severity*
    a) at baseline (i.e. start of pregnancy) with different look-back time, depending on DAP data availability
        i. During the total study period
        ii. By year
        iii. By maternal age

We hypothesize that different look-back time will have an impact the prevalence of migraine at baseline.

    b) Overall during pregnancy, and in each trimester of pregnancy
        i. pregnancies observed at any time in gestation
        ii. pregnancies observed in the 1st trimester
        iii. pregnancies observed in the 2nd trimester
        iv. pregnancies observed in the 3rd trimester

2. To quantify overlap between the following algorithms:
    a) Migraine events based on diagnosis codes only (Mig_A1) and Triptan prescription only (Mig_A2) at baseline and during pregnancy.
    b) Migraine types (Mig_T) by migraine severity (Mig_S) at baseline and during pregnancy.

*The distribution of year of LMP and maternal age across the various migraine event-finding algorithms will solely be done for Mig_A2 and Mig_A4, as these are considered the most relevant ones.

3. Study design, population and data sources

This is a cross-country comparative study, using data from national healthcare databases regulated by seven European countries and/or regions: Norway, France, United Kingdom, Finland, Spain, Germany, and Italy. Table 1 and 2 provides information on participating databases and relevant periods for which data are provided in each database. The primary look-back period in which pregnancy history is measured covers the 12 months prior to LMP date (3 months if 12 months is not available in the database), as this history window is available in most databases and migraine is a chronic/long-term condition. Using maternal unique identification numbers, we link all local databases to capture information related to pregnancy, medication use, and maternal migraine features and characteristics.

Table 1. Overview of data sources and study period

Country	Data coverage	DAP	Cohort entry date (CED)*	End date	First LMP date*	Number of pregnancies
Finland	Nationwide	THL	01/01/2008	31/12/2018	CED + 3m	804,000
France	Nationwide	SNDS	01/01/2015	31/12/2020	CED + 12m	3,500,000
France	Haute-Garonne	EFEMERIS	01/01/2008	31/12/2019	CED + 3m	83,964
Germany	Nationwide (~17%)	GePaRD	01/01/2008	31/12/2018	CED + 12m	1,800,000
Italy	Emilia Romagna	UNIFE	01/01/2008	31/12/2019	CED + 12m	225,000
Italy	Tuscany	ARS	01/01/2008	31/12/2019	CED + 12m	275,000
Norway	Nationwide	USLO	01/01/2008	31/12/2019	CED + 12m	876,000
Spain	Valencian Region	FISABIO	01/01/2010	31/12/2020	CED + 12m	310,000
UK	Wales	SAIL	01/01/2008	31/12/2020	CED + 12m	350,000

CED: Cohort entry date.

*Note on start date: We adjust start date according to the different look-back time we want to explore (i.e. 3 months, 12 months, and 5 years, depending on DAP data availability). 5-year look back time: Only pregnancies with estimated LMP date ≥ 1 January 2013 and onwards are included, to ensure that all pregnancies have a 5-year history data available.

Table 2. Availability of data by data sources

Note on DAP selection: Depending on results from the Data characterization/ data fit for purpose.

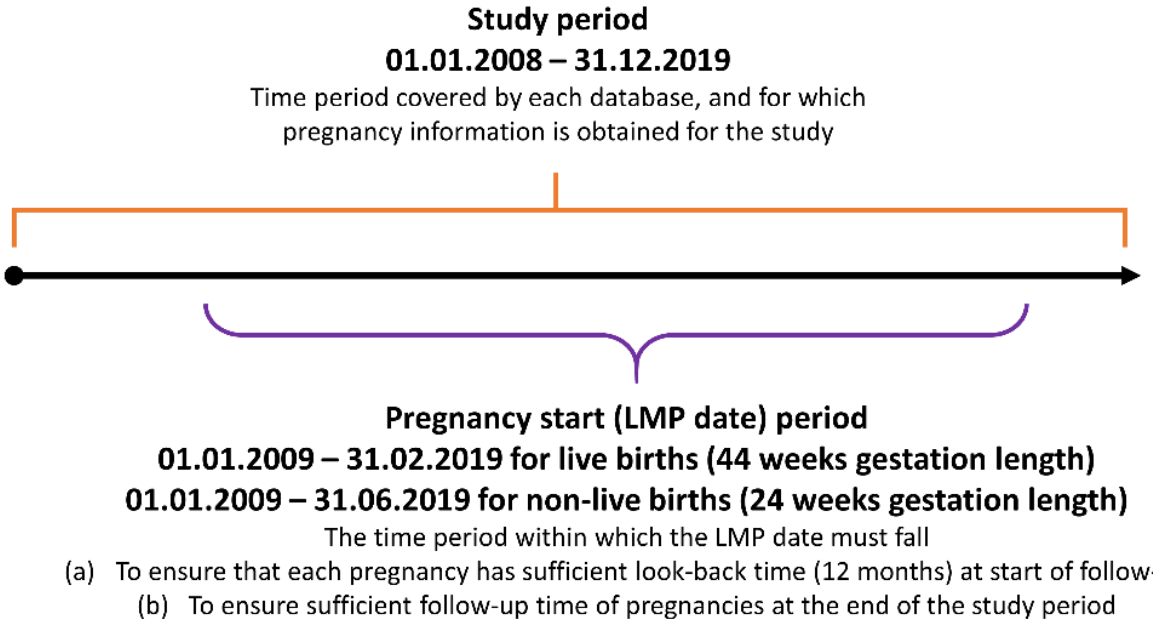
Data source	5 years prior to pregnancy			12 months prior to pregnancy			3 months prior to pregnancy			In pregnancy		
	Migraine Dx	Triptan Rx	Migraine procedure	Migraine Dx	Triptan Rx	Migraine procedure	Migraine Dx	Triptan Rx	Migraine procedure	Migraine Dx	Triptan Rx	Migraine procedure
Finland	☒	☐	☐	☒	☐	☐	☒	☒	☒	☒	☒	☒
France (Haute Garonne)	☐	☐	☐	☐	☐	☐	☒	☒	☐	☒	☒	☐
France (SNDS)	☐	☒	☐	☐	☒	☐	☒	☒	☐	☒	☒	☐
Germany	☐	☒	☐	☒	☒	☐	☒	☒	☐	☒	☒	☐
Italy (Emilia Romagna)	☐	☒	☐	☐	☒	☐	☒	☒	☐	☒	☒	☐
Italy (Tuscany)	☐	☒	☐	☐	☒	☐	☒	☒	☐	☒	☒	☐
Norway	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Spain (Valencian Region)	☒	☒	☐	☒	☒	☐	☒	☒	☐	☒	☒	☐
UK (Wales)	☒	☒	☐	☒	☒	☐	☒	☒	☐	☒	☒	☐

The study period is 01.01.2008 – 31.12.2019, except for Spain, Finland, UK, Germany and France (SNDS), as shown in Table 1. Figure 1 below shows the definition of the study period as well as the definition of the pregnancy start period (i.e., first and last LMP date). These dates have been set using the ultimate criterion for the look-back time period of 12 months prior to LMP (when not available, 3 months prior to LMP depending on data source). To ensure adequate follow-up of pregnancies with LMP at the end of the study period (i.e., in the year 2019), the LMP date must be within 44 weeks prior to end date of the study period for livebirths, and 24 weeks prior to end date of the study period for non-live births. These week numbers are conservative, and ensure full follow-up of shorter gestations.

The pregnancy period spans from 01.01.2009 to different dates of 2019 depending on birth outcomes, as shown in Figure 1. These dates may vary according to databases; to ease the SAP, we use hereafter the dates 01.01.2008 – 31.12.2019 for the study period, and the dates from 01.01.2009 to 31.06.2019 or 31.02.2019 depending on birth outcome, for the pregnancy period. The years of these dates change in specific databases, i.e. Finland, Spain, Germany, UK and France (SNDS).

Appendix 1 contains information about characteristics of databases, data collection setting, data domain, coding system, and data format. Pregnancy is the unit of analysis.

Figure 1. Illustration of the study period and pregnancy period definitions



We will use the same definition of the study population, inclusion and exclusion criteria as in DP4. These are the following:

Inclusion criteria:

➢ Pregnancies with LMP date between 01.01.2009 and 31.02.2019 (live births), or between 01.01.2009 and 31.06.2019 for non-live births* will be included (See Fig. 1)

- Data base coverage of both Rx and diagnostic codes of 12 months prior to pregnancy, or at least 3 months if 12 are not available (depending on data source)

➢ Known pregnancy outcome (live and non-live births)

➢ Age at pregnancy start between 15 and 49 years

*Except for specific databases, see Table 1.

Exclusion criteria:

➢ According to the results of the ConcePTION Data characterization task (7.6/7.7), we will exclude participants with missing or unrealistic information on pregnancy status, gestational age, date of the last menstrual period, and/or date of pregnancy end/delivery.

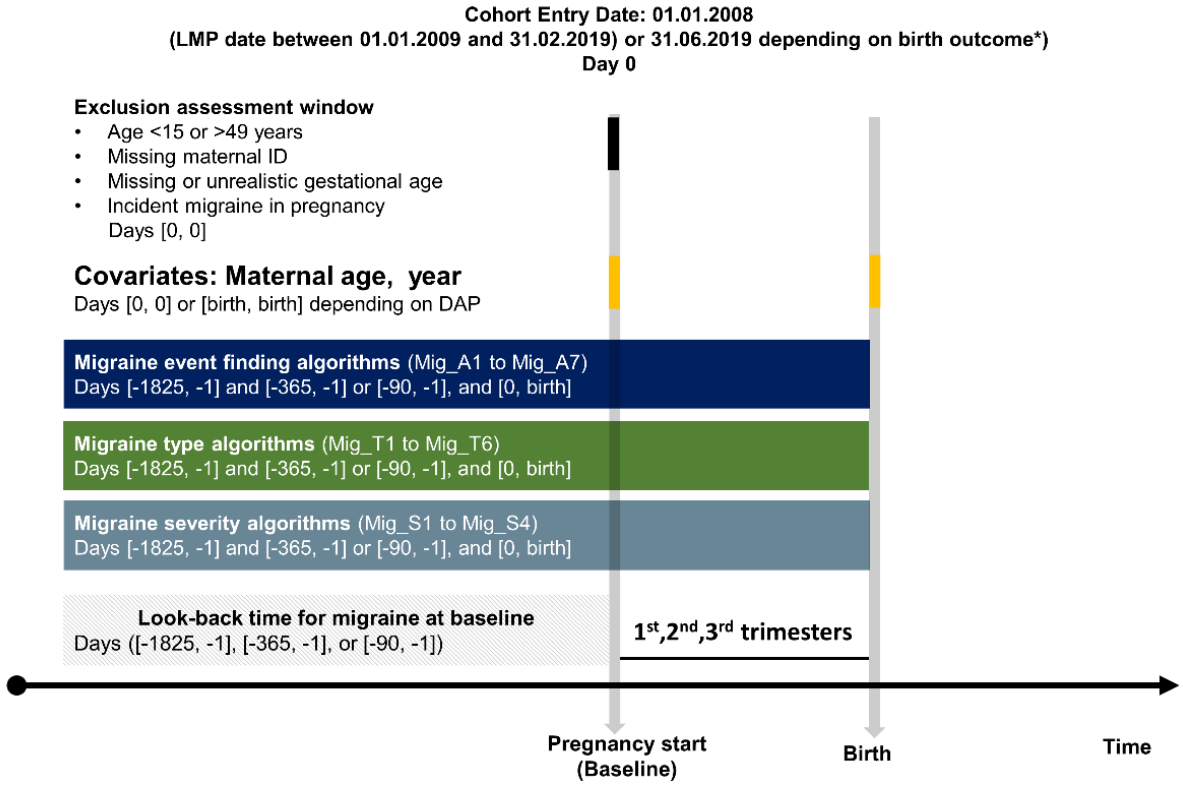
➢ Maternal age <15 or > 49 years

➢ Pregnancies with new migraine in pregnancy: having a new migraine diagnosis and/or a new triptan prescription, and/or a new procedure code in the pregnancy window, but not in the 12 months prior to pregnancy. This is an operational definition, as also used in prior drug in pregnancy research.

Figure 2 below depicts the study process. We define pregnancy start as the study baseline. We begin with implementing migraine event-finding algorithms, and calculate the prevalence of migraine identified at baseline and separately during pregnancy (and in each trimester). We repeat the same procedure for migraine type algorithms. For migraine severity algorithms, the

assessment is performed for the periods before and during pregnancy, by adapting the window of Rx patterns in each periods. The very severe migraine can only be assessed during pregnancy.

Figure 2. The study process using a design diagram (www.repeatinitiative.org/projects.html)



We vary look-back time as follows: 5 years, 12 months, and 3 months prior to pregnancy depending on the DAP. As stated earlier, the 12 months look-back time prior to pregnancy start is considered as the ultimate criterion ultimate criterion (when not available, 3 months prior to LMP are used depending on data source).

In the analysis exploring the 3 months or the 5-year look back time, the definitions of LMP start date are as follows:

- LMP date from 01.01.2013 for 5 years look-back time, to ensure that all pregnancies have a 5-year history data available;
- LMP date from 01.04.2008 for 3 months look-back time, to ensure that all pregnancies have a 3-month history data available.

Nb! When varying look-back time, study period will be restricted accordingly to ensure full coverage of the data base, e.g. for the 5 year look-back time, we will require coverage of both Rx and diagnostic codes at least 5 years prior to pregnancy. Example: in Norway we include only pregnancies with cohort entry in 2013 (instead of 2008) when we require 5 years look back time.

4. Migraine algorithms

We have designed three groups of algorithms to characterize perinatal migraine in healthcare databases:

- **Migraine-event finding algorithms** (Mig_A1-15). They include diagnostic, medication and procedure codes (ICD, ATC, ICPC, Read codes), which indicate the presence of migraine.
- **Migraine type algorithms**: (Mig_T1-6). They include diagnostic codes (ICD-10, ICD-9, ICPC, Read codes), which indicate the types of migraine.
- **Migraine severity algorithm by Rx:** (Mig_S1-4). This group of algorithms classifies migraine events into different levels of severity according to pharmacological treatment before or during pregnancy (14). This is based on the study by Tauqeer et al (14), and amended in line of the NICE and ANN guidelines for treatment of migraine (15-16).

Table 3. Migraine algorithms and their components

Algorithms	Name	Components
Migraine event-finding algorithm		
Mig_A1	Migraine event-finding algorithm 1	Migraine diagnostic code: ICD-10 (G43), ICD-9 (346), RCD (F26), ICPC (N89)
Mig_A2	Migraine event-finding algorithm 2	Triptan prescription: ATC code (N02CC)
Mig_A3	Migraine event-finding algorithm 3	Migraine procedure: ATC code (M03AX01)
Mig_A4	Migraine event-finding algorithm 4	Mig_A1 and/or Mig_A2
Mig_A5	Migraine event-finding algorithm 5	Mig_A1 and/or Mig_A3
Mig_A6	Migraine event-finding algorithm 6	Mig_A2 and/or Mig_A3
Mig_A7	Migraine event-finding algorithm 7	Mig_A1 and/or Mig_A2, and/or Mig_A3
Migraine type algorithms*		
Mig_T1	Migraine without aura	ICD-10: G43.0; ICD-9: 346.1, 346.7; RCD: F261
Mig_T2	Migraine with aura	ICD-10: G43.1; ICD-9: 346.0, 346.5, 346.6; RCD: F260
Mig_T3	Migraine status migrainosus	ICD-10: G43.2; ICD-9: 346.12; RCD: X007R
Mig_T4	Complicated migraine	ICD-10: G43.3; RCD: F26y3
Mig_T5	Other migraine (Ophthalmologic/Retinal)	ICD-10: G43.8; ICD-9: 346.8; RCD: F262, Fyu53, F26y, X0070
Mig_T6	Migraine unspecified	ICD-10: G43.9; ICD-9: 346.9, 346.2; ICPC: N89; RCD: F26z
Migraine severity algorithms**		
Mig_S1	Mild	Mig_A1 and ATC codes (M01A, N02BE01, N05AB04)
Mig_S2	Moderate	Mig_A2 (prior to, and/or during pregnancy), excluding N02CC01 injection

Algorithms	Name	Components
Mig_S3	Severe	N02CC01 injection prior to and/or during pregnancy; And/or migraine prophylaxis prior to, but not during pregnancy.
Mig_S4	Very severe	Mig_A7 and migraine prophylaxis during pregnancy, indicating by one or more of the following ATC codes: N02CD: CGRP-antagonists N02CX: other antimigraine preparations, incl. pizotifen C07A: beta blockers, specifically metoprolol, propranolol, bisoprolol and timolol C09A: ACE-inhibitors C09C: AII-blockers M03AX: botulinum toxin N03A: antiepileptics topiramate, valproate, carbamazepine N06AA: tricyclic antidepressants: amitriptyline N06AX16: venlafaxine N07CA03: flunarizine N02CB: Corticosteroid derivatives (short term prophylactic use) C08DA: Phenylalkylamine derivatives (e.g. Verapamil)

*The migraine types are not mutually exclusive and no hierarchy of diagnosis types is made. The migraine types will be considered as reported (e.g., one pregnancy may have more than one migraine type diagnosis reported); in addition the total number of different migraine types recorded in the window of interest (at baseline, during pregnancy) is computed. If a pregnancy has two different types of migraine diagnosis registered at baseline, both are shown and counted.

**These are mutually exclusive categories, meaning that for each pregnancy we assigned the highest severity category whenever more than one severity criterion is met.

To define specifically the timing of exposure, the components of the algorithms above can be expanded to include pregnancy periods as specified in Table 7. Lookback time in the algorithms can be 3 or 12 months prior to pregnancy, depending on the information provided by the databases to ConcePTION. Details on the components of each algorithm are shown in Tables 4-6.

Table 4. Migraine-event finding algorithms (Mig_A1-A15) (depending on data availability)

Algorithm	Name		Component	
		ICD-9, ICD-10, RCD, ICPC	ATC	Procedure
		As in Table 3	N02CC	M03AX01
		Diagnosis	Triptan	Botulinum toxin
Mig_A1	Migraine-event finding algorithm 1	≥1		
Mig_A2	Migraine-event finding algorithm 2		≥1	
Mig_A3	Migraine-event finding algorithm 3			≥1
Mig_A4	Migraine-event finding algorithm 4	≥1 AND/OR	≥1 AND/OR	
Mig_A5	Migraine-event finding algorithm 5	≥1 AND/OR		≥1 AND/OR
Mig_A6	Migraine-event finding algorithm 6		≥1 AND/OR	≥1 AND/OR
Mig_A7	Migraine-event finding algorithm 7	≥1 AND/OR	≥1 AND/OR	≥1 AND/OR

Not all DAPs will be able to provide data for all algorithms.

Table 5. Migraine type algorithmes (Mig_T1-6)

Algorithm	Name	Component (at least one of the listed codes has to be present)					
		ICD-10: G43.0; ICD-9: 346.1, 346.7; RCD: F261	ICD-10: G43.1; ICD-9: 346.0, 346.5, 346.6; RCD: F260	ICD-10: G43.2; ICD-9: 346.12; RCD: X007R	ICD-10: G43.3; RCD: F26y3	ICD-10: G43.8; ICD-9: 346.8; RCD: F262, Fyu53, F26y, X0070	ICD-10: G43.9; ICD-9: 346.9, 346.2; ICPC: N89; RCD: F26z*
Mig_T1	Migraine without aura	≥1					
Mig_T2	Migraine with aura		≥1				
Mig_T3	Migraine status migrainosus			≥1			
Mig_T4	Complicated migraine				≥1		
Mig_T5	Other migraine (Ophthalmoplegic/Retinal)					≥1	
Mig_T6	Migraine unspecified						≥1

Not all DAPs will be able to provide data for all algorithms. *ICPC code N89 measures "migraine"; because the type is unspecified, we classify this diagnosis into "migraine unspecified".

Table 6. Migraine severity algorithms based on Rx, Tauqeer et al. 2021 (14) and treatment guidelines (15-16) (Mig_S1-S4)

Algorithm	Severity	N02BE01	M01A	N02CC, exclude injecting N02CC01	N02CC01 injection		Prophylactic medication	
					Before pregnancy	During pregnancy	Only Before pregnancy, not during pregnancy	(before and / or) During pregnancy
Mig_S1	Mild	≥1 + migraine Dx AND/OR	≥1 + migraine Dx	0	0	0	0	0
Mig_S2	Moderate	-	-	≥1	0	0	0	0
Mig_S3	Severe	-	-	-	≥1 AND/OR	≥1, AND/OR	≥1 + migraine Dx	0
Mig_S4	Very severe	-	-	-	-	-	-	≥1 + migraine Dx

Not all DAPs will be able to provide data for all algorithms. These are mutually exclusive categories, meaning that for each pregnancy we assigned the highest severity category whenever more than one severity criterion is met.

The combination across criteria with "AND/OR" in Table 6 must be read from left to right. The symbol "-" means that the criterion is not essential for the severity definition. "0" means that the criterion must not be present. For instance, for Mig_S3, it is required that a pregnancy has exposure to triptan injection before and/or during pregnancy (depending on the window assessed) and/or exposure to prophylactic medication only before pregnancy in the presence of a migraine diagnosis. The requirement for a migraine diagnosis for mild and very severe migraine is included to limit capturing pregnancies using analgesics and prophylactic drugs for reasons other than migraine.

5. Covariate

5.1 Pregnancy periods

Definition of pregnancy periods are shown in Table 7.

Table 7. Definitions of pregnancy periods*

Pregnancy period	Definition
0-5 years prior to pregnancy	-1825 to -1 days prior to start date of pregnancy
0-12 months prior to pregnancy	-365 to -1 days prior to start date of pregnancy
0-3 months prior to pregnancy	-90 to -1 days prior to start date of pregnancy
Start of pregnancy	Day 0, i.e. 1st day of the Last Menstrual Period (LMP)
Overall during pregnancy	Start date of pregnancy to end date of pregnancy (day 0)
First trimester of pregnancy (T1)	From day 0 (=LMP date) to day 97
Second trimester of pregnancy (T2)	From day 98 after LMP to day 195 after LMP
Third trimester of pregnancy (T3)	From day 196 after LMP onwards

LMP=Last menstrual period. The time spans for the trimesters are according to the ACOG definition.
*LMP date may be directly available or calculated via use of date of delivery and gestational length.

5.2 Year of pregnancy start

Starting from 2009, we explore the prevalence migraine using one-year intervals: 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, and 2019. As shown in task 7.7, all pregnancies will have a reported/estimated/imputed pregnancy start (LMP) date and pregnancy end date.

5.3 Maternal age

We categorize maternal age at start of pregnancy into three age groups: 15-24, 25-39, 40-49 years of age.

6. Analysis

Each DAP will perform the following analyses according to their data availability:

6.1 Prevalence of pregnancies with ≥ 1 event of migraine

6.1.1 At baseline

Prevalence of migraine during the study period (2009-2019) according to algorithms Mig_A1 to Mig_A7 =

$$\frac{\text{No. of pregnancies among women with migraine according to Mig\_A1 to Mig\_A7}}{\text{All pregnancies in the study population}}$$

Shell Table 1: Prevalence of migraine events at baseline using different look-back time windows: (1) 5 years prior, (2) 12 months prior, and (3) 3 months prior to pregnancy start

	Look-back window 1: 5 years < pregnancy start N= XXX,XXX* **N pregnancies with ≥ 1 migraine event (%)**	**Look-back window 2: 12 months < pregnancy start N= XXX,XXX** **N pregnancies with ≥ 1 migraine event (%)**	**Look-back window 3: 3 months < pregnancy start N= XXX,XXX** **N pregnancies with ≥ 1 migraine event (%)**
Mig_A1			
Mig_A2			
Mig_A3			
Mig_A4			
Mig_A5			
Mig_A6			
Mig_A7			

*Only pregnancies with estimated LMP date ≥ 1 January 2013 and onwards are included in the denominator, to ensure that all pregnancies have a 5-year history data available.

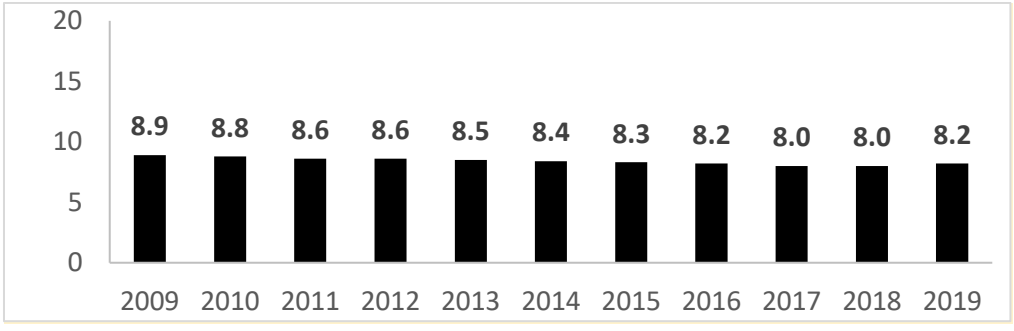
6.1.2. Stratifications

To reduce the number of analyses, we will only perform stratifications by LMP year and maternal age at start of pregnancy for migraine event algorithm Mig_A2 and Mig_A4 at baseline.

Prevalence of migraine according to $\mathrm{Mig_{A2}}$ and Mig_A4 stratified by **LMP year**=

$$\frac{\text{No. of pregnancies among women according to } \mathrm{Mig_{A2}} \text{ and } \mathrm{Mig_{A4}} \text{ with LMP date } in\ year\ 20XX}{\text{All pregnancies in the study population with LMP date } in\ year\ 20XX}$$

Shell figure 1: Example: Triptan Rx (Mig_A2)



Prevalence of migraine according to Mig_A2 and Mig_A4 stratified by **maternal age at pregnancy start**=

$$\frac{\text{No. of pregnancies among women at the age xx with migraine according to Mig\_A2 and Mig\_A4}}{\text{All pregnancies at the age XX in the study population}}$$

Shell Table 2: Prevalence of migraine events at baseline (i.e., in the 12 months prior to pregnancy start) by maternal age for Mig_A2 and Mig_A4

	Migraine algorithm, Mig_A2 Rx	**Migraine algorithm, Mig_A4 Dx & Rx**
Maternal age at pregnancy start in years	**N pregnancies with ≥ 1 migraine event (%)**	**N pregnancies with ≥ 1 migraine event (%)**
15-24		
25-39		
40-49		
Total		

Prevalence of migraine according to Mig_A1 to Mig_A7 **stratified by pregnancy period**=

$$\frac{\text{No. of pregnancies among women with migraine according to Mig\_A1 to Mig\_A7 at time } t}{\text{All pregnancies at time period } t \text{ in the study population}}$$

***t*:** specific pregnancy periods as described in Table 7**.** E.g., to estimate the prevalence of migraine in the second trimester, the denominator includes all pregnancies that have "survived" until the end of second trimester.

Shell Table 3: Prevalence of migraine events during pregnancy and by trimester, in pregnancies identified using 12 months prior to pregnancy start as look back-time

	Look-back window 1: 12 months < pregnancy start N= XXX,XXX			
	Overall during pregnancy N=XXX,XXX	**Pregnancies observed in 1. Trimester, N=XXX,XXX**	**Pregnancies observed in 2. Trimester, N= XXX,XXX**	**Pregnancies observed in 3. Trimester, N= XXX,XXX**
	N pregnancies with ≥ 1 migraine event (%)	**N pregnancies with ≥ 1 migraine event (%)**	**N pregnancies with ≥ 1 migraine event (%)**	**N pregnancies with ≥ 1 migraine event (%)**
Mig_A1				
Mig_A2				
Mig_A3				
Mig_A4				
Mig_A5				
Mig_A6				
Mig_A7				

6.2 Prevalence of migraine types and severity

We will assess migraine types and severity at baseline (incl. varying look back times) and in pregnancy.

We will assess prevalence of migraine types and severity using the following formula:

Prevalence of migraine types during the study period (2009-2019) according to algorithms Mig_T1 to T6=

$$\frac{\text{No. of pregnancies among women with migraine type according to Mig\_T1 to T6}}{\text{All pregnancies in the study population}}$$

Prevalence of migraine severity during the study period (2009-2019) according to algorithms Mig_S1 to S4=

$$\frac{\text{No. of pregnancies among women with migraine type according to Mig\_S1 to S4}}{\text{All pregnancies in the study population}}$$

We will also calculate the percentage of the same type of migraine types and severity in both time periods: in the 12 months prior to pregnancy start and in pregnancy.

Shell Table 4: Prevalence of migraine type and severity at baseline and during pregnancy in pregnancies identified using 12 months look-back time windows.

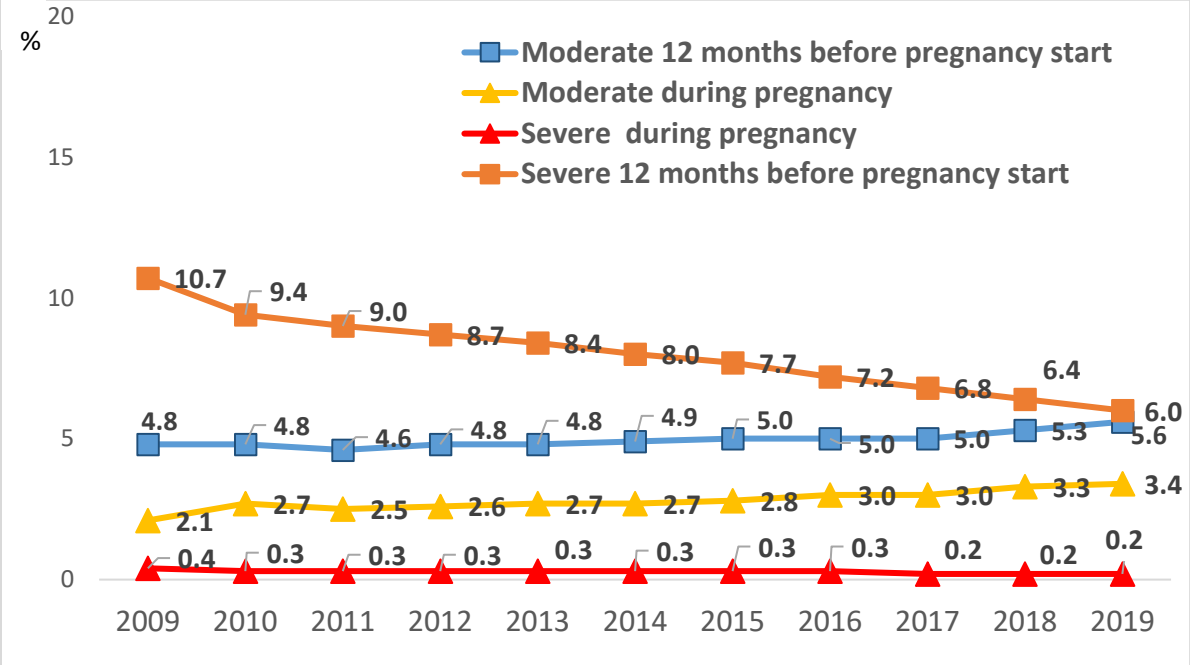
	Look-back window 1: 12 months < pregnancy start, N= XXX,XXX		
Migraine type (Dx)	**N pregnancies with ≥ 1 events (%) within 12 months < pregnancy start**	**N pregnancies with ≥ 1 events (%) during pregnancy**	**Same type in both periods**
Migraine without aura (Mig_T1)			
Migraine with aura (Mig_T2)			
Migraine status migrainosus (Mig_T3)			
Complicated migraine (Mig_T4)			
Other migraine (Mig_T5)			
Migraine unspecified (Mig_T6)			
Migraine severity (Rx and Dx) **	**N pregnancies with ≥ 1 events (%) within 12 months < pregnancy start**	**N pregnancies with ≥ 1 events (%) during pregnancy**	**Same severity in both periods**
Mild (Mig_S1)			
Moderate (Mig_S2)			
Severe (Mig_S3)			
Very severe (Mig_S4)			

*Only pregnancies with estimated LMP date ≥ 1 January 2013 and onwards are included in the denominator, to ensure that all pregnancies have a 5-year history data available.
**Very severe migraine at baseline cannot be measured as the algorithm used requires use of migraine prophylaxis during pregnancy specifically.

6.2.2 Stratifications

To reduce the number of analyses, we will only perform stratifications by year for migraine severity at baseline and in pregnancy.

Shell Figure 2: Example. Prevalence (as %) of migraine severity at baseline (i.e., in the 12 months prior to pregnancy start) and during pregnancy by year of birth (2009-2019) (the denominator varies by total births per year)



6.3. Quantifying overlap between algorithms

Through cross-tabulating, we quantify overlapping migraine events captured by diagnostic code only (Mig_A1) and Triptan prescription only (Mig_A2), at baseline and overall in pregnancy. Overlapping events are defined as the events which are found in both algorithms.

Shell Table 6: Pregnancies with ≥ 1 migraine events (n, %) based on diagnosis only (Mig_A1) and Triptan prescription only (Mig_A2) at baseline in the (i) 5 years (ii) 12 months, and (ii) 3 months prior to pregnancy, and (iv) during pregnancy

	At baseline, 5 years prior to pregnancy start N= XXXXX*	**At baseline, 12 months prior to pregnancy start N= XXXXX***	**At baseline, 3months prior to pregnancy start N= XXXXX***	**During pregnancy N=XXXXX***
Only triptan prescription (Mig_A2)				
Only diagnostic code (Mig_A1)				
Both prescription & diagnostic code				

*Number of pregnancies identified as having migraine in the time period, using the broader definition Mig_A7. Numbers do not add up to total due to additional pregnancies captured using procedure codes in Mig_A7.

We also perform the same assessment between migraine types (Mig_T1-T6) versus migraine severity (Mig_S1-S4) at baseline and in pregnancy.

Shell Table 7: Prevalence of migraine type by severity at baseline (12 months prior to pregnancy) and during pregnancy*

	N pregnancies with ≥1 severity events (%) at baseline by migraine type**			**N pregnancies with ≥1 severity events (%) during pregnancy by migraine type****			
Migraine type	**Mild N=xxx**	**Moderate N=xxx**	**Severe N=xxx**	**Mild N=xxx**	**Moderate N=xxx**	**Severe N=xxx**	**Very severe N=xxx**
Migraine without aura (Mig_T1)							
Migraine with aura (Mig_T2)							
Migraine status migrainosus (Mig_T3)							
Complicated migraine (Mig_T4)							
Other migraine (Mig_T5) (Ophthalmologic/Retinal)							
Migraine unspecified (Mig_T6)							

*Both the migraine and severity are measured in the same time window, i.e. both during the 12 months prior to pregnancy or both during pregnancy. **Very severe migraine at baseline cannot be measured at baseline as the algorithm used requires use of migraine prophylaxis during pregnancy specifically.

7. List of appendices

Appendix 1: Characteristics of databases

8. Reference

1. Cutrer FM, Huerter K. Migraine Aura. The Neurologist. 2007;13(3):118-25.
2. Ng N, Cox S, Maiti S. Headache in pregnancy: an overview of differential diagnoses. J Preg Child Health. 2015;2(130):2.
3. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? The Journal of Headache and Pain. 2018;19(1):17.
4. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1211-59.
5. Allais G, Chiarle G, Sinigaglia S, Mana O, Benedetto C. Migraine during pregnancy and in the puerperium. Neurological Sciences. 2019;40(1):81-91.
6. Parikh SK, Delbono MV, Silberstein SD. Managing migraine in pregnancy and breastfeeding. Progress in Brain Research. 2020;255:275-309.
7. Aukes AM, Yurtsever FN, Boutin A, Visser MC, de Groot CJ. Associations between migraine and adverse pregnancy outcomes: Systematic review and meta-analysis. Obstetrical & gynecological survey. 2019;74(12):738-48.
8. World Health Organization. International statistical classification of diseases and related health problems 10th Revision: 10th Revision: World Health Organization; 2010.
9. Bentsen BG. International classification of primary care. Scandinavian journal of primary health care. 1986;4(1):43-50.
10. World Health Organization. Guidelines for ATC classification and DDD assignment. 1996.
11. NHS NB. What are the Read Codes? Health Libraries Review. 1994;11(3):177-82.
12. Hägg D, Brenner P, Reutfors J, Li G, DiBernardo A, Bodén R, et al. A register-based approach to identifying treatment-resistant depression—Comparison with clinical definitions. Plos one. 2020;15(7):e0236434.
13. Thurin NH, Pajouheshnia R, Roberto G, et al. From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin Pharmacol Ther. 2021 Nov 26. doi: 10.1002/cpt.2476.
14. Tauqeer F, Wood M, Hjorth S, Lupattelli A, Nordeng H. Perinatal use of triptans and other drugs for migraine—A nationwide drug utilization study. Plos one. 2021;16(8):e0256214.
15. National Institute for Health and Care Excellence (NICE) Clinical Guidelines, No. 150. Headaches in over 12s: diagnosis and management. London; 2021 May 12. ISBN-13: 978-1-4731-1533-0.
16. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. Neurology. 2014; 78: 1337-1345.

Appendix 1. Characteristics of databases (needs to be updated by DAPs – from the questionnaires)

Country	Data coverage	Data banks */data sources*	Setting	Data domain *E.g. diagnosis, medication, laboratory test, procedure or other*	Vocabulary *Vocabulary for categorical variable e.g. ICD10, ICD10CM, ICD9, RCD2, ATC or other*
Finland	Nationwide	Care Register for Health Care (HILMO) Register of Primary Health Care visits (Avohilmo) Medical Birth Register Register on Reimbursed Drug Purchases			ICD10, ICPC2, ATC
Norway	Nationwide	Patient registry: NPR	Secondary care including inpatient and outpatient	Diagnosis during hospitalization	ICD-10, ATC, procedural codes
		Outpatient care: KUHR	Outpatient care	Diagnosis Reason for GP visit	ICD-10 ICPC2
		Birth registry: MBRN	Specialist clinics, hospital maternity wards, or midwifery-led units	Diagnosis at birth Year of delivery Maternal age at delivery	1=yes
		Prescription registry	Community pharmacies	Drug dispensation	ATC
France	Haute Garonne	EFEMERIS			ICD-10 , ATC
	Nationwide	SNDS			ICD-10, ATC
Italy	Emilia Romagna	Inhabitant registry Drug dispensations from community pharmacies and from hospital pharmacies Hospital discharge records Emergency admissions Outpatient services Birth registry IMER Registry of Congenital anomalies			ICD9/10, ATC

	Tuscany	Inhabitant registry Drug dispensations from community pharmacies and from hospital pharmacies Hospital discharge records Emergency admissions Outpatient services Birth registry Congenital anomaly register			ICD9/10, ATC
Wales	Nationwide	SAIL			Read codes, ICD10, ATC (Read code CV2 converted to ATC using lookup table provided by NHS TRUD)
Spain	Valencian Region	Prescription and dispensations dataset Hospital discharge records Mortality registry Perinatal Mortality registryCongenital anomalies registry Birth registry			In Hospital discharges: ICD-9 UP TO 2016. After 2016 ICD10-ES (Spanish version). Mortality Registry and Perinatal Mortality Registry and Congenital anomalies registry use ICD-10. For medication , ATC codes are used
Germany	Nationwide	GePaRD			ICD10, ATC