Medication use during Pregnancy and Outcomes Associated with Preterm Birth

Perinatal pharmacoepidemiological studies based on data from the PHARMO Perinatal Research Network (PPRN)

Eline Houben

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Geneesmiddelengebruik tijdens de zwangerschap

en uitkomsten geassocieerd met vroeggeboorte

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uit het PHARMO Perinataal Onderzoeksnetwerk (PPRN)

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veur papa

CONTENTS

CHAPTER 1

Introduction

1.1 Background

Medication use during pregnancy
The potentially harmful effects on the mother and child of medication used before and during pregnancy have been widely acknowledged and can lead to major birth defects. It is therefore undisputed that safe pharmaceutical care around pregnancy is of vital importance.[1,2] Despite this, drug exposure during pregnancy is common in Europe and the US.[3-5] A multinational study showed that, compared to other countries, prevalence of medication use during pregnancy was also high in the Netherlands.[4] Taking this into account, the public health importance of monitoring drug use around pregnancy has been recognized from a national as well as from an EU perspective.[6,7] However, recent long-term population-based data on drug utilization before, during and after pregnancy in the Netherlands are lacking. Evidence generation in this area would also support national action plans that are currently active aiming to protect vulnerable populations, such as women with chronic disease who use potentially harmful medication.[8]

Pregnancy care in the Netherlands
Current national action programs of the Netherlands focus on a healthy start of life, knowing that child health before, during and after birth is an important driver of health problems later in life.[8,9] Pregnancy care in the Netherlands is different from most other countries, because of the structure of the Dutch health care system with a clear boundary between primary, secondary and tertiary care. Community midwives have the lead in providing care during uncomplicated pregnancy and childbirth. In case of (increased risk of) medical or obstetric pathology, responsibility is taken over by obstetricians and gynaecologists in the hospital.[10] Next to that, general practitioners act as gatekeeper to hospital- and specialist care and they have been shown to be important providers of routine – non pregnancy-related – medical primary care for pregnant women.[11]

Preterm birth
A common concern in pregnancy care is gestational age, by which prenatal care is guided. Increasing evidence demonstrates increased risks of adverse outcomes for children born prematurely, such as perinatal death, cerebral palsy, neurodevelopmental disorders, hearing loss and visual impairment.[12,13] The risk of complications has been shown to decrease with increasing gestational age. Four stages of preterm birth are defined: late preterm, moderately preterm, very preterm and extremely preterm. There are limited population data available on the real-world outcomes and resource use of children born to mothers with spontaneous preterm labour, as well as the healthcare burden associated with the various stages of preterm birth. Observational population-based research using RWD may also have great prospects in this specific vulnerable population and the possibilities should be explored further.

Need for a new data source for perinatal studies
Clinical trials have well-known limitations to study drug safety in vulnerable populations, including pregnant women and their offspring. Alternatively, real-world data (RWD) and related observational population-based research have the potential to fill this gap as a non-invasive method for studies

in these groups. Until now, there were no large-scale registrations available in the Netherlands that include routinely collected data on maternal, pregnancy and child outcomes. Medical records are documented during the perinatal period by different involved caregivers using separate non-linked information systems. The separation of these registrations not only complicates information exchange during pregnancy between involved caregivers, it also makes it difficult to perform outcome research if potential risk factors are registered elsewhere. Even broader, such linked information sources are scarcely available in Europe and thus ask for pioneer initiatives. Besides the challenge to link data on a personal level given the restriction of privacy laws that limits use of citizen service number, a second challenge is the sheer unlimited large size of the databases needed to study drug effects that are, fortunately, most often rare.

In the Netherlands specifically, two RWD sources including routinely collected data exist that have the potential to contribute to related observational population-based research: The PHARMO Database Network (PHARMO) and the Netherlands Perinatal Registry (Perined). PHARMO is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. Perined is a nationwide registry that contains data on pregnancy, obstetric history and pregnancy outcomes.

Aims of this thesis
The key objectives of this studies described in this thesis can be summarized as follows:

1. To explore whether the linkage of the PHARMO Database Network and Perined would establish a valuable data source for perinatal pharmacoepidemiological studies in the Dutch population.
2. To examine medication use before, during and after pregnancy, specifically focusing on potentially harmful medication and trends over time, among pregnant women in the established PHARMO Perinatal Research Network (PPRN).
3. To assess morbidities, healthcare utilisation and cost burden associated with preterm birth, among children in the PPRN.

1.2 Outline
This thesis consists of four parts. In **Part I** the PHARMO Perinatal Research Network (PPRN) is described, which is the infrastructure that was established based on the linkage of PHARMO and Perined. In **Chapter 2** the cohort profile of the PPRN is described, including the background, setting, underlying data sources, linkage, data captured, findings to date, strengths and limitations and potential collaborations.

Next, the chapters in **Part II** and **Part III** of this thesis concern applications of the PPRN exploring it as a data source for perinatal pharmacoepidemiological studies. In **Part II** medication use during pregnancy, with a specific focus on potentially harmful medication and trends over time, is examined. In **Chapter 3** the prevalence of drug exposure during the preconception, pregnancy and postpartum periods is examined, with special emphasis on trends of potentially harmful medication over the

years. In **Chapter 4** evidence is compiled on the trends in use of anti-seizure medication among pregnant women according to their safety profile. In **Chapter 5** general practitioners' awareness of pregnancy and its association with prescribing medication with potential safety risks is investigated.

Part III of this thesis concerns the application of the PPRN for studying real-world outcomes associated with preterm birth. In **Chapter 6** the morbidities and healthcare utilisation in children born following preterm labour are compared to those born from full-term labour. In **Chapter 7** a closer look is taken at respiratory morbidity, healthcare resource use, and cost burden associated with extremely preterm birth.

Lastly, **Part IV** includes the general discussion of the main findings from the previous chapters, the methodological considerations, practical implications, future recommendations and conclusions (**Chapter 8**). Furthermore, in **Chapter 9** a summary of this thesis is provided in English as well as in Dutch.

chapter 1

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PART I

CHAPTER 2

Cohort profile: the PHARMO Perinatal Research Network (PPRN) in the Netherlands: a population-based mother-child linked cohort

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ABSTRACT

Purpose
Observational population-based research is a very suitable non-invasive method for studies in the vulnerable populations of pregnant women and children. Therefore, the PHARMO Perinatal Research Network (PPRN) was set up as a resource for life course perinatal and paediatric research by linking population-based data from existing registrations.

Participants
From 1999 to 2017, the PPRN captures approximately 542,900 pregnancies of 387,100 mothers ('Pregnancy Cohort'). Additionally, mother-child linkage is currently available for a quarter of these pregnancies ('Child Cohort'). The PPRN contains preconceptional information on maternal healthcare, as well as detailed pregnancy and neonatal data, extending into long-term follow-up and outcomes after birth for both mother and child up to nearly 20 years. It includes linked data from different primary and secondary healthcare settings.

Findings to date
Through record linkage of the Netherlands Perinatal Registry and the PHARMO Database Network, we have established a large population-based research network including data on demographics, medication use, medical conditions and details concerning labour, birth and neonatal outcomes. Here, we provide an overview of record types available from the PPRN, available database follow-up and pregnancy characteristics of the PPRN cohorts. The PPRN has been used for a number of different pharmacoepidemiological studies, for example, to confirm that preterm-born infants were more likely than full-term infants to be hospitalised or use medication. Similar long-term comparisons showed that children born following spontaneous preterm labour were at increased risk of neurodevelopmental and respiratory conditions. Most recently, the PPRN provided important evidence on the trends in use of potentially harmful medication during pregnancy.

Future plans
The PPRN provides a unique and rich data set facilitating large-scale observational pharmacoepidemiological perinatal research. The patient-level linkage of many different healthcare data sources allows for long-term follow-up of mother and child, with ongoing annual updates.

Strenghts and limitations of this study

- The main strength of the PHARMO Perinatal Research Network (PPRN) lies in the ongoing assembly of detailed, population-based, anonymized data from existing registrations which makes it an invaluable resource for life course perinatal and paediatric research.
- Evidence from clinical trials is often lacking behind for pregnant women and children, as researchers are often hesitant to include these subjects due to a variety of reasons. Hence, the PPRN provides a very suitable, non-invasive method that stays within the many risks and objections of studies in the vulnerable populations of pregnant women and children.
- The PPRN covers a considerable proportion of pregnancies from 1999 onwards that has been shown to reflect true estimates of the Dutch population captured in Netherlands Perinatal Registry (Perined), ensuring a high level of generalisability.
- Data collection periods and catchment areas vary between the linked databases and therefore the size of the study population depends on the databases included.
- Currently, we rely on probabilistic linkage methods as the number of records that include a social security number is currently too limited to allow for deterministic record linkage between the PHARMO Database Network and Perined.

INTRODUCTION

Observational population-based research is a very suitable non-invasive method for studies in the vulnerable populations of pregnant women and children. Therefore, the PHARMO Perinatal Research Network (PPRN) was set up as a resource for life course perinatal and paediatric research by linking population-based data from existing registrations. It was initiated around 2010 at the PHARMO Institute for Drug Outcomes Research in collaboration with Netherlands Perinatal Registry (Perined). At that time it was set up to study the relation between medication exposure during pregnancy and pregnancy outcomes, but the applications of the PPRN have extended considerably over the years, along with the continuous expansion of the underlying databases.

COHORT DESCRIPTION

Setting

The PPRN is a unique linkage of the Perined and the PHARMO Database Network (PHARMO). With data collection starting in 1999, the linkage of these population-based data sources facilitates large-scale observational pharmacoepidemiological perinatal research. It contains preconceptional information on maternal healthcare extending into long-term follow-up and outcomes after birth for both mother and child, with ongoing annual updates of the routinely collected data.

Data sources

Perined is a nationwide registry in which medical data around pregnancy and birth are included from pregnancies with a gestational age of at least 16 weeks (including terminated pregnancies and stillborns).[1] It is a linked database combining medical registries from four professional groups that provide perinatal care: general practitioner, midwives, gynaecologists and neonatologists/ paediatricians. Among the items reported are maternal demographics and medical conditions, pregnancy complications and details concerning labour, birth and neonatal outcomes. Linking the records is a complex operation—especially when it comes to records that originate from different data sets. Probabilistic linkage based on matching data is performed in the absence of unique identification of mother and/or child. There is a firm basis for deciding whether two records describe the same case or have a lot of resemblance. The threshold value for such a decision depends on the situation and is statistically substantiated.[2] The established registry reflects virtually all deliveries in the Netherlands (~99% agreement with the municipal administration), that is, including home as well as hospital births. The frequency of data collection and processing is four times a year. The average lag time of the data is half a year. PHARMO is a population-based network of databases combining subnational data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms.[3] Data are retrieved directly from the source, that is, the electronic medical records of the healthcare providers who agree to contribute to PHARMO. All patients registered at the contributing healthcare providers are included, unless the patient requested to opt out. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymisation of the data are performed by the foundation 'Stichting Informatievoorziening voor Zorg en Onderzoek' (STIZON). STIZON is an independent ISO/IEC 27001 certified foundation, which acts as a trusted third party (TTP) between the data sources and the PHARMO Institute. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere.[4,5] PHARMO covers approximately a quarter of the Dutch population and is shown to be representative of the Dutch population with regard to age and sex; however, data collection period, catchment area and overlap between data sources differ. The PHARMO databases are linked on an annual basis, the average lag time of the data is 1 year.

Perined-PHARMO linkage

STIZON also acts as a TTP for the linkage between Perined and PHARMO. This specific linkage is primarily based on the birth date of the mother and child, their gender and their zip codes. In case multiple possible links are established, these determinants are supplemented with hospital admission records around delivery as well as obstetrician or gynaecologist-prescribed medication. Furthermore, home codes that indicate mother and child live on the same address are used to verify established pairs and improve linkage specificity.

Data collection

From 1999 to 2017, the PPRN captures approximately 542 900 pregnancies of 387 100 mothers for which a PHARMO–Perined link could be established (ie, 'Pregnancy Cohort'). Additionally, an individual mother– child linkage is currently available for a quarter of these pregnancies allowing subjects to be followed over time up to nearly 20 years after birth and studying associations with pregnancy or neonatal-specific outcomes (ie, 'Child Cohort'). A schematic overview of data captured in the PPRN for mothers and children and how these two cohorts inter-relate is included in figure 1 and table 1. Further characterisation of the PPRN is included in table 2, including the total Perined population as a reference, considering that only a subsample of the Netherlands is represented by the PHARMO Database Network. Figure 2 presents the number of pregnancies included in the Pregnancy Cohort and Child Cohort by calendar year. Details on the available database follow-up for the children included in the Child Cohort are presented in figure 3, with end of follow-up defined by either end of database registration (ie, the patient moves out of the PHARMO catchment area), death or end of study period (31 December 2018), whichever occurred first.
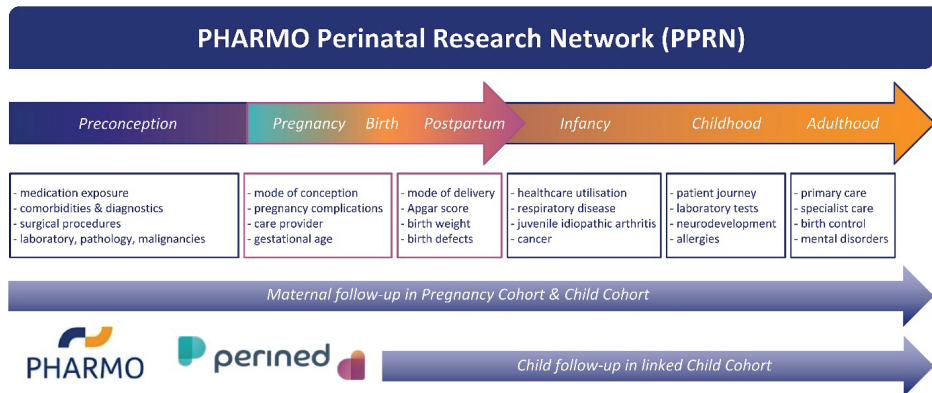
FIGURE 1 Schematic overview of data captured in the PHARMO–Perined linked PHARMO Perinatal Research Network (PPRN)

Patient and public involvement

No patients were involved in the described linkage between existing registries providing an anonymous data set.

FINDINGS TO DATE

Through record linkage of Perined and PHARMO, we have established a large population-based research network including data on demographics, medication use, medical conditions, pregnancy complications and details concerning labour, birth and neonatal outcomes. The PPRN has been used for a number of different pharmacoepidemiological studies (see online supplemental appendix 1 for a citation list of work published on the PPRN). Its applicability can be centred on the mother, the child or both (ie, assessing the association between maternal characteristics and child outcomes). As an example, medication use during first year of life and hospital admission rates have been assessed and compared between premature and term infants.[6] Preterm-born infants were up to two times more likely than full-term infants to be hospitalised or use medication, especially related to respiratory disease. Similar long-term comparisons of morbidities and healthcare utilisation have been made which showed that children born following spontaneous preterm labour (irrespective of gestational age at delivery) were at increased risk of neurodevelopmental and respiratory conditions compared with those from full-term labour pregnancies.[7] Most recently, data from the PPRN have been used to determine population-based trends over the last two decades in the use of potentially harmful medication among pregnant women.[8]

TABLE 1 Schematic overview of data captured in the PHARMO–Perined linked PHARMO Perinatal Research Network (PPRN)

Record type	Description	Data availability
Pregnancy/neonatal	Maternal and neonatal characteristics and perinatal care from pregnancies with a gestational age of at least 16 weeks captured by midwife practices, gynaecologists, paediatricians and neonatologists (maintained by Perined).	From 1999 onwards (full coverage for PPRN cohorts)
Medication	General practitioner or specialist prescribed healthcare products including information on type of product, date, strength, dosage regimen, route of administration, prescriber specialty and costs dispensed by out-patient pharmacy. In-patient medication available for a subcohort.	From 1998 onwards (full coverage for PPRN cohorts for out-patient medication; in-patient medication only for a subcohort)
General practitioner	Patient records registered by general practitioners (gatekeeper of the Dutch healthcare system) including information on diagnoses and symptoms, laboratory test results, general practitioner visits and referrals to specialists.	From 2003 onwards (partial coverage for PPRN cohorts)
Laboratory tests	Results of laboratory tests performed on clinical specimens, requested by general practitioners or medical specialists including information on date and time of testing, test result, unit of measurement and type of clinical specimen.	From 1998 onwards (partial coverage for PPRN cohorts)
Hospital admissions	Hospital admissions (i.e. in-patient hospital records) for more than 24 hours and admissions for less than 24 hours for which a bed is required including information on hospital admission and discharge dates, discharge diagnoses and procedures (maintained by the Dutch Hospital Data Foundation[9]).	From 1998 onwards (full coverage for PPRN cohorts up to 2015; partial coverage for PPRN cohorts from 2016 onwards) after permission is granted by the Dutch Hospital Data Foundation.
Ambulatory care	Ambulatory care (i.e. out-patient hospital records, e.g. by pediatrician), including diagnosis, number of visits, involved specialist (maintained by the Dutch Hospital Data Foundation[9]).	From 2016 onwards (partial coverage for PPRN cohorts) after permission is granted by the Dutch Hospital Data Foundation.
Pathology reports	Data on excerpts of histological, cytological and autopsy examinations, obtained through linkage with the national Pathology Registry[10] (maintained by the PALGA Foundation).	From 1998 onwards (full coverage for PPRN cohorts) after permission is granted by the PALGA Foundation.
Malignancies	Data on all newly diagnosed cancer cases including information on cancer diagnosis, tumour staging, tumour site, morphology and initial treatment, obtained through linkage with the national Netherlands Cancer Registry[11] (maintained by the Netherlands Comprehensive Cancer Organisation).	From 1998 onwards (full coverage for PPRN cohorts) after permission is granted by the Netherlands Comprehensive Cancer Organisation.

TABLE 2 Pregnancy characteristics in the Pregnancy Cohort and the Child Cohort of the PPRN

	PHARMO Perinatal Research Network (PPRN) 1999-2017		Perined 1999-2017 (reference)
	Pregnancy Cohort	**Child Cohort**	**Total population**
Number of pregnancies	~542,900	~126,200	~3,200,000
Number of mothers	~387,100	~101,400	-
Maternal characteristics			
Age at delivery (mean ± SD; years)	31.0 ± 4.8	30.8 ± 4.7	31.0 ± 4.9
Nulliparous (%)	46	57	47
Dutch ethnicity (%)	79	84	79
Database history before delivery (mean ± SD; years)	6.0 ± 4.3	6.1 ± 4.3	-
Database follow-up after delivery (mean ± SD; years)*	7.9 ± 5.0	7.7 ± 4.7	-
Infant characteristics			
Male sex (%)	51	53	51
Gestational age at birth (mean ± SD; weeks)	39.1 ± 3.5	39.2 ± 2.7	39.3 ± 2.3
Preterm birth (%)	8	7	8
Multiple birth (%)	2	<0.5	4
Database follow-up after birth (mean ± SD; years)*	7.8 ± 4.7	7.8 ± 4.7	-

*Current censoring: 31 December 2018.
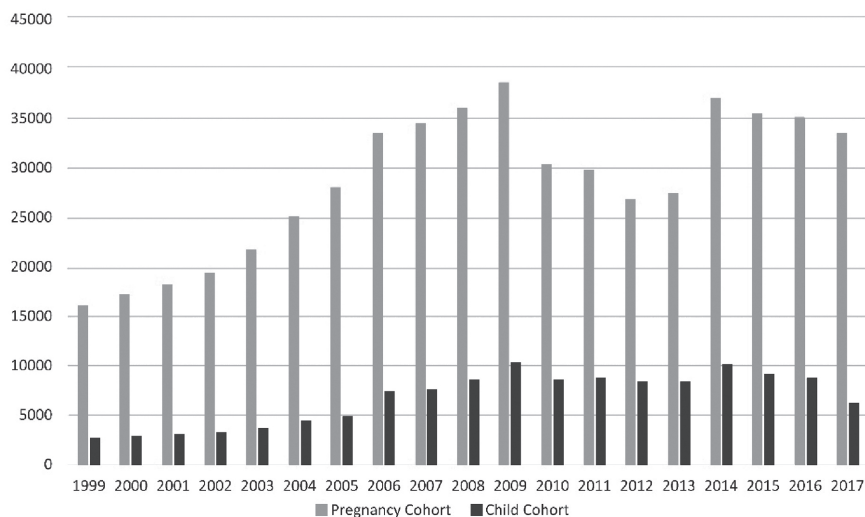
FIGURE 2 Number of pregnancies included in the Pregnancy Cohort and Child Cohort by calendar year
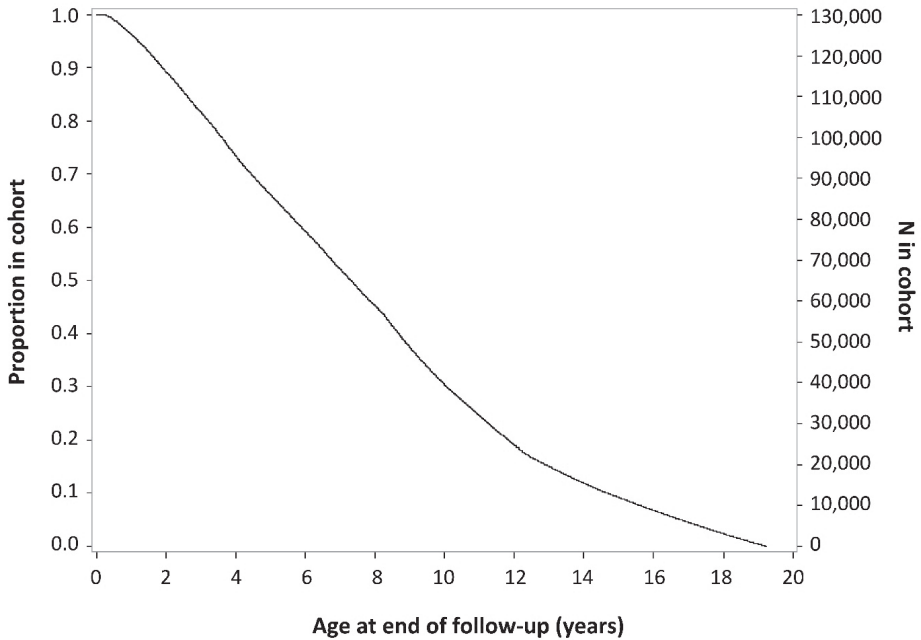
FIGURE 3 Proportion and number of children included in the PPRN Child cohort, with age in years at end of follow-up (current censoring: 31 December 2018)

STRENGTHS AND LIMITATIONS

The main strength of the PPRN lies in the ongoing assembly of detailed, population-based, anonymised data from existing registrations which makes it an invaluable resource for life course perinatal and paediatric research. Evidence from clinical trials is often lacking behind for pregnant women and children, as researchers are often hesitant to include these subjects due to a variety of reasons, including the fear of harm to the fetus and threat of legal liability.[12,13] Therefore, the PPRN provides a very suitable, non-invasive method that stays within the many risks and objections of studies in the vulnerable populations of pregnant women and children. The PPRN covers a considerable proportion of pregnancies from 1999 onwards that has been shown to reflect true estimates of the Dutch population captured in Perined,[14] ensuring a high level of generalisability. The patient-level linkage of many different healthcare data sources provides a very rich data set allowing long-term follow-up of mother and child, with data continuously being collected. The PPRN brings together data from various sources. Data collection periods and catchment areas vary between these databases and therefore the size of the study population depends on the databases included. The 542 900 pregnancies linked in the data cut up to 2017 allow for assessment of drug use during the 9-month preconception, pregnancy and 9-month postpartum periods. Inclusion of other databases (eg, general practitioner records or hospital admissions) will reduce the cohort size. As with any database, identification of medical events is limited to data that are captured as part of the medical records or

other linked data sources in daily clinical practice. These data are not primarily collected for research purposes and rely on appropriate diagnostic coding. Also, the lag time for the PHARMO–Perined linked data to become available is currently approximately 1 year. Furthermore, the number of records that include a social security number is currently too limited to allow for deterministic record linkage between PHARMO and Perined. This availability is steadily increasing and will in the future improve the ability to differentiate between siblings in case of multiple birth pregnancies, which are now under-represented in the Child Cohort. The current linkage methods particularly gain a high specificity, and including these unique patient identifiers the sensitivity is expected to increase further as well. The seeming under-representation of multiple births in the Pregnancy Cohort is caused by the fact that the presented reference proportion for the total Perined population includes all pregnancies (including terminated pregnancies and stillborns); however, comparisons by gestational age indeed show agreement between the two (data not presented). Furthermore, the higher proportion of nulliparous women in the Child Cohort compared with the other two cohorts is mainly influenced by families more often moving houses shortly after delivery of a second child compared with their first child, and due to the new address it is less likely that the child can be traced back in the PHARMO Database Network.

COLLABORATION

Access to the PPRN is, by governance regulations of the data collection and contractually agreed between the PHARMO Institute and Perined, restricted to researchers of the PHARMO Institute, Perined and academic affiliates. Academic affiliates from universities, hospitals or other research institutes are encouraged to apply for access to the anonymised data for scientific study purposes. The data are handled in accordance with data protection, privacy regulations and ISO certification schemes. Each data request is checked against these policies and requires permission of the applicable compliance and privacy boards of both PHARMO and Perined. Permission to external databases is requested from the database holders (eg, Dutch Hospital Data Foundation or PALGA Foundation) on a project basis. As it concerns database research with anonymous data, no Institutional Review Board or ethics committee approval is required. An overview of the variables included in the different databases, the terms and conditions and data application forms are available on http:// pharmo. nl/ whatwe- have/ data- request- PHARMO/ and (in Dutch) www. perined. nl/ registratie/ faciliteren- onderzoek. Data sets are processed in SAS version 9.4 (SAS Institute), but can be converted to other data formats. Only a 10% subsample of the requested data can be downloaded by the researcher from a secure FTP server; access to the full data set can be granted to researchers guesting at the PHARMO office.

CONTRIBUTORS

EH and RH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EH, LB, EAPS and RH contributed to the plan and design of the study. EH performed the data analyses and drafted the manuscript and was in charge of the study planning. EH, LB, EAPS and RH contributed to the interpretation of the results and critical

revision of the manuscript for important intellectual content and approved the final version of the manuscript. EH and RH are the guarantors of this paper.

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None declared.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

PATIENT CONSENT FOR PUBLICATION

Not required.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Requests for sharing study data must be made on specific grounds, either (1) with the aim of corroborating the study results in the interest of public health or (2) in the context of an audit by a competent authority. Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a sound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable.

OPEN ACCESS

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PART II

MEDICATION USE DURING PREGNANCY

CHAPTER 3

**Dutch trends in the use
of potentially harmful
medication during pregnancy**

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ABSTRACT

Aims

Recent population-based data on drug utilization around pregnancy are lacking. This study aims to examine the prevalence of drug exposure in the Netherlands during the preconception, pregnancy and postpartum periods, with special emphasis on trends of potentially harmful medication over the years.

Methods

A population-based study was conducted using records from the PHARMO Perinatal Research Network. From 1999 to 2017, the proportion of pregnancies during which women used any medication or potentially harmful medication was assessed, overall and stratified by timing of exposure relative to pregnancy and by the year of delivery.

Results

Overall, 357,226 (73%) and 166,484 (34%) of 487 122 selected pregnancies were exposed to any and potentially harmful medication, respectively. Among these 487,122 pregnancies, preconception prevalence for use of potentially harmful medication was 43%, 24% during the first trimester, 19% during the second, 16% during the third, and 45% postpartum. A declining trend was observed for exposure to any medication, from 84% in 1999 to 68% in 2017. No clear changes were observed over time for the proportion of pregnancies exposed to potentially harmful medication.

Conclusions

Our study shows that the use of potentially harmful medication was high over the last two decades. Although there was a declining trend over the years in overall medication use, during a steady one-third of pregnancies, women used potentially harmful medication. Our findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding potential risks associated with pharmacological treatment during pregnancy.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- The potentially harmful effects on the mother, embryo or fetus, and newborn of some medication used before, during and after pregnancy are well known.
- Despite this, drug exposure during pregnancy is common in Europe and the US.
- Recent long-term population-based data on drug utilization before, during and after pregnancy in the Netherlands are lacking.

WHAT THIS STUDY ADDS
- Over all the study years, potentially harmful medication was used during a steady one-third of pregnancies.
- Our findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding the potential risks associated with pharmacological treatment during pregnancy.

chapter **3**

INTRODUCTION

The potentially harmful effects on the mother, embryo or fetus, and newborn of medication used before, during and after pregnancy are well known and can lead to major birth defects. It is therefore undisputed that safe pharmaceutical care around pregnancy is of vital importance. There are critical time points during a pregnancy when medication is likely to impact pregnancy outcomes. In the first trimester, risk of spontaneous abortion and birth defects are highest because of organogenesis. However, after the first trimester, teratogens can still affect development of fetal organs and tissues such as the brain.[1,2]

Despite this, drug exposure during pregnancy is common in Europe and the US.[3-5] Prior drug utilization studies have revealed an overall prescription rate of up to 79% during pregnancy in the period 1994 to 2013 in the Netherlands.[6,7] A multinational study showed that compared to other (European) countries, prevalence of any medication use during pregnancy was high in the Netherlands (95% vs. on average 81%).[4] For certain chronic conditions like epilepsy or diabetes medical treatment cannot be easily avoided. In case of potential teratogenicity, switching to alternative (pharmaceutical) treatment, lowering thable 1e dose or temporary cessation should be considered. However, it remains a matter of balancing fetal and maternal risks, especially in case of chronic conditions.[8]

The public health importance of monitoring drug use around pregnancy has been recognized from a national as well as from an EU perspective.[9,10] Recent long-term population-based data on drug utilization before, during and after pregnancy in the Netherlands are lacking. Such data would allow for more intense future interventions targeted at preventing use of potentially harmful medication during pregnancy. The objective of the current study was to examine, at a population level, the prevalence of drug exposure during the preconception, pregnancy and postpartum periods in the Netherlands, with special emphasis on potentially harmful medication, and to assess trends over the years.

METHODS

Study design and data sources

This population-based study was performed using the PHARMO Perinatal Research Network (PPRN), which combines records from the Netherlands Perinatal Registry (Perined) and the PHARMO Database Network (PHARMO).[11] Perined is a nationwide registry that contains validated data from pregnancies with a gestational age (GA) of at least 16 weeks.[12] PHARMO comprises a dynamic cohort of participants and includes, among other information, drug-dispensing records from community pharmacies for more than three million individuals (approximately 25% of the Dutch population) collected since 1998.[13,14] The Out-patient Pharmacy Database contains the following information per filled prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, dose regimen, prescribing physician, quantity dispensed and estimated duration of use.[15] The Out-patient Pharmacy Database represents the Dutch population that has picked up prescription drugs or has registered with a pharmacy and has been shown to be representative of the general Dutch population in terms of age and gender. The linkage between PHARMO and Perined has been described in detail elsewhere but was generally based on the birth date of the mother and child and their addresses and could be established for about 20% of the pregnancies in Perined.[11,16] Women who gave birth between 1999 and 2017 were selected from the PPRN, including both live and stillbirths (GA ≥22 weeks). No exclusion criteria were applied in order to increase the generalizability of the results. To allow for women's medication use to be assessed during the preconception, pregnancy and postpartum periods, their details needed to be registered in the Out-patient Pharmacy Database from 40 weeks before the conception date (based on ultrasound or first day of the last menstrual period [LMP]) until 40 weeks after the delivery date as recorded in Perined. For the current database research with anonymous data, no Institutional Review Board or ethics committee approval was required.

Drug exposure during the preconception, pregnancy and postpartum periods

All drug dispensing records of the women in the PPRN were selected from the Out-patient Pharmacy Database and the length of each dispensing was calculated by dividing the total number of dispensed units by the number of units to be taken per day. Dispensings were converted into treatment episodes of uninterrupted use to be able to determine drug exposure over time. Drug exposure preconception was defined as an active treatment episode within 40 weeks before the conception date. Drug exposure during pregnancy was similarly assessed from on or after the conception date until delivery date and classified by pregnancy trimester: up to the week 12 of amenorrhea (first), 13-27 weeks (second) and 28 weeks to delivery (third). Drug exposure postpartum was assessed during the 40 weeks after delivery. Although the conventional definition of the periconceptional period is shorter, these periods were defined in order to have time windows of similar length and thereby allow comparability of drug exposure between the three periods. Sensitivity analyses were performed in which drug exposure during these periods was based on drug dispensings rather than treatment episodes. Drug exposure to medication not indicated as safe (hereafter referred to as "potentially harmful medication") was classified according to categories 2-6 of the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (see Table 1 and

Supplementary Table 1).[17] Although this classification system is directed specifically at drug use during pregnancy, the same classification was applied to the postpartum period in order to visualize periconceptional exposure patterns (i.e. without applying breastfeeding-specific risk classification).

TABLE 1 Overview of medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

Category	Label	Description*
1.	Wide experience; can be used	Medicines used in research or in practice without showing a raised prevalence of congenital defects, or (in)direct harmful effects in the embryo, fetus, or newborn. This category is not taken into account separately in the current study.
2.	Pharmacological effects; require monitoring	Medicines known or suspected to result in pharmacological effects in the embryo, fetus, or newborn. The use of these medicines must be considered carefully. When used, monitoring for side effects is needed.
3.	Pharmacological effects; avoid (temporarily)	Medicines known or suspected to result in pharmacological effects in the embryo, fetus, or newborn. These medicines should not be used during this hazardous period; an alternate medicine should be chosen.
4.	Teratogenic effects; require monitoring	Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage or that can have harmful pharmacological effects in the embryo, fetus, or newborn. Usage must be considered carefully, and if so, monitoring for undesirable effects is needed.
5.	Teratogenic effects; avoid (temporarily)	Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage and that can have harmful pharmacological effects in the embryo, fetus, or infant. These medicines should not be used during this hazardous period; an alternate medicine should be chosen.
6.	Unknown risk	Medicines of which the risk for the embryo, fetus, or newborn cannot be determined because there are insufficient data on their effect in humans. The use of these medicines must be considered carefully and when possible; another medicine should be chosen.

*See Supplementary Table 1 for detailed overview of the medication that is included per category.

Outcome assessment

Maternal and obstetric characteristics assessed included age at delivery, neighbourhood socioeconomic status (SES)[18,19], year of delivery, ethnicity, preconceptional use of medication for chronic conditions (see Supplementary Table 2), parity, and GA at birth (ultrasound- or LMP-based). The proportion of pregnancies during which potentially harmful as well as any medication was used was determined and stratified by the timing of exposure relative to pregnancy (i.e. preconception, first trimester, second trimester, third trimester and postpartum). Risk classification categories were presented separately and combined as "potentially harmful" (Categories 2-6) and "known risk" (Categories 2-5) medication. The medication most often used during pregnancy was assessed per medication category (2, 3, 4, 5, 6 and none) and the top 5 presented by pregnancy trimester (excluding reproductive hormonal drugs). In order to assess developments over the years, the proportion of pregnancies during which potentially harmful as well as any medication was used was stratified by the year of delivery. Any medication included all ATC-coded drugs, in case they

chapter

3

were dispensed in the out-patient pharmacy and not purchased over-the-counter (including folic acid and vitamin D, although these are nearly always purchased over-the-counter).

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were used to calculate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) to estimate associations between maternal and obstetric characteristics and use of potentially harmful medication. Missing categories were created for SES, ethnicity and parity. Trends over time were tested by Poisson regression at *P*-value < 0.05.

RESULTS

In total, 487,122 pregnancies were selected from the PPRN between 1999 and 2017 for inclusion in the study (Table 2). During 357,226 (73%) of all the pregnancies women used any medication at least once. Overall, women used potentially harmful medication during 166,484 (34%) of these pregnancies. This was 43% preconception, 24% during the first trimester, 19% during the second trimester, 16% during the third trimester and 45% postpartum (Figure 1). The highest prevalence was observed for medication with unknown risk (Category 6; ranging from 9-31%) and the lowest for medication with teratogenic effects that require monitoring (Category 4; ranging from <0.5-1%), regardless of the timing relative to pregnancy. Similar periconceptional patterns were observed for any medication with overall higher prevalence (preconception: 71%, first trimester: 58%, second trimester: 55%, third trimester: 53%, postpartum: 80%). Sensitivity analyses in which drug exposure prevalence during these periods was based on drug dispensings rather than treatment episodes showed very similar results: all percentage differences in recalculated prevalences were smaller than 0.5% (data not presented).
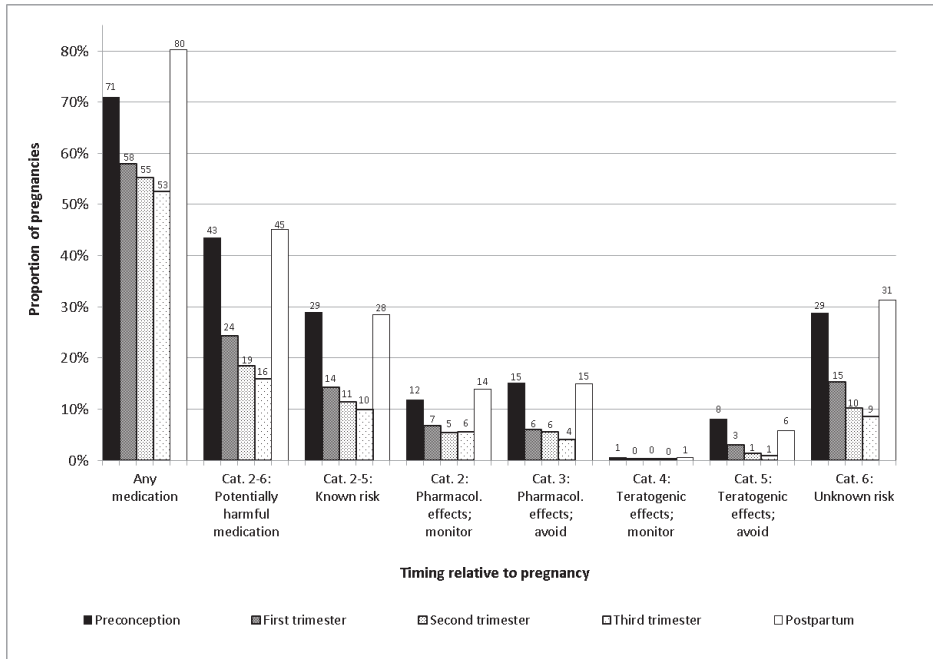
FIGURE 1 Medication use during the preconception, pregnancy and postpartum periods categorized according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

All trends over time were statistically significant at *P*-value < 0.05.

Table 2 shows that preconceptional use of medication for chronic conditions was strongly associated with potentially harmful medication use (OR 3.82, 95% CI 3.77-3.86), particularly antipsychotics and drugs used in diabetes. The use of potentially harmful medication was observed to a significantly larger extent among women of non-Dutch ethnicity compared with Dutch women (OR Moroccan/Turkish: 1.41, 95% CI 1.38-1.44; OR other European/Western: 1.09, 95% CI 1.05- 1.12; OR Other: 1.25, 95% CI 1.22-1.28).

TABLE 2 Maternal and obstetric characteristics of included pregnancies, stratified by use of potentially harmful medication during pregnancy

Characteristic	Study cohort	Use of potentially harmful medication (Cat. 2-6)	No use of potentially harmful medication (Cat. 2-6)	OR (95% CI) Use vs. No use
	N = 487,122 n (%)	N = 166,484 (34%) n (%)	N = 320,638 (66%) n (%)	
Age at delivery (years)				
≤20	7,837 (2)	2,900 (2)	4,937 (2)	1.18 (1.13 to 1.24)
21-30	213,153 (44)	70,742 (42)	142,411 (44)	1 (reference)
31-40	254,949 (52)	87,868 (53)	167,081 (52)	1.06 (1.05 to 1.07)
≥41	11,183 (2)	4,974 (3)	6,209 (2)	1.61 (1.55 to 1.68)
Mean ± SD	31 ± 5	31 ± 5	31 ± 5	1.06 (1.06 to 1.07)[a]

TABLE 2 Maternal and obstetric characteristics of included pregnancies, stratified by use of potentially harmful medication during pregnancy (continued)

Characteristic	Study cohort	Use of potentially harmful medication (Cat. 2-6)	No use of potentially harmful medication (Cat. 2-6)	OR (95% CI) Use vs. No use
	N = 487,122	N = 166,484 (34%)	N = 320,638 (66%)	
	n (%)	n (%)	n (%)	
SES				
Low	171,623 (35)	61,490 (37)	110,133 (34)	1.12 (1.11 to 1.14)
Normal	151,123 (31)	50,165 (30)	100,958 (31)	1 (reference)
High	162,414 (33)	54,114 (33)	108,300 (34)	1.01 (0.99 to 1.02)
Unknown	1,962 (<0.5)	715 (<0.5)	1,247 (<0.5)	-
Year of delivery				
1999-2003	74,812 (15)	24,833 (15)	49,979 (16)	1 (reference)
2004-2008	134,370 (28)	45,639 (27)	88,731 (28)	1.04 (1.02 to 1.05)
2009-2013	142,759 (29)	51,685 (31)	91,074 (28)	1.14 (1.12 to 1.16)
2014-2017	135,181 (28)	44,327 (27)	90,854 (28)	0.98 (0.96 to 1.00)
Ethnicity				
Dutch	388,723 (80)	128,584 (77)	260,139 (81)	1 (reference)
Moroccan/Turkish	35,400 (7)	14,550 (9)	20,850 (7)	1.41 (1.38 to 1.44)
Other European/ Western[b]	16,025 (3)	5,601 (3)	10,424 (3)	1.09 (1.05 to 1.12)
Other[c]	44,609 (9)	17,036 (10)	27,573 (9)	1.25 (1.22 to 1.28)
Unknown	2,365 (<0.5)	713 (<0.5)	1,652 (1)	-
Medication for chronic conditions[d]	150,232 (31)	83,418 (50)	66,814 (21)	3.82 (3.77 to 3.86)
Drugs used in diabetes	2,677 (1)	2,360 (1)	317 (<0.5)	14.53 (12.92 to 16.34)
Corticosteroids, dermatological preparations	47,269 (10)	25,508 (15)	21,761 (7)	2.48 (2.44 to 2.53)
Corticosteroids for systemic use	7,036 (1)	5,004 (3)	2,032 (1)	4.86 (4.61 to 5.12)
Thyroid therapy	8,517 (2)	4,362 (3)	4,155 (1)	2.05 (1.96 to 2.14)
Anti-inflammatory and antirheumatic products	70,340 (14)	37,632 (23)	32,708 (10)	2.57 (2.53 to 2.61)
Antimigraine medication	8,730 (2)	6,136 (4)	2,594 (1)	4.69 (4.48 to 4.91)
Antiepileptics	2,937 (1)	2,508 (2)	429 (<0.5)	11.42 (10.30 to 12.65)
Antipsychotics	3,185 (1)	2,913 (2)	272 (<0.5)	20.92 (18.48 to 23.69)
Antidepressants	19,583 (4)	16,563 (10)	3,020 (1)	11.62 (11.17 to 12.08)
Antiasthmatics	24,602 (5)	14,153 (9)	10,449 (3)	2.76 (2.69 to 2.83)

TABLE 2 Maternal and obstetric characteristics of included pregnancies, stratified by use of potentially harmful medication during pregnancy (continued)

Characteristic	Study cohort	Use of potentially harmful medication (Cat. 2-6)	No use of potentially harmful medication (Cat. 2-6)	OR (95% CI) Use vs. No use
	N = 487,122	N = 166,484 (34%)	N = 320,638 (66%)	
	n (%)	n (%)	n (%)	
Parity				
0	219,670 (45)	76,845 (46)	142,825 (45)	1 (reference)
1	24,802 (5)	7,884 (5)	16,918 (5)	0.87 (0.84 to 0.89)
2	161,309 (33)	52,764 (32)	108,545 (34)	0.90 (0.89 to 0.92)
≥3	81,295 (17)	28,975 (17)	52,320 (16)	1.03 (1.01 to 1.05)
Unknown	46 (<0.5)	16 (<0.5)	30 (<0.5)	-
GA at birth (weeks)				
≤24	1,875 (<0.5)	803 (<0.5)	1,072 (<0.5)	1.48 (1.35 to 1.62)
25-<28	1,455 (<0.5)	648 (<0.5)	807 (<0.5)	1.58 (1.43 to 1.76)
28-<33	5,679 (1)	2,327 (1)	3,352 (1)	1.37 (1.30 to 1.44)
33-<37	29,385 (6)	11,702 (7)	17,683 (6)	1.30 (1.27 to 1.34)
≥37	448,728 (92)	151,004 (91)	297,724 (93)	1 (reference)
Mean ± SD	39.2 ± 2.2	39.0 ± 2.4	39.3 ± 2.1	0.75 (0.75 to 0.76)[a]

OR = odds ratio; CI = confidence interval; SD = standard deviation; SES = neighbourhood socioeconomic status; GA = gestational age; [a]OR for 5 units change; [b]including North American and Canadian; [c]Creole, Hindu, Asia and other; [d]Medication use for chronic conditions was assessed preconception (see Appendix Table 2 for definitions).

An overall declining trend over the years for any medication use was observed, from 84% in 1999 to 68% in 2017 (Figure 2). However, no clear long-term linear trend is apparent for the potentially harmful medication categories presented in this figure. Combining this information, the proportion of "potentially harmful medication" relative to "any medication" increased from 39% in 1999 to about 50% from 2011 onwards (data not presented in figure). Pregnancies during which women used potentially harmful medication were predominantly in Category 6 (63%), followed by Category 3 (33%), Category 2 (29%), Category 5 (11%) and Category 4 (1%).
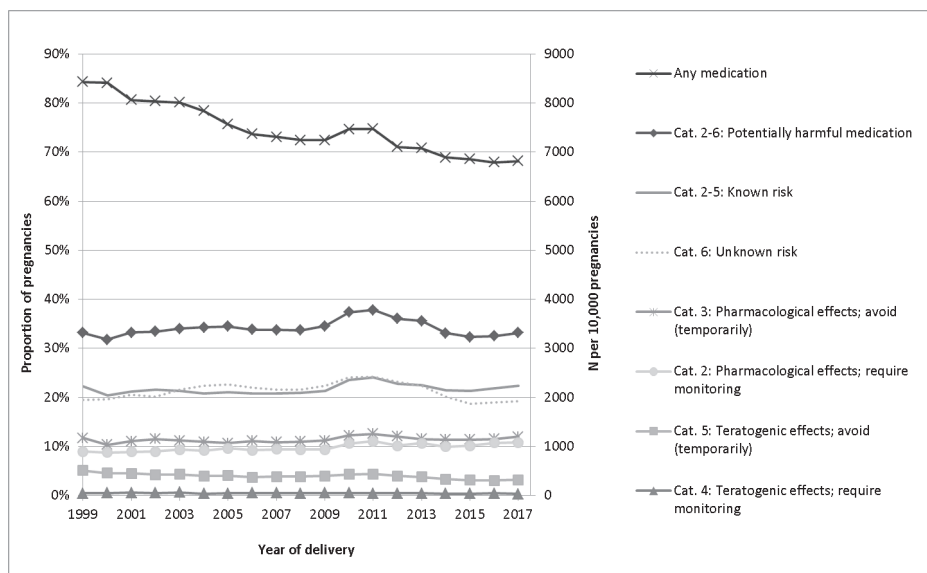
FIGURE 2 Trends in medication use during pregnancy, categorized according to 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

The top five medications used in each category are presented in Table 3. The table shows that among drugs with pharmacological effects that require monitoring (Category 2), the nervous system drugs (psycholeptics and psychoanaleptics) were at the top. A marked increase for temazepam was observed in the third trimester, which is used for short-term treatment of insomnia and is one of the preferred choices during pregnancy. Nitrofurantoin, which should be avoided only around the due date, was most often used within Category 3, including drugs with pharmacological effects that should be (temporarily) avoided, followed by ibuprofen (contraindicated in third trimester), naproxen (contraindicated in third trimester), acetylsalicylic acid (contraindicated in third trimester at daily dose >80 mg) and promethazine (should be avoided in last weeks of pregnancy, however known for its sedating side effect in favour of other sleep medication). Overall the prevalence of drugs with teratogenic effects that require monitoring (Category 4) was low across all trimesters (≤0.1%). Of those Category 5 drugs with teratogenic effects that should be (temporarily) avoided, doxycycline (should be avoided in second and third trimester) was most often used, followed by minocycline (contraindicated in second and third trimester), valproic acid (contraindicated during pregnancy, unless other epilepsy treatment is inadequate), acenocoumarol (should be avoided from 6 weeks GA onwards) and enalapril (contraindicated in second and third trimester). In Category 6 including drugs with unknown risk, a clear decrease in prevalence was observed reflecting patients who switched or stopped nonpreferred treatment. For cabergoline, used to suppress lactation, a high increase was observed in the third trimester. Among medication without a category assigned, pregnancy-related drugs were most apparent. For example, a clear increase was observed in meclozine use in the first trimester, which is prescribed for nausea and vomiting in pregnancy. Use of ferrous fumarate also increased over the trimesters, which is recommended for maternal anaemia.

TABLE 3 Top 5 medication used during pregnancy trimesters according to 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

Medication (ATC)ᵃ	Preconception N = 487,122 n (%)	First Trimester N = 487,122 n (%; changeᶜ)	Second Trimester N = 487,122 n (%; changeᵈ)	Third Trimester N = 483,799 n (%; changeᵉ)
Cat. 2: Pharmacological effects; require monitoring				
#1 Temazepam (N05CD07)	6,347 (1)	2,402 (0.5; -62%)	2,016 (0.4; -16%)	5,328 (1; +166%)
#2 Oxazepam (N05BA04)	9,781 (2)	3,999 (0.8; -59%)	2,774 (0.6; -31%)	2,541 (0.5; -8%)
#3 Paroxetine (N06AB05)	5,328 (1)	3,756 (0.8; -30%)	2,875 (0.6; -23%)	2,529 (0.5; -11%)
#4 Betamethasone (D07AC01)	5,338 (1)	2,566 (0.5; -52%)	1,901 (0.4; -26%)	1,406 (0.3; -26%)
#5 Prednisolone (H02AB06)	3,705 (0.8)	1,644 (0.3; -56%)	1,570 (0.3; -5%)	1,487 (0.3; -5%)
Cat. 3: Pharmacological effects; avoid (temporarily)				
#1 Nitrofurantoin (J01XE01)	23,101 (5)	10,851 (2; -53%)	14,904 (3; +37%)	9,852 (2; -33%)
#2 Ibuprofen (M01AE01)	25,081 (5)	6,784 (1; -73%)	3,216 (0.7; -53%)	2,344 (0.5; -27%)
#3 Naproxen (M01AE02)	17,088 (4)	4,472 (0.9; -74%)	1,836 (0.4; -59%)	1,358 (0.3; -26%)
#4 Acetylsalicylic Acid (B01AC06)	842 (0.2)	2,514 (0.5; +199%)	3,174 (0.7; +26%)	2,878 (0.6; -9%)
#5 Promethazine (R06AD02)	1,266 (0.3)	840 (0.2; -34%)	1,167 (0.2; +39%)	1,416 (0.3; +22%)
Cat. 4: Teratogenic effects; require monitoring				
#1 Carbamazepine (N03AF01)	591 (0.1)	485 (<0.1; -18%)	474 (<0.1; -2%)	457 (<0.1; -3%)
#2 Valproic Acid (N03AG01)	589 (0.1)	446 (<0.1; -24%)	393 (<0.1; -12%)	367 (<0.1; -6%)
#3 Propylthiouracil (H03BA02)	314 (<0.1)	373 (<0.1; +19%)	393 (<0.1; +5%)	289 (<0.1; -26%)
#4 Lithium (N05AN01)	299 (<0.1)	271 (<0.1; -9%)	242 (<0.1; -11%)	259 (<0.1; +8%)
#5 Thiamazole (H03BB02)	460 (<0.1)	258 (<0.1; -44%)	207 (<0.1; -20%)	139 (<0.1; -32%)
Cat. 5: Teratogenic effects; avoid (temporarily)				
#1 Doxycycline (J01AA02)	17,909 (4)	3,625 (0.7; -80%)	1,704 (0.3; -53%)	1,178 (0.2; -30%)
#2 Minocycline (J01AA08)	1,651 (0.3)	623 (0.1; -62%)	374 (<0.1; -40%)	315 (<0.1; -15%)
#3 Valproic Acid (N03AG01)	589 (0.1)	446 (<0.1; -24%)	393 (<0.1; -12%)	367 (<0.1; -6%)
#4 Acenocoumarol (B01AA07)	510 (0.1)	347 (<0.1; -32%)	351 (<0.1; +1%)	288 (<0.1; -17%)
#5 Enalapril (C09AA02)	391 (<0.1)	258 (<0.1; -34%)	193 (<0.1; -25%)	119 (<0.1; -38%)
Cat. 6: Unknown risk				
#1 Desloratadine (R06AX27)	12,018 (2)	4,855 (1.0; -60%)	2,571 (0.5; -47%)	1,721 (0.4; -33%)
#2 Ketoconazole (D01AC08)	7,046 (1)	3,986 (0.8; -43%)	3,367 (0.7; -16%)	2,453 (0.5; -27%)
#3 Levocetirizine (R06AE09)	9,555 (2)	4,382 (0.9; -54%)	2,548 (0.5; -42%)	1,666 (0.3; -34%)

chapter

3

TABLE 3 Top 5 medication used during pregnancy trimesters according to 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (continued)

Medication (ATC)[a]	Preconception N = 487,122 n (%)	First Trimester N = 487,122 n (%; change[c])	Second Trimester N = 487,122 n (%; change[d])	Third Trimester N = 483,799 n (%; change[e])
#4 Mometasone (R01AD09)	7,372 (2)	4,207 (0.9; -43%)	2,773 (0.6; -34%)	1,831 (0.4; -34%)
#5 Cabergoline (G02CB03)	1,291 (0.3)	448 (<0.1; -65%)	513 (0.1; +15%)	4,098 (0.8; +704%)
Medication without category assigned[b]				
#1 Ferrous Fumarate (B03AA02)	11,519 (2)	7,465 (2; -35%)	24,705 (5; +231%)	45,553 (9; +86%)
#2 Miconazole (G01AF04)	25,417 (5)	15,827 (3; -38%)	27,272 (6; +72%)	28,675 (6; +6%)
#3 Amoxicillin (J01CA04)	23,321 (5)	11,769 (2; -50%)	20,160 (4; +71%)	19,530 (4; -2%)
#4 Meclozine, Combinations (R06AE55)	1,439 (0.3)	27,419 (6; +1,805%)	19,263 (4; -30%)	3,140 (0.6; -84%)
#5 Folic Acid (B03BB01)	16,747 (3)	22,168 (5; +32%)	19,257 (4; -13%)	9,521 (2; -50%)

Note: top 5 determined during entire pregnancy combining first, second and third trimester; [a]Excluding reproductive hormonal drugs (ATC G03); [b]According to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb; Percentage change in proportion that used medication calculated relative to: [c] preconception; [d] first trimester and [e] second trimester.

DISCUSSION

This study shows a high prevalence of exposure to potentially harmful medication during pregnancy in the Netherlands from 1999 to 2017. Over all the study years, potentially harmful medication was used during approximately one-third of pregnancies, including drugs with known and unknown risks to a similar extent. Although there was a declining trend in overall medication use, no such trend was observed for potentially harmful medication, indicating an increasing share of potentially harmful medication relative to all medication used. Most notably, potentially harmful medication use was significantly higher among women with preconceptional use of medication for chronic conditions and women of non-Dutch ethnicity. Exposure was most common during the first trimester for all risk categories. Although in particular the use of drugs with known teratogenic effects dropped most markedly in the second and third trimester, exposure to harmful medications such as non-steroidal anti-inflammatory drugs (NSAIDs), tetracyclines or valproic acid remained common.

The current study findings are in line with those in previous Dutch studies on medication exposure during pregnancy. Our estimate of overall medication use was somewhat lower than observed in a study published in 2006 (73% vs. 79%).[6] This is probably due to differences in patient selection (e.g. their restriction to first pregnancies), as well as the extension of our study into more recent years. A recent Dutch, tertiary academic centre study of pregnant and lactating women showed that 68.2% used prescribed medication.[7] However, next to the difference in study setting, participants using only vitamin D, folic acid, and/or multivitamins during pregnancy were classified as nonmedication users,

contrary to the current study. We observed a decreasing trend for any medication use over the years. Similar recent studies focusing on Dutch population-based trends are limited. Increasing multinational trends were described in two papers published in the last decade, and attributed to older maternal age and associated pre-existing medical conditions that require pharmacotherapy.[5,20] In addition to international differences, the study period differed and the main focus was on the number of medications used (i.e. polypharmacy) rather than the binomial outcome of medication use applied in this study. Focusing on potentially harmful medication specifically, other recently reported rates were somewhat higher than those presented here.[7] As well as the different make-up of their study population, they used a questionnaire design taking into account over-the-counter drugs. Studies assessing medication use during preconception, pregnancy and postpartum periods and classified per risk category are limited. In a Dutch study from 2006, decreasing exposure to potentially harmful medication was reported from 30% in the first trimester to 14% in the third trimester, increasing to 45% postpartum.[6] This is very similar to the patterns we observed for all risk categories together. Contrary to the current study, an increase in overall prescription rates during pregnancy trimesters was observed. This can be attributed to their exclusion of contraceptive prescriptions, the main drugs used before pregnancy.[21]

Our results have important implications for public health. The unchanged high use of medication with known risks suggests a potential deficit of risk perception among healthcare providers and pregnant women. The increased relative share of potentially harmful medication together with the decline in overall medication use implies that patients with high-risk conditions requiring pharmaceutical treatment continue their therapy, supported also by the strong associations with chronic medication use in this study. This is in line with the abovementioned increase in maternal age and pre-existing medical conditions (e.g. diabetes) over the years, as recorded in the annual Perined reports and substantiated in this study cohort.[22] Healthcare providers, including pharmacists, have to recognize and shoulder their responsibility for drug use surveillance among women of reproductive age. A recent Dutch study has shown that pregnant women perceived most drugs relatively low in risk and high in benefit. This should be taken into account when counselling them.[23] The higher use among women of non-Dutch ethnicity suggests that these patients in particular have difficulty obtaining, understanding and implementing health information as demonstrated also in previous research.[24] Treating physicians rely on available evidence on risks when making decisions and daily face difficulties balancing drugs' risks and benefits.[25] A high proportion of drugs are labelled as "unknown risk", lacking specific recommendations for use during pregnancy.[26] As exposure rates were highest in early pregnancy, which can be expected as sometimes pregnancy is still unknown, preconception counselling of the general population would in theory make women more aware of the risks of certain pharmacological treatments in relation to pregnancy. This could help to improve prevention of potentially harmful medication use. However, the implementation of preconception care in European countries is still very limited.[26-28] In order to achieve speedy and scalable benefits to public health it was recently suggested that an advocacy coalition of groups interested in preconception health should be developed to harness the political will and leadership necessary to turn high-level policy into effective coordinated action.[29]

These results highlight the need for an expansion of medication-risk knowledge and communication by means of targeted preventive interventions, research and education programmes, so that specific recommendations can be made for medication use during pregnancy. Novel insights on the consequences of drug exposure during pregnancy should and can be gained, for example from the nearly twenty years of follow-up data currently available in the PPRN and other registries such as pREGnant.[30] Next to that, drug-centric research would enable assessment of dose-response relationships and provide insight on patient-level pregnancy-centred treatment patterns and alternatives (i.e. individualised care). Based on the current results, NSAIDs, tetracyclines, valproic acid or, more generally, medication for chronic conditions would be eligible for prioritisation in such studies. Future research should focus on the challenge of actually achieving the desired risk perception, responsibility and activism in the context of risk management.

This observational study used nearly 20 years of data from a large population-based cohort, combining drug dispensing and pregnancy records and was shown to be representative of the Dutch population.[11] The timing of drug exposure relative to pregnancy staging could be accurately assessed based on LMP, ultrasound, exact delivery date, drug dispensing dates and intended duration of use. A limitation of Perined is that 1st trimester miscarriages were unable to be included, thereby potentially underestimating miscarriage-inducing medication.

A common challenge in using administrative data is defining drug exposure or compliance. Treatment episodes based on dispensing records can only approximate actual exposure and particularly during pregnancy drugs may be discontinued. Drug exposure could therefore have been overestimated, although sensitivity analyses using dispensing dates showed similar exposure rates. Underestimated drug exposure is likely because hospital-administered drugs and over-the-counter drugs sold outside pharmacies were not captured.

Of importance in this study was the use of a risk classification system for drugs in pregnancy that did not take into account individualized care in which drug risks are balanced with benefits. Also, the proportion of drugs with unknown risks was relatively high and therefore a statement could only be made on potentially harmful medication. In addition, risk classifications have evolved and been revised over time, and we specifically designed our study to use recent insights. Although some risk classification categories only apply during specific parts of pregnancy, no distinction was made between pregnancy trimesters for the trends in medication use during pregnancy over time. To put this into perspective, we also determined periconceptional patterns of exposure to risk classification categories. The risks of medication used in relation to breastfeeding were beyond the scope of this paper.

Our study shows that the use of potentially harmful medication was high over the last two decades, especially among ethnic minorities and women with chronic medical conditions. Although there was a declining trend over the years in overall medication use, during a steady one-third of pregnancies women used potentially harmful medication. Our findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding the potential

risks associated with pharmacological treatment during pregnancy. In order to be able to make specific recommendations, medication-risk knowledge needs to be expanded and readily accessible. Political will and leadership are needed to turn high-level policy on preconception care into effective coordinated action.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

E.H. and R.H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the plan and design of the study. E.H. performed the data analyses and drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. E.H. and R.H. are the guarantors of this paper. The corresponding author attests that all listed authors meet all ICMJE authorship criteria and that no others meeting the criteria have been omitted.

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chapter

3

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb

Category	Name	ACT
1. Wide experience; can be used *Medicines used in research or in practice without showing a raised prevalence of congenital defects, or (in)direct harmful effects in the embryo, fetus, or newborn.*	N.A. (category not included in current study)	N.A.
2. Pharmacological effects; require monitoring *Medicines known or suspected to result in pharmacological effects in the embryo, fetus, or newborn. The use of these medicines must be considered carefully. When used, monitoring for side effects is needed.*	Dexamethasone	A01AC02
	Epinephrine	A01AD01
	Atropine	A03BA01
	Prednisolone	A07EA01
	Betamethasone	A07EA04
	Quinidine	C01BA01
	Lidocaine	C01BB01
	Propranolol	C07AA05
	Metoprolol	C07AB02
	Atenolol	C07AB03
	Labetalol	C07AG01
	Nifedipine	C08CA05
	Betamethasone	D07AC01
	Desoximetasone	D07AC03
	Diflucortolone	D07AC06
	Amcinonide	D07AC11
	Mometasone	D07AC13
	Fluticasone	D07AC17
	Clobetasol	D07AD01
	Fenoterol	G02CA03
	Fludrocortisone	H02AA02
	Betamethasone	H02AB01
	Dexamethasone	H02AB02
	Methylprednisolone	H02AB04
	Prednisolone	H02AB06
	Prednisone	H02AB07
	Triamcinolone	H02AB08
	Hydrocortisone	H02AB09
	Cortisone	H02AB10
	Rifampicin	J04AB02
	Trastuzumab	L01XC03
	Trastuzumab Emtansine	L01XC14
	Ciclosporin	L04AD01
	Azathioprine	L04AX01
	Suxamethonium	M03AB01
	Atracurium	M03AC04
	Rocuronium Bromide	M03AC09
	Mivacurium Chloride	M03AC10

SUPPLEMENTARY TABLE 1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (continued)

Category	Name	ACT
2. Pharmacological effects; require monitoring continued *Medicines known or suspected to result in pharmacological effects in the embryo, fetus, or newborn. The use of these medicines must be considered carefully. When used, monitoring for side effects is needed.*	Cisatracurium	M03AC11
	Enflurane	N01AB04
	Isoflurane	N01AB06
	Desflurane	N01AB07
	Sevoflurane	N01AB08
	Thiopental	N01AF03
	Fentanyl	N01AH01
	Alfentanil	N01AH02
	Sufentanil	N01AH03
	Remifentanil	N01AH06
	Ketamine	N01AX03
	Etomidate	N01AX07
	Propofol	N01AX10
	Nitrous Oxide	N01AX13
	Morphine	N02AA01
	Hydromorphone	N02AA03
	Nicomorphine	N02AA04
	Oxycodone	N02AA05
	Dihydrocodeine	N02AA08
	Dihydrocodeine, Combinations	N02AA58
	Pethidine	N02AB02
	Fentanyl	N02AB03
	Dextromoramide	N02AC01
	Pentazocine	N02AD01
	Buprenorphine	N02AE01
	Dihydrocodeine And Paracetamol	N02AJ01
	Dihydrocodeine And Acetylsalicylic Acid	N02AJ02
	Dihydrocodeine AndOther Non-opioid Analgesics	N02AJ03
	Tramadol	N02AX02
	Haloperidol	N05AD01
	Oxazepam	N05BA04
	Lorazepam	N05BA06
	Temazepam	N05CD07
	Zopiclone	N05CF01
	Zolpidem	N05CF02
	Imipramine	N06AA02
	Clomipramine	N06AA04
	Amitriptyline	N06AA09
	Nortriptyline	N06AA10
	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10

chapter

3

SUPPLEMENTARY TABLE 1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (continued)

Category	Name	ACT
2. Pharmacological effects; require monitoring continued *Medicines known or suspected to result in pharmacological effects in the embryo, fetus, or newborn. The use of these medicines must be considered carefully. When used, monitoring for side effects is needed.*	Bupropion	N06AX12
	Venlafaxine	N06AX16
	Buprenorphine	N07BC01
	Methadone	N07BC02
	Fenoterol	R03AC04
	Salbutamol	R03CC02
	Fenoterol	R03CC04
	Theophylline	R03DA04
	Aminophylline	R03DA05
	Prednisolone	S01BA04
	Timolol	S01ED01
	Betaxolol	S01ED02
	Levobunolol	S01ED03
	Carteolol	S01ED05
	Ciclosporin	S01XA18
	Diazoxide	V03AH01
3. Pharmacological effects; avoid (temporarily) *Medicines known or suspected to result in pharmacological effects in the embryo, fetus, or newborn. These medicines should not be used during this hazardous period; an alternate medicine should be chosen.*	Tetracycline	A01AB13
	Magnesium Silicate	A02AA05
	Atropine	A03BA01
	Liquid Paraffin	A06AA01
	Senna Glycosides	A06AB06
	Acetylsalicylic Acid	B01AC06
	Carbasalate Calcium	B01AC08
	Amiodarone	C01BD01
	Norepinephrine	C01CA03
	Phenylephrine	C01CA06
	Ephedrine	C01CA26
	Indometacin	C01EB03
	Ibuprofen	C01EB16
	Hydrochlorothiazide	C03AA03
	Furosemide	C03CA01
	Positonen-Iodine	D08AG02
	Iodine	D08AG03
	Positonen-Iodine	G01AX11
	Iodine Therapy	H03CA
	Thiamphenicol	J01BA02
	Thiamphenicol, Combinations	J01BA52
	Sulfamethoxazole	J01EC01
	Sulfadiazine	J01EC02
	Sulfamethoxazole And Trimethoprim	J01EE01
	Sulfametrole And Trimethoprim	J01EE03
	Fusidic Acid	J01XC01
	Nitrofurantoin	J01XE01
	Phenylbutazone	M01AA01
	Indometacin	M01AB01

SUPPLEMENTARY TABLE 1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (continued)

Category	Name	ACT
3. Pharmacological effects; avoid (temporarily) continued	Proglumetacin	M01AB14
Medicines known or suspected to result	Aceclofenac	M01AB16
in pharmacological effects in the embryo,	Piroxicam	M01AC01
fetus, or newborn. These medicines should	Tenoxicam	M01AC02
not be used during this hazardous period;	Meloxicam	M01AC06
an alternate medicine should be chosen.	Ibuprofen	M01AE01
	Naproxen	M01AE02
	Ketoprofen	M01AE03
	Flurbiprofen	M01AE09
	Tiaprofenic Acid	M01AE11
	Dexketoprofen	M01AE17
	Nabumetone	M01AX01
	Nimesulide	M01AX17
	Ibuprofen	M02AA13
	Diclofenac	M02AA15
	Nimesulide	M02AA26
	Acetylsalicylic Acid	N02BA01
	Carbasalate Calcium	N02BA15
	Chlorpromazine	N05AA01
	Ephedrine	R01AA03
	Pseudoephedrine	R01BA02
	Flurbiprofen	R02AX01
	Combinations	R05CA10
	Promethazine	R06AD02
	Chloramphenicol	S01AA01
	Ketorolac	S01BC05
	Phenylephrine	S01FB01
	Phenylephrine	S01GA05
	X-Ray Contrast Media, Iodinated	V08A
4. Teratogenic effects; require monitoring	Propylthiouracil	H03BA02
Medicines known or suspected to cause a	Carbimazole	H03BB01
higher prevalence of congenital defects or	Thiamazole	H03BB02
other permanent damage or that can have	Phenobarbital	N03AA02
harmful pharmacological effects in the	Primidone	N03AA03
embryo, fetus, or newborn. Usage must be	Phenytoin	N03AB02
considered carefully, and if so, monitoring	Carbamazepine	N03AF01
for undesirable effects is needed.	Valproic Acid	N03AG01
	Topiramate	N03AX11
	Lithium	N05AN

chapter

3

SUPPLEMENTARY TABLE 1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (continued)

Category	Name	ACT
5. Teratogenic effects; avoid	Doxycycline	A01AB22
(temporarily)	Misoprostol	A02BB01
	Neomycin	A07AA01
Medicines known or suspected to cause	Nandrolone	A14AB01
a higher prevalence of congenital defects	Warfarin	B01AA03
or other permanent damage and that can	Phenprocoumon	B01AA04
have harmful pharmacological effects	Acenocoumarol	B01AA07
in the embryo, fetus, or infant. These	Captopril	C09AA01
medicines should not be used during this	Enalapril	C09AA02
hazardous period; an alternate medicine	Lisinopril	C09AA03
should be chosen.	Perindopril	C09AA04
	Ramipril	C09AA05
	Quinapril	C09AA06
	Benazepril	C09AA07
	Cilazapril	C09AA08
	Fosinopril	C09AA09
	Zofenopril	C09AA15
	Losartan	C09CA01
	Eprosartan	C09CA02
	Valsartan	C09CA03
	Irbesartan	C09CA04
	Candesartan	C09CA06
	Telmisartan	C09CA07
	Olmesartan Medoxomil	C09CA08
	Acitretin	D05BB02
	Isotretinoin	D10BA01
	Alitretinoin	D11AH04
	Nomegestrol And Estradiol	G03AA14
	Lynestrenol	G03AC02
	Progesterone	G03DA04
	Norethisterone	G03DC02
	Lynestrenol	G03DC03
	Cyproterone	G03HA01
	Danazol	G03XA01
	Demeclocycline	J01AA01
	Doxycycline	J01AA02
	Lymecycline	J01AA04
	Tetracycline	J01AA07
	Minocycline	J01AA08
	Tigecycline	J01AA12
	Tobramycin	J01GB01
	Gentamicin	J01GB03
	Kanamycin	J01GB04
	Neomycin	J01GB05

SUPPLEMENTARY TABLE 1 ATC codes for medication categories according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (continued)

Category	Name	ACT
5. Teratogenic effects; avoid (temporarily) continued *Medicines known or suspected to cause a higher prevalence of congenital defects or other permanent damage and that can have harmful pharmacological effects in the embryo, fetus, or infant. These medicines should not be used during this hazardous period; an alternate medicine should be chosen.*	Amikacin	J01GB06
	Spectinomycin	J01XX04
	Methotrexate	L01BA01
	Fluorouracil	L01BC02
	Megestrol	L02AB01
	Medroxyprogesterone	L02AB02
	Tamoxifen	L02BA01
	Mycophenolic Acid	L04AA06
	Thalidomide	L04AX02
	Methotrexate	L04AX03
	Lenalidomide	L04AX04
	Pomalidomide	L04AX06
	Penicillamine	M01CC01
	Dihydroergotamine	N02CA01
	Ergotamine	N02CA02
	Dihydroergotamine, Combinations	N02CA51
	Valproic Acid	N03AG01
	Topiramate	N03AX11
	Nicotine	N07BA01
	Quinine	P01BC01
6. Unknown risk *Medicines of which the risk for the embryo, fetus, or newborn cannot be determined because there are insufficient data on their effect in humans. The use of these medicines must be considered carefully and when possible; another medicine should be chosen.*	In total, 733 substances were included in this category according to the 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb (examples: ciprofloxacin, infliximab, ketanserin, midazolam).	

Note: adapted from 2016 risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb.1

chapter

3

SUPPLEMENTARY TABLE 2 ATC codes for use of medication for chronic conditions

Chronic condition	ATC
Drugs used in diabetes	A10
Corticosteroids, dermatological preparations	D07
Corticosteroids for systemic use	H02
Thyroid therapy	H03
Anti-inflammatory and antirheumatic products	M01
Antimigraine medication	N02C
Antiepileptics	N03A
Antipsychotics	N05A, excl. N05AB04
Antidepressants	N06A
Antiasthmatics	R03

Note: preconceptional use was defined similar to all other medication classes assessed (i.e. an active treatment episode within 40 weeks before the conception date).

CHAPTER 4

Twenty-year trends in the use of anti-seizure medication among pregnant women in the Netherlands

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ABSTRACT

Background

Anti-seizure medications (ASMs) are used to treat conditions such as epilepsy and bipolar disorder. Some of these drugs are associated with an increased risk of congenital malformations and adverse developmental outcomes.

Objectives

To examine trends in use of ASMs among pregnant women in the Netherlands according to medication safety profile.

Methods

Using population-based data from the PHARMO Perinatal Research Network, we assessed trends in use of ASMs among pregnant women in the Netherlands between 1999 and 2019, stratified by medication safety profile. Individual treatment patterns were also assessed.

Results

In total, 671,709 pregnancies among 446,169 women were selected, of which 2405 (3.6 per 1000) were ASM-exposed. Over the study period, a significant increase was observed for use of known safest ASMs (0.7–18.0 per 10,000 pregnancies) as well as for those with uncertain risk (5.3–13.4 per 10,000 pregnancies). Use of ASMs with higher risk of congenital malformations decreased significantly (24.8–14.5 per 10,000 pregnancies), except for topiramate (0–6.7 per 10,000 pregnancies). Switches between ASM safety risk categories before and during pregnancy were uncommon; women rather discontinued treatment or switched within the same category. There was no clear change for the proportion using polytherapy during pregnancy (12% overall), however a non-significant trend toward inclusion of known safest ASMs was observed over time (1.9–3.6%).

Conclusions

Over the last two decades, there has been an increase in use of known safest ASMs among pregnant women, together with a trend toward newer ASMs with uncertain risk. Only a small proportion of women switched to a safer alternative before or during pregnancy. Altogether, this highlights the need for an expansion of ASM risk knowledge and communication to healthcare providers and women of reproductive age to improve preconception counseling.

HIGHLIGHTS

- Significant trends toward known safest anti-seizure medications (ASMs) observed.
- Use of ASMs with higher risk of congenital malformations significantly decreased.
- Shift toward use of ASMs with uncertain risk highlights need for future research.
- Switches to safer medication alternatives before or during pregnancy seem uncommon.
- Multi-disciplinary, collaborative care for women using ASMs is essential.

INTRODUCTION

Anti-seizure medications (ASMs) are used to treat conditions such as epilepsy and bipolar disorder.[1] Some of these drugs are associated with an increased risk of congenital malformations and adverse developmental outcomes.[2-4] However, with the continued need to manage chronic medical conditions, the majority of women remain on ASMs during pregnancy, at times, more than one drug (i.e. polytherapy).[5] Pharmacotherapeutic management during pregnancy is a subject of concern challenged by many gender-related issues, in which the drug-imposed risks must be weighed against the risks associated with the disorder treated.[3,6]

Various new ASMs have entered the market over the last decades. For some, a lower risk of teratogenicity is demonstrated, whereas for others, safety profiles are yet to be fully determined. This challenges prescribers, as recommendations are often still lacking for newer drugs.[3,7] For the first-generation ASMs, the safety risks have been explored in more detail and resulted in a valproate pregnancy prevention program and a recommendation against polytherapy with ASMs.[7,8] Understanding the trends in the use of higher or uncertain risk agents will provide useful information to advise clinical practice guidelines.

Several international studies have been published assessing ASM exposure among pregnant women over time[9-14] and our study showed that valproic acid use remained common.[14] However, recent long-term population-based data on the full spectrum of ASMs are lacking. The objective of the current study was to examine the trends in use of ASMs among pregnant women in the Netherlands, stratified by medication safety profile. Individual treatment patterns were also assessed, including the extent of changing from one ASM to another and use of polytherapy.

MATERIAL AND METHODS

Data sources

This population-based study was performed using the PHARMO Perinatal Research Network (PPRN), which includes linked records from both the Netherlands Perinatal Registry (Perined) and the PHARMO Database Network (PHARMO).[15] Perined is a nationwide registry that contains validated data from pregnancies with a gestational age (GA) of at least 16 weeks.[16] PHARMO comprises a dynamic cohort of participants and includes, among other information, drug-dispensing records

from community pharmacies for more than three million individuals (approximately 25% of the Dutch population).[17,18] The Out-patient Pharmacy Database (OPD) contains the following information per filled prescription: the Anatomical Therapeutic Chemical (ATC) classification of the drug, dispensing date, dose regimen, prescribing physician, quantity dispensed and estimated duration of use.[19] The OPD represents the Dutch population that has picked up prescription drugs or has registered with a pharmacy. The linkage between PHARMO and Perined has been described in more detail elsewhere but was generally based on the birth date of the mother and child and their addresses and could be established for about 20% of the pregnancies in Perined.[15] For the current database research with anonymous data, no Institutional Review Board or ethics committee approval was required.

Study population

Women who gave birth between 1999 and 2019 were selected from the PPRN. No exclusion criteria were applied to increase the generalisability of the results. To allow for women's medication use to be assessed before and during pregnancy, their details needed to be registered in the OPD from 3 months before the conception date (based on ultrasound or first day of the last menstrual period) until the delivery date as recorded in Perined. Women of all ages and women of reproductive age (15-49 years) registered in the OPD were selected as reference populations, excluding pregnant women as recorded in the PPRN from the latter population.

Maternal and obstetric characteristics

Selected maternal and obstetric characteristics included age at delivery, neighbourhood socioeconomic status (SES)[20,21], year of delivery, ethnicity, parity and GA at birth. These characteristics were assessed for all included pregnancies as well as for those exposed to ASMs during pregnancy.

Exposure

Anti-seizure medications dispensing records, defined by ATC group N03A 'Antiepileptics', were selected from the OPD.[22] ASM use during pregnancy was defined as at least one dispensing from the conception date until the delivery date. ASM use before pregnancy was defined as at least one dispensing in the 3 months before the conception date. In addition to the drug-level analysis, ASMs were grouped according to their safety profile as classified by the Dutch Teratology Information Service Lareb (see Table 1).[7] According to this classification, we categorised ASMs into 3 levels: known safest, uncertain risk, and higher risk of congenital malformations. This information system was selected as it is deemed applicable to clinical practice in the Netherlands and is being used as the main information body in decision making on medication use during pregnancy by clinicians. It focuses mainly on congenital malformations. Recently, knowledge on adverse developmental outcomes is being incorporated in the recommendations.

TABLE 1 Overview of ASM safety profile according to Dutch Teratology Information Service Lareb

Category	Label in current study	ASMs included
Green	Known safest	lamotrigine ('most safe'), levetiracetam ('probably safe')
Orange	Uncertain risk	brivaracetam, felbamate, gabapentin, lacosamide, oxcarbazepine, perampanel, pregabalin, rufinamide, stiripentol, vigabatrin, zonisamide, clonazepam, ethosuximide and all remaining N03A drugs for which no recommendation is available
Red	Higher risk of congenital malformations	valproic acid, phenytoin, carbamazepine, topiramate, primidone, phenobarbital

Source: Dutch Teratology Information Service Lareb[7]

Among women who were exposed to an ASM before or during pregnancy, changes in safety category were assessed as well as timing of these medication changes by trimester (first: up to week 12 of amenorrhea; second: 13–27 weeks; third: 28 weeks to delivery). The highest risk category was assigned in case multiple categories were used in the period of interest. For those using medication with higher risk of congenital malformations before pregnancy, the type of ASM used during pregnancy was assessed.

Patient-level switching was defined as discontinuation of one ASM and initiation of another ASM in the period from two years before pregnancy until the end of pregnancy. This was operationalised as at least one dispensing for the first ASM in the 3 months before the introduction of the second ASM (i.e. switch date), no dispensing for the second ASM in the 3 months before the switch date, and no dispensing for the first ASM in the 3 months after the switch date. The safety profiles of ASMs used during pregnancy were also stratified by prescriber type (general practitioner, neurologist, psychiatrist, other mental health specialist, other specialist or other). Use of monotherapy vs. polytherapy was assessed before and during pregnancy. It was based on the number of distinct ASMs in the 3 months before pregnancy or in a single pregnancy trimester, respectively. Women using more than one ASM anywhere during the period of interest were classified as being on polytherapy. Similarly, women using an ASM with higher risk of congenital malformations anywhere during the period of interest were classified as using either "monotherapy incl. higher risk" or "polytherapy incl. higher risk".

Statistical analysis

Trends over time were analysed for the top 10 most used ASMs per year (1998-2019), separately for women of all ages, women of reproductive age (excluding pregnant women) and pregnant women. Trends were also assessed for the number of exposed pregnancies per 10,000 pregnancies per year of delivery (1999-2019), by safety risk category as well as by ASM (for those with at least 100 women exposed during pregnancy over all years). The class-level switches between ASM safety risk categories are presented in a Sankey diagram, showing the proportion of women moving between categories over the selected trimesters. The top 5 most common patient-level ASM switches were determined for the ASM most often switched from, most often switched to and most often switched between, and presented overall and by timing of switch (before pregnancy/during pregnancy).

For those with a switch prior to pregnancy, the median time to pregnancy was assessed. Trends in ASM monotherapy and polytherapy were presented before and during pregnancy, categorised by year of delivery. All trends over time were tested by Poisson regression at P-value <0.05. Separate categories were created for missing maternal and obstetric characteristics.

Sensitivity analyses

A sensitivity analysis was performed in which dispensings were converted into treatment episodes of uninterrupted use to define ASM exposure. This method was not chosen for the main analysis as it is known to overestimate exposure, because particularly during pregnancy, drugs may be discontinued.[14] Another sensitivity analysis was performed in which use before pregnancy was defined as at least one dispensing in the year before the conception date. To assess the robustness of the definition of monotherapy vs. polytherapy, two sensitivity analyses were performed in which polytherapy was based on 1) overlapping treatment episodes and 2) same day dispensings.

RESULTS

In total, 671,709 pregnancies among 446,169 women were selected from the PPRN of which 2405 (3.6 per 1000) were ASM-exposed, increasing from 3.0 per 1000 in 1999 to 4.2 per 1000 in 2019. Pregnancies were categorized according to the level of risk of the medications used; in 1030 pregnancies (1.5 per 1000) women were exposed to ASMs with higher risk of congenital malformations, 636 (0.9 per 1000) to ASMs with uncertain risk and 723 (1.1 per 1000) to known safest ASMs. Sensitivity analyses based on treatment episodes of uninterrupted use yielded 2849 pregnancies with maternal ASM exposure (4.2 per 1000; 18% higher). Maternal and obstetric characteristics of included pregnancies are summarised in Table 2.

TABLE 2 Maternal and obstetric characteristics of included pregnancies and those exposed to ASMs

Characteristic	All pregnancies N = 671,709 n (%)	ASM-exposed pregnancies N = 2,405 n (%)
Age at delivery (years)		
≤20	9,984 (1)	25 (1)
21-30	291,427 (43)	925 (38)
31-40	354,232 (53)	1,358 (56)
≥41	16,066 (2)	97 (4)
Mean ± SD	31 ± 5	32 ± 5
SES		
Low	232,761 (35)	937 (39)
Normal	208,996 (31)	708 (29)
High	227,507 (34)	751 (31)
Unknown	2,445 (<0.5)	9 (<0.5)
Year of delivery		
1999-2004	104,977 (16)	354 (15)
2005-2009	170,226 (25)	628 (26)

TABLE 2 Maternal and obstetric characteristics of included pregnancies and those exposed to ASMs (continued)

Characteristic	All pregnancies N = 671,709 n (%)	ASM-exposed pregnancies N = 2,405 n (%)
2010-2014	204,186 (30)	683 (28)
2015-2019	192,320 (29)	740 (31)
Ethnicity		
Dutch	527,026 (78)	1,837 (76)
Moroccan/Turkish	46,386 (7)	210 (9)
Other European/Western[a]	24,168 (4)	109 (5)
Other[b]	65,701 (10)	220 (9)
Unknown	8,428 (1)	29 (1)
Parity		
0	295,352 (44)	1,069 (44)
1	242,188 (36)	840 (35)
2	92,755 (14)	330 (14)
≥3	39,451 (6)	160 (7)
Unknown	1,963 (<0.5)	6 (<0.5)
GA at birth (weeks)		
≤24	20,327 (3)	79 (3)
25-<28	2,532 (<0.5)	11 (<0.5)
28-<33	8,904 (1)	31 (1)
33-<37	40,618 (6)	161 (7)
≥37	599,328 (89)	2,123 (88)
Mean ± SD	38.8 ± 3.9	38.6 ± 4.0

SD = standard deviation; SES = neighbourhood socioeconomic status; GA = gestational age; [a] including North American and Canadian; [b] Creole, Hindu, Asia and other.

Figure 1 shows the trends in use of ASMs among all women, women of reproductive age and pregnant women. Notable trends over time for all groups include decreased use of carbamazepine and valproic acid, and increased use of pregabalin, gabapentin, levetiracetam, topiramate and lamotrigine. Lamotrigine shows the highest differences between these three groups with a 24% increase in use over time in pregnant women compared to 3% and 8% in all women and women of reproductive age, respectively. Second highest differences were observed for pregabalin (+36% and +24% in all women and women of reproductive age, respectively, compared to +9% in pregnant women). Third, carbamazepine showed a higher decrease in pregnant women (-37%) compared to all women and women of reproductive age (both -24%). Valproic acid ranked fourth with an approximate 10% higher decrease in pregnant women compared to the other groups, followed by levetiracetam with an approximate 10% higher increase in pregnant women compared to the other groups. Other ASMs not presented in Figure 1 represented a very small proportion over the years, from approximately 0.5% in 1998 to 1.5% in 2019.

The trends in use of ASMs during pregnancy are again presented in Figure 2, stratified by risk category and individually for selected ASMs. A significant decrease over time was observed for

chapter

4

ASMs with higher risk of congenital malformations, whereas use of known safest ASMs as well as ASMs with uncertain risk increased significantly. Of note, a significant increase was observed for topiramate (market entry in 1999), which has a higher risk of congenital malformations. The biggest changes over time were observed for carbamazepine (decreased), followed by levetiracetam (market entry in 2000) and lamotrigine (both increased).
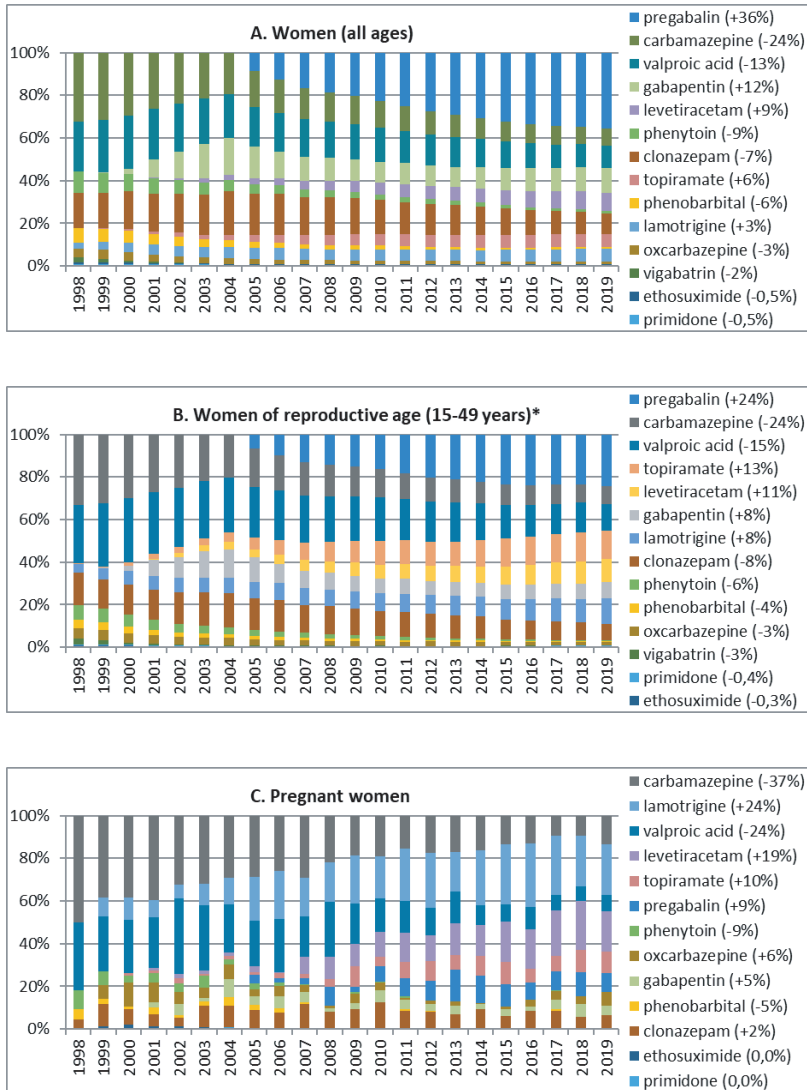
FIGURE 1 Trends in use of ASMs among (A) all women; (B) women of reproductive age and (C) pregnant women

* Excluding pregnant women as included in the PPRN
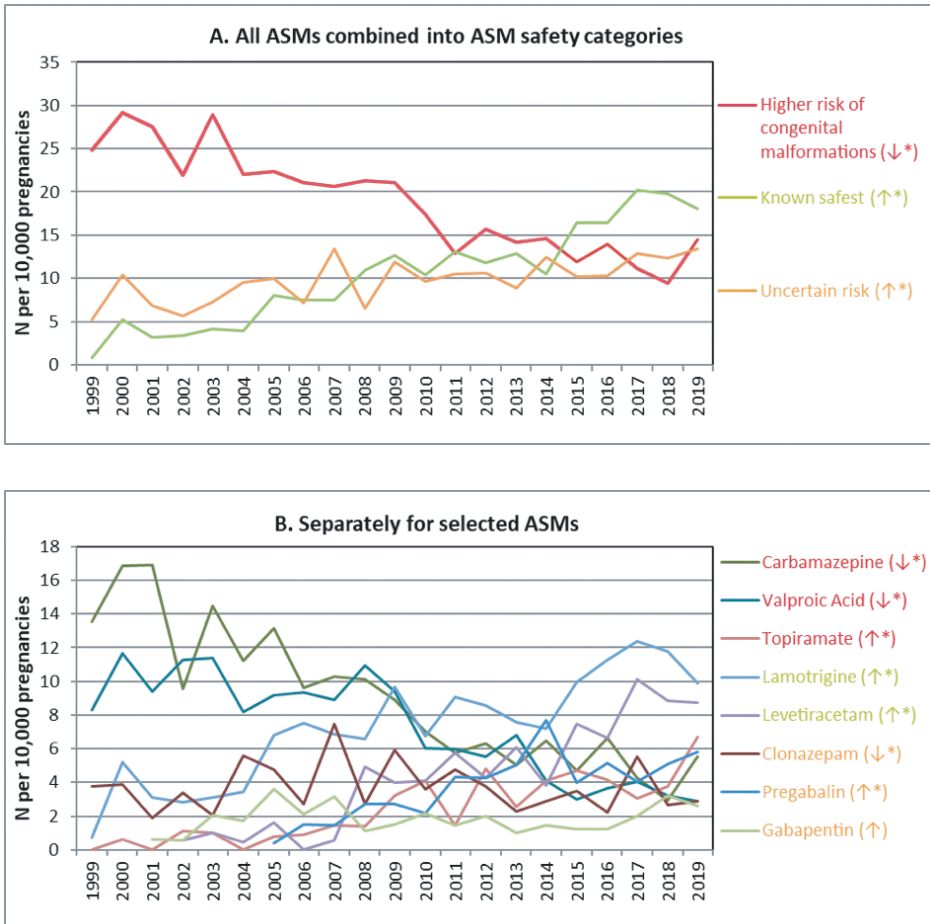
FIGURE 2 Trends in use of ASMs during pregnancy, separately for (A) all ASMs combined into ASM safety risk categories and (B) selected ASMs

↑ Trendline with positive slope; ↓ Trendline with negative slope; * Trend over time was statistically significant at P-value <0.05.

Class-level switches during pregnancy are presented in Figure 3. The proportion of women on known safest ASMs remains relatively stable throughout pregnancy (about 17% before and during all trimesters). A 10-percent decrease was observed for the proportion using ASMs with uncertain risk. Use of ASMs with higher risk of congenital malformations decreased from 35% before pregnancy to 26% in the third trimester. Overall, switching between safety risk categories was uncommon and the changes observed mostly concerned discontinuation of treatment. Of the women using ASMs with higher risk of congenital malformations before pregnancy, the majority continued their therapy during pregnancy (87%) and those remaining either discontinued treatment (5%), switched to other therapy that includes an ASM with higher risk of congenital malformations (3%) or switched to other ASMs (5%), most often being lamotrigine and levetiracetam (data not presented). The sensitivity analysis including the year before pregnancy generally shows the same patterns, only increased

proportions without treatment during pregnancy, which may indicate that treatment discontinuation generally occurs more than 3 months before pregnancy. The sensitivity analysis on treatment episodes of uninterrupted use also shows similar patterns, but with higher exposure rates for ASM with uncertain risk and with higher risk of congenital malformations. This might indicate that the overestimation of exposure due to unfinished medication fills applies more to the higher risk ASM.
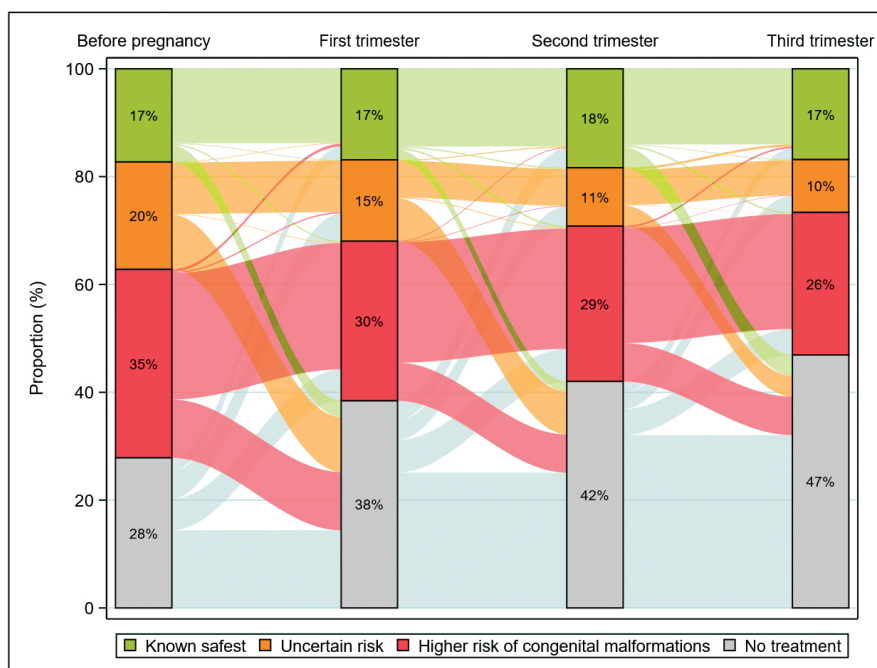
FIGURE 3 Switches between ASM safety risk categories before and during pregnancy

The patient-level switching analysis from two years before pregnancy until the end of pregnancy showed at least one switch in 7% of all ASM users (Supplementary Table S1). Most switches took place before pregnancy (82%), with a median time to pregnancy of 369 days (interquartile range: 186-568 days). Similar to the class-level analysis, this analysis demonstrates that most switches occur within the same safety risk category. Overall, women switched most often from valproic acid (20%) or carbamazepine (16%) and most often to lamotrigine (14%) or levetiracetam (14%).

For all ASMs dispensed during pregnancy, the majority were prescribed by the general practitioner (Supplementary Table S2). This proportion was higher for the ASMs with uncertain risk (65%) and ASMs with higher risk of congenital malformations (61%) compared to known safest ASMs (54%). Similarly, the proportion prescribed by psychiatrists and mental health specialists was higher for ASMs with uncertain risk and ASMs with higher risk of congenital malformations (9% each) compared to known safest ASMs (3%). The proportion of neurologists prescribing known safest ASMs (22%) was

higher than for ASMs with uncertain risk (9%) and ASMs with higher risk of congenital malformations (17%).

Overall, 12% of the pregnancies exposed to ASMs included polytherapy and no significant trend over time was observed for the distribution between monotherapy and polytherapy (Figure 4). A significant trend was observed for the proportion of monotherapy including ASMs with higher risk of congenital malformations (decreased over time) vs. monotherapy excluding ASMs with higher risk of congenital malformations (increased over time). Although non-significant, Figure 4 shows an increasing proportion of polytherapy excluding ASMs with higher risk of congenital malformations compared to polytherapy including ASMs with higher risk of congenital malformations over time. Comparing before vs. during pregnancy, no clear pattern exists for the distribution between monotherapy and polytherapy.
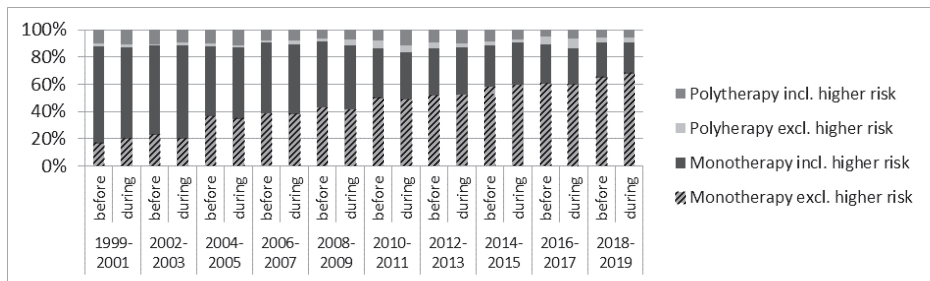
FIGURE 4 Trends in ASM monotherapy and polytherapy before and during pregnancy

The most common polytherapy was a combination of lamotrigine and levetiracetam, followed by lamotrigine and carbamazepine and then by lamotrigine and valproic acid. Numbers did not allow assessment of trends over time, however when comparing pregnancies from 1999-2009 with those from 2010-2019 there seems a clear decrease in polytherapy including carbamazepine toward the inclusion of levetiracetam. Similar conclusions can be drawn from the sensitivity analyses (data not presented).

DISCUSSION

Over the last two decades, a significant increase was observed for use of ASMs with uncertain risk from 5.3 to 13.3 per 10,000 pregnant women. A significant increase was also observed for known safest ASMs, from 0.8 to 18.0 per 10,000 pregnant women. Use of ASMs with higher risk of congenital malformations decreased significantly from 24.8 to 14.5 per 10,000 pregnant women. The decrease in use of carbamazepine and valproic acid was more pronounced in pregnant women compared to all women and women of reproductive age. In pregnant women, lamotrigine use increased over time to a greater degree than all women and women of reproductive age. Pregabalin, which has uncertain risk, showed increased use over time, moreso for all woman and women of

reproductive age, compared to pregnant women. There was an increase in use of topiramate over time from 0 to 6.7 per 10,000 pregnant women, which has known higher risk of congenital malformations. Switches between ASM safety risk categories before and during pregnancy were not very common; women rather discontinued treatment or switched within the same category. Results indicate that treatment switches more often occurred longer than 3 months before pregnancy. Before and during pregnancy taken together, women switched most often from valproic acid or carbamazepine and most often to lamotrigine or levetiracetam. About one in ten women used ASM polytherapy rather than monotherapy during pregnancy without a clear change over time, however a non-significant trend toward known safest ASMs was observed.

The current findings are in line with those in previous studies on use of ASMs in pregnancy. Our estimate of overall ASM exposure during pregnancy was somewhat lower than observed in a study published in 2015 (3.6 vs. 4.3 per 1000) in which a broader ASM definition was applied.[11] General trends observed were also very similar to previous multinational studies: increases in the known safest ASMs lamotrigine and levetiracetam[11,13,23,24] as well as in ASMs with uncertain risk, often referred to as the "second-generation" drugs.[9,10,13] Similar declining trends were observed for the higher risk medications, valproic acid and carbamazepine[9,11,24,25], with the exception of the newer topiramate.[1,11,13] In addition to other studies, we compared these trends with female reference populations. Few studies have been published on medication changes around pregnancy, however a multinational study concluded that patients switched mostly from valproate or topiramate.[13] We observed a higher tendency to switch from carbamazepine than from topiramate, potentially because overall use of topiramate was lower in our study. A previous study in women of childbearing age with epilepsy demonstrated that medication changes should be initiated early prior to conception.[26] This is in line with our observation that most medication changes were made prior to pregnancy. The high rates of ASM discontinuation observed during pregnancy were comparable to those observed in other countries.[13,25] Our study provides additional evidence on ASM switching patterns in relation to their safety profile. The proportion of women on polytherapy during pregnancy was the same as demonstrated in a recent multinational study.[13] A clear trend in polytherapy was also lacking in other studies.[23,24,27,28] Similar to our study, there has been a reported decrease in polytherapy including ASMs with higher risk of congenital malformations, with a larger proportion of polytherapy regimens including lamotrigine and levetiracetam.[12,13,24] These findings are in line with recent beliefs that some polytherapy combinations may not have an elevated risk of malformations.[29,30]

A common medication management issue is choosing ASM with lower teratogenic potential in women of reproductive age.[30] Our data show that non-pregnant women of reproductive age are more likely to use medications with higher risk of congenital malformation, compared to pregnant women. Also, we demonstrated that there is a small proportion of women who switch to a preferred agent before or during pregnancy. These findings highlight the need for more preconception counseling to encourage timely and safe treatment adjustments before pregnancy, as many pregnancies are unplanned.[31] Use of ASMs with uncertain risk increased over time, possibly reflecting a shift from drugs with known teratogenicity to those with unknown risk profiles. Treating physicians rely on available evidence when balancing drugs' risks and benefits.[32] Therefore, there is a need for an expansion of research on

ASM teratogenicity for these agents. Switches from valproate to topiramate or carbamazepine were relatively common, despite these all having known higher risk of congenital malformations. This might be explained by the awareness that has been specifically raised for valproate over the last decades, for instance by means of a pregnancy prevention program. The switch to topiramate may be in part due to shared indications for seizures as well as migraines. A switch to carbamazepine may relate to a more favorable profile of cognitive and behavioral outcomes, compared with valproate.[33,34] Switching to lamotrigine can be limited by the required slow titration due to risk of Stevens-Johnson Syndrome[35], and switching to levetiracetam can be limited by mood side effects.[36] Outcome research can guide targeted preventive interventions and education programs, and specific recommendations can be made for each ASM.[14,37] There seems to be more need to educate certain groups such as GPs who prescribed the majority of ASMs. Altogether, this asks for a collaborative, multidisciplinary approach with key roles for neurologists, obstetricians, primary care doctors, clinical pharmacists and nurses in ASM management.[30]

Strengths of this study included the use of over 20 years of data from a unique and large population-based cohort, which was shown to be representative of the Dutch population.[15] The timing of drug exposure relative to pregnancy staging could be accurately assessed based on last menstrual period, ultrasound, exact delivery date, drug dispensing dates and intended duration of use, allowing patient-level analyses of treatment patterns on the full spectrum of ASMs. A common challenge in using administrative data is defining drug exposure or compliance. Treatment episodes of uninterrupted use were not applied in the current study as it is known to overestimate exposure, particularly during pregnancy.[14] Underestimated drug exposure is therefore likely, also because hospital-administered drugs were not captured. Another limitation was the use of a risk classification system for ASMs in pregnancy that did not take into account individualized care, in which weighed treatment decisions are made. The reasons for staying on treatment were unknown, however for conditions like epilepsy and bipolar disorder treatment adjustments often may not be the safest choice.[38,39] Data on indication were not available in the databases used for this study, which may have demonstrated different patterns per condition treated. However, this study was intended predominantly to characterize medication use according to its safety profile, regardless of the indication. This may have limited the generalizability to the population with epilepsy alone. We recognize that safety profiles have evolved and been revised over time. For example, although the Dutch Teratology Information Service Lareb classifies oxcarbazepine as having uncertain risk, recent international data show oxcarbazepine having low risk for congenital malformations, similar to levetiracetam and lamotrigine.[40] However, we specifically designed our study to use insights linked to current daily practice in the Netherlands (i.e. the Dutch Teratology Information Service Lareb). Although ASM dose adjustments are captured in the PPRN, this was beyond the scope of this paper. The same applies to reporting on similar trends in male patients or on pregnancy outcomes, which would be interesting to study in follow-up research.

chapter

4

CONCLUSIONS

In conclusion, this study shows an increase in use of known safest ASMs and a decrease for most of the ASMs with higher risk of congenital malformations among pregnant women over the last two decades. However, there also seems to be a trend toward prescribing newer ASMs with uncertain risk. Only a small proportion of women switched to a safer alternative before or during pregnancy. Altogether, this highlights the need for an expansion of ASM risk knowledge and communication to healthcare providers and women of reproductive age and thus improvement of preconception counseling. The observed trends were very similar to those observed in other countries and suggest a collective responsibility at an international level. Future efforts could strive to collaborate or standardize pregnancy registries to maximize data collection and the power of subsequent analyses. Considering the many facets of ASM management and the consequences of untreated underlying conditions, a collaborative, multidisciplinary approach is required for timely, safe and well-weighed treatment decisions.

FUNDING

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENTS

For the current database research with anonymous data, no Institutional Review Board or ethics committee approval was required.

DATA AVAILABILITY

Data are available upon reasonable request. Requests for sharing study data must be made on specific grounds, either (1) with the aim of corroborating the study results in the interest of public health or (2) in the context of an audit by a competent authority. Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a sound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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chapter

4

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chapter

4

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 Top 5 most common ASM switches in the period from two years before pregnancy until the end of pregnancy, overall and by timing of switch

Overall (N$_{switches}$ = 371)		
ASM most often switched from	**ASM most often switched to**	**ASM most often switched between**
#1 Valproic acid (20%)	Lamotrigine (14%)	Pregabalin to Gabapentin (7%)
#2 Carbamazepine (16%)	Levetiracetam (14%)	Valproic acid to Topiramate (6%)
#3 Levetiracetam (13%)	Valproic acid (12%)	Levetiracetam to Lamotrigine (6%)
#4 Lamotrigine (12%)	Carbamazepine (12%)	Valproic acid to Carbamazepine (4%)
#5 Pregabalin (11%)	Gabapentin (11%)	Gabapentin to Pregabalin (4%)

Before pregnancy (N$_{switches}$ = 303)		
ASM most often switched from	**ASM most often switched to**	**ASM most often switched between**
#1 Valproic acid (21%)	Lamotrigine (14%)	Valproic acid to Topiramate (8%)
#2 Carbamazepine (17%)	Pregabalin (13%)	Pregabalin to Gabapentin (7%)
#3 Levetiracetam (13%)	Valproic acid (13%)	Levetiracetam to Lamotrigine (6%)
#4 Pregabalin (11%)	Levetiracetam (12%)	Gabapentin to Pregabalin (5%)
#5 Lamotrigine (10%)	Topiramate (12%)	Topiramate to Valproic acid (5%)

During pregnancy (N$_{switches}$ = 68)		
ASM most often switched from	**ASM most often switched to**	**ASM most often switched between**
#1 Lamotrigine (19%)	Carbamazepine (25%)	Pregabalin to Gabapentin (9%)
#2 Valproic acid (14%)	Levetiracetam (22%)	Lamotrigine to Levetiracetam (7%)
#3 Clonazepam (13%)	Lamotrigine (15%)	Valproic acid to Carbamazepine (7%)
#4 Levetiracetam (13%)	Gabapentin (12%)	Levetiracetam to Lamotrigine (6%)
#5 Pregabalin (13%)	Valproic acid (10%)	Lamotrigineto Carbamazepine (4%)

SUPPLEMENTARY TABLE 2 Prescribers of ASMs used during pregnancy, by ASM safety risk categories

ASM of preferred choice	Ill-defined pregnancy risks	Risk of congenital malformations
General practitioner (54%)	General practitioner (65%)	General practitioner (61%)
Neurologist (22%)	Neurologist (9%)	Neurologist (17%)
Other specialist (17%)	Other specialist (15%)	Other specialist (10%)
Unknown (4%)	Unknown (2%)	Unknown (3%)
Psychiatrist (3%)	Psychiatrist (7%)	Psychiatrist (7%)
Other (<0.5%)	Other (1%)	Other (1%)
Other mental health specialist (<0.5%)	Other mental health specialist (2%)	Other mental health specialist (2%)

CHAPTER 5

General practitioners' awareness of pregnancy: trends and association with hazardous medication use

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ABSTRACT

Background
GPs have been shown to be important providers of medical care during pregnancy, however little evidence exists on their awareness of pregnancy when prescribing medication to women.

Aim
To assess GPs' awareness of pregnancy and its association with prescribing medication with potential safety risks.

Design and Setting
Population-based study using confirmed pregnancy records linked to GP records from the PHARMO Perinatal Research Network.

Method
GPs' awareness of pregnancy, defined as the presence of a pregnancy confirmation in the GP information system during pregnancy, was assessed from 2004 to 2020. GP prescriptions of medication with potential safety risks were selected during pregnancy and its association with GPs' awareness of pregnancy was assessed using multivariable logistic regression.

Results
A pregnancy confirmation was present in the GP records for 48% (n = 67 496/140 976) of selected pregnancies, increasing from 28% (n = 34/121) in 2004 to 63% in 2020 (n = 5763/9124). During 3% (n = 4489/140 976) of all pregnancies, the GP prescribed highly hazardous medication with teratogenic effects that should have been (temporarily) avoided. Pregnancy was GP confirmed for only 13% (n = 585/4489) at the first occurrence of such a prescription. Comparative analyses showed that women without a pregnancy confirmation were 59% more likely to be prescribed this highly hazardous medication (OR 95%CI: 1.59 1.49-1.70) compared to those with.

Conclusion
Results of this study indicate a potential GP awareness issue at the time medication with potential safety risks is prescribed. Although pregnancy registration by GPs improved over the years, still inadequate use seems to be made of the available information systems for appropriate drug surveillance.

HOW THIS FITS IN

The role of Dutch general practitioners (GPs) in pregnancy care has been an item for debate for some time. GPs have been shown to be important providers of medical care during pregnancy, however little evidence exists on GPs' awareness of pregnancy when prescribing medication to women. This study indicates a potential issue with GP awareness of pregnancy status at the time medication with potential safety risks is prescribed, placing women and their babies at avoidable risk of exposure to teratogens. Although pregnancy registration by GPs improved over the years, still inadequate use seems to be made of the available information systems for appropriate drug surveillance.

INTRODUCTION

The role of general practitioners (GPs) in pregnancy care has been an item for debate for some time in Europe.[1] Although GPs act as gatekeeper to hospital- and specialist care in the Netherlands, midwives have the lead in providing pregnancy care. In case of medical or obstetric pathology, responsibility is taken over by the obstetrician.[2] Currently, only 2-6% of all GPs still provide obstetric care.[3] Despite their declined involvement[1,4], GPs have been shown to be important providers of routine medical care for pregnant women.[3] For example, they are still responsible for the large majority of drug prescriptions during pregnancy, including medication with potential safety risks in one-third of Dutch pregnancies.[5,6] A substantial part of repeat prescribing by GPs occurs without any direct patient contact, thus without assessing pregnancy status or intention.[7,8] This underscores the GPs' vital role in optimisation of pregnancy care.[9] Collaboration between GPs and midwives has been widely encouraged and GPs acknowledge their role in shared perinatal care.[10-14]

In practice the involvement of GPs in this collaborative preconception and antenatal care needs further reinforcement, for instance by their greater involvement in preconception care.[3,11,12,15] Guidelines state that midwives should inform the GP about pregnancy[16], however no automatic link exists between the information system of the midwife and de GP. There is little evidence on actual clinical practice in forwarding, recording and using this information.

This study aimed to fill this evidence gap, to allow for more directed future interventions targeted at preventing use of potentially harmful medication during pregnancy. Therefore, the objectives were to assess GPs' awareness of pregnancy, the way it is registered in GP records as well as the trends over time. Furthermore, the association between GPs' awareness and prescribing medication with potential safety risks was assessed.

chapter

5

METHODS

Data source

This population-based study was performed using the PHARMO Perinatal Research Network (PPRN), including linked records from the Netherlands Perinatal Registry (Perined) and the PHARMO Database Network (PHARMO).[17] Perined is a nationwide registry that contains validated data from pregnancies with a gestational age of at least 16 weeks.[18] PHARMO is a population-based, patient-level network of healthcare databases linking data from different health-care settings of approximately 25% of the Dutch population.[19-21] For the current study two PHARMO databases linked to Perined were selected: the GP Database, comprising data from electronic patient records registered by GPs, and the Out-patient Pharmacy Database, containing detailed drug information from both GP- and specialist-prescribed dispensings. Mandatory health insurance and required registration with a GP makes the GP Database representative of the general Dutch population.[22,23] The Out-patient Pharmacy Database represents the Dutch population that has picked up prescription drugs or has registered with a pharmacy and has been shown to be representative of the general Dutch population in terms of age and gender. The linkage between PHARMO and Perined has been described in more detail elsewhere (including arrangements for data oversight), but was generally based on the birth date of the mother and child and their addresses.[17] For the current database research with anonymous data, no ethics committee approval was required.

Study population

Women who gave birth between 2004 and 2020 were selected from the PPRN. No exclusion criteria were applied to increase the generalisability of the results. Women's medical details needed to be registered in the selected PHARMO databases from one year before the conception date (based on ultrasound or first day of the last menstrual period) until the delivery date as recorded in Perined.

Characteristics

Characteristics included age at delivery, neighbourhood socioeconomic status (SES)[24,25], year of delivery, ethnicity, preconceptional use of medication for chronic conditions (see Supplementary Table 1 for included medication), parity, gestational age, care setting at the start of pregnancy and birth weight. Furthermore, women's healthcare utilisation in primary care was assessed in the year before conception as well as during pregnancy, defined by the number of GP visits, GP prescriptions and incoming specialist letters. The type of electronic GP information system used for keeping the maternal medical file was also assessed, as multiple different systems are available for use in GP practices with varying options for registration of patient records in different reference tables.

GPs' awareness

The concept of GPs' awareness of pregnancy was quantified by using all available information from the women's electronic patient records, considering that this is the information caregivers rely on in daily practice. It was defined at multiple levels of pregnancy indicators recorded in the GP information system: 1) <u>Pregnancy confirmation</u>: the presence of a specific coded diagnosis on confirmed pregnancy; 2) <u>Pregnancy indicator</u>: the presence of any record indicating that the women

is pregnant in all digitally available GP records (for example an uncoded text note about pregnancy as recorded by the GPs assistant after a telephone consultation) ; 3) <u>Pregnancy contra-indication</u>: the presence of a recorded pregnancy contra-indication in this specific GP reference table that need to be linked actively and is intended for drug surveillance (i.e. without this additional data entry no popup will appear warning about contra-indicated medication, even when there is an entry for pregnancy as a diagnostic code). The timing of pregnancy confirmation was grouped by pregnancy trimester according to the first recorded occurrence. The occurrence of GPs providing formal individual preconception care was assessed by means of a recorded preconceptional GP consultation specifically set up and coded for preconception counselling. Exact underlying definitions and GP reference tables of the defined indicators are detailed in Supplementary Table 2.

Use of hazardous medication

Use of medication with potential safety risks was determined by means of GP prescriptions recorded or continuing during the pregnancy period. Medication was grouped according to the risk classification system for drugs in pregnancy of the Dutch Teratology Information Service Lareb[26]. These safety profiles were used to define 'hazardous medication' (i.e. medication with pharmacological or teratogenic effects that requires monitoring or should be (temporarily) avoided) as well as 'highly hazardous medication' (i.e. medication with teratogenic effects that should be (temporarily) avoided). Prescriptions with a recorded pregnancy-driven indication were excluded (e.g. progesterone used to try to reduce the risk of preterm birth). Availability of a pregnancy confirmation or pregnancy indicator was assessed at the time (highly) hazardous mediation was first prescribed. For those women with a pregnancy confirmation, the proportion that used (highly) hazardous medication before and after confirmation was assessed. Sensitivity analyses were performed in which use of (highly) hazardous medication was defined by medication fills as recorded in the Out-patient Pharmacy Database, which includes both GP- and specialist-prescribed dispensings. Also, we performed separate analyses per categorised year of delivery (2004-2009, 2010-2014, 2015-2020).

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to estimate unadjusted associations between characteristics and pregnancy confirmation. Trends over time for defined GP-recorded pregnancy indicators were tested by Poisson regression ($P < 0.05$). The association between GP-recorded pregnancy indicators and use of hazardous medication was assessed by means of logistic regression analyses, providing ORs and 95% CIs adjusted for age, GP information system and all other characteristics that remained significant using backward selection ($P < 0.05$). Similarly, adjusted logistical models were created to assess the association between pregnancy confirmation and the drug-level use of highly hazardous medication.

chapter 5

RESULTS

Study population and characteristics

A total of 140 976 pregnancies among 96 182 women were selected from the PPRN between 2004 and 2020. During 48% of these pregnancies a pregnancy confirmation was identified in the GP records, indicating GPs' (potential) awareness of pregnancy. Characteristics of included pregnancies are summarised in Table 1 and stratified by pregnancy confirmation. Particularly SES, year of delivery, ethnicity, preconceptional use of medication for chronic conditions, gestational age and women's healthcare utilisation in primary care were associated with GP's being aware of pregnancy. A total of seven different electronic systems were used in the included GP practices. The type of GP information system showed to be significantly associated with GPs' awareness (data not presented).

TABLE 1 Maternal and obstetric characteristics of included pregnancies, stratified by presence of a GP-recorded pregnancy confirmation

Characteristic	Study cohort	GP-recorded pregnancy confirmation	No GP-recorded pregnancy confirmation	OR (95% CI) With vs. without GP-recorded pregnancy confirmation
	N = 140 976	N = 67 496 (48%)	N = 73 480 (52%)	
	n (%)	n (%)	n (%)	
Age at delivery (years)				
≤20	1532 (1)	526 (1)	1006 (1)	0.57 (0.51-0.64)
21-30	59 350 (42)	28 343 (42)	31 007 (42)	1 (reference)
31-40	76 629 (54)	37 043 (55)	39 586 (54)	1.02 (1.00-1.05)
≥41	3465 (2)	1584 (2)	1881 (3)	0.92 (0.86-0.99)
Mean ± SD	31 ± 5	31 ± 4	31 ± 5	1.03 (1.02-1.04)
SES				
Low	38 618 (27)	17 183 (25)	21 435 (29)	0.78 (0.76-0.80)
Normal	52 758 (37)	26 734 (40)	26 024 (35)	1 (reference)
High	49 210 (35)	23 449 (35)	25 761 (35)	0.89 (0.86-0.91)
Unknown	390 (<0.5)	130 (<0.5)	260 (<0.5)	-
Year of delivery				
2004-2009	19 005 (13)	6606 (10)	12 399 (17)	1 (reference)
2010-2015	63 351 (45)	27 558 (41)	35 793 (49)	1.45 (1.40-1.49)
2016-2020	58 620 (42)	33 332 (49)	25 288 (34)	2.47 (2.39-2.56)
Ethnicity				
Caucasian	122 630 (87)	59 233 (88)	63 397 (86)	1 (reference)
Non-caucasian	16 733 (12)	7534 (11)	9199 (13)	0.88 (0.85-0.91)
Unknown	1613 (1)	729 (1)	884 (1)	-
Preconceptional use of medication for chronic conditions[a]	46 825 (33)	23 816 (35)	23 009 (31)	1.20 (1.17-1.22)

TABLE 1 Maternal and obstetric characteristics of included pregnancies, stratified by presence of a GP-recorded pregnancy confirmation (continued)

Characteristic	Study cohort	GP-recorded pregnancy confirmation	No GP-recorded pregnancy confirmation	OR (95% CI) With vs. without GP-recorded pregnancy confirmation
	N = 140 976	N = 67 496 (48%)	N = 73 480 (52%)	
	n (%)	n (%)	n (%)	
Parity				
0	58 771 (42)	28 333 (42)	30 438 (41)	1 (reference)
1	54 431 (39)	25 850 (38)	28 581 (39)	0.97 (0.95-0.99)
2	19 543 (14)	9368 (14)	10 175 (14)	0.99 (0.96-1.02)
≥3	7731 (5)	3736 (6)	3995 (5)	1.00 (0.96-1.05)
Unknown	500 (<0.5)	209 (<0.5)	291 (<0.5)	-
Gestational age (weeks)				
≤24	10 064 (7)	2854 (4)	7210 (10)	0.40 (0.39-0.42)
25-<28	352 (<0.5)	172 (<0.5)	180 (<0.5)	0.97 (0.79-1.20)
28-<33	1480 (1)	693 (1)	787 (1)	0.90 (0.81-0.99)
33-<37	7765 (6)	3689 (5)	4076 (6)	0.92 (0.88-0.97)
≥37	121 315 (86)	60 088 (89)	61 227 (83)	1 (reference)
Mean ± SD	38.0 ± 5.3	38.5 ± 4.3	37.5 ± 6.0	1.22 (1.21-1.23)[b]
Care setting at start pregnancy				
Primary care	120 592 (86)	57 685 (85)	62 907 (86)	1 (reference)
Secondary care	20 109 (14)	9694 (14)	10 415 (14)	1.02 (0.99-1.05)
Unknown	275 (<0.5)	117 (<0.5)	158 (<0.5)	-
Birth weight (grams)				
Mean ± SD	3384 ± 653	3392 ± 641	3377 ± 665	1.02 (1.01-1.03)[c]
Healthcare utilisation in primary care				
Year before conception (mean ± SD)				
Number of GP visits	1.2 ± 2.4	1.4 ± 2.5	1.0 ± 2.2	1.09 (1.08-1.09)
Number of GP prescriptions	3.9 ± 4.7	4.2 ± 4.8	3.7 ± 4.7	1.02 (1.02-1.02)
Number of incoming specialist letters	1.7 ± 2.2	1.8 ± 2.3	1.5 ± 2.1	1.07 (1.07-1.08)
During pregnancy (mean ± SD)				
Number of GP visits	1.0 ± 1.9	1.3 ± 2.1	0.8 ± 1.7	1.17 (1.16-1.18)
Number of GP prescriptions	2.8 ± 3.7	3.1 ± 3.7	2.5 ± 3.6	1.05 (1.04-1.05)
Number of incoming specialist letters	1.8 ± 2.1	2.3 ± 2.2	1.4 ± 1.9	1.23 (1.23-1.24)

CI = confidence interval; OR = odds ratio; SD = standard deviation; SES = neighbourhood socioeconomic status; [a]Based on both GP- and specialist-prescribed medication dispensed in the out-patient pharmacy in the year before conception (see Supplementary Table 1 for included medication); [b]OR for 5 weeks change; [c]OR for 500 grams change.

chapter **5**

GPs' awareness

Figure 1 presents the GP-recorded pregnancy indicators reflecting GPs' awareness of pregnancy over time. A strong increase was observed for the proportion of pregnancies with confirmation from 28% in 2004 to 63% in 2020 (48% overall). In total, 78% (n = 52 640/67 496) of these pregnancy confirmations happened first during the first trimester, then 17% (n = 11 426/67 496) during the second, and the remaining 5% (n = 3430/67 496) in the third trimester. Using all available GP records (that is, coded as well as based on search terms occurring in free text) as a pregnancy indicator, this proportion was 70% (n = 99 289/140 976) and increased from 50% (n = 61/121) in 2004 to 77% (n = 7025/9124) in 2020. Even though recording pregnancy as a contraindication clearly increased during the second half of the study period, such a registration was observed for only 13% (n = 17 643/140 976) of pregnancies. Overall, only 1% (n = 1626/140 976) of pregnancies were preceded by a GP consultation specifically set up and coded for preconception counselling.
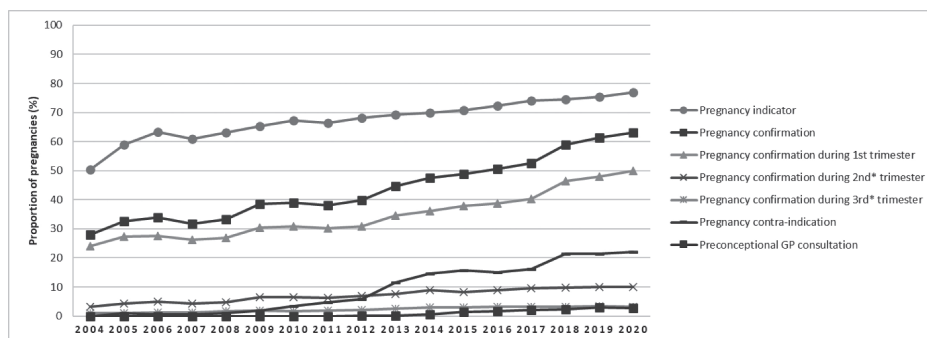
FIGURE 1 Selected GP-recorded pregnancy indicators reflecting GPs' awareness of pregnancy over time

*First recorded, i.e. without recorded pregnancy confirmation in the prior trimester(s); All trends over time were statistically significant at P-value < 0.0001.

Use of hazardous medication

During 22% (31 523 out of 140 976) of included pregnancies GPs prescribed hazardous medication. At the point in which such hazardous medication was prescribed for the first time, pregnancy was confirmed in the GP records for only 29% (n = 9265/31 523). Any indicator was recorded for less than half of the women prescribed hazardous medication (n = 14 212/31 523, 45%). For highly hazardous medication, which was prescribed in 3% (n = 4489/140 976) of pregnancies, these proportions were even lower: pregnancy was confirmed for only 13% (n = 585/4489) and any indicator was available for 26% (n = 1171/4489). Comparing GP prescriptions of highly hazardous medication during pregnancy before and after pregnancy confirmation, only 11% (n = 127/1160) of women with such a prescription before confirmation also had such a prescription after confirmation (data not shown).

GPs' awareness and hazardous medication

Figure 2 shows the likelihood of (highly) hazardous medication being prescribed during pregnancy by the defined pregnancy indicators. Women without a pregnancy confirmation were 25% more likely to be prescribed hazardous medication during pregnancy compared to those with confirmation, with an adjusted OR of 1.25 (95% CI 1.21-1.29). No significant association between pregnancy confirmation and prescribed hazardous medication was found if confirmation occurred for the first time during the second (OR 95%CI: 1.01 0.96-1.07) or third (OR 95%CI: 1.04 0.94-1.14) trimester. For highly hazardous medication, the absence of a pregnancy confirmation was associated with a 59% higher odds of prescribing highly hazardous medication (OR 95%CI: 1.59 1.49-1.70). The absence of a recorded contra-indication for pregnancy significantly increased the prescription of hazardous medication (OR 95%CI: 1.12 1.07-1.18), particularly for highly hazardous medication including drugs actually contra-indicated during pregnancy (OR 95%CI: 1.41 1.26-1.59).
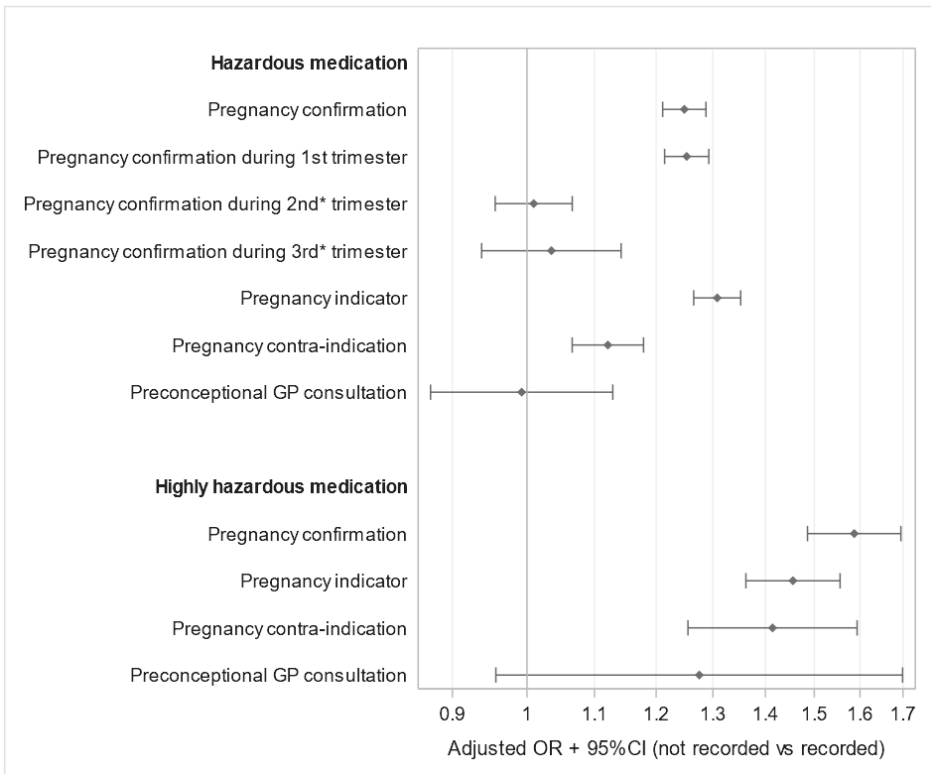
FIGURE 2 Likelihood of (highly) hazardous medication being prescribed during pregnancy by selected GP-recorded pregnancy indicators reflecting GPs' awareness

*First recorded, i.e. without recorded pregnancy confirmation in the prior trimester(s)

Taking a closer look at the type of medication, Figure 3 presents the highly hazardous medication that was significantly more often prescribed by GPs unaware of pregnancy compared to those aware. Absolute numbers per drug were generally below 10 per 10 000 pregnancies, however the top 3 relative differences were: isotretinoin (used to treat severe acne) which was prescribed about 30 times more often by GPs not aware of pregnancy, followed by methotrexate (used to treat inflammatory conditions and certain types of cancer) and mycophenolic acid (used to treat autoimmune conditions and to prevent organ rejection after transplant). In terms of absolute prescription rates, the top 3 consisted of doxycycline (used for bacterial infections such as acne), followed by misoprostol (used to prevent stomach ulcers, but also to induce abortion) and norethisterone (used for various menstrual problems).

Sensitivity analyses using medication dispensed in the pharmacy and by categorised year of delivery provided similar results for the analyses on GPs' awareness and hazardous medication (Supplementary Figure 1 and 2).
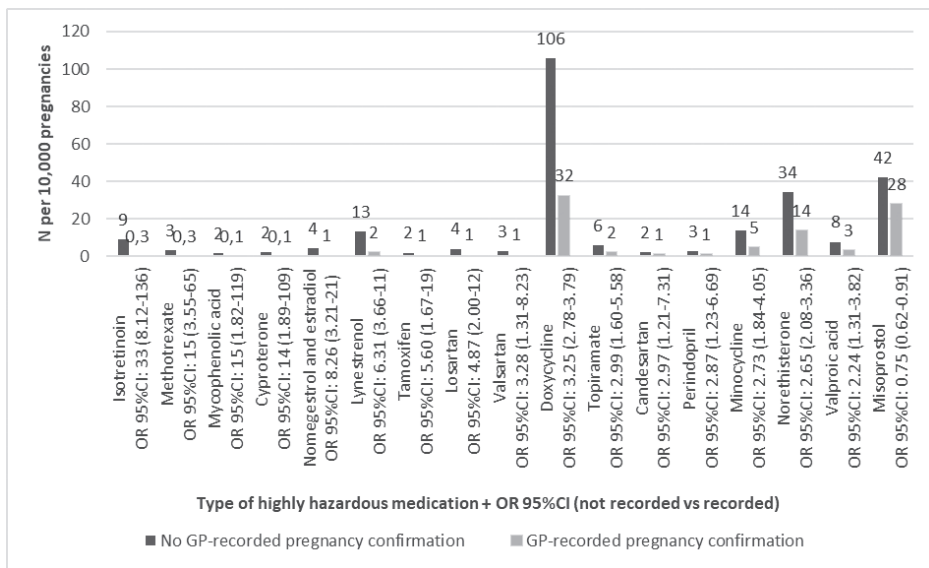
FIGURE 3 GP prescriptions of highly hazardous medication during pregnancy, stratified by presence of a GP-recorded pregnancy confirmation

DISCUSSION

Summary

Among 140 976 selected pregnancies, for only 48% a pregnancy confirmation was recorded in the GP records, indicating GPs' (potential) awareness of pregnancy. A statistically significant increase was observed from 28% in 2004 to 63% in 2020. The large majority (80%) of these confirmations happened during the first trimester. In about 3% of all included pregnancies, the GP prescribed highly hazardous medication with teratogenic effects that should have (temporarily) been avoided, with pregnancy being GP-confirmed for only 13% at the first occurrence of such a prescription. In 11% of patients with a highly hazardous prescription before pregnancy confirmation this prescriptions was repeated after confirmation. Comparative analyses showed that women without a GP-recorded pregnancy confirmation were 59% more likely to be prescribed this highly hazardous medication. Even though this study demonstrated that the absence of a recorded pregnancy contraindication in the GP system for automatic drug surveillance significantly increased the odds by 41% of prescribing highly hazardous medication, such an active link was created in only 13% of pregnancies (increasing from 0% to 22% during the study period). When using all available coded and uncoded electronic records from the GP information system, a pregnancy indicator was available for 70% of pregnancies. Still, in 2020, 23% of the pregnancies were not registered in the GP information system. Only 1% had a GP consultation specifically set up for preconception counselling recorded in the 12 months preceding pregnancy.

Strengths and limitations

A major strength of this study was the use of over 15 years of routinely collected data from a unique and large population-based linked cohort, shown to be representative of the Dutch population.[17] The timing of registered records relative to pregnancy could be accurately assessed based on information from the different databases. This study thereby provides a unique, contemporary perspective on GP involvement in pregnancy in real-world clinical practice. There are, however, several limitations. The qualitative concept of GPs' awareness was quantified by using available electronic patient records from the women's medical file, however, this should be regarded as 'potential' awareness. GPs may have been aware of pregnancy, but did not record this due to a variety of reasons (e.g. time constraints, deemed redundant, system difficulties or because no letter was even received from the midwife). It has been acknowledged, however, that GPs rely on the information registered in their systems for providing accurate patient care, for example in case of transfers to other caregivers.[27,28] A common challenge in using administrative data is defining drug exposure or compliance. Prescription records can only approximate actual exposure and, particularly during pregnancy, prescriptions may not be filled or drugs may be discontinued. Although use of hazardous medication could therefore have been overestimated, it is not expected to have altered the conclusions in relation to GPs' awareness, since sensitivity analyses using medication that was dispensed in the pharmacy provided similar results. Underestimated drug exposure is likely because specialist-prescribed and over-the-counter drugs were not included, however the intended focus of the current paper was on GPs' prescription practices. Confounding by indication could not be ruled out in the definition of hazardous medication. Although we specifically excluded pregnancy-driven prescriptions where

possible, some of the hazardous medication may still have been prescribed because of pregnancy. For example, as observed in the drug-level assessment, misoprostol may have been prescribed to induce abortion. However, since prescribing for these reasons would normally occur in secondary care, they are assumed to be prescribed for other indications in most of the cases. Unfortunately, data on the indication of use was only available for a small proportion of prescriptions. Absolute rates presented as part of the drug-level assessment should therefore be interpreted with caution and conclusions can be drawn from relative comparisons by GPs' awareness status.

Comparison with existing literature

The study contributes valuable new evidence to the role of GPs in daily clinical practice during pregnancy. Although existing literature on the outcomes of interest is scarce, one previous Dutch study reported a recorded diagnosis for pregnancy in the GP records for 41% of births in 2007-2009, which is very similar to what we observed.[3] Taking into account slight differences in study period and design, the findings of prescribed (highly) hazardous medication were in agreement with previous studies.[29-32] To the authors' knowledge, this is the first study to assess the association between GPs' awareness of pregnancy and prescribing hazardous medication. Although no comparison information is available on the registration of pregnancy as a contra-indication in the GP information system, efforts have been made to measure the quality of GP registrations by defining a set of quality indicators, such as the proportion with a recorded contra-indication. This was reported to vary among GP practices and thus they were instructed to critically review their daily habits for registering contra-indications.[33] More generally, maintaining medical records has been acknowledged as a fundamental part of a doctor's duties in providing patient care and despite this importance, it is often given low priority.[27,28] Similar to this study, many other previous studies have concluded that delivery of preconception care is inadequate.[11,12,34-36] A Dutch survey conducted among GPs and midwives reported that only 0.7% of GPs systematically invited patients for a formal preconception care consultation.[11] Although this is similar to the 1% that we observed, 20% of those GPs indicated that they performed preconception care in a standardised manner, which is probably not captured by the strict definitions used for a preconceptional GP consultation in the current study. For example, it is likely that the GP may counsel women preconceptionally as part of a consultation (coded) for something else, e.g. the underlying condition. Although Dutch guidelines have clearly advocated standardised preconception care for some time[34], collaboration between GPs and other caregivers is advised. There seems to be a shift towards a more public, programmatical approach incorporated in the provided daily care that may explain the low occurrence of systematic preconceptional GP consultations observed in the current study.[37,38] In comparison to other countries with similar health care systems, among which the United Kingdom, similar conclusions have been drawn on the need for shared, multidisciplinary pregnancy-related care programs in which preconception care should be offered.[10,13,14,39]

Implications for research and/or practice

The finding that women without a GP-recorded pregnancy confirmation were significantly more likely to be prescribed hazardous medication indicates a potential awareness issue at the time these drugs are prescribed, placing women and their babies at avoidable risk of exposure to teratogens. Although pregnancy registration by GPs improved over the years, still inadequate use seems to be

made of the available information systems for appropriate drug surveillance. The key challenge for improved registration lies with the shared responsibility, in which collaborative care is pivotal. The authors pose three main implications based on the study findings in combination with the existing evidence. First, caregivers should be supported and educated in maintaining accurate and readily available patient records for effective communication and information transfer to other involved caregivers. Specifically in pregnancy, this requires continuity of care by documenting medical records on a daily basis to prevent use of harmful medication due to delayed or incomplete record keeping. To achieve this, the second implication relates to the electronic information systems used to maintain records. There should be clear and standardised procedures for recording and communicating information so that healthcare providers know what is expected. The differences in GPs' awareness observed between GP information systems suggest the need for further standardisation of systems. The increased availability of pregnancy indicators when using all available records from the GP information system implies difficulties in choosing the appropriate GP reference tables for registering pregnancy, obstructing GPs' awareness. Further simplification would be helpful, for example by automatically establishing an active contra-indication in that specific GP reference table in case of pregnancy confirmation, blocking the prescription of certain high risk drugs and avoiding alert fatigue among caregivers. A financial impulse was provided by the Dutch government in 2012 and 2013 for improvement of coded registration in GP practices[40], which is also reflected in the increased coded pregnancy indicators in the second half of the study period. During the study period, also the conversion of GP records from handwritten to computerised took place. Third, public awareness about the potential risks of medication used during pregnancy should be improved by means of population-wide education incorporating collaborative preconception care. In addition to caregivers acknowledging their duty here, this would ultimately increase women's self-awareness recognising their own responsibility in timely informing caregivers about (planned or unplanned) pregnancy, so that appropriate action can be taken. When prescribing hazardous medication, raised awareness would make prescribers more actively inquire about pregnancy, even in case of repeat prescriptions. Interventions should be set up in such a way that women are informed about the potential pregnancy risks of the medicines they use as early as possible, so that the patient is alert if she considers to conceive. Whether interventions have the intended positive effects should be evaluated according to predefined targets. Pregnancy prevention programs for highly hazardous drugs should be continuously evaluated and set up as needed.[41] Future qualitative research among GPs, midwives and pharmacists would be very useful to further estimate the scale of the posed awareness issue and associated aspects, such as the women's lack of awareness of pregnancy, shortcomings of information systems and the barriers perceived in collaborative care.

chapter 5

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ETHICAL APPROVAL

For the current database research with anonymous data, no ethical approval was required.

DATA

Data are available on reasonable request. Requests for sharing study data must be made on specific grounds, either 1) with the aim of corroborating the study results in the interest of public health, or 2) in the context of an audit by a competent authority. Sufficient information needs to be provided to confirm that the request is made for one of the above- mentioned purposes, including a sound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable.

PROVENANCE

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COMPETING INTERESTS

None of the authors has any conflict of interest to disclose.

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chapter

5

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chapter 5

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 ATC codes for use of medication for chronic conditions

Chronic condition	ATC
Drugs used in diabetes	A10
Corticosteroids, dermatological preparations	D07
Corticosteroids for systemic use	H02
Thyroid therapy	H03
Anti-inflammatory and antirheumatic products	M01
Antimigraine medication	N02C
Antiepileptics	N03A
Antipsychotics	N05A, excl. N05AB04
Antidepressants	N06A
Antiasthmatics	R03

SUPPLEMENTARY TABLE 2 Definitions of different levels of GP-recorded pregnancy indicators reflecting GPs' awareness of pregnancy

Type of indicator	Operationalisation	Code(s)	Search terms
Pregnancy confirmation	At least one record during pregnancy (i.e. conception date ≤ record date ≤ delivery date) with any of the defined ICPC codes or search terms in any of the GP reference tables of interest: EPI, EXA, COR, MED, JRN or INV. The timing of pregnancy trimester was additionally grouped by pregnancy trimester according to the first recorded occurrence as follows: - First trimester: conception date ≤ record date < conception date + (13*7) - Second trimester: conception date + (13*7) ≤ record date < conception date + (28*7) - Third trimester: conception date + (28*7) ≤ record date ≤ delivery date	**ICPC:** W78 Pregnancy W79 Unwanted pregnancy	-
Pregnancy indicator	At least one record during pregnancy (i.e. conception date ≤ record date ≤ delivery date) with any of the defined ICPC codes or search terms in any of the GP reference tables of interest: EPI, EXA, COR, MED, JRN, INV or CIA.	**ICPC:** W02 Fear of pregnancy W03 Antepartum bleeding W05 Pregnancy vomiting/nausea W17 Post-partum bleeding W18 Post-partum symptom/complaint oth. W19 Breast/lactation symptom/complaint W21 Concern body image in pregnancy W27 Fear complications of pregnancy W28 Limited function/disability (w) W29 Pregnancy symptom/complaint other W70 Puerperal infection/sepsis	All search terms indicating pregnancy (e.g. 'zwangerschap', 'moeder geworden', 'bevallen', 'gravida', 'gynaecologist') excl. those indicating the wish to get pregnant (e.g. 'zwangerschaps-wens', 'wil zwanger worden')

chapter 5

SUPPLEMENTARY TABLE 2 Definitions of different levels of GP-recorded pregnancy indicators reflecting GPs' awareness of pregnancy (continued)

Type of indicator	Operationalisation	Code(s)	Search terms
Pregnancy indicator continued		W71 Infection complicating pregnancy W72 Malignant neoplasm relate to preg. W73 Benign/unspec. neoplasm/ pregnancy W75 Injury complicating pregnancy W76 Congenital anomaly complicate preg. W78 Pregnancy W79 Unwanted pregnancy W80 Ectopic pregnancy W81 Toxaemia of pregnancy W82 Abortion spontaneous W83 Abortion induced W84 Pregnancy high risk W85 Gestational diabetes W90 Uncomplicate labour/delivery live W91 Uncomplicate labour/delivery still W92 Complicate labour/ delivery livebirth W93 Complicate labour/delivery stillbirth W94 Puerperal mastitis W95 Breast disorder in pregnancy other W96 Complications of puerperium other W99 Disorder pregnancy/delivery, other **WCIA**: 439 Urine pregnancy test (positive) 1282 Rhesus (screening pregnancy) 1883 Duration pregnancy 2030 Pregnancy (comorbidity) 2187 Urine pregnancy test stick (positive) 2349 Uterine ultrasound pregnancy 2997 Date planned ultrasound pregnancy 3271 Fetal rhesus D typing (screening pregnancy) 3753 HCG Pregnancy Urine POC test	
Pregnancy contra-indication	At least one record during pregnancy (i.e. conception date ≤ record date ≤ delivery date) with any of the defined ICPC codes or search terms in the CIA GP reference table.	**CIA:** 1320 Pregnancy	'Pregnancy' (only in case CIA code is empty)

SUPPLEMENTARY TABLE 2 Definitions of different levels of GP-recorded pregnancy indicators reflecting GPs' awareness of pregnancy (continued)

Type of indicator	Operationalisation	Code(s)	Search terms
Preconceptional GP consultation	At least one record in the year before pregnancy (i.e. conception date - 365 ≤ record date < conception date) with any of the defined ICPC codes or search terms in the EPI GP reference table.	**ICPC:** A97.02 Wish to have children	-

CIA = contra-indications, for recording diagnoses part of drug surveillance; COR = correspondence, for recording correspondence to and from other care providers; EPI = episodes, for recording the patient's health problem during an encounter; EXA = examinations, for recording diagnostics such as laboratory results; ICPC = International Classification of Primary Care; INV = invoices, for recording actions and the associated financial reimbursement; JRN = journals, recording all patient contacts as well as the undertaken action according to the SOEP-system (Subjective, Objective, Evaluation, Plan); MED = medication, including all medication records as prescribed by the GP; WCIA = Werkgroep Coördinatie Informatie Automatisering.

PART III

**OUTCOMES ASSOCIATED
WITH PRETERM BIRTH**

CHAPTER 6

Increased risk of morbidities and health-care utilisation in children born following preterm labour compared with full-term labour: A population-based study

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ABSTRACT

Aim
Recent evidence is emerging indicating long-term effects in infants born after an episode of preterm labour (PTL), even if birth is at term. This population-based study compared long-term rates of outcomes and health-care utilisation (HCU) in children born following spontaneous preterm labour, irrespective of gestational age at delivery or of an uncomplicated pregnancy (SPTLu), with children born following full-term labour (FTL), overall stratified by comorbidity status and assessed using a composite morbidity measure (CM).

Methods
Retrospective data on mother–neonate pairs were collected from a patient-linked dataset from the Netherlands Perinatal Registry and the PHARMO Database Network. Children born between 2000 and 2010 were followed until 2012.

Results
Of pregnancies in 134,006 mother–neonate pairs, 122,894 (92%) pregnancies resulted in FTL, and 11,112 (8%) resulted in PTL. Of the PTL pregnancies, 6599 (59%) were SPTLu. Mean follow-up after birth was 6.6–6.7 years. Children from SPTLu pregnancies were at increased risk of neurodevelopmental and respiratory conditions compared with those from FTL pregnancies. In children from SPTLu pregnancies, the presence of the CM was associated with an increased risk of respiratory conditions and failure to thrive. Post-natal hospitalisations (incidence rate (IR) per 100 patient-years: 18.1 vs. 11.7) and specialist referrals (IR per 1000 patient-years: 290.6 vs. 184.5) occurred significantly more frequently in children from SPTLu versus FTL pregnancies.

Conclusion
The increased risk of morbidities and HCU in children born following SPTLu pregnancy in this population-based setting reinforces the need for safe interventions that can effectively halt labour and lead to an improvement in childhood outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Many studies have reported sustained poorer outcomes for children born preterm compared with those born full term, with increased risk of death, short-term medical complications, longterm disabilities and neurodevelopmental problems.
- The subtype of preterm birth confers differing risks of outcomes; this study is focused on mothers with spontaneous preterm labour (SPTL) in an uncomplicated pregnancy, a population that has not been well-studied before.

WHAT THIS PAPER ADDS

- This study provides real-world insight into the risk of a range of outcomes and health-care utilisation (HCU) in children born following SPTL compared with children born full term.
- Using a uniquely rich set of population-based antenatal and post-natal data, we have followed these children through various health-care settings into late childhood and report the long-term medical burden affecting them.
- Children born after an SPTL event in an uncomplicated pregnancy have an increased risk of morbidities and HCU compared with children born full term, taking into account gestational age.

INTRODUCTION

Preterm labour (PTL), defined as labour occurring before 37 weeks gestation, is the most common cause of hospitalisations among pregnant women[1] and often leads to preterm birth. In 2010, 11% of live births world-wide (15 million) were preterm,[2] of which two-thirds occurred following an uncomplicated pregnancy.[3] Increasing evidence demonstrates sustained adverse outcomes for children born preterm, with increased risks of perinatal death, cerebral palsy, neurodevelopmental disorders, hearing loss and visual impairment.[4] Existing preventive measures target women with pregnancy complications at higher risk of PTL or preterm birth, but characteristics of women with uncomplicated pregnancies who remain at risk of PTL are less well-understood. In addition, there are limited population data available on the outcomes and resource use of children born to mothers with spontaneous preterm labour (SPTL), and especially SPTL following an uncomplicated pregnancy (SPTLu). New evidence is emerging indicating long-term effects in infants born after an episode of PTL, even if birth is at term.[5] Tocolytics are used to delay delivery, but there is little evidence that they extend pregnancy long enough to improve neonatal outcomes.[6] However, new randomised controlled trials (RCTs) to demonstrate this have been started.[7,8] The assessment of outcomes in real-world settings allows early contextualisation and interpretation of potential safety signals that may arise during RCTs in this population. Using data from a population-based network of health-care databases in the Netherlands, the objective of this study was to compare realworld outcomes and health-care utilisation (HCU) between children born from SPTLu pregnancies (irrespective of

gestational age (GA) at delivery) compared to those born from fullterm labour (FTL). A composite morbidity measure (CM) of several neonatal morbidities, which was used as an endpoint in RCTs to assess neonatal benefit,[7,8] was used to stratify children to determine whether morbidity at birth impacted the risk of longer-term outcomes.

METHODS

Study design
A retrospective cohort analysis was conducted using mother– infant linked pairs from a combined dataset of the Netherlands Perinatal Registry (PRN) and the PHARMO Database Network (PHARMO). The PRN comprises validated data on maternal, pregnancy and birth/neonatal outcome data from approximately 95% of pregnancies in the Netherlands.[9] PHARMO is a population-based, patient-level network of healthcare databases linking data from different health-care settings (including in- and outpatient pharmacies, hospitals and general practice).[10,11] PRN and PHARMO linkage was based on birth dates (mother and child) and addresses.[12] Children in this analysis were born between 2000 and 2010 and were followed until 2012, end of database registration or death, whichever occurred first. This study was conducted in accordance with the Declaration of Helsinki. As a retrospective review of databases with deidentified data, patient consent was not required.

Study populations
The study included two cohorts: the study cohort and the general practice (GP) sub-cohort. The study cohort consisted of mother– infant pairs for all singleton live births from the PRN, where both the mother and child were registered in the PHARMO Outpatient Pharmacy Database and Hospitalisation Database. Mother–infant pairs in which the mother had <12 months history in PHARMO before delivery were excluded as complete coverage of these pregnancies could not be ensured. Mother–infant pairs in which the infant had specific congenital anomalies (Supplementary Table 1) were excluded due to the higher risk of adverse outcomes.[13] The GP sub-cohort was created to assess longer-term outcomes (e.g. diagnosis, referrals, HCU) captured in the primary care records and included study cohort children where linkage to the GP Database was available. Children in the study and GP sub-cohorts were grouped according to labour status into FTL and SPTLu. SPTLu was defined as an uncomplicated pregnancy based on the exclusion of specific pregnancy complications (Supplementary Table 2) with either an International Classification of Diseases- Ninth Revision-Clinical Modification (ICD-9-CM) or International Classification of Diseases-Tenth Revision-Clinical Modification (ICD-10-CM) diagnosis code for PTL (irrespective of GA at delivery) or a preterm delivery identified by GA at birth (Supplementary Table 3). The SPTLu group from the GP sub-cohort was stratified according to the presence of ≥1 comorbidity from a CM endpoint used in RCTs.[7,8] The CM included respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia with cysts and/or porencephaly, necrotising enterocolitis, retinopathy of prematurity, cerebellar haemorrhage, sepsis and confirmed meningitis. The presence of the CM was assessed during hospitalisation for birth and, if discharged, during readmissions in the first 28 days after birth.

Baseline characteristics and demographics

Maternal and obstetric characteristics recorded included age at delivery, ethnicity, parity, delivery mode and socio-economic status. Characteristics recorded for neonates were gender, birth year, years of follow-up, birthweight and GA at birth.

Outcomes

The rates of common childhood morbidities or those associated with prematurity were assessed based on hospitalisations (ICD- 9-CM and ICD-10-CM codes) and GP-recorded diagnoses (international classification of primary care codes and free-text searches) (Supplementary Table 4). Morbidities were recorded from birth until the end of follow-up in the overall SPTLu and FTL cohorts and from 29 days after birth in the CM-based sub-cohorts. In addition, outcomes were assessed by age: <1, 1–2, 3–5 and 6+ years.

Health-care utilisation

Rates of hospitalisations (number of children with ≥1 post-natal hospitalisation and total number and total days of post-natal hospitalisation) and prescriptions filled (defined as unique medication prescriptions actually collected from the outpatient pharmacy; number of children with ≥1 prescription filled; total number of prescriptions filled) were assessed from birth until the end of follow-up. Post-natal hospitalisations were defined as hospitalisations after birth (excluding birth date), or when a child was hospitalised from birth onwards for more than 28 days, hospitalisation was regarded as being post-natal from the 29th day onwards. HCU in the study cohort was also assessed by age. GP referrals to specialists were assessed in the GP sub-cohort. These included referrals to any specialist and referrals for imaging, use of therapies, visual impairment services, surgeries or mental health services (Supplementary Table 5).

Analyses

Rates of outcomes and HCU were compared between the SPTLu and FTL groups and between children with and without the CM within the SPTLu group. Poisson regression analyses and Cox regression analyses were used for comparisons of rates of HCU and outcomes, respectively, to provide adjusted rate ratios and hazard ratios with 95% confidence intervals. For all comparative analyses, relevant maternal, obstetric and neonatal characteristics (e.g. GA and other parameters known to be confounders according to literature) recorded in ≥5% of the population, and with univariate P values <0.1, were considered eligible for the multivariable (adjusted) regression models using a backward stepwise approach.

RESULTS

Baseline characteristics and demographics

A total of 290 133 singleton pregnancies were identified from the PRN between 2000 and 2010 and could be linked to mothers registered in PHARMO. After exclusions, the study cohort comprised 134 006 eligible mother–infant pairs (Figure 1). Of these, 122 894 (92%) pregnancies resulted in FTL, and 11 112 (8%) resulted in PTL (with birth either before or after 37 weeks' gestation). Of the

PTL pregnancies, 6599 (59%) demonstrated SPTLu. Children born following SPTLu pregnancies had lower median (interquartile range) birthweight than those born following FTL (2781 (2375−3200) g and 3515 (3200−3850) g, respectively). The mean follow-up in the study cohort was 6.6−6.7 years (Table 1). Maternal mean age at delivery (Table 1) and socio-economic status (data not shown) were similar between SPTLu and FTL pregnancies. Of mothers with SPTLu, 53% were pregnant with their first child. Most mothers (87%) had a vaginal delivery (Table 1). Within the study cohort, 13% of children (n = 17 903) could be linked to the GP Database and formed the GP sub-cohort, of whom 1510 (8%) were born after a PTL pregnancy. Of children born following PTL, 847 (56%) were born following SPTLu. Infant characteristics suggested that the GP sub-cohort was representative of the study cohort (Table 1). The mean follow-up in the GP sub-cohort was 5.7−6.1 years. Among children in the GP sub-cohort born following SPTLu, 7.6% (n = 64) had ≥1 component of the CM at birth. There was no difference in gender distribution or follow-up time between those with or without the CM (Table 1). A higher proportion of children with the CM were born very or moderately preterm (24−<28 and 28−<33 weeks GA) compared to those without (5 vs. 0% and 41 vs. 3%, respectively).
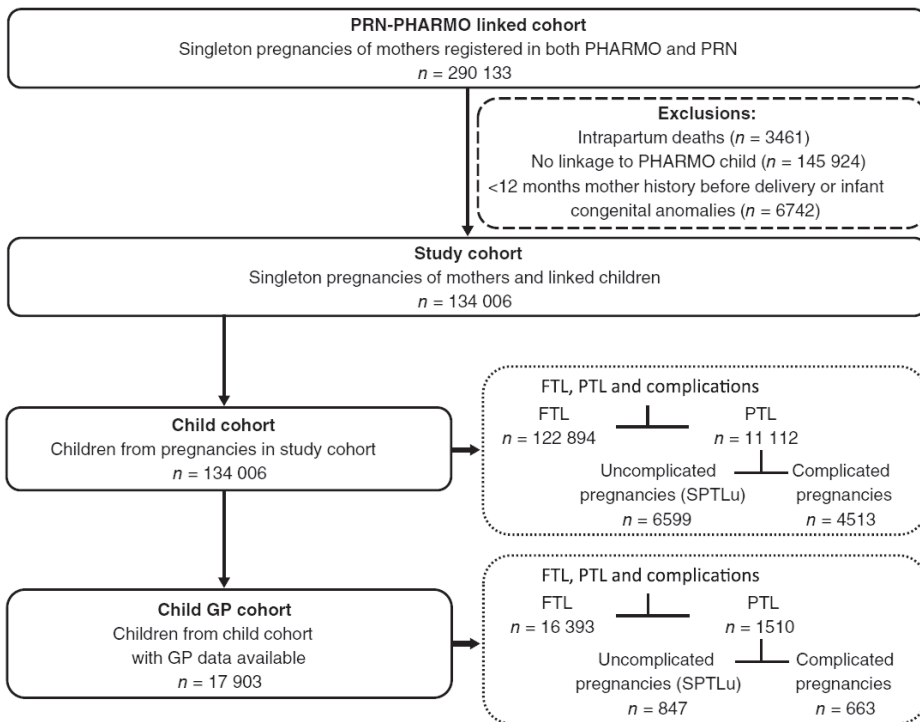
FIGURE 1 Patient flow chart

FTL, full-term labour; GP, general practice; PHARMO, PHARMO Database Network; PRN, Netherlands Perinatal Registry, PTL, preterm labour; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy

Outcomes

Respiratory conditions, particularly reactive airway disease, and infectious diseases were the most commonly observed outcomes among all pregnancies (Table 2). Children from SPTLu pregnancies were at an increased risk of arrhythmias, gastroesophageal reflux disease, any infectious disease, adverse behavioural outcomes in childhood and motor impairment compared with children from FTL pregnancies adjusted for GA and other relevant characteristics (Table 2). Outcomes by age are shown in Supplementary Table 6 including additional subclassification of selected age-dependent outcomes. Sensitivity analyses assessing outcomes by GA indicated that, predominantly, rates of infectious diseases such as pneumonia and sepsis/bacteraemia were higher for children born very preterm (<28 weeks GA) compared with children born at 28 to <33, 33 to ≤36 and ≥37 weeks GA (data not shown). For children born from SPTLu pregnancies, the CM at birth was associated with a substantially increased risk of failure to thrive and several respiratory conditions during infancy. The highest rates of most outcomes were during the first year of life and decreased thereafter. The only exception was sensory conditions, which had the highest incidence in children aged 6+ years (data not shown).

Health-care utilisation

More post-natal hospitalisations were seen in children from SPTLu pregnancies compared with children from FTL pregnancies (Table 3); mean (standard deviation (SD)) numbers of hospitalisations were 1.2 (2.8) and 0.8 (2.2), respectively. Children from SPTLu pregnancies were also in hospital for longer than those from FTL pregnancies, with mean (SD) number of days of hospitalisation of 5.0 (15.3) and 2.0 (7.6), respectively. The total number of prescriptions filled was also higher among children from SPTLu pregnancies compared with children from FTL pregnancies (mean (SD): 23.9 (36.4) vs. 19.3 (27.7), respectively). All differences were apparent across age categories (Supplementary Table 7). In the GP sub-cohort, children from SPTLu pregnancies were referred to specialist services significantly more often than children from FTL pregnancies (Table 4), including significantly more referrals for therapies, surgeries and mental health services. These differences were most apparent in the first year, except for mental health services, which were generally utilised in later childhood (Supplementary Table 8). The incidence of specialist referrals overall did not differ among the children from SPTLu pregnancies, irrespective of the CM at birth (Table 4). The exception to this was the use of therapies that were less frequent among those with the CM compared to those without. However, this pattern was not observed across all age groups, with referrals for therapies being higher in children with the CM compared with those without the CM in the <1 year and 6+ years age groups.

chapter

6

TABLE 1 Infant and maternal/obstetric characteristics for spontaneous preterm labour following an uncomplicated pregnancy (SPTLu) and full-term labour (FTL) and pregnancies (study and general practice (GP) sub-cohorts)

	Study cohort		GP sub-cohort			
	SPTLu	FTL	SPTLu			FTL
			Overall	With CM	Without CM	
	N = 6,599	N = 122,894	N = 847	N = 64	N = 783	N = 16,393
Infant characteristics						
Gender, n (%)						
Male	3,570 (54)	63,549 (52)	432 (51)	32 (50)	400 (51)	8,559 (52)
Female	3,029 (46)	59,345 (48)	415 (49)	32 (50)	383 (49)	7,834 (48)
Birth weight, g						
Median (IQR)	2,781 (2,375–3,200)	3,515 (3,200–3850)	2,800 (2,400–3,190)	2,028 (1,480–2,480)	2,845 (2,450–3,220)	3,500 (3,190–3,830)
Gestational age at birth, n (%)						
24–<28 weeks	77 (1)	–	3 (<0.5)	3 (5)	0 (0)	–
28–<33 weeks	495 (8)	–	51 (6)	26 (41)	25 (3)	–
33–<36 weeks	3,955 (60)	–	493 (58)	35 (55)	458 (58)	–
≥37 weeks	2,057 (31)	122,415 (100)	299 (35)	0 (0)	299 (38)	16,377 (100)
Unknown	15 (<0.5)	479 (<0.5)	1 (<0.5)	0 (0)	1 (<0.5)	16 (<0.5)
Follow-up, years						
Mean ± SD	6.6 ± 3.0	6.7 ± 3.0	5.7 ± 2.5	6.1 ± 2.5	5.7 ± 2.5	6.1± 2.5
Maternal characteristics						
Age at delivery, n (%)						
<18 years	34 (1)	254 (<0.5)	1 (<0.5)	0 (0)	1 (<0.5)	18 (<0.5)
18–25 years	1,201 (18)	16,310 (13)	143 (17)	9 (14)	134 (17)	1,691 (10)
26–30 years	2,438 (37)	43,358 (35)	339 (40)	26 (41)	313 (40)	5,931 (36)
31–35 years	2,118 (32)	45,874 (37)	279 (33)	24 (38)	255 (33)	6,537 (40)

TABLE 1 Infant and maternal/obstetric characteristics for spontaneous preterm labour following an uncomplicated pregnancy (SPTLu) and full-term labour (FTL) and pregnancies (study and general practice (GP) sub-cohorts) (continued)

	Study cohort		GP sub-cohort			
	SPTLu	FTL	SPTLu			FTL
			Overall	With CM	Without CM	
	N = 6,599	N = 122,894	N = 847	N = 64	N = 783	N = 16,393
36–40 years	728 (11)	15,596 (13)	77 (9)	4 (6)	73 (9)	2,044 (12)
≥41 years	80 (1)	1502 (1)	8 (1)	1 (2)	7 (1)	172 (1)
Mean ± SD	29.8 ± 4.9	30.6 ± 4.6	29.7 ± 4.6	29.7 ± 5.0	29.7 ± 4.6	30.8 ± 4.3
Parity, n (%)						
0	3,520 (53)	52,422 (43)	492 (58)	35 (55)	457 (58)	7,046 (43)
1	2,120 (32)	48,802 (40)	251 (30)	21 (33)	230 (29)	6,764 (41)
2	695 (11)	16,370 (13)	82 (10)	6 (9)	76 (10)	2,032 (12)
≥3	264 (4)	5,288 (4)	22 (3)	2 (3)	20 (3)	548 (3)
Unknown	0 (0)	12 (<0.5)	0 (0)	0 (0)	0 (0)	3 (<0.5)
Median (IQR)	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–1)
Mode of delivery, n (%)						
Vaginal (with or without induction)	5,534 (84)	106,376 (87)	706 (83)	53 (83)	653 (83)	14,032 (86)
Caesarean section (primary or secondary)	1,063 (16)	16,405 (13)	141 (17)	11 (17)	130 (17)	2,350 (14)
Unknown	2 (<0.5)	113 (<0.5)	0 (0)	0 (0)	0 (0)	11 (<0.5)

CM, composite morbidity measure; FTL, full-term labour; GP, general practice; IQR, interquartile range; SD, standard deviation; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy

chapter

6

TABLE 2 Incidence rates of selected outcomes any time during follow-up for spontaneous preterm labour following an uncomplicated pregnancy (SPTLu) and full-term labour (FTL) pregnancies (general practice (GP) sub-cohort)

Outcome	SPTLu IR per 1,000 PY (95% CI)			FTL IR per 1,000 PY (95% CI)	HR adjusted* (95% CI)	
	Overall $N_{at\,risk}$ = 847	Without CM $N_{at\,risk}$ = 783	With CM $N_{at\,risk}$ = 64	$N_{at\,risk}$ = 16,393	Overall SPTLu vs FTL	SPTLu with CM vs SPTLu without CM
Any cancer	0.2 (0.0, 0.8)	–	–	0.2 (0.1, 0.3)	1.0 (0.1, 7.2)	–
Cardiovascular/cerebro-vascular events						
Arrhythmias	1.5 (0.6, 2.8)			0.4 (0.3, 0.5)	**4.3 (1.9, 9.7)**	
GI conditions						
GERD	3.4 (1.9, 5.3)	2.5 (1.2, 4.3)	5.2 (0.4,15.2)	1.8 (1.5, 2.1)	**1.8 (1.1, 3.0)**	1.6 (0.2, 10.5)
Growth parameters						
Failure to thrive	2.9 (1.6, 4.7)	1.8 (0.8, 3.4)	16.5 (5.8, 32.8)	2.3 (2.0, 2.6)	1.3 (0.8, 2.2)	**7.1 (1.7, 29.2)**
Infectious diseases/serious infections						
Any infectious disease**	35.9 (30.2, 42.1)	27.0 (22.0, 32.6)	38.8 (20.3, 63.4)	20.8 (19.9, 21.8)	**1.5 (1.1, 2.0)**	0.9 (0.5, 1.8)
Neurodevelopmental conditions						
Adverse behavioural outcome in childhood	1.0 (0.3,2.2)	–	–	0.3 (0.2, 0.4)	**2.9 (1.1, 7.8)**	–
Motor impairment	3.5 (2.0, 5.5)	2.8 (1.4, 4.6)	13.2 (4.0, 27.6)	1.6 (1.3, 1.8)	**2.5 (1.5, 4.2)**	3.6 (0.9, 14.5)
Respiratory conditions						
Adverse respiratory outcomes including asthma	16.1 (12.5, 20.1)	14.2 (10.8, 18.2)	40.2 (21.0, 65.5)	10.1 (9.5, 10.8)	**1.5 (1.2, 1.9)**	**3.1 (1.5, 6.2)**
Asthma	15.8 (12.3, 19.8)	13.9 (10.5, 17.9)	40.0 (20.9, 65.3)	10.0 (9.4, 10.7)	**1.5 (1.2, 1.9)**	**3.0 (1.5, 6.1)**
Chronic lung disease	2.7 (1.4, 4.4)	2.3 (1.1, 4.0)	5.3 (0.5, 15.6)	1.0 (0.8, 1.2)	**2.6 (1.4, 4.7)**	1.9 (0.3, 11.9)
Pneumonia	17.5 (13.8, 21.6)	16.6 (12.8, 20.8)	29.2 (13.7, 50.7)	9.9 (9.3, 10.5)	**1.7 (1.3, 2.1)**	1.2 (0.6, 2.7)
Reactive airway disease	97.4 (87.2,108.2)	98.0 (87.2, 109.4)	91.8 (59.9, 130.5)	72.0 (70.1,74.0)	**1.3 (1.1, 1.4)**	0.8 (0.5,1.3)

TABLE 2 Incidence rates of selected outcomes any time during follow-up for spontaneous preterm labour following an uncomplicated pregnancy (SPTLu) and full-term labour (FTL) pregnancies (general practice (GP) sub-cohort) (continued)

Outcome	SPTLu IR per 1,000 PY (95% CI)			FTL IR per 1,000 PY (95% CI)	HR adjusted* (95% CI)	
	Overall $N_{at\ risk}$ = 847	Without CM $N_{at\ risk}$ = 783	With CM $N_{at\ risk}$ = 64	$N_{at\ risk}$ = 16,393	Overall SPTLu vs FTL	SPTLu with CM vs SPTLu without CM
Sensory conditions						
Blindness	0.2 (0.0, 0.8)	–	–	0.1 (0.1, 0.2)	1.6 (0.2, 12.1)	–
Hearing impairment or deafness	4.2 (2.5, 6.2)	–	–	3.1 (2.8, 3.5)	1.5 (1.0, 2.4)	–

CM, composite morbidity measure; CI, confidence interval; FTL, full-term labour; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HR, hazard ratio; IR, incidence rate; PY, patient-years; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy. *Relevant characteristics present in at least 5% of the population and with univariate p-values <.1 were considered eligible for the multivariable (adjusted) regression model, using a backward stepwise approach. Items in bold italics were significant for the relevant comparison; **Over 2,000 diseases were included, for example, chickenpox, diphtheria, gastroenteritis, group B streptococcus, herpes, influenza, measles, meningitis, pertussis, pneumonia, rotavirus, rubella, sepsis/bacteraemia and septic shock.

chapter

6

TABLE 3 Post-natal hospitalisations and prescriptions filled following spontaneous preterm labour following an uncomplicated pregnancy (SPTLu) and full-term labour (FTL) pregnancies (study cohort)

Outcome	SPTLu IR per 100 PY (95% CI) $N_{at\ risk}$ = 6,599	FTL IR per 100 PY (95% CI) $N_{at\ risk}$ = 122,894	RR adjusted* (95% CI)
Postnatal hospitalisations			
Total number of hospitalisations	18.1 (17.7, 18.5)	11.7 (11.7, 11.8)	1.5 (1.4, 1.5)
Total days of hospitalisation	75.7 (74.8, 76.5)	29.9 (29.8, 30.0)	1.7 (1.5, 1.9)
Prescriptions filled			
Total number of prescriptions filled	363.5 (361.6, 365.3)	286.5 (286.1, 286.8)	1.2 (1.2, 1.3)

CI, confidence interval; FTL, full-term labour; IR, incidence rate measured per 100 patient years; PY, patient-years; RR, rate ratio; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy. *Relevant characteristics present in at least 5% of the population and with univariate p-values <.1 were considered eligible for the multivariable (adjusted) regression model, using a backward stepwise approach.

TABLE 4 Incidence rates of specialist referrals following SPTLu and FTL pregnancy (GP sub-cohort)

Outcome	SPTLu IR per 1,000 PY (95% CI)			FTL IR per 1,000 PY (95% CI)	HR adjusted* (95% CI)	
	Overall N_at-risk = 847	Without CM N_at-risk = 783	With CM N_at-risk = 64	N_at-risk = 16,393	Overall SPTLu vs FTL	SPTLu with CM vs SPTLu without CM
Any referral	290.6 (266.7, 315.5)	285.5 (261.0, 311.0)	366.9 (265.7, 484.4)	184.5 (180.7, 188.3)	**1.5 (1.4, 1.7)**	1.0 (0.7, 1.4)
Imaging	38.8 (33.0, 45.1)	39.1 (33.1, 45.7)	35.6 (18.0, 59.2)	33.2 (32.0, 34.5)	1.1 (0.9, 1.3)	0.8 (0.4, 1.7)
Therapies**	35.7 (30.2, 41.6)	35.8 (30.0, 42.0)	34.3 (17.4, 57.0)	24.0 (23.0, 25.1)	**1.4 (1.2, 1.7)**	***0.5 (0.2, 0.9)***
Visual impairment services	21.0 (16.9, 25.5)	19.5 (15.5, 24.1)	38.5 (20.1, 62.8)	16.4 (15.6, 17.3)	0.9 (0.6, 1.3)	1.6 (0.8, 3.3)
Surgeries	22.5 (18.3, 27.3)	21.8 (17.4, 26.6)	31.7 (15.5, 53.7)	15.1 (14.4, 16.0)	**1.5 (1.2, 1.8)**	0.6 (0.3, 1.5)
Mental health services	11.9 (8.9, 15.3)	10.8 (7.9, 14.2)	25.0 (11.1, 44.4)	6.0 (5.5, 6.5)	**2.1 (1.6, 2.8)**	1.8 (0.7, 4.5)

CM, composite morbidity measure; CI, confidence interval; FTL, full-term labour; GP, general practice; IR, incidence rate; PY, patient-years; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy.
* Relevant characteristics present in at least 5% of the population and with univariate p-values <.1 were considered eligible for the multivariable (adjusted) regression model, using a backward stepwise approach;
** therapies includes therapeutic interventions such as physical therapy, speech therapy, respiratory therapy, feeding therapy, etc. (see Supplementary Table 5). Items in bold italics were significant for the relevant comparison.

DISCUSSION

The population-based network of health-care databases used in this retrospective study allowed access to a uniquely rich set of antenatal and post-natal clinical data across several different sources, including GP records, in- and outpatient medications and hospital admission records. Combining patient-level data from diverse sources, linked between mothers and children, provided an effective way to determine the relationship between SPTLu in mothers with a wide range of infant perinatal outcomes. The study demonstrated increased risk for a range of morbidities and HCU in children from SPTLu pregnancies (irrespective of GA at delivery) compared with those from FTL pregnancies. This is one of the first studies to determine longterm outcomes in this specific population of patients. Numerous previous studies have demonstrated an increased risk of intellectual disability, speech and language disorders, cognitive delay and respiratory conditions seen in early childhood in preterm compared with full-term babies, including all aetiologies of PTL.[4,14,15] In our study, comorbidities occurring more frequently in children from SPTLu pregnancies compared with FTL pregnancies included neurodevelopmental and respiratory conditions. Recent evidence has indicated that PTL is a risk factor for neurodevelopment deficits at 2 years of age[16]; our data provide supportive evidence for this. Given the longitudinal nature of the databases used in the present study, we were able to assess outcomes for over 6 years on average. Most outcomes had the highest rates during the first year of life. However, there was also evidence of persistent disability, with the highest rates of cognitive impairment and sensory conditions seen in older children, possibly as these issues may be more likely to be detected at school age. In addition, and probably related, to the adverse effect of SPTLu on childhood outcomes, an increased risk for HCU was seen among children from SPTLu pregnancies compared with those from FTL pregnancies. Higher hospitalisation and medication use rates occurred in all years. The timing of increased risk for specialist referrals varied, with referrals to therapy and surgery occurring more frequently during the first year, but referrals to mental health services increasing as children became older, likely reflecting cognitive development. The presence of comorbidity at birth (as assessed by the CM) in SPTLu children was associated with an increased risk of several outcomes and HCU. However, as the CM occurred in only 7.6% of mother–infant pairs, comparative analyses were not possible for infrequent outcomes, and results for HCU lacked statistical significance. The rare occurrence of the CM also illustrates the potential difficulty in powering RCTs to demonstrate neonatal benefit. Epidemiological studies therefore provide important data to inform future RCTs, particularly in populations that are challenging to study. Due to its retrospective design, this study was inherently limited by the risk of under-recording of outcomes in health-care records, which may have caused an underestimation of the incidence rates. Morbidities at/around birth and outcomes were captured using the hospitalisation database; hence, any events that did not require hospitalisation would be under-reported. For outcomes in infancy, completeness depends on whether the outcome was recorded and coded by the GP, as is the case for all studies using routinely collected health-care information from daily practice. Therefore, we focused on comparative analyses between groups producing relative ratios, without interpretation of absolute rates per comparator group. Adjustment of outcomes for relevant characteristics was also limited by information available in the database. As deaths recorded in the PRN database could not be linked to PHARMO, which includes live children only, some mother–neonate pairs with more severe neonatal outcomes may

have been excluded. In addition, it should be noted that the FTL group included both complicated and uncomplicated pregnancies, whereas the SPTLu group included only uncomplicated pregnancies. By design, only mother–neonate pairs that could be linked between the PRN and PHARMO databases were included in the analysis, excluding those for whom missing data prevented linkage. Only 13% of children could be included in the GP subcohort due to the partial geographical overlap between the pharmacy and GP databases. We do not expect any selection bias to have occurred given that all individuals in the Netherlands should be registered with a GP as a requirement of mandatory health insurance. Additional assessments (manuscript in preparation) have shown the linkable populations to PRN as well as the GP Database to be representative of the national population.

CONCLUSION

The outcomes seen in this real-world setting provide relevant long-term information about an increased risk for comorbidities, neurodevelopment impact and HCU in children born following SPTLu pregnancies. This information provides evidence of the continued medical burden in this population, which reinforces the need for effective interventions and can be used to provide contextual information for the long-term safety of medication in this area.

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chapter

6

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 List of congenital abnormalities, used as exclusion criteria

Condition
A-V malformation
Achondrogenesis Type II
Acrania
Alobar holoprosencephaly
Anencephaly
Autosomal recessive polycystic kidney disease
Bilateral dysplastic kidneys
Bilateral renal agenesis
Congenital renal abnormality/agenesis
Craniorachischisis
Diaphragmatic hernia
Duodenal atresia
Exencepthaly
Exstrophy of bladder
Genitourinary cystic/dysplastic obstruction
Gastroschisis
Harlequin foetus
Hydranencephaly/congenital hydrocephaly
Hydrocephalus with shunt
Hydronephrosis
Hydrops fetalis
Hypoplastic left heart
Imperforate anus
Inborn error metabolism
Iniencephaly
Lethal skeletal dysplasia
Major cardiac defects
Meckel–Gruber syndrome
Mixed dysplastic/cystic/agenic disorders
Myelomeningocele
Omphalocele
Osteogenesis imperfecta Type II
Potters
T-E fistula/oesophageal atresia
Total Anomalous Pulmonary Venous Return
Tetralogy of Fallot
Transposition of the great arteries
Triploidy
Trisomy 13
Trisomy 18
Trisomy 21

chapter 6

SUPPLEMENTARY TABLE 2 Pregnancy complications used as exclusion criteria to define an uncomplicated pregnancy

Complication
Abruptio placentae
Active liver disease
Antepartum haemorrhage
Arrhythmias
Cardiomyopathy
Congenital heart disease
Eclampsia
Foetal distress
HELLP syndrome
IUGR
Intra-amniotic infection
Ischaemic cardiac disease
Oligohydramnios
Placenta praevia
Polyhydramnios
Premature preterm rupture of membrane
Pulmonary hypertension
Severe pre-eclampsia
Severe or pregnancy affecting alcohol use
Severe or pregnancy affecting drug use
Unstable liver disease
Valvular heart disease

HELLP, haemolysis, elevated liver enzymes, low platelet count; IUGR, intrauterine growth restriction.

SUPPLEMENTARY TABLE 3 Diagnosis codes for identification of threatened preterm labour

Record source	Description	Code
PRN		**Local code lists**
LVR1- problems during pregnancy/ reason for consulting gynaecologist	Threatened preterm labour	430
LVR1 – problems during labour/ reason for consulting gynaecologist	Preterm labour	517
	Threatened preterm labour	518
LVR2 – reason for transfer to gynaecologist	Threatened preterm labour	63
LVR2 – details pregnancy	Medication to stop contraction with hospitalisation	54
	Medication to stop contraction without hospitalisation	55
LVR1–LVR2	Pregnancies with GA, <37 weeks	GA
PHARMO		**ICD-9-CM**
Hospitalisation database	Threatened premature labour	644.0
	Early onset of delivery	644.2

GA, gestational age; ICD-9-CM, International Classification of Diseases-Ninth Revision-Clinical Modification; LVR1, midwives; LVR2, gynaecologists; PRN, Netherland Perinatal Registry.

SUPPLEMENTARY TABLE 4 Selected outcomes assessed during follow-up

Outcomes	
Infant death (outside the initial birth episode)	
Respiratory conditions	Chronic lung disease
	Reactive airway disease
	Vocal cord paralysis
	Asthma
	Adverse respiratory outcomes including asthma and chronic obstructive pulmonary disease
Neurological conditions	Cerebral palsy
	Seizure disorders
	Epilepsy
	Hydrocephalus with shunt
Sensory conditions	Visual impairment
	Blindness
	Hearing impairment and deafness
Gastrointestinal conditions	Gastroesophageal reflux disease
	Short bowel syndrome
Renal conditions	Renal impairment
	Renal impairment needing dialysis
Birth/congenital comorbidities	
Growth parameters	Poor weight gain
	Reduced length
	Reduced head circumference
	Failure to thrive
Neurodevelopmental conditions	Autism spectrum disorder
	Attention deficit disorder
	Attention deficit disorder with hyperactivity
	Developmental delays (learning difficulties, developmental delay in speech or language, developmental coordination disorders, other developmental delays)
	Cognitive impairment
	Motor impairment
	Adverse behavioural outcome in childhood (difficulties with attachment, socialisation, attention, feeding, hyperactivity)
	Adverse mental health including psychotic and mood disorders (anxiety and depression, neuroses, psychogenic symptoms, compulsive obsessive disorder, psychosis, schizophrenia)
Cardiovascular/ cerebrovascular events	Arrhythmias
	Valvulopathy
	Pulmonary hypertension
	Stroke
	Transient ischaemic attack
	Hypertension
	Adverse vascular health including hypertension/reduced renal function

SUPPLEMENTARY TABLE 4 Selected outcomes assessed during follow-up (continued)

Outcomes	
Infectious diseases/serious infections	Any infectious disease
	Pneumonia
	Meningitis
	Sepsis
	Septic shock
	Chickenpox
	Herpes simplex virus
	Herpes zoster
	Rotavirus
	Gastroenteritis requiring hospitalisation
	Group B streptococcus
	Measles
	Rubella
	Diphtheria
	Pertussis
	Influenza requiring hospitalisation
Cancers	Any cancer/malignant tumour
	Acute lymphocytic leukaemia
	Hepatoblastoma
	Neuroblastoma
	Wilms' tumour

SUPPLEMENTARY TABLE 5 Specialist referrals assessed during follow-up

Specialist referrals	
Imaging	Electrocardiography
	Radiography
	Radiology
	Sonography
Therapies	Cesar therapy (active practice therapy to relieve and prevent problems resulting from incorrect posture)
	Ergotherapy/occupational therapy (assessment and treatment to develop or maintain daily living skills)
	Manual therapy (physical therapy to treat musculoskeletal pain and disability)
	Mensendieck therapy (therapeutic posture and movement technique)
	Physiotherapy
	Speech therapy
Visual impairment services	Ophthalmology
	Optometry
Surgeries	Anaesthesia
	Neuro surgery
	Oral surgery
	Plastic surgery
	Surgery
	Vascular surgery
Mental health services	Mental health centre
	Psychiatry
	Psychological care
	Psychotherapy

chapter 6

SUPPLEMENTARY TABLE 6 Postnatal outcomes by age (GP sub-cohort)

Outcome	SPTLu IR per 1000 PY (95% CI)				FTL IR per 1000 PY (95% CI)			
	<1 years $N_{at\ risk} = 847$	1–2 years $N_{at\ risk} = 846$	3–5 years $N_{at\ risk} = 730$	6+ years $N_{at\ risk} = 347$	<1 year $N_{at\ risk} = 16,393$	1–2 years $N_{at\ risk} = 16,384$	3–5 years $N_{at\ risk} = 14,404$	6+ years $N_{at\ risk} = 7,980$
Any cancer	–	–	0.6 (0.0, 2.5)	–	0.4 (0.1, 0.7)	0.3 (0.1, 0.5)	0.2 (0.1, 0.4)	0.4 (0.2, 0.8)
Cardiovascular/cerebro-vascular events								
Arrhythmias	5.9 (1.8, 12.4)	–	1.3 (0.1, 3.7)	–	1.0 (0.5, 1.5)	0.1 (0.0, 0.2)	0.4 (0.2, 0.7)	0.4 (0.2, 0.8)
Valvulopathy	4.7 (1.2, 10.7)	–	–	–	1.2 (0.7, 1.8)	0.4 (0.2, 0.7)	0.1 (0.0, 0.3)	–
GI conditions								
GERD	15.5 (8.1, 25.4)	1.8 (0.3, 4.6)	0.6 (0.0, 2.5)	1.3 (0.0, 5.2)	9.8 (8.3, 11.5)	0.4 (0.2, 0.7)	0.1 (0.0, 0.3)	0.2 (0.0, 0.4)
Growth parameters								
Failure to thrive	8.3 (3.2, 15.8)	1.8 (0.3, 4.6)	1.3 (0.1, 3.7)	2.6 (0.2, 7.6)	4.1 (3.2, 5.2)	2.3 (1.8, 2.8)	1.7 (1.3, 2.2)	1.8 (1.2, 2.5)
Infectious diseases/serious infections								
Any infectious disease	105.6 (83.7, 130.1)	31.1 (22.8, 40.6)	17.4 (11.4, 24.8)	7.9 (2.8, 15.7)	54.5 (50.8, 58.2)	23.9 (22.2, 25.7)	12.9 (11.7, 14.2)	4.9 (3.9, 6.0)
Sepsis/bacteraemia	32.9 (21.5, 46.8)	–	–	–	8.4 (7.0, 9.9)	0.3 (0.1, 0.5)	0.0 (0.0, 0.1)	0.1 (0.0, 0.3)
Neurodevelopmental conditions								
Cognitive impairment	–	0.6 (0.0, 2.4)	1.9 (0.3, 4.7)	2.6 (0.2, 7.6)	0.2 (0.1, 0.5)	0.3 (0.1, 0.5)	0.5 (0.3, 0.8)	2.1 (1.4, 2.8)
Adverse behavioural outcome in childhood	–	0.6 (0.0, 2.4)	1.9 (0.3, 4.7)	1.3 (0.0, 5.2)	0.1 (0.0, 0.2)	0.3 (0.1, 0.5)	0.4 (0.2, 0.6)	0.7 (0.3, 1.1)
Developmental delays – speech and language disorder	–	5.5 (2.5, 9.8)	11.5 (6.7, 17.5)	6.6 (2.0, 13.7)	0.1 (0.0, 0.4)	4.0 (3.3, 4.7)	6.6 (5.8, 7.6)	3.9 (3.1, 5.0)
Motor impairment	–	3.1 (0.9, 6.4)	3.1 (1.0, 6.6)	9.2 (3.5, 17.4)	1.3 (0.8, 2.0)	1.4 (1.0, 1.8)	1.6 (1.2, 2.0)	2.3 (1.7, 3.1)

SUPPLEMENTARY TABLE 6 Postnatal outcomes by age (GP sub-cohort) (continued)

Outcome	SPTLu IR per 1000 PY (95% CI)				FTL IR per 1000 PY (95% CI)			
	<1 years $N_{at\,risk}$ = 847	1–2 years $N_{at\,risk}$ = 846	3–5 years $N_{at\,risk}$ = 730	6+ years $N_{at\,risk}$ = 347	<1 year $N_{at\,risk}$ = 16,393	1–2 years $N_{at\,risk}$ = 16,384	3–5 years $N_{at\,risk}$ = 14,404	6+ years $N_{at\,risk}$ = 7,980
Respiratory conditions								
Adverse respiratory outcomes including asthma	42.1 (29.1, 57.5)	12.4 (7.5, 18.5)	13.4 (8.2, 19.8)	5.2 (1.3, 11.7)	26.6 (24.1, 29.2)	9.2 (8.1, 10.3)	6.8 (5.9, 7.7)	3.9 (3.1, 5.0)
Asthma	40.9 (28.0, 56.1)	11.8 (7.0, 17.8)	13.4 (8.2, 19.8)	5.2 (1.3, 11.7)	26.1 (23.7, 28.7)	9.0 (8.0, 10.1)	6.8 (5.9, 7.7)	3.9 (3.1, 5.0)
Chronic lung disease	7.1 (2.5, 14.1)	1.2 (0.1, 3.6)	2.5 (0.6, 5.7)	1.3 (0.0, 5.2)	2.3 (1.6, 3.1)	1.4 (1.0, 1.8)	0.4 (0.2, 0.7)	0.1 (0.0, 0.3)
Reactive airway disease	234.8 (200.9, 271.5)	113.3 (96.3, 131.7)	64.4 (51.8, 78.4)	31.1 (19.5, 45.4)	182.5 (175.6, 189.6)	81.2 (77.9, 84.5)	44.4 (42.1, 46.8)	26.3 (23.9, 28.9)
Sensory conditions								
Blindness	1.2 (0.0, 4.7)	–	–	–	–	0.1 (0.0, 0.2)	0.3 (0.1, 0.5)	–
Hearing impairment or deafness	1.2 (0.0, 4.7)	2.5 (0.6, 5.5)	8.2 (4.3, 13.4)	2.6 (0.2, 7.6)	0.7 (0.4, 1.2)	1.7 (1.2, 2.2)	4.9 (4.2, 5.7)	5.2 (4.1, 6.3)

CI, confidence interval; FTL, full-term labour; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GP, general practitioner; IR, incidence rate; PY, patient-years; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy.

chapter

6

SUPPLEMENTARY TABLE 7 Healthcare utilisation by age (study cohort)

Outcome	SPTLu IR per 1000 PY (95% CI)				FTL IR per 1000 PY (95% CI)			
	<1 year	1–2 years	3–5 years	6+ years	<1 year	1–2 years	3–5 years	6+ years
	$N_{at\,risk}$ = 6,599	$N_{at\,risk}$ = 6,587	$N_{at\,risk}$ = 5,812	$N_{at\,risk}$ = 3,411	$N_{at\,risk}$ = 122,894	$N_{at\,risk}$ = 122,750	$N_{at\,risk}$ = 108,902	$N_{at\,risk}$ = 67,172
Postnatal hospitalisations								
Total number of hospitalisations	98.3 (95.9, 100.8)	13.2 (12.6, 13.7)	5.5 (5.3, 5.8)	6.9 (6.4, 7.5)	63.4 (63.0, 63.9)	9.1 (9.0, 9.2)	4.3 (4.3, 4.4)	5.3 (5.2, 5.4)
Total days of hospitalisation	864.3 (857.1, 871.6)	28.8 (28.1, 29.6)	9.8 (9.5, 10.2)	15.7 (14.9, 16.5)	238.0 (237.1, 238.9)	18.3 (18.1, 18.4)	7.2 (7.1, 7.2)	9.0 (8.8, 9.1)
Prescriptions filled								
Total number of prescriptions filled	676.8 (670.4, 683.2)	262.4 (260.0, 264.7)	117.4 (116.2, 118.6)	227.3 (224.3, 230.3)	509.3 (508.0, 510.6)	209.8 (209.3, 210.3)	95.6 (95.3, 95.8)	192.0 (191.3, 192.6)

CI, confidence interval; FTL, full-term labour; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IR, incidence rate; PY, patient-years; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy.

SUPPLEMENTARY TABLE 8 Specialist referrals by age (GP sub-cohort)

Referrals	SPTLu IR per 1000 PY (95% CI)				FTL IR per 1000 PY (95% CI)			
	<1 year N$_{atrisk}$ = 847	1–2 years N$_{atrisk}$ = 846	3–5 years N$_{atrisk}$ = 730	6+ years N$_{atrisk}$ = 347	<1 year N$_{atrisk}$ = 16,393	1–2 years N$_{atrisk}$ = 16,384	3–5 years N$_{atrisk}$ = 14,404	6+ years N$_{atrisk}$ = 7980
Any	912.6 (827.6, 1001.8)	276.5 (247.0, 307.7)	266.1 (236.1, 297.8)	277.6 (233.0, 326.2)	546.7 (533.0, 560.6)	188.4 (183.0, 193.8)	198.3 (192.7, 203.9)	205.3 (197.4, 213.4)
Imaging	75.2 (57.2, 95.8)	30.8 (22.6, 40.3)	36.2 (27.1, 46.6)	47.5 (32.6, 65.2)	76.0 (71.7, 80.5)	23.1 (21.4, 24.9)	26.4 (24.6, 28.2)	35.1 (32.2, 38.0)
Therapies*	57.4 (41.9, 75.4)	22.6 (15.7, 30.8)	51.2 (40.1, 63.6)	53.6 (37.7, 72.5)	32.6 (29.8, 35.5)	15.6 (14.2, 17.0)	34.1 (32.0, 36.1)	42.6 (39.5, 45.9)
VI services	21.4 (12.5, 32.7)	20.7 (14.1, 28.5)	29.4 (21.3, 38.8)	14.5 (7.1, 24.6)	11.3 (9.7, 13.1)	12.3 (11.1, 13.6)	24.3 (22.6, 26.1)	20.0 (17.9, 22.2)
Surgeries	38.8 (26.3, 53.7)	21.3 (14.6, 29.2)	20.7 (14.0, 28.7)	18.7 (10.0, 30.0)	15.8 (13.9, 17.8)	15.8 (14.4, 17.3)	16.5 (15.1, 18.0)	18.7 (16.7, 20.9)
Mental health services	2.4 (0.2, 6.9)	6.8 (3.3, 11.5)	18.5 (12.3, 26.1)	30.9 (19.4, 45.2)	0.6 (0.3, 1.1)	0.1 (0.8, 1.5)	7.0 (6.1, 7.9)	21.9 (19.7, 24.3)

CI, confidence interval; FTL, full-term labour; IR, incidence rate; PY, patient-years; SPTLu, spontaneous preterm labour following an uncomplicated pregnancy; VI, visual impairment. *Therapies includes therapeutic interventions such as physical therapy, speech therapy, respiratory therapy, feeding therapy, etc.

chapter 6

CHAPTER 7

Respiratory morbidity, healthcare resource use, and cost burden associated with extremely preterm birth in The Netherlands

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ABSTRACT

Background

Extremely preterm (EP) infants have high rates of respiratory morbidity and correspondingly high healthcare resource utilization.

Objectives

Data from the PHARMO Perinatal Research Network were analyzed to quantify the burden of EP birth in the Netherlands.

Methods

A retrospective analysis included infants <28 weeks gestational age with a birth record in the Perinatal Registry (1999–2015) and data in the PHARMO Database Network. Outcomes of interest included select comorbidities, hospital readmissions, and costs of hospitalization and medication up to 1- and 2-years corrected age. Outcomes were stratified by birth period (1999–2005, 2000–2009, 2010–2015) and by diagnosis of bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD).

Results

The cohort included 168 EP infants (37 born 1999–2005, 51 born 2006–2009, 80 born 2010–2015). Median (Q1–Q3) birth weights decreased by birth period from 970 (840–1,035) g in 1999–2005 to 853 (695–983) g in 2010–2015. Overall, BPD and CLD were reported during the birth hospitalization in 40% and 29% of infants, respectively; rates of BPD increased and rates of CLD decreased by birth period. Eighty-four percent of EP infants had an additional comorbidity. Mean (standard deviation) costs of birth hospitalization were €110,600 (€73,000) for 1999–2005, €119,350 (€60,650) for 2006–2009, and €138,800 (€130,100) for 2010–2015. Birth hospitalization and total costs for up to 1- and 2-years corrected age were higher for infants with BPD and/or CLD than for those without either complication.

Conclusion

Healthcare resource utilization and costs for EP infants, especially for those with respiratory morbidities, increased between 1999 and 2015. Future cost-effectiveness analyses are essential to determine the economic impact of this change and underscore the need for new therapeutic interventions to decrease clinical sequelae in this vulnerable population.

INTRODUCTION

Infants born before 28 weeks gestational age (GA), termed extremely preterm (EP), have high rates of morbidity and mortality.[1-4] Survival to discharge of EP infants has increased in developed countries as a result of advances in neonatal and maternal care practices, such as antenatal corticosteroid use, less aggressive ventilation, and strict infection control practices.[5-9] The incidence of comorbidities of preterm birth has also improved, except for bronchopulmonary dysplasia (BPD), which has either remained steady or increased over time.[5,9-11] Greater use of active resuscitation and improvements in intensive care have led to increased survival and therefore persistence of BPD.[9,12] Because BPD is the most common complication of preterm birth[13] and is associated with prolonged hospitalization for pulmonary complications and development of chronic lung diseases (CLDs)[14-16], increased survival has resulted in increased healthcare resource utilization (HCRU) and costs. In 2010, Dutch guidelines lowered the recommend active care of neonates from 25 weeks GA to 24 weeks GA, with comfort care recommended for live births below this threshold. Two studies characterized the consequence of this change: Geurtzen et al.[17] surveyed physician's preferences on treatment decisions, and van Beek et al.[12] evaluated the impact of guideline implementation on neonatal survival, mortality, and timing of death. From the physician survey, the widest variation in individually preferred treatment options was around care at 24 and 25 weeks GA. Views differed on the lowest GA limit for interventions such as cesarean section and neonatologist presence at birth. Factors for restricting active treatment included congenital malformations, sub-normal GA size, and incomplete course of steroids, with a median of optional comfort care at parental request.[17] As expected, implementation of the guidelines on neonates led to an increase in NICU admissions at 24 weeks GA (27% for the 2007–2009 reference group to 69% for the 2011–2017 post-guideline change group, p<0.001) resulting in increased survival to discharge from 13% (reference group) to 34% (post-guideline change group, p<0.001). A downstream effect of the guideline change was a decrease in deaths attributed to respiratory insufficiency (respiratory distress syndrome [RDS] and BPD combined) from 34% for 2011–2014 to 23% for 2015–2017 (p=0.006). Overall (2011–2017), the cause of death for 29.9% of the non-surviving infants was due to respiratory issues (19.1% RDS, 10.8% BPD).[12] Characterizing the burden of BPD is critical for providing parents and healthcare providers with decision-making information and for developing strategies to improve outcomes. Because HCRU data are compiled based on local standards, developing data representative of an entire country is challenging. The PHARMO Perinatal Research Network (PPRN)[18], established by linkage of the Netherlands Perinatal Registry (Perined)[19] and the PHARMO Database Network (PHARMO)[20], uniquely captures birth and treatment information, including longitudinal pharmacy usage and hospital discharge records. This study was undertaken to broaden understanding of the burden of EP birth, using the Netherlands as a model. The main objective was to assess respiratory morbidities, hospital length of stay (LOS), HCRU, and costs for infants born <28 weeks GA. To assess the impact of respiratory complications, data were stratified by the presence of BPD and CLD and by birth period.

chapter **7**

METHODS

Study design and conduct

This retrospective analysis of PPRN data[18] included infants with a birth record in Perined and data in PHARMO. The latter is a population-based, patient-level network of healthcare databases (including inpatient and outpatient pharmacies, hospitals, and general practices). The longitudinal nature of PHARMO enables retrospective studies of >4 million residents (25%) of a well-defined population in the Netherlands for an average of 10 years.[21,22] For this study, the PHARMO Out-patient Pharmacy Database and Hospitalization Database were used. Perined contains validated data from ~95% of pregnancies in the Netherlands.[23] Data acquisition complied with rules governing the use of patient-level healthcare data in the Netherlands.

Analysis population

Data in the PPRN for all infants born preterm (24–37 weeks GA) from 1 January 1999 to 31 December 2015 were selected. To eliminate the effect of congenital malformations on the burden of EP birth, infants with one or more major congenital malformations, such as central nervous system malformations, diaphragmatic hernia, or gastroschisis, were excluded from the analysis. Infants were followed from birth until transfer out of the database, death, or the end of the study period (31 December 2016), whichever occurred first. Eligible infants were divided into four subgroups: EP, <28 weeks GA; very preterm, 28–<32 weeks GA; moderately preterm, 32–<34 weeks GA; and late preterm, 34–<37 weeks GA. This analysis focused on the subgroup of EP infants.

Outcome measures

BPD was defined as requiring supplemental oxygen for >28 days from the day of birth or still requiring supplemental oxygen at 36 postmenstrual weeks; this group also included infants identified through the ICD-10 hospitalization discharge code for BPD (P27.1). This definition was based on the literature and expert opinion (Supplementary Table 1). The severity of BPD could not be differentiated. CLD comprised several respiratory diagnoses (Supplementary Table 2) and was also identified by recorded use of pulmonary medications (i.e. furosemide, hydrochlorothiazide, inhaled steroids, systemic corticosteroids, inhaled bronchodilators, or inhaled mucolytics). The definition of CLD used in this study was based on the literature and expert opinion (Supplementary Table 1). We assessed CLD that occurred up to 1- and 2-years corrected age (CA; chronological age minus the number of weeks the infant was preterm). LOS was determined for the birth hospitalization and was categorized as short or long based on the median LOS. The number, rate, and LOS of all-cause hospital readmissions and pulmonary-related hospital readmissions were assessed at 1- and 2-years CA. Costs (in Euros [€]) are presented for the birth hospitalization, all hospitalizations (excluding the birth hospitalization), all outpatient dispensed medication, and total costs (hospitalizations and medication) up to and including 1- and 2-years CA per person-year (PY). Hospitalization costs were based on standard tariffs for nursing days in 2014 as prescribed by the Dutch Healthcare Authority[24], indexed to the year of hospital admission according to annual changes in the Netherlands Consumer Price Index (CPI).[25] The annual change in CPI is measured as the increase in the CPI compared to the corresponding

period in the previous year. Costs of outpatient dispensed medication were based on claim amounts recorded in the PHARMO Out-patient Pharmacy Database.[20]

Statistical analysis

Outcomes were stratified by birth period (1999–2005; 2006–2009; 2010–2015). Additional comorbidities (intraventricular hemorrhage, necrotizing enterocolitis, periodic limb movement, RDS, retinopathy of prematurity, and sepsis) were also summarized by birth period. No imputations were performed for missing data. Predictors of long versus short LOS of birth hospitalization were assessed using a multivariable Poisson regression model to yield relative risk. Potential predictors included BPD during birth hospitalization, CLD during birth hospitalization, birth weight, 5-min Apgar score, birth year, type of birth, mode of delivery, age and ethnicity of mother, parity, and the presence of at least one pregnancy risk factor. Significant predictors were identified from the sex- and GA-adjusted model when the lower bound of the 95% CI for the relative risk exceeded unity. Because of the descriptive nature of this study based on real-world data, no formal power analysis was performed, and no a priori hypotheses were tested.

Ethics approval and consent to participate

This article reports on a retrospective analysis of anonymized healthcare data and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Study population and available data

Of 101,329 infants born between 1999 and 2015, 7,328 (7%) were born preterm (<37 weeks GA). After exclusion of infants with congenital malformations (329/7,328 [4%]), the analysis cohort comprised 168 EP infants (very, moderate, and late preterm total sample sizes are shown in Figure 1). Based on Dutch perinatal guidelines, infants born <24 weeks GA were not identified. Of the 168 EP infants, 37 were born in 1999–2005, 51 in 2006–2009, and 80 in 2010–2015. Median (interquartile range, Q1–Q3) birth weights decreased over time: 970 (840–1,035) g for 1999–2005, 915 (750–1,090) g for 2006–2009, and 853 (695–983) g for 2010–2015. Birth hospitalization data were available for 76% of EP infants. Overall, 90% and 80% of EP infants had follow-up data available from birth until ≥1-year CA and ≥2-years CA, respectively (median = 5.0 years; interquartile range = 2.6–8.1). Total PYs of follow-up were 203 and 346 at 1- and 2-years CA, respectively. Infant and maternal characteristics of the population are summarized in Table 1. In this cohort, BPD and CLD were reported during the birth hospitalization in 40% and 29% of EP infants, respectively. The incidence of BPD increased with later birth periods (24% in 1999–2005, 41% in 2006–2009, 46% in 2010-2015) and the prevalence of CLD decreased (46% in 1999–2005, 33% in 2006–2009, 19% in 2010–2015). Birth weight for infants with BPD (alone or with CLD) was lower than the median for the overall cohort. While additional comorbidities (IVH, ROP, NEC, sepsis, PVL, or RDS) were reported in 83% (n=65) of infants without BPD or CLD, this rate rose to >90% for infants with BPD and/or CLD (Table 1). The rates of any additional comorbidities, and particularly RDS and

ROP, increased over successive birth periods, whereas the rates of other comorbidities remained mainly consistent across birth periods (Figure 2).

Pulmonary complications

Of 168 EP infants, 43% (rate/PY = 0.51) and 47% (rate/PY = 0.33) were diagnosed with other pulmonary complications during 1- and 2-years CA, respectively. Commonly recorded pulmonary complications included apnea (1- and 2-years CA = 18%), hypoxemia/hypoxia (1- and 2-years CA = 18%), respiratory infection (1-year CA = 13%; 2-years CA = 16%), and acute respiratory distress (1- and 2-years CA = 12%). During the 1- and 2-years CA periods, 50% (rate/PY = 0.41) and 59% (rate/PY = 0.29) of EP infants, respectively, received medication for pulmonary complications at least once. Inhaled bronchodilators (1-year CA = 36%; 2-years CA = 46%) were the most frequently recorded medications dispensed for pulmonary complications (1-year CA rate/PY = 0.30 and 2-years CA rate/PY = 0.22), followed by diuretics (1- and 2-years CA = 20%) and inhaled corticosteroids (1-year CA = 18%; 2-years CA = 24%).

					Source cohort						
					All infants born 1999–2015 from the PPRN with data available in the Out-patient Pharmacy and Hospitalisation Database N=101,329						

Source cohort born preterm (<37 weeks GA)
n=7328

Excluded
Infants with congenital malformations
n=329

Overall cohort
n=6999

	Extremely preterm[a] n=168 (2%)				Very preterm n=753 (11%)				Moderately preterm n=933 (13%)		Late preterm n=5145 (74%)		
GA	24[b]	25	26	27	28	29	30	31	32	33	34	35	36
n	14	24	46	84	122	154	206	271	372	561	954	1454	2737
(%)	(8)	(14)	(27)	(50)	(16)	(20)	(27)	(36)	(40)	(60)	(19)	(28)	(53)

FIGURE 1 Flow diagram showing the study population identified in the PPRN

[a] Infants born <28 weeks GA are the primary focus of the analyses reported in this article.
[b] Given the restrictive treatment policy of infants born at <24 weeks GA in the Netherlands, the study cohort only included pregnancies from 24 weeks GA onwards.
Abbreviations. GA, gestational age; PPRN, PHARMO Perinatal Research Network.

TABLE 1 Selected infant and maternal characteristics by morbidity status during birth hospitalization of infants in the PHARMO Perinatal Research Network born EP (<28 weeks GA) from 1999 to 2015

Status	Overall (N=168)	No BPD or CLD (n=78)	BPD only (n=41)	CLD only (n=23)	BPD and CLD (n=26)
GA at birth (weeks), n (%)					
24	14 (8)	3 (4)	7 (17)	2 (9)	2 (8)
25	24 (14)	10 (13)	6 (15)	3 (13)	5 (19)
26	46 (27)	18 (23)	10 (24)	5 (22)	13 (50)
27	84 (50)	47 (60)	18 (44)	13 (57)	6 (23)

TABLE 1 Selected infant and maternal characteristics by morbidity status during birth hospitalization of infants in the PHARMO Perinatal Research Network born EP (<28 weeks GA) from 1999 to 2015 (continued)

| Status	Overall (*N*=168)	No BPD or CLD (*n*=78)	BPD only (*n*=41)	CLD only (*n*=23)	BPD and CLD (*n*=26)
Birth period, *n* (%)					
1999–2005	37 (22)	16 (21)	4 (10)	12 (52)	5 (19)
2006–2009	51 (30)	23 (29)	11 (27)	7 (30)	10 (38)
2010–2015	80 (48)	39 (50)	26 (63)	4 (17)	11 (42)
Male, *n* (%)	81 (48)	36 (46)	14 (34)	16 (70)	15 (58)
Median (IQR) birth weight, g	900 (743–1,038)	955 (790–1,080)	815 (715–940)	900 (835–1,160)	775 (655–945)
5-min Apgar score, *n* (%)					
0–4	8 (5)	2 (3)	3 (7)	2 (9)	1 (4)
5–7	76 (45)	36 (46)	20 (49)	8 (35)	12 (46)
8	41 (24)	17 (22)	10 (24)	6 (26)	8 (31)
9	33 (20)	17 (22)	7 (17)	4 (17)	5 (19)
10	10 (6)	6 (8)	1 (2)	3 (13)	0
Follow-up, years CA					
≥1, *n* (%)	152 (90)	71 (91)	36 (88)	22 (96)	23 (88)
≥2, *n* (%)	135 (80)	64 (82)	29 (71)	22 (96)	20 (77)
Median (IQR)	5.0 (2.6–8.1)	5.0 (2.9–7.7)	3.2 (1.8–5.8)	8.9 (4.8–13.8)	5.4 (2.6–8.7)
Mode of delivery, *n* (%)					
Vaginal[a]	81 (48)	37 (47)	18 (44)	12 (52)	14 (54)
Primary caesarean section	65 (39)	28 (36)	18 (44)	9 (39)	10 (38)
Secondary caesarean section	21 (13)	12 (15)	5 (12)	2 (9)	2 (8)
Unknown	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Mother's age at delivery, mean (SD), y	31 (5)	31 (5)	30 (5)	30 (5)	33 (5)
Parity, *n* (%)					
0	126 (75)	58 (74)	30 (73)	17 (74)	21 (81)
1	27 (16)	14 (18)	5 (12)	4 (17)	4 (15)
2	11 (7)	5 (6)	3 (7)	2 (9)	1 (4)
≥3	4 (2)	1 (1)	3 (7)	0	0
Most frequent pregnancy risk factors, *n* (%)[b]					
Prior preterm delivery	28 (17)	9 (12)	11 (27)	2 (9)	6 (23)
Hypertension	21 (13)	8 (10)	8 (20)	3 (13)	2 (8)
Antepartum hemorrhage	10 (6)	6 (8)	2 (5)	1 (4)	1 (4)

chapter

7

TABLE 1 Selected infant and maternal characteristics by morbidity status during birth hospitalization of infants in the PHARMO Perinatal Research Network born EP (<28 weeks GA) from 1999 to 2015 (continued)

Status	Overall (N=168)	No BPD or CLD (n=78)	BPD only (n=41)	CLD only (n=23)	BPD and CLD (n=26)
Presence of additional comorbidities, n (%)					
Any	148 (88)	65 (83)	38 (93)	21 (91)	24 (92)
RDS	118 (70)	47 (60)	34 (83)	16 (70)	21 (81)
Sepsis	95 (57)	34 (44)	30 (73)	15 (65)	16 (62)
ROP	32 (19)	9 (12)	10 (24)	2 (9)	11 (42)
NEC	21 (13)	10 (13)	8 (20)	1 (4)	2 (8)
IVH	19 (11)	6 (8)	5 (12)	4 (17)	4 (15)
PVL	17 (10)	4 (5)	5 (12)	5 (22)	3 (12)

Abbreviations: BPD, bronchopulmonary dysplasia; CA, corrected age; CLD, chronic lung disease; EP, extremely preterm; GA, gestational age; IQR, interquartile range; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

[a]No vaginal deliveries were induced.

[b]At least one of the following pregnancy risk factors was recorded: placental abruption; antepartum hemorrhage; blood clotting disorders; diabetes (including gravidarum); eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; hypertension; intrauterine growth restriction; intra-amniotic infection; placenta previa; pre-eclampsia; prior caesarean delivery; prior preterm delivery; severe or pregnancy affecting alcohol use; severe or pregnancy affecting drug use; recurrent urinary tract infection; or uterine fibroid.
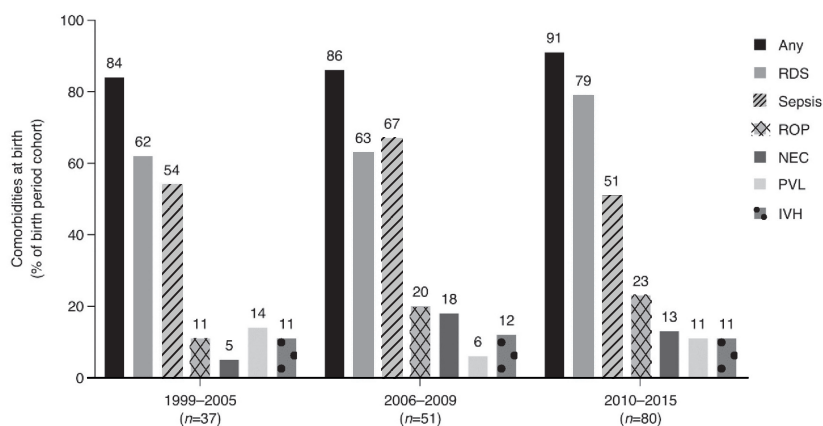
FIGURE 2 Percentage of infants with additional comorbidities at birth by birth period

Birth hospitalization and readmissions

Median LOS of birth hospitalization for EP infants was 81 days. Mean (standard deviation [SD]) of short and long birth hospitalization LOS was 57 (25) and 107 (19) days, respectively. In the adjusted model, CLD during birth hospitalization, GA at birth, and maternal pregnancy risk factors were significantly predictive of long LOS (Table 2). Among the infants born EP, 61% (rate/PY = 0.51) and 68% (rate/PY = 0.33) developed CLD in the periods up to 1- and 2-years CA, respectively. For infants with CLD up to 1- year CA, 47 (46%) were also diagnosed with BPD. Rates of all-cause

and pulmonary-related hospital readmissions were highest in the subgroup with both BPD and CLD (Figure 3(a)). Compared with infants without BPD or CLD, all-cause and pulmonary readmission rates were higher for infants with CLD alone but not for infants with BPD alone. The rates of all-cause and pulmonary-related hospital readmissions showed a trend of increase by birth period (Figure 3(b)).

TABLE 2 Adjusted model predicting long LOS of birth hospitalization[a] among EP infants (<28 weeks GA) in the PHARMO Perinatal Research Network born from 1999 to 2015

Variable	Short LOS[b] (n=63)	Long LOS[b] (n=64)	Adjusted[c] RR (95% CI)
LOS, days			
Mean (SD)	57 (25)	107 (19)	
Median (IQR)	68 (47–75)	105 (91–118)	
BPD during birth hospitalization, n (%)[d]			
No	46 (73)	30 (47)	
Yes	17 (27)	34 (53)	
CLD during birth hospitalization, n (%)			
No	52 (83)	27 (42)	
Yes	11 (17)	37 (58)	2.13 (1.51–3.01)
GA at birth (weeks), n (%)			
24	3 (5)	7 (11)	1.83 (1.07–3.15)
25	5 (8)	13 (20)	1.83 (1.25–2.69)
26	11 (17)	20 (31)	1.43 (0.94–2.17)
27	44 (70)	24 (38)	1 (reference)
Sex, n (%)			
Female	29 (46)	34 (53)	1.34 (0.99–1.82)
Male	34 (54)	30 (47)	1 (reference)
Birth weight, g, n (%)[d]			
<600	1 (2)	8 (13)	
600 to <700	5 (8)	10 (16)	
700 to <800	4 (6)	12 (19)	
800 to <900	5 (8)	12 (19)	
900 to <1,000	16 (25)	11 (17)	
1,000 to <1,100	13 (21)	5 (8)	
≥1,100	19 (30)	6 (9)	
Pregnancy risk factors,[e] n (%)			
No	44 (70)	31 (48)	1 (reference)
Yes	19 (30)	33 (52)	1.49 (1.07–2.07)

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CLD, chronic lung disease; EP, extremely preterm; GA, gestational age; IQR, interquartile range; LOS, length of stay; RR, relative risk; SD, standard deviation.
[a]Birth hospitalization data were available for 127 EP infants (76%).
[b]Birth hospitalization LOS was categorized based on its median (81 days).
[c]Sex and gestational age at birth were forced into the adjusted model. Variables with a crude association at *p*<0.10 were retained in the adjusted model at *p*<0.05. In addition to variables presented, tested variables included 5-minute Apgar score, birth year, type of birth, mode of delivery, mother's age and ethnicity, and parity.
[d]Not included in the adjusted model after backward selection.
[e]At least one of the following pregnancy risk factors was recorded: placental abruption; antepartum hemorrhage; blood clotting disorders; diabetes (including gravidarum); eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; hypertension; intrauterine growth restriction; intra-amniotic infection; placenta previa; pre-eclampsia; prior caesarean delivery; prior preterm delivery; severe alcohol use/pregnancy affecting alcohol use; severe drug use/pregnancy affecting drug use; recurrent urinary tract infection; or uterine fibroid.
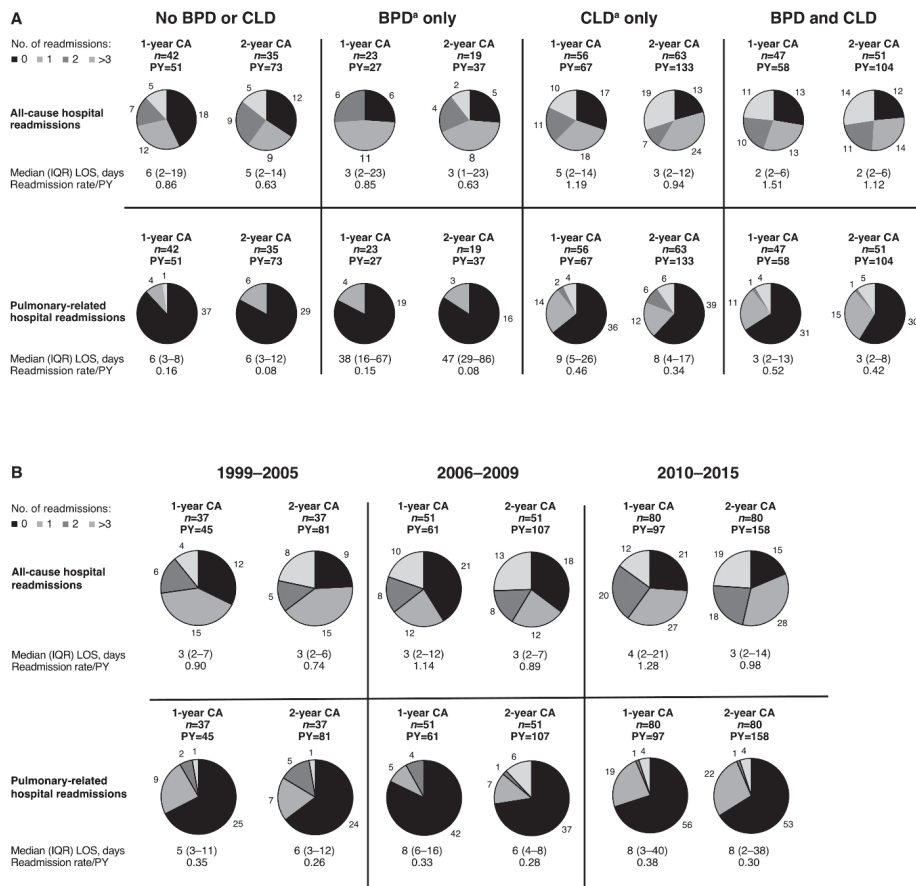
FIGURE 3 Frequency of hospital readmissions at 1- and 2-years CA after birth among EP (<28 weeks gestational age) infants in the PHARMO Perinatal Research Network.

(a) Infants with a birth record from 1999 to 2015 by pulmonary morbidity cohort.

(b) Frequency of hospital readmissions at 1- and 2-years CA after birth among EP infants in the PHARMO Perinatal Research Network with a birth record from 1999 to 2005, 2006 to 2009, and 2010 to 2015.

[a] Within the time periods of outcome assessment (note: cohort sizes can therefore be larger than those presented at birth).

Abbreviations. BPD, bronchopulmonary dysplasia; CA, corrected age; CLD, chronic lung disease; EP, extremely preterm; IQR, interquartile range; LOS, length of stay; PY, person-year.

Costs of healthcare resource utilization

The mean (SD) costs of birth hospitalization for the overall cohort of EP infants was €126,350 (€101,900) and increased by birth period (€110,600 [€73,000] in 1999–2005; €119,350 [€60,650] in 2006–2009; €138,800 [€130,100] in 2010–2015 [Figure 4(b)]). Costs for birth hospitalization were higher for infants with BPD or CLD (or both) than for those without either respiratory complication (Figure 4(a)); for EP infants with neither BPD nor CLD, mean (SD) birth hospitalization costs were €85,050 (€65,600), compared with €188,650 (€156,300) for infants with BPD and CLD. In the periods up to 1- and 2-years CA, total costs (including non-birth hospitalizations

and medication) for all causes were higher for EP infants with both BPD and CLD than without BPD or CLD, BPD alone, or CLD alone (Figure 5(a)). At 1- year CA, hospitalization costs per PY (excluding birth hospitalization) were €3,800, €3,650, €3,450, and €12,950 for infants with neither BPD nor CLD, BPD alone, CLD alone, and both BPD and CLD, respectively. At 2-years CA, hospitalization costs were €2,350, €2,650, €2,500, and €8,300, respectively. In the periods up to 1- and 2-years CA, total costs increased by birth period (Figure 5(b)).
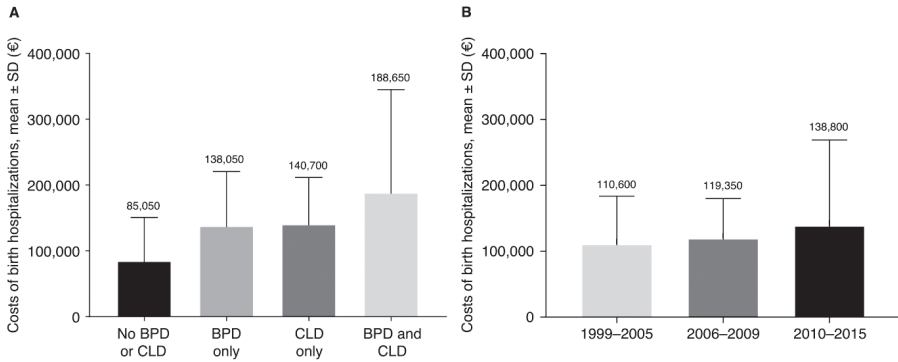
FIGURE 4 Mean costs of birth hospitalization for EP infants (<28 weeks gestational age).

(a) by pulmonary morbidity;
(b) by birth period.
Abbreviations. BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; EP, extremely preterm; SD, standard deviation.
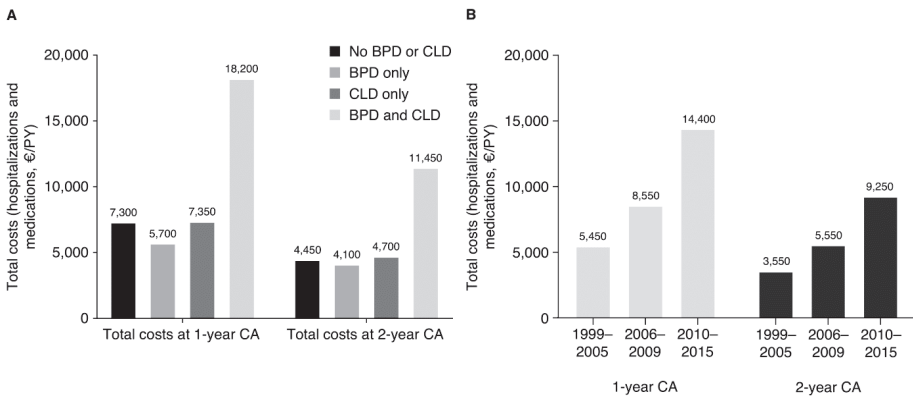
FIGURE 5 Costs of health care resource utilization among EP infants (<28 weeks gestational age).

(a) by pulmonary morbidity;
(b) by birth period.
Costs are for infants with data available on birth hospitalization.
Abbreviations. BPD, bronchopulmonary dysplasia; CA, corrected age; CLD, chronic lung disease; EP, extremely preterm; PY, person-year.

chapter

7

DISCUSSION

Results of this population-based study using data from the PPRN provide insight into the pulmonary outcomes, resource needs, and cost impact associated with preterm birth, adding to previous evidence that greater burdens are associated with pulmonary complications[12]. Taken as an example, these data from the Netherlands also provide support for institutional estimates of HCRU in Europe within the context of EP birth with and without BPD or CLD. This study quantified the respiratory burden and HCRU among EP infants born in the Netherlands between 1999 and 2015. It demonstrates the high prevalence of BPD and CLD among EP infants (40% and 29%, respectively, during birth hospitalization), and high hospital readmission rates particularly among infants with CLD alone and infants with both BPD and CLD. Significant predictors of a long LOS for the birth hospitalization were CLD during birth hospitalization, GA at birth, and pregnancy risk factors. Analysis of these data by birth period suggested lower mean birth weights, higher rates of BPD, lower rates of CLD, and an increase in hospitalization and medication costs with more recent birth periods. On the other hand, rates of individual comorbidities that are often observed in preterm infants, such as IVH and NEC, did not seem to change over time. A lower incidence of BPD was estimated by de Waal et al.[26], who performed a prospective, population-based cohort study of preterm infants born in the Netherlands in 2007. In a cohort of 215 infants who survived long enough to receive neonatal care, 33.3%, 29.1%, and 20.9% of infants born at 24, 25, and 26 weeks GA, respectively, were diagnosed with BPD. BPD based on "oxygen dependency at 36 post-menstrual weeks" was identified in the study using 2001 guidelines, but the use of International Classification of Diseases, 10th Revision (ICD-10) codes[27] was not specified in the publication. The present study identified BPD as needing supplemental oxygen for either >28 days or at 36 postmenstrual weeks (based on Perined records) and also included infants identified through the ICD-10 hospitalization discharge code for BPD, which may explain the higher incidence of BPD in our study compared with the incidence of BPD in the earlier study in the Netherlands.[23] Data from Europe on outcomes of preterm birth are limited. A retrospective evaluation performed in the Netherlands that compiled postpartum (up to 1 year) neonatal HCRU data from a prospective cohort study and three randomized clinical trials showed higher neonatal care costs were associated with lower GA.[28] Mean costs of €60,783–€88,052 for singleton infants born at 24–28 weeks GA were primarily driven by LOS in a neonatology ward, particularly in intensive and medium care units. Maier et al.[29] observed LOS of birth hospitalization for preterm infants ranging from 52.4 to 76.5 days across 10 regions in nine European countries. The median LOS was 55 days in 2011–2012 for infants born between 22þ0 and 31þ6 weeks GA. For infants born 25–29 weeks GA, the adjusted mean LOS was 61.6 days. Our analyses support that a main driver of increased LOS is respiratory complications. The analyses by birth period, carried out in an effort to highlight where evolving treatment strategies were having an effect, were limited somewhat by the small numbers of infants following stratification. Not surprisingly, though, the change in Dutch guidelines in 2010 to provide active care as early as 24 weeks GA resulted in an increase in the number of hospital readmissions within the first 2 years CA, and higher overall costs, especially for infants with both BPD and CLD. Our study generates a unique set of longitudinal data combining multiple settings of care by linkage of Perined to the PHARMO Database Network for analysis of preterm birth complications and real-world HCRU. Our definitions of BPD and CLD

may be useful for future researchers in determining cost drivers of preterm birth. We used standard tariffs for nursing days for the calculation of costs of hospitalizations. In the Netherlands, these tariffs are based on average costs of diagnostics, associated specialist fees, and inpatient medication.[24] As our data indicate, the individual costs may vary significantly depending on the presence and number of comorbidities being treated. Another limitation of this study is that our data set did not include complete birth hospitalization data for all infants; transfers from the birth hospital to a separate site with a neonatal intensive care unit were recorded but such transfers may have been recorded differently at different institutions. If transfers were recorded as readmissions rather than a continuation of the birth hospitalization, this would have confounded estimated readmissions and/or LOS. Additionally, infants who died shortly after birth (i.e. the most severe cases of preterm birth) are under-represented in the study cohort because they were less likely to be linked from Perined to the PHARMO Database Network. Under-representation of these infants could have resulted in an overestimate of the overall costs but an underestimate of BPD as well as CLD. Lastly, pulmonary outcomes may have been under-recorded. The Hospitalization Database requires only one primary discharge diagnosis, whereas secondary diagnoses are optional. Under-recording of events along with misclassification of infants with BPD or CLD in the "no BPD or CLD" group could have resulted in underestimation of HCRU and cost differences.

CONCLUSION

These data highlight and quantify over time the healthcare burden associated with EP birth and the associated increase in pulmonary complications. Our findings of high prevalence of BPD and CLD among EP infants, along with accompanying high HCRU which has increased over time, underscore the need for new interventions in this vulnerable population and provide a basis for future cost-effectiveness analyses.

TRANSPARENCY

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EH, JO, and FP-vB are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. CS and VN are employees of Takeda and own stocks/options in Takeda. SPS was an employee of Takeda at the time of the study. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions
EH, JO, FP-vB, CS, and SPS contributed to the study conception and design. Data collection, analysis, and interpretation were performed by EH, JO, and FP-vB. CS, VN, and SPS participated in data

interpretation. All authors participated in the drafting and revision of this manuscript, and each gave their final approval prior to its submission.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 Overview of BPD and CLD definitions in clinical practice and clinical trials

	Definition	Source	Notes
BPD	Oxygen requirement at 36 weeks PMA in infants with birth weight <1.5 kg	Shennan AT, Dunn MS, Ohlsson A, et al. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. *Pediatrics.* 1988;82:527–532. Vermont Oxford Network. Manual of operations: Part 2. Data definitions & infant data forms. Release 23.2. 2019. https://vtoxford.zendesk.com/hc/en-us/article_attachments/360024732954/Manual_of_Operations_Part_2_v23.2.pdf. Accessed 30 September 2021.	Definition adopted by Vermont Oxford Network
	In newborns with <32 weeks gestational age, oxygen support requirement (>21%) for ≥28 days and a subsequent assessment at 36 weeks PMA or discharge, whichever criterion is met first	Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;63:1723–1729.	Definition adopted by Eunice Kennedy Shriver National Institute of Child Health and Development Neonatal Research Network (NICHD)
	Infants (corrected age 36 ± 1 weeks) treated with mechanical ventilation, continuous positive airway pressure, or with supplemental oxygen concentration >0.30 or supplemental oxygen <0.30 who failed a timed stepwise reduction to room air	Walsh MC, Wilson-Costello D, Zadell A, et al. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol.* 2003;23:451–456.	BPD physiological definition with a room-air challenge

SUPPLEMENTARY TABLE 1 Overview of BPD and CLD definitions in clinical practice and clinical trials (continued)

	Definition	Source	Notes
CLD	Defined based on validated algorithm shown to be more accurate than the oxygen at 36 weeks measure and coded as follows: 1. In infants at 36 weeks PMA, CLD is equal to the value of oxygen at 36 weeks. This may include infants who: • Were never transferred to another hospital or infants who were readmitted to a centre following initial transfer • Were in the "transferred to" hospital on the Date of Week 36 and who were subsequently readmitted to a centre 2. In infants discharged home at ≥34 weeks PMA and before the date of 36 weeks PMA, CLD is equal to the value of oxygen at discharge 3. In infants transferred to another hospital at ≥34 weeks PMA and before the date of 36 weeks PMA, CLD is equal to oxygen at discharge, unless the infant is re-admitted, and Definition 1 applies	Vermont Oxford Network. Chronic lung disease (CLD). https://nightingale.vtoxford.org/help/!SSL!/WebHelp/CLD36.htm. Accessed 25 August 2019. Birenbaum HJ, Pfoh ER, Helou S, et al. Chronic lung disease in very low birth weight infants: persistence and improvement of a quality improvement process in a tertiary level neonatal intensive care unit. *J Neonatal-Perinatal Med.* 2016;9:187–194.	Definition adopted by Vermont Oxford Network
	Analysis of all systematic reviews completed by the Cochrane Neonatal Review Group and published in the Cochrane Library (up to November 2013) reported CLD definitions, including oxygen requirement at: • 36 weeks PMA • 28 days postnatal age	Ioannidis JPA, Horbar JD, Ovelman CM, et al. Completeness of main outcomes across randomized trials in entire discipline: survey of chronic lung disease outcomes in preterm infants. *BMJ.* 2015;350:h72.	Overview of CLD definitions in clinical trials identified substantial variability in how CLD is defined

BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; PMA, postmenstrual age.

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications

Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
Bronchopulmonary dysplasia (BPD)	6310 Bronchopulmonale dysplasie >28 dagen O2			P27.1	Bronchopulmonary dysplasia originating in the perinatal period
	6320 Bronchopulmonale dysplasie na week 36 nog O2				
Chronic lung disease (CLD)ª	6330 Chron. Pulm insuff. Preamat. CPIP	770.7	Chronic respiratory disease arising in the perinatal period	P27 (excl. P27.1)	Chronic respiratory disease originating in the perinatal period
	6340 Mikity Wilson	277.0	Cystic fibrosis	E84	Cystic fibrosis
	6390 Overige chronische longziekten	416	Chronic pulmonary heart disease	I27.8	Other specified pulmonary heart diseases
		490	Bronchitis, not specified as acute or chronic	I27.9	Pulmonary heart disease, unspecified
		491	Chronic bronchitis	J40	Bronchitis, not specified as acute or chronic
		492	Emphysema	J41	Simple and mucopurulent chronic bronchitis
		494	Bronchiectasis	J42	Unspecified chronic bronchitis
		496	Chronic airway obstruction, not elsewhere classified	J43	Emphysema
		500	Coal workers' pneumoconiosis	J44	Other chronic obstructive pulmonary disease
		501	Asbestosis	J47	Bronchiectasis
		502	Pneumoconiosis due to other silica or silicates	J60	Coal workers' pneumoconiosis
		503	Pneumoconiosis due to other inorganic dust	J61	Pneumoconiosis due to asbestos and other mineral fibres
		505	Pneumoconiosis, unspecified	J62	Pneumoconiosis due to dust containing silica
		506.4	Chronic respiratory conditions due to fumes and vapours	J63	Pneumoconiosis due to other inorganic dusts

chapter 7

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
		515	Postinflammatory pulmonary fibrosis	J64	Unspecified pneumoconiosis
Chronic lung disease (CLD)ᵃ continued		516	Other alveolar and parietoalveolar pneumonopathy	J65	Pneumoconiosis associated with tuberculosis
				J68.4	Chronic respiratory conditions due to chemicals, gases, fumes, and vapours
				J84	Other interstitial pulmonary diseases
				J96	Respiratory failure, not elsewhere classified
Intraventricular hemorrhage (IVH)	4130 Intraventriculair >50 % ventrikel gevuld	772.1	Intraventricular haemorrhage of foetus or newborn	P52	Intracranial non-traumatic haemorrhage of foetus and newborn
	4131 Links				
	4132 Rechts				
	4133 Beide				
	4140 Parenchymbloeding				
	4141 Links				
	4142 Rechts				
	4143 Beide				
Retinopathy of prematurity (ROP)	4600 Retinopathy of prematurity	362.2	Retinopathy of prematurity	H35.1	Retinopathy of prematurity
	4610 Graad I				
	4620 Graad II				
	4630 Graad III				
	4639 Overig				
	4640 Graad IV, ook graad V				
	4611 Links nasaal				

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
	4612	Links temporaal			
	4613	Rechts nasaal			
Retinopathy of prematurity (ROP) continued	4614	Rechts temporaal			
	4619	Overig			
	4621	Links nasaal			
	4622	Links temporaal			
	4623	Rechts nasaal			
	4624	Rechts temporaal			
	4629	Overig			
	4631	Links nasaal			
	4632	Links temporaal			
	4633	Rechts nasaal			
	4634	Rechts temporaal			
	4641	Links nasaal			
	4642	Links temporaal			
	4643	Rechts nasaal			
	4644	Rechts temporaal			
	4649	Overigv			
	4690	Graad niet gespecificeerd			
	4691	Links nasaal			
	4692	Links temporaal			
	4693	Rechts nasaal			
	4694	Rechts temporaal			

chapter

7

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

	Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
	4699	Overig				

Other complications

	Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
Necrotizing enterocolitis (NEC)	7400	Necrotiserende enterocolitis	777.5	Necrotizing enterocolitis in newborn	P77	Necrotizing enterocolitis of foetus and newborn
	7410	Suspect				
	7420	Pneumatosis				
	7430	Perforatie				
Sepsis	1200	Sepsis	036.2	Meningococcaemia	A39.1	Waterhouse-Friderichsen syndrome
	1210	Streptococcus	036.3	Waterhouse-Friderichsen syndrome, meningococcal	A39.2	Acute meningococcaemia
	1211	Bèta-hemolytische Streptococcus	038	Septicaemia	A39.3	Chronic meningococcaemia
	1219	Andere Streptococcus	054.5	Herpetic septicaemia	A39.4	Meningococcaemia, unspecified
	1220	Staphylococcus	112.5	Disseminated candidiasis	A40	Streptococcal septicaemia
	1221	Staphylococcus aureus			A41	Other septicaemia
	1222	MRSA			B00.7	Disseminated herpes viral disease
	1223	Staphylococcus epidermidis			B37.7	Candidal sepsis
	1229	Andere Staphylococcus				
	1230	Listeria monocytogenes				
	1240	Andere Gram-positieve bacterie				
	1250	Gram-negatieve bacterie				
	1251	E. coli				
	1252	Pseudomonas				
	1253	Klebsiella				

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

	Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
Sepsis continued	1254	Enterobacter				
	1259	Andere Gram-negatieve bacterie				
	1261	Chlamydia				
	1262	Ureaplasma urealyticum				
	1270	Schimmel / gist				
	1280	Virus				
	1281	Herpesvirus				
	1289	Ander virus				
	1290	Overige en onbekende verwekker				
	1291	Niet nader gespecificeerde bacterie				
	1292	Overige gespecificeerde verwekker				
	1293	Niet gespecificeerde verwekker				
	1294	Onbekende verwekker				
Periventricular leukomalacia	4210	PVL graad I				
	4220	PVL graad II				
	4230	PVL graad III				
	4240	PVL graad IV				
Respiratory distress syndrome	6100	IRDS	769	Respiratory distress syndrome in newborn	P22.0	Respiratory distress syndrome of newborn
Other pulmonary complications						
Pulmonary hypertension			416.0	Primary pulmonary hypertension	I27.0	Primary pulmonary hypertension
Respiratory infection (including bronchitis, bronchiolitis, and croup [barking cough])			460-466	Acute respiratory infections	J00-J06	Acute upper respiratory infections
					J20-J22	Other acute lower respiratory infections

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
Pneumonia (including respiratory syncytial virus)		079.6, 480-486	Pneumonia/respiratory syncytial virus	J12-J18, J21.0, B97.4	Pneumonia/respiratory syncytial virus
Influenza		487	Influenza	J09-J11	Influenza
Asthma		493	Asthma	J45, J46	Asthma Status asthmaticus
Reactive airway disease		493.9	Asthma, unspecified	J45.9	Asthma, unspecified
		519.9	Other diseases of respiratory system, not elsewhere classified	J98.9	Respiratory disorder, unspecified
Respiratory failure		518.8	• Other diseases of lung, including: • acute respiratory failure • other pulmonary insufficiency, not elsewhere classified • chronic respiratory failure • acute and chronic respiratory failure • other diseases of lung, not elsewhere classified	P28.5	Respiratory failure of newborn
Acute respiratory distress		518.8	See above	P22	Respiratory distress of newborn
Tracheostomy complications		519.0	Tracheostomy complications		
Tachypnoea		770.6	Transitory tachypnoea of newborn	P22.1	Transient tachypnoea of newborn

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
Hypoxaemia/hypoxia		770.8	Other respiratory problems after birth, including: • primary apnoea of newborn • other apnoea of newborn • cyanotic attacks of newborn • respiratory failure of newborn • aspiration of postnatal stomach contents with/without respiratory symptoms • respiratory arrest of newborn • hypoxemia of newborn • other respiratory problems after birth	R09.0	Asphyxia and hypoxaemia
		799.0	Asphyxia and hypoxaemia		
Apnoea		770.8	Other respiratory problems after birth, including: • primary apnoea of newborn • other apnoea of newborn • cyanotic attacks of newborn • respiratory failure of newborn • aspiration of postnatal stomach contents with/without respiratory symptoms • respiratory arrest of newborn • hypoxemia of newborn • other respiratory problems after birth	P28.3	Primary sleep apnoea of newborn
				P28.4	Other apnoea of newborn

chapter

7

SUPPLEMENTARY TABLE 2 Diagnosis codes for complications (continued)

Perined (LNR)	Description (Dutch)	ICD-9-CM	Description (English)	ICD-10	Description
Cyanosis		782.5	Cyanosis	R23.0	Cyanosis
Dyspnoea		786.09	Other symptoms involving respiratory system and other chest symptoms	R06.0	Dyspnoea
Wheezing		786.09	Other symptoms involving respiratory system and other chest symptoms	R06.2	Wheezing
Stridor		786.1	Stridor	R06.1	Stridor

chapter 7

PART IV

CHAPTER 8

General discussion

INTRODUCTION

The general aim of this thesis was to set up and explore a research network facilitating population-based perinatal pharmacoepidemiological studies in both mother and child, focusing on potentially harmful medication use during pregnancy and outcomes associated with preterm birth. This chapter will provide a general discussion of the main findings of this thesis. Furthermore, methodological considerations, practical implications and future recommendations are provided.

NEEDS AND POSSIBILITIES IN PERINATAL PHARMACOEPIDEMIOLOGICAL RESEARCH

Clinical trials have well-known limitations to study drug safety in vulnerable populations, including pregnant women and their offspring. Alternatively, real-world data (RWD) and related observational population-based research have the potential to fill this gap as a non-invasive method for studies in these groups. Until now, there were no large-scale registrations available in the Netherlands that include routinely collected data on maternal, pregnancy and child outcomes. Medical records are documented during the perinatal period by different involved caregivers using separate non-linked information systems. Even broader, such linked information sources are scarcely available in Europe and thus ask for pioneer initiatives. Therefore, the PHARMO Perinatal Research Network (PPRN) was set up as a resource for perinatal and paediatric real-world evidence (RWE) research by linking data from existing registrations (**Chapter 2**). Using the population-based PPRN we can perform pharmacoepidemiological research in linked mother and child populations, studying life course outcomes up to more than 20 years after birth. As one of the main ambitions, evidence can be compiled on the potential risks associated with specific medication used before and during pregnancy. Treating physicians rely on this information, incorporated into treatment guidelines, when balancing drugs' risks and benefits. This applies not only to new drugs or those for which evidence is scarce, but also to drugs that have been available for many years and considered safe.[1] Altogether, the PPRN provides many possibilities for perinatal pharmacoepidemiological research and applications much broader than those described in the current thesis. With yearly updates, the PPRN currently comprises detailed information on more than 1.3 million pregnancies from 1999 onwards, which can be linked to electronic health records originating from thousands of GPs, hundreds of pharmacies and dozens of clinical laboratories that are part of the PHARMO Database Network. Furthermore, they can be linked to other national registries, including hospital admissions and out-patient hospital visits[2], the nationwide registry of histo- and cytopathology[3], and the Netherlands Cancer Registry[4].

POTENTIALLY HARMFUL MEDICATION USE

The potentially harmful effects on the mother and child of medication used before and during pregnancy have been widely acknowledged and can lead to major birth defects. It is therefore undisputed that safe pharmaceutical care around pregnancy is of vital importance.[5,6] Despite this, drug exposure during pregnancy is common in Europe and the US.[7-9] In this thesis, a high prevalence

of exposure to potentially harmful medication during pregnancy over the last two decades was found. Most notably, medication use was highest among vulnerable groups, such as women with chronic disease or those of lower socioeconomic status (**Chapter 3**). Also noticeable was the trend towards the use of newer drugs with still ill-defined pregnancy risks. For anti-seizure medication specifically, only a small proportion of women switched to a safer alternative before or during their pregnancy. There seemed to be a need to educate certain groups, such as GPs, who prescribed the majority of anti-seizure medication (**Chapter 4**). Altogether, these findings on potentially harmful medication use are of sufficient clinical importance to prompt a call towards safer medication management around pregnancy, especially early in pregnancy. The unchanged high use of medication with known risks suggests a potential deficit of risk perception among healthcare providers and pregnant women. In daily clinical practice, treating physicians rely on available evidence on risks when making decisions and daily face difficulties balancing drugs' risks and benefits.[10] These results highlight the need for an expansion of medication risk knowledge and communication by means of targeted preventive interventions, research and education programs, so that specific recommendations can be made for medication use during pregnancy.

AWARENESS ISSUE

Although GPs act as gatekeeper to hospital- and specialist care in the Netherlands, midwives have the lead in providing pregnancy care.[11] Despite GPs declined involvement in obstetric care[12,13], they remain important providers of routine medical care for pregnant women parallel to the antenatal care provided by midwives and gynaecologists.[14] They are still responsible for the large majority of drug prescriptions during pregnancy, which includes medication with potential safety risks in one-third of Dutch pregnancies (**Chapter 3 & 4**). This underscores the GPs' vital role in optimisation of pregnancy-related care.[15] Collaboration between GPs and midwives has been widely encouraged and GPs acknowledge their role in accomplishing safe pregnancy care.[16-20] In practice, it is suggested that the involvement of GPs in this collaborative care needs further reinforcement.[14,17,18,21] In one of the studies that was part of this thesis a potential awareness issue was demonstrated: women without a GP-recorded pregnancy confirmation were significantly more likely to be prescribed hazardous medication than women with such a confirmation (**Chapter 5**). A similar awareness issue may exist among secondary care providers, since switching to safer anti-seizure medication alternatives was not common in one of the other studies that was part of this thesis (**Chapter 4**). Although pregnancy registration by GPs improved over the years, still suboptimal use seems to be made of the available information systems for appropriate drug surveillance.

PRECONCEPTION CARE

The key challenge for improved registration lies with shared responsibility, in which collaborative care is pivotal. Caregivers should be supported and educated in maintaining accurate and readily available patient records for effective communication and information transfer to other involved caregivers. The role of pharmacists should not be forgotten, as they also need to be aware of potential safety risks when dispensing medication. Also, through standardisation of information systems there

chapter

8

should be clear procedures for recording and communicating information so that healthcare providers know what is expected from them. Public awareness should be improved by means of population-wide education incorporating collaborative preconception care, which is currently inadequate.[17,18,22-24] In addition to caregivers acknowledging their duty here, this would ultimately increase women's self-awareness recognising their own responsibility in timely informing caregivers about (planned and unplanned) pregnancy, so that appropriate action can be taken. Interventions should be set up in such a way that women are informed about the potential pregnancy risks of the medicines they use as early as possible, so that the patient is alert if she considers to conceive.

OUTCOMES ASSOCIATED WITH PRETERM BIRTH

A common concern in pregnancy care is gestational age, by which prenatal care is guided. Increasing evidence demonstrates sustained adverse outcomes for children born from preterm birth or labour, with increased risks of perinatal death, cerebral palsy, neurodevelopmental disorders, hearing loss and visual impairment.[25,26] The risk of complications has been shown to decrease with increasing gestational age. Four stages of preterm birth are defined: late preterm, moderately preterm, very preterm and extremely preterm. In the current thesis it was demonstrated that children born from preterm labour pregnancies are at increased risk for a range of morbidities and healthcare utilisation, irrespective of gestational age at delivery, compared with those from full-term labour pregnancies (**Chapter 6**). Focusing on the group of extremely preterm infants (gestational age <28 weeks), a high healthcare burden was demonstrated, especially caused by pulmonary complications. An increase in healthcare resource utilisation and costs was observed between 1999 and 2015 (**Chapter 7**). The medical burden continuing into adulthood reinforces the need for interventions that can effectively halt labour and decrease clinical sequelae in this vulnerable population.

METHODOLOGICAL CONSIDERATIONS

A common challenge in using administrative data is defining drug exposure or compliance. Although we have access to records of prescribed or dispensed drugs, there is no prove that woman take these drug accordingly. Continuous treatment based on dispensing records can therefore only approximate actual exposure and, particularly during pregnancy, drugs may be discontinued (**Chapter 3**). For this reason, drug exposure could have been overestimated. On the other hand, underestimated drug exposure is likely because hospital-administered drugs and over-the-counter drugs sold outside pharmacies were not captured. In-patient medication use can be additionally linked from other data sources of the PHARMO Database Network, however this was beyond the scope of this thesis. Validation of exposure would be required to obtain information concerning actual exposure, however patients often cannot recall if they truly used a drug at a particular date. Fortunately, exposure misclassification is assumed to be non-differential for the relative comparisons made in this thesis, so it is not expected that this would have altered the conclusions that were drawn. As with any retrospective database study, identification of medical events is limited to data captured as part of the medical records or other linked data sources in daily clinical practice. The routinely collected records used for the studies in this thesis are not primarily administrated for research purposes, and rely on

appropriate diagnostic coding to detect events or characteristics. For this reason, the studies were inherently limited by the risk of under-recording of outcomes in the PHARMO Database Network and Perined. For example, in **Chapter 6** morbidities were captured using the PHARMO Hospitalisation Database; hence, events that did not require hospitalisation would be under-reported. Congenital anomalies that were part of the exclusion criteria depended on whether they were recorded in Perined. The outcomes of interest were captured from the GP Database and completeness depended on whether the outcome was recorded and coded accordingly by the GP. Therefore, for interpretation of this type of studies there should be a focus on comparative analyses between groups, producing relative ratios. Adjustment of outcomes for relevant characteristics was also limited by information available in the database. In order to answer research questions to the best ability by means of the PPRN, the first step when setting up a study should always be selecting the appropriate databases that allows capturing the event of interest; i.e. hospitalisations for severe events and the GP primary care data for softer outcomes.

Pregnancies included in the PPRN were representative for those included in the nation-wide perinatal registry (Perined) (**Chapter 2**). However, we showed that in the linked PPRN multiple births were under-represented due to overlapping linkage parameters. The current probabilistic linkage methods particularly gain a high specificity. In the future the increasing number of records that include a citizen service number will allow for improved record linkage between PHARMO and Perined, by which the sensitivity is expected to increase further as well, for example for multiple births. Moreover, linkage between Perined and PHARMO was more successful for the most recent years, which might be explained by time-dependent linkage variables (e.g. zip code) that have changed in one of the two registries over time, hindering linkage in the earliest years. For proper data application and interpretation, all these factors should be considered in studies based on the PPRN. All sources of potential bias should be taken into account when outlining research approaches, particularly selection bias, confounding by indication and protopathic bias. Similar to what is stated above, absolute rates should be interpreted with caution, but rather the focus should be on relative comparisons.

PRACTICAL IMPLICATIONS AND FUTURE RECOMMENDATIONS

Based on the findings in this thesis practical implications and associated future recommendations can be formulated. First of all, there is the importance of medical record keeping. Electronic health records are a permanent account of a patient's disease. Their accuracy, clarity, completeness and interchangeability is paramount for effective communication between healthcare providers and patients. Maintaining medical records properly ensures that patient's medical needs are met comprehensively.[27] Demonstrated in this thesis, inadequate use seems to be made of the available information systems for appropriate drug surveillance (**Chapter 5**). There is room for improvement, which can be achieved by means of proper education, standardised procedures and increased public awareness. National instances should play a pioneering role here. These medical records are the foundation for scientific research based on registries such as the PPRN, which provides infinite possibilities for perinatal pharmacoepidemiological research. Medical records from other data sources part of the PPRN can be additionally linked in setting up studies, such as data from

chapter

8

clinical laboratories, hospitals or the registry of histo- and cytopathology. These routinely collected data should be used more systematically in drug surveillance, making efficient use of the fact that the majority of these registries are updated at least every month. Specifically, there is a need for comparative outcome analyses in pregnant women, assessing potential risks of use during pregnancy for medication lacking specific recommendations. A systematic analytic system could be set up for this, making use of automatic data-driven evaluations rather than studying specific hypotheses separately. As a broader application of the PPRN, the data can be transferred into a common data model for use in EU-wide pharmacoepidemiological studies. Currently this is done together with other European countries, as part of the large collaborative project 'ConcePTION' launched in 2019. The goal of this project is to build an ecosystem for medicine safety in pregnancy and breastfeeding.[28] Analysing data as part of a common data model allows pooling data from multiple countries, thereby providing a treasure trove of information. Eventually, this framework can be expanded to other countries joining the network, allowing EU-wide analyses. Then, the high use of potentially harmful medication, especially in the first trimester of pregnancy (**Chapter 3**), in combination with the awareness issue when prescribing medication (**Chapter 5**), together indicate the importance of primary prevention of drug-induced teratogenic exposure. This should be the principal goal of collaborative preconception counselling and care, for which population-wide education and would be helpful. In addition to caregivers acknowledging their duty here, perhaps even by legally establishing so, this would ultimately increase women's self-awareness to make them recognise their own responsibility in timely informing caregivers about (planned or unplanned) pregnancy, so that appropriate action can be taken. Interventions should be set up in such a way that women are informed about the potential pregnancy risks of the medicines they use as early and often as possible, so that the patient is alert if there is a change to trying to conceive. For example, informed consent forms at the initiation of hazardous medication could be helpful here or eye-catching stickers on the outside of medicine boxes. Upon visiting their healthcare provider or pharmacist, women of reproductive age should be repeatedly informed about the potential hazardous effects of their medication so that the need for either preconception or contraception care can be properly assessed. Also, this should be more tailored to the general population so that all women can be reached and the uptake of information is increased. This would improve protection of ethnic minorities, who have been shown to have difficulty obtaining, understanding and implementing health information.[29] For closing the circle, measuring effectiveness of interventions should be part of the picture, for example by incorporating the evaluation of preconception care in the quality assessments performed by professional associations. Other future recommendations are directed at qualitative research among GPs, midwives, pharmacists and women to further estimate the scale of the posed awareness issue and associated aspects. Moreover, assessing the daily practices in balancing risk and benefits of medication during pregnancy would be useful. This should also provide information on the shortcomings of information systems and the barriers perceived in collaborative care. Finally, linkage to other external registries such as the questionnaire-based "pREGnant"[30], maintained by the Dutch Teratology Information Service Lareb ("Moeders van Morgen"), could further complement the information in the PPRN with self-reported outcomes and provide new opportunities for research. Table 1 presents a summary of posed practical implications and future recommendations, categorised per topic.

TABLE 1 Summary of practical implications and future recommendations posed in this thesis

Topic	Recommendations
Medical record keeping	**Aim: accuracy, clarity, completeness and interchangeability of electronic health records** • Proper support and education of caregivers • Simplification and standardisation of electronic information systems • Setting up standardised procedures for recording and communicating information • Setting up systems so that information from different caregivers can be interchanged and accessed through the same channel.
Generation & implementation of new knowledge	**Aim: expansion of medication risk knowledge** • Pharmacoepidemiological research based on the PPRN • Systematic set-up of these studies for efficient drug surveillance, e.g. automatic data-driven evaluations • Linkage to other (external) registries, e.g. pREGnant • Pooling data in EU-wide collaborations by means of common data models • Qualitative research in focus groups • Implementing evidence in knowledge systems used in daily practice, e.g. the Dutch Pregnancy Drug Register ("Moeders van Morgen")

Increased awareness	**Aim: primary prevention of drug-induced teratogenic exposure**
	• Knowledge transfer tailored to the general population, i.e. population-wide education
	  ◦ Secure collaborative preconception care and counselling in daily clinical practice, e.g.:
	  ◦ Informing patients about potential pregnancy risks of medicines as early and often as possible
	  ◦ Introducing informed consent forms at the initiation of hazardous medication
	  ◦ Eye-catching information on medication boxes
	  ◦ Using the One Key Question approach[31] for asking the question 'Do you plan to become pregnant in the next year?' according to the national action programs focusing on a healthy start of life[32]
	  ◦ Legally establishing caregivers roles and responsibilities in preconception care

Evaluation of interventions	**Aim: a closed ongoing action cycle of planning, implementation and evaluation**
	• Evaluating current daily clinical practice in pregnancy-related care, e.g.:
	  ◦ Shortcomings of information systems
	  ◦ Barriers perceived in collaborative pregnancy care
	  ◦ Risks associated with women's lack of awareness of pregnancy
	• Re-evaluating clinical practice in pregnancy-related care, e.g. evaluation of preconception care as part of quality assessments performed by professional associations
	• Pioneering role by national instances, e.g. develop an advocacy coalition to harness political will and leadership necessary to turn high-level policy into effective coordinated action

chapter

8

CONCLUSIONS

The PPRN demonstrated in this thesis provides endless possibilities for perinatal pharmacoepidemiological research. Real-world data (RWD) and related observational population-based research is a very suitable non-invasive method for studies in pregnant women and their offspring, underscoring the importance of medical record keeping. Especially in vulnerable populations, such as preterm infants, the PPRN serves as an invaluable resource for perinatal and paediatric real-world evidence (RWE) research, extending into long-term follow-up and life course outcomes up to more than 20 years after birth. At this point, inadequate use seems to be made of the available information systems. The key challenge for improved registration lies with shared responsibility, in which collaborative pregnancy care is pivotal. It asks for a multidisciplinary approach with key roles for midwives, gynaecologists, primary care doctors and women themselves. Public awareness about the potential risks of medication used during pregnancy should be improved by means of population-wide education incorporating collaborative preconception care. National instances should play a pioneering role here. In addition to caregivers acknowledging their duty here, this would ultimately increase women's self-awareness to make them recognise their own responsibility in timely informing caregivers about pregnancy, so that appropriate action can be taken. Altogether, the observed high use of potentially harmful medication is of sufficient clinical importance to prompt a call towards safer medication management around pregnancy, especially among ethnic minorities, among women with chronic medical conditions, and early in pregnancy. The unchanged high use of medication with known risks suggests a potential deficit of risk perception among healthcare providers and pregnant women. However, treating physicians rely on available evidence when making decisions on medication use during pregnancy and daily face difficulties balancing foetal and maternal risks.

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chapter 8

CHAPTER 9

Summary
Samenvatting

SUMMARY

Part I of this thesis gives an introduction to the pharmacoepidemiological studies included in this thesis, by describing the linkage of the PHARMO Database Network (PHARMO) and Perined, the PHARMO Perinatal Research Network (PPRN), in more detail. More specifically, **Chapter 1** provides the background for this thesis as an introduction. Clinical trials have well-known limitations to study drug safety in vulnerable populations, including pregnant women and their offspring. Alternatively, real-world data (RWD) and related observational population-based research have the potential to fill this gap as a non-invasive method for studies in these groups. Therefore, the PPRN was set up as a resource for perinatal and paediatric real-world evidence (RWE) research by linking data from existing registrations. The main aim of this thesis was to set up and explore a research network facilitating population-based perinatal pharmacoepidemiological studies in both mother and child, focusing on potentially harmful medication use during pregnancy and outcomes associated with preterm birth.

In **Chapter 2** the PPRN is described as a new data source to facilitate large-scale observational pharmacoepidemiological perinatal research. It contains preconceptional information on maternal healthcare extending into long-term follow-up and outcomes after birth for both mother and child, with ongoing annual updates of the routinely collected data. Introducing the two data sources, Perined is a nationwide registry in which medical data around pregnancy and birth are included. PHARMO is a population-based network of databases combining subnational data from different primary and secondary healthcare settings in the Netherlands. At the time of this research, the linked PPRN consisted of more than 0.5 million pregnancies from 1999 onwards.

Then, in **Part II** of this thesis the first applications of the PPRN are demonstrated, studying medication use during pregnancy with a specific focus on potentially harmful medication and trends over time. In **Chapter 3** the prevalence of drug exposure during the preconception, pregnancy and postpartum periods in the Netherlands was examined, with special emphasis on potentially harmful medication. Furthermore, trends over the years were assessed. A high prevalence of exposure to potentially harmful medication during pregnancy from 1999 to 2017 was shown. Over all the study years, potentially harmful medication was used during approximately one-third of pregnancies, including drugs with known and unknown risks to a similar extent. Most notably, potentially harmful medication use was significantly higher among women with chronic medical conditions and women of non-Dutch ethnicity. These findings highlight the need for an increased sense of urgency among both healthcare providers and women of reproductive age regarding the potential risks associated with pharmacological treatment during pregnancy.

In **Chapter 4** the trends in use of anti-seizure medications (ASMs) among pregnant women in the Netherlands were examined, stratified by medication safety profile. Individual treatment patterns were also assessed, including the extent of changing from one ASM to another. Over the last two decades, a significant increase was observed for use of ASMs with uncertain risk. A significant increase was also observed for known safest ASMs. Use of ASMs with higher risk of congenital

malformations decreased significantly. Switches between ASM safety risk categories before and during pregnancy were not very common; women rather discontinued treatment or switched within the same category. Altogether, this highlighted the need for an expansion of ASM risk knowledge and communication to healthcare providers and women of reproductive age to improve preconception counseling.

In **Chapter 5** GPs' awareness of pregnancy, the way it is registered in GP records as well as the trends over time are explored. Furthermore, the association between GPs' awareness and prescribing medication with potential safety risks was assessed. A pregnancy confirmation was present in the GP records for 48% of the pregnancies, increasing from 28% in 2004 to 63% in 2020. During 3% of all pregnancies, the GP prescribed highly hazardous medication with teratogenic effects that should have been (temporarily) avoided. Comparative analyses showed that women without a pregnancy confirmation were 59% more likely to be prescribed this highly hazardous medication compared to those with. Results of this study indicate a potential GP awareness issue at the time medication with potential safety risks is prescribed. Although pregnancy registration by GPs improved over the years, still suboptimal use seems to be made of the available information systems for appropriate drug surveillance.

Part III of this thesis concerns the application of the PPRN for studying real-world outcomes associated with preterm birth. In **Chapter 6** the long-term rates of outcomes and health-care utilisation in children born following uncomplicated spontaneous preterm labour (SPTLu) were assessed and compared to rates among children born following full-term labour (FTL). A composite morbidity measure of several neonatal morbidities was used to stratify children to determine whether morbidity at birth impacted the risk of longer-term outcomes. The study demonstrated increased risk for a range of morbidities and HCU in children from SPTLu pregnancies. Comorbidities that occured more frequently in children from SPTLu pregnancies compared with FTL pregnancies included neurodevelopmental and respiratory conditions. The presence of comorbidity at birth in SPTLu children was associated with an increased risk of HCU and several outcomes, such as respiratory conditions and failure to thrive. This information provided evidence of the continued medical burden in children born following SPTLu pregnancies, which reinforces the need for safe interventions that can effectively halt labour and lead to an improvement in childhood outcomes.

In **Chapter 7** respiratory morbidities, hospital length of stay, healthcare resource utilisation, and costs for infants born <28 weeks gestational age, i.e. extremely preterm infants, are described. To assess the impact of respiratory complications, data were stratified by the presence of bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD) and by birth period. This chapter highlights and quantifies over time the healthcare burden associated with extremely preterm birth and the associated increase in pulmonary complications. Our findings of high prevalence of BPD and CLD among extremely preterm infants, along with accompanying high healthcare resource utilisation which has increased over time, underscore the need for new interventions in this vulnerable population and provide a basis for future cost-effectiveness analyses.

chapter

9

In **Chapter 8** the main findings and conclusions of this thesis are discussed. This thesis demonstrates the PPRN as an invaluable resource for perinatal and paediatric research. First, a high prevalence of exposure to potentially harmful medication during pregnancy was shown, most notably among vulnerable groups. Also noticeable was the trend towards newer drugs with ill-defined pregnancy risks. These findings on potentially harmful medication use are of sufficient clinical importance to prompt a call towards safer medication management around pregnancy, especially early in pregnancy. Although pregnancy registration by GPs improved over the years, still suboptimal use seems to be made of the available information systems for appropriate drug surveillance. As a second application, the studies presented in this thesis provide evidence for the medical burden of preterm birth continuing into adulthood. It reinforces the need for interventions that can effectively halt labour and decrease clinical sequelae in this vulnerable population. Altogether, it was concluded that collaborative pregnancy care is pivotal, asking for a multidisciplinary approach with key roles for obstetricians, medical specialists, primary care doctors and women themselves. Treating physicians rely on available evidence when making decisions on medication use during pregnancy and daily face difficulties balancing foetal and maternal risks.

SAMENVATTING

In **Deel I** van dit proefschrift wordt een introductie gegegeven op de farmacoepidemiologische studies gepresenteerd in dit proefschrift, door de koppeling van het PHARMO Database Network (PHARMO) en Perined, ook wel het PHARMO Perinatal Research Network (PPRN), in meer detail te beschrijven. Als specifieke introductie wordt in **Hoofdstuk 1** de achtergrond bij het huidige proefschrift gepresenteerd. Van klinische trials is alom bekend dat ze beperkingen hebben voor studies naar de veiligheid van geneesmiddelen in kwetsbare populaties, waaronder zwangere vrouwen en hun kinderen. 'Real-world data' (RWD) en gerelateerd observationeel populatiegebaseerd onderzoek bieden een veelbelovend alternatief, als een niet-invasieve methode voor studies in deze groepen. Daarom is het PPRN opgezet als een bron voor perinataal en pediatrisch 'real-world evidence' (RWE) onderzoek door gegevens uit bestaande registraties te koppelen. Het belangrijkste doel van dit proefschrift was het opzetten en verkennen van een onderzoeksnetwerk dat populatiegebaseerde perinatale farmacoepidemiologische studies in zowel moeder als kind faciliteert, met de nadruk op mogelijk schadelijke geneesmiddelen tijdens de zwangerschap en uitkomsten die geassocieerd zijn met vroeggeboorte.

In **Hoofdstuk 2** wordt het PPRN beschreven als een nieuwe databron om grootschalig observationeel farmacoepidemiologisch perinataal onderzoek mogelijk te maken. Het bevat preconceptionele informatie over medische zorg tijdens de zwangerschap tot aan lange termijn uitkomsten na de geboorte voor zowel moeder als kind, met jaarlijkse updates van de gegevens die routinematig verzameld worden. Om de twee databronnen te introduceren: Perined is een landelijke registratie waarin medische gegevens rondom de zwangerschap en geboorte zijn opgenomen. PHARMO is een populatiegebaseerd netwerk van databanken waarin zorggegevens van verschillende primaire en secundaire zorgsystemen gecombineerd worden. Ten tijde van dit onderzoek bestond het gekoppelde PPRN uit meer dan 0,5 miljoen zwangerschappen vanaf 1999.

Vervolgens worden in **Deel II** van dit proefschrift de eerste toepassingen van het PPRN gedemonstreerd, waarbij geneesmiddelengebruik tijdens de zwangerschap bestudeerd wordt, met de nadruk op mogelijk schadelijke geneesmiddelen en trends over de tijd. In **Hoofdstuk 3** is de prevalentie van geneesmiddelengebruik voor, tijdens en na zwangerschap onderzocht, met de nadruk op mogelijk schadelijke geneesmiddelen. Verder zijn in dit hoofdstuk ook de trends over de tijd in kaart gebracht. Tijdens de zwangerschap werd een hoge prevalentie van het gebruik van mogelijk schadelijke geneesmiddelen aangetoond, tussen 1999 en 2017. Gedurende alle studiejaren werden mogelijk schadelijke geneesmiddelen gebruikt tijdens ongeveer een derde van de zwangerschappen, waaronder geneesmiddelen met bekende en onbekende risico's in vergelijkbare mate. Het was opvallend dat het gebruik van mogelijk schadelijke geneesmiddelen significant hoger was onder vrouwen met chronische medische aandoeningen en vrouwen van niet-Nederlandse etniciteit. Deze bevindingen benadrukken het belang van erkenning van de potentiële risico's geassocieerd met medicamenteuze behandeling tijdens de zwangerschap, door zowel zorgverleners als vrouwen van vruchtbare leeftijd.

In **Hoofdstuk 4** zijn de trends in anti-epileptica onder zwangere vrouwen in Nederland onderzocht en gestratificeerd naar veiligheidsprofiel. Individuele behandelpatronen werden ook bekeken, waaronder het overstappen van het ene naar het andere anti-epilepticum. In de afgelopen twee decennia werd een significante toename waargenomen voor het gebruik van anti-epileptica met onzeker risico. Er was ook een significante toename voor de anti-epileptica waarvan bekend is dat ze veilig zijn tijdens de zwangerschap. Het gebruik van anti-epileptica met een hoger risico op aangeboren afwijkingen nam significant af. Het overstappen van de ene naar de andere risicocategorie voor en tijdens de zwangerschap was niet erg gebruikelijk; vrouwen bleken vaker te stoppen met de behandeling of over te stappen binnen dezelfde risicocategorie. De bevindingen van deze studie duiden op het belang van de uitbreiding van kennis en communicatie over de mogelijke risico's van anti-epileptica, naar zowel zorgverleners als vrouwen in de vruchtbare leeftijd, om preconceptionele voorlichting te verbeteren.

Hoofdstuk 5 laat zien in hoeverre het bekend is bij de huisarts dat een vrouw zwanger is, de manier waarop dit wordt geregistreerd in de informatiesystemen van de huisarts, alsook de trends over de tijd. Verder is de associatie tussen het bekend zijn bij de huisarts en het voorschrijven van mogelijk schadelijke geneesmiddelen onderzocht. Een zwangerschapsbevestiging was geregistreerd in het informatiesysteem van de huisarts voor 48% van de zwangerschappen, met een stijging van 28% in 2004 naar 63% in 2020. Tijdens 3% van alle zwangerschappen schreef de huisarts hoog risico geneesmiddelen voor met teratogene effecten die (tijdelijk) vermeden hadden moeten worden. Vergelijkende analyses toonden aan dat vrouwen zonder een zwangerschapsbevestiging 59% meer kans hadden om deze hoog risico geneesmiddelen voorgeschreven te krijgen, in vergelijking met degenen mét een zwangerschapsbevestiging. De resultaten van deze studie wijzen op een mogelijk bewustzijnsprobleem bij de huisarts op het moment dat de mogelijk schadelijke geneesmiddelen worden voorgeschreven. Ook al verbeterde de registratie van zwangerschap door de huisarts over de jaren, het gebruik van de beschikbare informatiesystemen lijkt toch nog suboptimaal voor effectieve medicatiebewaking.

Deel III van dit proefschrift betreft de toepassing van het PPRN voor het bestuderen van 'real-world' uitkomsten geassocieerd met vroeggeboorte. In **Hoofdstuk 6** werden lange termijn uitkomsten en zorggebruik in kinderen geboren na ongecompliceerde vroeggeboorte (SPTLu) in kaart gebracht en vergeleken met kinderen geboren na een voldragen zwangerschap (FTL). Een samengestelde uitkomstmaat van verschillende neonatale morbiditeiten werd gebruikt om te kijken of morbiditeit bij de geboorte het risico op lange termijn uitkomsten beïnvloedde. De studie toonde een verhoogd risico op een reeks morbiditeiten en zorggebruik in kinderen van SPTLu zwangerschappen. Uitkomsten die vaker voorkwamen bij kinderen van SPTLu zwangerschappen in vergelijking met FTL zwangerschappen waren onder andere neurologische ontwikkelings- en respiratoire aandoeningen. De aanwezigheid van morbiditeit bij de geboorte was geassocieerd met een verhoogd zorggebruik en verhoogd risico op uitkomsten zoals respiratoire aandoeningen en groeiachterstand. Deze studie leverde bewijs van de aanhoudende medische belasting in kinderen geboren na een SPTLu zwangerschap, en daarmee het belang van veilige medische interventies om de bevalling uit te stellen, om zo de lange termijn uitkomsten bij kinderen te kunnen verbeteren.

In **Hoofdstuk 7** worden respiratoire aandoeningen, ziekenhuisopnameduur, zorggebruik en kosten beschreven voor baby's die geboren zijn na een zwangerschapsduur van minder dan 28 weken, ook wel extreme vroeggeboorte genoemd. Om de impact van respiratoire complicaties te beoordelen, werden de resultaten gestratificeerd naar de aanwezigheid van bronchopulmonale dysplasie (BPD), chronische longziekte (CLD) en geboorteperiode. Dit hoofdstuk belicht en kwantificeert over de tijd de zorglast die gepaard gaat met extreme vroeggeboorte en de bijbehorende toename van longcomplicaties. De bevonden hoge prevalentie van BPS en CLD na extreme vroeggeboorte, samen met het bijbehorende hoge zorggebruik dat in de loop van de tijd is toegenomen, duiden op het belang van nieuwe interventies in deze kwetsbare populatie en bieden een basis voor toekomstige kosteneffectiviteitsanalyses.

In **Hoofdstuk 8** worden de belangrijkste bevindingen en conclusies van dit proefschrift bediscussieerd. Dit proefschrift laat zien dat het PPRN een bron van onschatbare waarde is voor het uitvoeren van perinataal en pediatrisch onderzoek. Allereerst werd een hoge prevalentie van het gebruik van mogelijk schadelijke geneesmiddelen tijdens de zwangerschap aangetoond, met name bij kwetsbare groepen. Verder was er ook een duidelijke trend richting het gebruik van nieuwere geneesmiddelen waarvoor de veiligheidsrisico's nog niet goed in kaart zijn gebracht. Deze bevindingen van mogelijk schadelijk geneesmiddelengebruik zijn van voldoende klinisch belang om een oproep te doen tot veiligere medicatiebewaking rondom de zwangerschap, vooral vroeg in de zwangerschap. Ook al verbeterde de registratie van zwangerschap door de huisarts over de jaren, het gebruik van de beschikbare informatiesystemen lijkt toch nog suboptimaal voor effectieve medicatiebewaking. Als een tweede toepassing leveren de studies uit dit proefschrift bewijs voor de aanhoudende medische belasting na vroeggeboorte, die doorgaat tot in de volwassenheid. Het versterkt de behoefte aan veilige medische interventies om de bevalling uit te stellen en daarmee de klinische gevolgen in deze kwetsbare populatie te verminderen. Alles samengenomen werd geconcludeerd dat collaboratieve zwangerschapszorg cruciaal is en vraagt om een multidisciplinaire aanpak met sleutelrollen voor verloskundigen, medisch specialisten, huisartsen en vrouwen zelf. Zorgverleners zijn afhankelijk van de beschikbare informatie bij het nemen van beslissingen over geneesmiddelengebruik tijdens de zwangerschap en worden dagelijks geconfronteerd met de afweging van foetale en maternale risico's.

chapter 9

ADDENDUM

CHAPTER 10

CONTRIBUTING AUTHORS

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Bernke te Winkel Teratology Information Service Netherlands, Pharmacovigilance Centre Lareb, s-Hertogenbosch, The Netherlands

chapter 10

LIST OF PUBLICATIONS

Publications in this thesis

1. **Houben E**, Broeders L, Steegers EAP, Herings RMC. Cohort profile: the PHARMO Perinatal Research Network (PPRN) in the Netherlands: a population-based mother-child linked cohort. *BMJ Open* 2020; 10(9): e037837.

2. **Houben E**, Te Winkel B, Steegers EAP, Herings RMC. Dutch trends in the use of potentially harmful medication during pregnancy. *Br J Clin Pharmacol* 2020.

3. **Houben E**, Benson RJ, Steegers EAP, Herings RMC. Twenty-year trends in the use of anti-seizure medication among pregnant women in the Netherlands. *Epilepsy Behav* 2022; 127: 108549.

4. **Houben E**, Swart KMA, Steegers EAP, Elders PJM, Herings RMC. GPs' awareness of pregnancy: trends and association with hazardous medication use. *Br J Gen Prac 2023; BJGP.2022.0193.*

5. **Houben E**, Smits E, Pimenta JM, Black LK, Bezemer ID, Penning-van Beest FJ. Increased risk of morbidities and health-care utilisation in children born following preterm labour compared with full-term labour: A population-based study. *J Paediatr Child Health* 2018.

6. **Houben E**, Siffel C, Overbeek J, Penning-van Beest F, Niklas V, Sarda SP. Respiratory morbidity, healthcare resource use, and cost burden associated with extremely preterm birth in The Netherlands. *J Med Econ* 2021; 24(1): 1290-8.

Other publications

1. Smits E, **Houben E**, De Smet P, et al. The availability of information on impaired renal function in the community pharmacy, a descriptive pilot study. *Journal of Nephrology and Renal Therapy* 2016.

2. **Houben E**, van Haalen HG, Sparreboom W, et al. Chemotherapy for ovarian cancer in the Netherlands: a population-based study on treatment patterns and outcomes. *Med Oncol* 2017; 34(4): 50.

3. Kuiper JG, Sanchez RJ, **Houben E**, et al. Use of Lipid-modifying Therapy and LDL-C Goal Attainment in a High-Cardiovascular-Risk Population in the Netherlands. *Clin Ther* 2017; 39(4): 819-27.e1.

4. Margulis AV, **Houben E**, Hallas J, et al. Ophthalmic nepafenac use in the Netherlands and Denmark. *Acta Ophthalmol* 2017; 95(5): 509-17.

5. **Houben E**, Johansson S, Nagy P, Penning-van Beest FJA, Kuipers EJ, Herings RMC. Observational cohort study: safety outcomes in children using proton pump inhibitors or histamine-2 receptor antagonists. *Curr Med Res Opin* 2018; 34(4): 577-83.

6. **Houben E**, Smits E, Overbeek JA, et al. No Evidence for an Association Between Renal Function and Serious Bleeding Events in Patients Treated With Coumarins: A Population-Based Study. *Ann Pharmacother* 2018; 52(3): 221-34.

7. Heintjes EM, **Houben E**, Beekman-Hendriks WL, et al. Trends in mortality, cardiovascular complications, and risk factors in type 2 diabetes. *Neth J Med* 2019; 77(9): 317-29.

8. Weersink RA, Taxis K, Drenth JPH, **Houben E**, Metselaar HJ, Borgsteede SD. Prevalence of Drug Prescriptions and Potential Safety in Patients with Cirrhosis: A Retrospective Real-World Study. *Drug Saf* 2019; 42(4): 539-46.

9. Rebordosa C, **Houben E**, Laugesen K, et al. No Evidence of Off-label Use of Olodaterol and Indacaterol in Denmark, France, and the Netherlands: A Drug Utilization Study. *Sci Rep* 2020; 10(1): 586.

10. Flinterman LE, Kuiper JG, Korevaar JC, et al. Impact of a Forced Dose-Equivalent Levothyroxine Brand Switch on Plasma Thyrotropin: A Cohort Study. *Thyroid* 2020; 30(6): 821-8.

11. Brand AR, **Houben E**, Bezemer ID, et al. Platelet aggregation inhibitor prescription for newly diagnosed peripheral arterial disease in the Netherlands: a cohort study. *BMJ Open* 2021; 11(1): e041715.

12. Arana A, Pottegård A, Kuiper JG, et al. Long-Term Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus and Pimecrolimus: Final Results from the Extension of the Cohort Study Protopic Joint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE). Clin Epidemiol 2021; 13: 1141-53.

13. Smits E, Andreotti F, **Houben E**, et al. Adherence and Persistence with Once-Daily vs Twice-Daily Direct Oral Anticoagulants Among Patients with Atrial Fibrillation: Real-World Analyses from the Netherlands, Italy and Germany. Drugs Real World Outcomes 2022; 9(2): 199-209.

chapter

10

CURRICULUM VITAE

Eline Houben werd geboren in Sittard op 7 juni 1989. In 2007 behaalde zij haar VWO diploma aan de Trevianum Scholengroep Sittard waarna zij begon met haar studie Voeding en Gezondheid aan de Wageningen Universiteit. Aan de Vrije Universiteit Amsterdam doorliep zij haar stage bij faculteit Aard- en Levenswetenschappen – Voeding en Gezondheid waar ze onderzoek deed naar de tevredenheid over de Voedselbank in combinatie met de ervaren gezondheid van het dieet. Tijdens haar tweede stage aan het Rijksinstituut voor Volksgezondheid en Milieu werkte ze mee aan de ontwikkeling van een monitoringssysteem voor het zout- en vetgehalte van voedingsmiddelen. Voor haar afstudeervak aan de Wageningen Universiteit deed ze onderzoek naar energie-smaak conditionering in jonge kinderen. In september 2012 behaalde zij haar Master-diploma Voeding en Gezondheid. Sinds september 2013 is Eline werkzaam bij het PHARMO Instituut, waar zij startte als Junior Onderzoeker. Als onderdeel van deze functie voerde zij farmaco-epidemiologisch onderzoek uit binnen diverse ziektegebieden, met een specialisatie op het gebied van moeder & kind op basis van gekoppelde gegevens uit het PHARMO Datanetwerk en de Perinatale Registratie. Ze werkte mee aan het tot stand komen van de koppeling van deze registraties. Op basis van deze gegevens startte zij in 2017 naast haar reguliere functie met een promotieonderzoek aan het Erasmus MC en voerde zij diverse studies uit op het gebied van medicatiegebruik en uitkomsten rondom de zwangerschap. De resultaten hiervan zijn gepresenteerd in dit proefschrift. In de periode 2015-2021 was ze werkzaam als Onderzoeker, waarbij ook projectleiding, het contact met opdrachtgevers en het ontwikkelen van onderzoeksprotocollen centraal stond. Vanaf 2021 werkt zij als Senior Onderzoeker bij het PHARMO Instituut. Eline woont in Utrecht samen met haar man Joris. Sinds november 2019 hebben zij samen een dochter Lot en in april 2022 is dochter Ellis geboren.

PHD PORTFOLIO

PhD Portfolio - Summary
Name PhD student: Eline Houben
Research school: NIHES
Erasmus MC Department: Obstetrics and Gynaecology
PhD period: 2017-2022
Promotors: Prof. dr. E.A.P. (Eric) Steegers & Prof. dr. R.M.C. (Ron) Herings
Supervisor: K. (Karin) Swart-Polinder, PhD

Training program	Year	Workload (hours/ECTS)
Courses - general		
Scientific Integrity	2018	8 hours (0.3 ECTS)
BROK	2022	42 hours (1.5 ECTS)
Courses - other		
NIHES Erasmus Winter Programme - Pharmaco-epidemiology and Drug Safety	2014	53 hours (1.9 ECTS)
Workshop Use of social media in epidemiologic research	2015	4 hours (0.1 ECTS)
Public training course: SAS ODS Statistical Graphics	2016	8 hours (0.3 ECTS)
Clinical prediction models	2018	56 hours (2.0 ECTS)
Workshop SAS Graph Template Language	2018	4 hours (0.1 ECTS)
Love2Speak - Management drives: Samen Succesvol Sterker & Klantcontact	2017, 2022	56 hours (2.0 ECTS)
Scientific writing (by training)	2017-2022	40 hours (1.4 ECTS)
Statistics (by training)	2017-2022	40 hours (1.4 ECTS)
Methodology (by attending monthly knowledge transfer meetings at PHARMO Institute)	2017-2022	72 hours (2.6 ECTS)
Methods in pharmacoepidemiology & Drug safety in pregnancy (by attending content-specific webinars)	2017-2022	24 hours (0.9 ECTS)
Seminars and conferences		
European Congress of Epidemiology - Healthy Living Conference	2015	28 hours (1.0 ECTS)
PhUSE Single Day Event: Data Visualisation	2016	8 hours (0.3 ECTS)
PRISMA symposium KNMP	2016	8 hours (0.3 ECTS)
Lareb bijwerkingendag Aandacht voor bijwerkingen van de geneesmiddelen bij kinderen	2016	8 hours (0.3 ECTS)
ZonMw startersbijeenkomst 'Zwangerschap & Geboorte II'	2017	5 hours (0.2 ECTS)
Minisymposium Integrale zorg en best practices bij de zorg voor kwetsbare zwangeren	2017	4 hours (0.1 ECTS)
34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management	2018	28 hours (1.0 ECTS)

Seminars and conferences continued

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conference Europe	2018	28 hours (1.0 ECTS)
IMI ConcePTION kick-off meeting	2019	8 hours (0.3 ECTS)
ICPE All Access 2020	2020	16 hours (0.6 ECTS)
ICPE All Access 2021	2021	16 hours (0.6 ECTS)

Presentations

One oral poster presentation at European Congress of Epidemiology - Healthy Living Conference	2015	28 hours (1.0 ECTS)
Two oral presentations at PRISMA symposium KNMP	2016	56 hours (2.0 ECTS)
Three poster presentations at ISPE's 33st International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE)	2017	48 hours (1.7 ECTS)
Three poster presentations at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conference Europe	2017	48 hours (1.7 ECTS)
Three poster presentations at ISPE's 34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE)	2018	48 hours (1.7 ECTS)
Four poster presentations at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conference Europe	2018	64 hours (2.3 ECTS)
One oral presentation at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conference Europe	2018	28 hours (1.0 ECTS)
One poster presentation at 54th EASD Annual Meeting	2018	16 hours (0.6 ECTS)
One poster presentation at 7th Congress of the European Academy of Paediatric Societies	2018	16 hours (0.6 ECTS)
Three presentations at Dutch Epidemiological Conference - WEON	2018	48 hours (1.7 ECTS)
Three poster presentations at ISPE's 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE)	2019	48 hours (1.7 ECTS)
Two poster presentations at Dutch Epidemiological Conference - WEON	2019	32 hours (1.1 ECTS)
Two oral presentations at 37th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID)	2019	32 hours (1.1 ECTS)
One poster presentation at ISPE's 36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE)	2020	16 hours (0.6 ECTS)
One oral presentation at MediQ webinar Hulpmiddelenzorg is meer dan de zorg voor het hulpmiddel	2021	28 hours (1.0 ECTS)

chapter **10**

Teaching tasks	Year	Workload (hours/ECTS)
Lecturing		
Three pharmacoepidemiological workshops during PHARMO research meetings	2017-2022	84 hours (3.0 ECTS)
Supervising Masters theses		
Internship 'PASS to characterize the risk of angioedema and other specific safety events of interest in association with use of sacubitril/valsartan in adult patients with heart failure'	2018	16 hours (0.6 ECTS)
Other		
Supporting PhD research on 'Antidepressants in the Perinatal Period: challenging choices in current practice' using data from the PHARMO Database Network	2017	32 hours (1.1 ECTS)
Supporting PhD research on 'Antidepressant use during pregnancy and development of preeclampsia' using data from the PHARMO Database Network	2017	16 hours (0.6 ECTS)
Supporting PhD research on 'Medication safety in patients with cirrhosis' using data from the PHARMO Database Network	2018	16 hours (0.6 ECTS)
Supervision and analytical support during (Junior) Traineeships at PHARMO Institute	2019-2022	72 hours (2.6 ECTS)
TOTAL		**1,356 hours (48.4 ECTS)**

DANKWOORD

Een dankwoord. Waarschijnlijk het meest gelezen hoofdstuk uit dit boek en mijn eerste gedachte is "als ik maar niemand vergeet". Ik ga mijn best doen.

Laat ik beginnen bij mijn sollicitatiegesprek in 2013 bij PHARMO met Myrthe en Irene. Jullie waren toen al, maar ook in de jaren erna, degenen die het eerste zaadje plantten voor een promotietraject bij PHARMO. Veel dank daarvoor, voor het voorbeeld dat jullie waren en ook voor het lobbyen bij Ernst, waardoor ik in 2018 echt officieel aan dit avontuur kon beginnen!

Zonder data zijn we nergens. Ik dank specifiek Leanne, Rients, Ger de Winter, Chantal Hukkelhoven en Lisa Broeders voor de toegang tot en het wegwijs maken in de Perined data en het opzetten van de eerste PHARMO-PRN koppeling. Dank voor het beantwoorden van al mijn vragen bij de verschillende variabelen. Zonder jullie zouden we dit goud nooit in handen hebben gehad.

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voor de gezellige, open sfeer en de getoonde interesse in mijn promotie-traject de afgelopen jaren. Het heeft allemaal meegeholpen!

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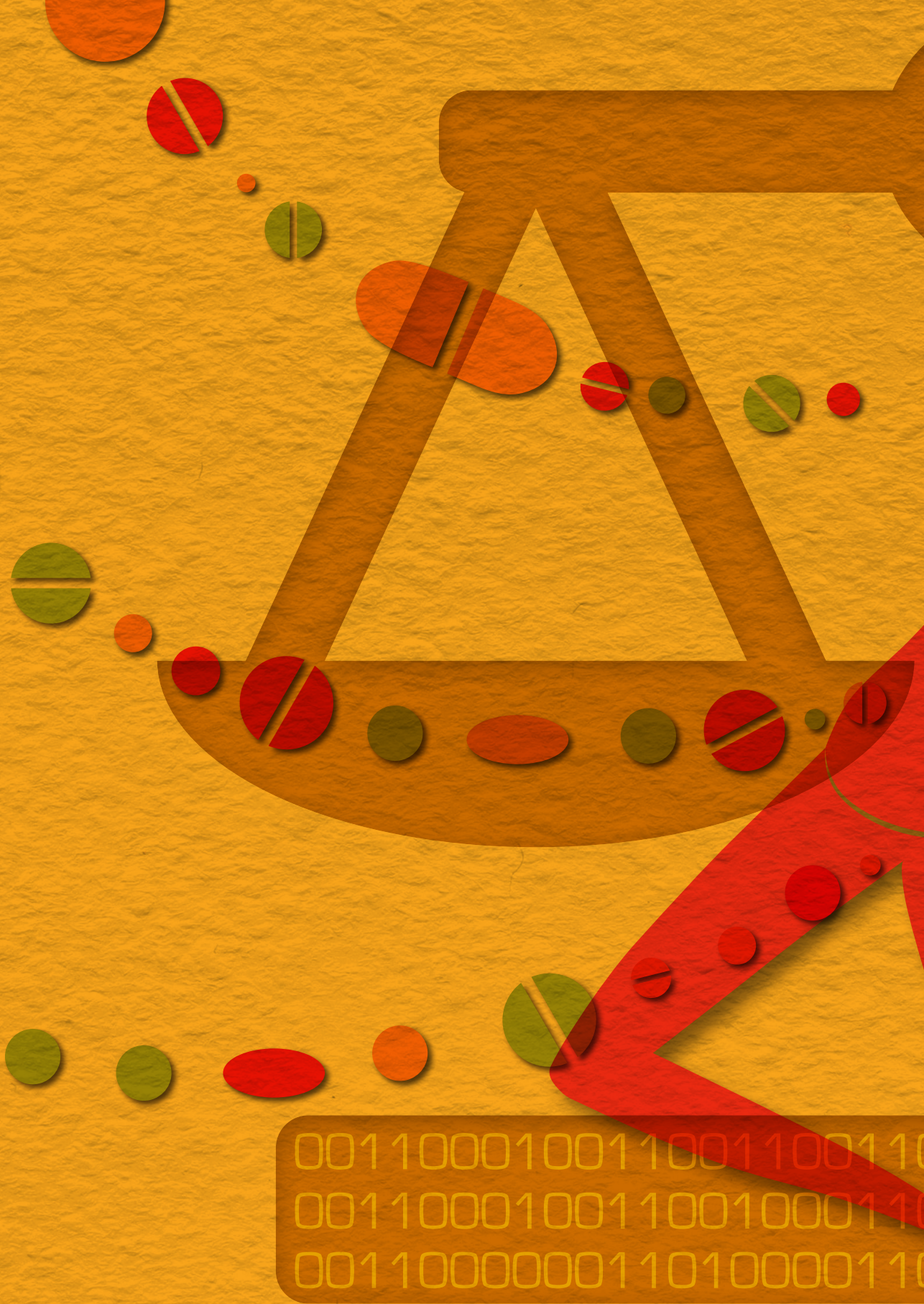
Een Limburgse afsluiting
Oma en oma, gaer hei ich dit nog same mit uch gevierd, mer dat moch nét neit zo zeen. Wat ben ich

dankbaar veur alles wat geer mich gegaeve höb en veural dat veer zo lang plezeier mit uch mochte höbbe! Dankzij uch zit doorzettingsvermogen in os bloud.

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Dankwoord