Cover Sheet

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Title:

The relationship between the month of birth and ADHD treatment

Principal investigators & Affiliations

L. Minjon MSc., dr. E.R. Heerdink, prof. dr. A.C.G. Egberts
Utrecht University
Utrecht Institute for Pharmaceutical Sciences (UIPS)
Department of Pharmaceutical Sciences
Pharmacoepidemiology and Clinical Pharmacy

Table of content

Protocol Electronic Approval Form 2
List of Abbreviations 3
Summary of protocol 4
Study Protocol 5
1. Introduction 5
2. Objective/hypothesis 5
3. Methodology 6
4. Study management 9
5. References 9
Checklist 11

Protocol Electronic Approval Form

Researcher	**Daily supervisor**	**Supervisor**
_____	_____	_____
Name	Name	Name
_____	_____	_____
Electronic signature & date	*Electronic signature & date*	*Electronic signature & date*

Data manager
(if applicable)

_____
Name

_____
Electronic signature & date

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical
CBS	Centraal Bureau voor de Statistiek
GIP	Genees- en hulpmiddelen Informatie Project

Summary of protocol

There seems to be a relationship between a child's month of birth and the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD). Both underdiagnosis as well as overdiagnosis of ADHD can have consequences for the future of a child. It is not clear if there is a relationship between the month of birth and use of ADHD medication in the Netherlands.

The objective of this study:
Is there a relationship between the month of birth and the pharmacological treatment of ADHD in children?

- Is there a relationship between the month of birth and the time until the first dispensing date for medication to treat ADHD?
- Is there a relationship between the month of birth and the period a child uses medication to treat ADHD?

To perform this study, the PHARMO Database Network is used. The study cohort includes children and adolescents ≤ 24 years old who use ADHD medication, dispensed for the first time between 2006-2016. The first dispensing date is the index date. The primary outcome is the start of ADHD medication. In the analysis the number of children and adolescents receiving ADHD medication with a different month of birth will be compared.

Study Protocol

1. Introduction

There seems to be a relationship between a child's month of birth and the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD).(1–6) Children born in the period prior to the cut-off date for entry to school are more likely to be diagnosed with ADHD (1–4,6) and to receive treatment for ADHD (2–6), compared to the children born right after the cut-off date. This can be due to the fact that the children who are born in a month preceding the cut-off date are the youngest within their grade. Because these younger children may be more immature, it is possible that they are more often diagnosed with ADHD. It is also possible that these children are treated just for a short period of time because of a false diagnosis.
Children who are the youngest within their grade may be overdiagnosed and their behaviour can be misinterpreted, but it can also be that children who are the oldest within their grade may be underdiagnosed.(3,6) So, the gap may seem larger than it actually is. It can be a problem that the behaviour of a child is compared to the behaviour of children within the same grade, instead of the behaviour of children of similar ages.(3) There can be an age span of twelve months within one classroom.
Underdiagnosis as well as overdiagnosis can both have consequences for the future of a child.

In the Netherlands children mostly attend primary school when they are four years old, but education is compulsory at an age of five. There is no official cut-off date to enter the next grade after kindergarten since 1985. The development and progress of a child is more important than the age or month of birth. A child should be able to finish primary school in eight years.(7) Although there is no clearly defined cut-off date, most schools use October 1st or January 1st as the cut-off date.(8) There seems to be a relationship between the month of birth and ADHD according to previous research, but it is not clear if this relationship is the same in the Netherlands.

2. Objective/hypothesis

Objective:
Is there a relationship between the month of birth and the pharmacological treatment of ADHD in children?

- Is there a relationship between the month of birth and the time until the first dispensing date for medication to treat ADHD?
- Is there a relationship between the month of birth and the period a child uses medication to treat ADHD?

Hypothesis:
There is a relationship between the month of birth and the pharmacological treatment of ADHD in children.

- There is a relationship between the month of birth and the time until the first dispensing date.
- There is a relationship between the month of birth and the period children use the medication to treat ADHD.

3. Methodology

Setting
This study will be performed within the Dutch PHARMO Database Network (PHARMO Institute for Drug Outcomes Research). This database is a population-based network of electronic healthcare databases in the Netherlands for approximately ten years. The PHARMO Database includes approximately 25% (± 4 million residents) of the population of the Netherlands.
For this study we will use the pharmacy records. It contains a complete medication history of residents, including the dispensed medication, dispensing date, prescriber, amount dispensed and the dosage regimen. In the PHARMO Database the medication is coded according to the Anatomical Therapeutic Chemical (ATC) classification.

Participants and exposure
In the database we include all children and adolescents of ≤ 24 years old who used ADHD medication between January 2006 - December 2016.
The study cohort will include children and adolescents (hereafter referred to as children) ≤ 24 years old who use ADHD medication for the first time (incident users).

The first dispensing date is the index date.
The follow-up period ends two years after the index date, at the end of the study period, after lost to follow-up or up to death, whichever comes first.

The first dispensing date is defined:
- As no use of any medication to treat ADHD during a six months period prior.
- When there is no previous record of the child at all and the amount of ADHD medication dispensed doesn't exceed 15 days of use. The duration of use of the dispensed medication can be calculated using the dosage regimen and amount dispensed.

Children are excluded if the first dispensing date cannot be defined.

To determine the period children use the ADHD medication, also children with no valid data 24 months after the index date are excluded. Valid data is defined as a (dispensing) record in the database.

The medication to treat ADHD:
- Methylphenidate (immediate and extended release) ATC code: N06BA04
- Dexamphetamine ATC code: N06BA02
- Atomoxetine ATC code: N06BA09

During the study period the treatment can change. Because we are interested in the period of time a child uses the medication to treat ADHD, and we are not interested in the specific medication, it doesn't matter if children switch to another treatment or other dosage regimen during the study period. Periods of treatment are calculated independent of switching between different types of ADHD medication.

Persistent users will be defined as patients with a maximum gap in the therapy no greater than then twice the duration of use (in days) of the dispensed medication. When the gap is bigger, the therapy will be defined as ended. The duration of use of the dispensed medication will be estimated by dividing the number of dispensed tablets/capsules by the number of tablets/capsules used per day.

Data needed:
- Month and year of birth
- Sex
- Dispensed medication
    - ADHD medication as well as co-medication (ATC codes)
    - Dispensing dates (full date)
    - Prescriber
    - Amount dispensed
    - Dosage regimen

When data needed is missing, the child is excluded. Exceptions: the dosage regimen and prescriber. When the dosage regimen is not clear, but the same amount of ADHD medication is dispensed every time, we can estimate the dosage regimen and the duration of use. Than the child will not be excluded.

Study design and type
Study design: retrospective cohort study
Study type: descriptive

Outcome
The primary outcome is the start of ADHD medication.

Data analysis
The data will be analysed using the independent t-test and ANOVA.

The children receiving ADHD medication with a different month of birth will be compared.
The age at which a child receives the treatment for the first time will be defined, it will be represented as the number of months from birth until the first dispensing date. The time until the first dispensing date (index date) of children with a different month of birth will be compared. Time period: 2006-2016.
Also the period the children use the ADHD medication will be analysed. The number of months from the first dispensing date (index date) until the last, within the study period, of children with a different month of birth will be compared. There are three time points at which the use of medication is compared and analysed. These time point will be defined when we know more about the available data, probably it will be after 6, 12 and 18 months of use. Time period: 2006-2016.
The measures of occurrence and association are the incidence rates and the relative risks.

In the analysis we will also determine if there is a relationship between the month of birth and:
- Switch in ADHD medication
- If the ADHD medication is only dispensed once
- The use of co-medication next to ADHD medication

Analyses are stratified according to sex, age categories and the calendar year the ADHD medication is dispensed for the first time.

Children with a different month of birth will be compared. It is possible that the number of births differs between different months/years. Therefore we compare the number of children receiving a treatment for ADHD with the number of births in the Netherlands, published by the *Centraal Bureau voor de Statistiek* (CBS), to correct for the number of births in a month/year.

Sample size
The Pharmo Database includes approximately 25% (4 million residents) of the population of the Netherlands. In 2015 the total users, 0-14 years old, of ADHD medication was approximately 84.000 (GIP databank). We expect that there will be approximately 20.000 children in the Pharmo Database who will use ADHD medication.

Data collection and management
The data will be stored on the secured research environment of the Utrecht University.
Before using the data, a data cleaning check is done. Abnormalities will be eliminated.

Covariates and confounding
Analyses are stratified according to sex and age categories.
It is possible that girls are more likely to enter the next grade and less likely to held back in kindergarten than boys, because the maturation of young girls is faster. This might influence the outcome of this study. Therefore analyses are stratified according to sex to determine if sex has an effect on the outcome.
The effect of the month of birth on the use of ADHD medication can differ between different ages. When children are > 12 years old, they will enter high school and the environment of the children will change, for example there will be new and more different teachers and the expectations of the children will differ compared to primary school. Therefore we compare age categories to determine if age has an effect on the outcome.

Analyses are also stratified according to the calendar year the ADHD medication is dispensed for the first time. Because the number of diagnoses and treatments of ADHD can be different between the calendar years within the study period, this may have an effect on the outcome of this study.

We compare the number of children receiving a treatment for ADHD with the number of births in the Netherlands, published by the *Centraal Bureau voor de Statistiek* (CBS), to correct for the number of births in a month/year.

Other factors that may influence the outcome of the study are the prescribers, teachers and the use of other medication. Because the database includes children across the entire country, the influence of differences between prescribers and individual teachers on the outcome will be minimal. The influence of the use of co-medication will be analysed.

Strength
The PHARMO Database Network includes approximately 25% of the population of the Netherlands, throughout the country. This will reduce selection and information bias.

Limitations
Because there is no official cut-off date for entering the next grade after kindergarten in the Netherlands, there will be different policies throughout the country. Some schools will use October 1st as the cut-off date, some January 1st and others will have no cut-off date at all. Therefore we don't know in which grade a child is and if the child is the oldest or youngest in class. We can't conclude if this influences the use of ADHD medication, it can only be considered if we will find a difference between children born in different months.

Schools can have a different policy in reporting a child with suspected ADHD. Teachers expectations of children can also differ. They might use other children in the same grade as the reference group, instead of children of similar ages.

When there is no record of the child before the first dispensed ADHD medication within the PHARMO Database, we cannot be sure that this is really the first dispensing date. When a patient receives medication for the first time, the amount dispensed it will be for approximately 15 days. Therefore we exclude children with no previous records and who receive medication for more than 15 days, because these children may have used the medication before this first record in the PHARMO Database. It is a limitation that we don't know for sure if the children who receive the ADHD medication for 15 days or less, haven't used the ADHD medication before.

The ADHD medication described in this protocol can be used for other indications, although this is rarely the case. There is no information about the indications or diagnoses available in the pharmacy records, so we can't verify the indication.

Other medication than described in this protocol can be used for ADHD, for example antipsychotics. Because this medication can be used for many other indications, we don't take them into account.

4. Study management

Ethical approval
The study is retrospective and anonymous. Patient records will be anonymized and de-identified by the Pharmo institute before the data is provided. Because we need the month and year of birth to perform this study, an independent Privacy Committee of Pharmo has to approve this study.

Study milestones

Registration in EU PAS register	April 2017
Start data collection	June 2017
Study progress report	July 2017
Start analysis	August 2017
Study progress report	October 2017
Start writing	November 2017
Article submission	December 2017

Study reporting and publications
We plan to publish our results in a peer-reviewed scientific journal. We will also present the findings at scientific meetings. Possible Dutch journals are *Tijdschrift voor Psychiatrie* and *Psyfar.* This study becomes part of a PhD thesis.

5. References

1. Boland MR, Shahn Z, Madigan D, Hripcsak G, Tatonetti NP. Birth month affects lifetime disease risk: A phenome-wide method. J Am Med Informatics Assoc. 2015;22(5):1042–53.
2. Halldner L, Tillander A, Lundholm C, Boman M, Långström N, Larsson H, et al. Relative immaturity and ADHD: Findings from nationwide registers, parent- and self-reports. J Child Psychol

Psychiatry. 2014;55(8):897–904.
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4. Morrow RL, Garland EJ, Wright JM, Maclure M, Taylor S, Dormuth CR. Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children. Can Med Assoc J. 2012;184(7):755–62.
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6. Evans WN, Morrill MS, Parente ST. Measuring inappropriate medical diagnosis and treatment in survey data: The case of ADHD among school-age children. J Health Econ [Internet]. Elsevier B.V.; 2010;29(5):657–73.
7. Huizinga J, Damstra G, Mulder L, Leest B, Veen A, Bollen I. Doorstroom van kleuters. 2016.
8. Smeets J, Resing W. Overgang van najaarsleerling naar groep 3 nader onderzocht. Tijdschr voor Orthop. 2013;52(2005):442–53.

Checklist

1. Introduction/objectives

	Yes	No	N/A
Does the formulation of the research question and objectives clearly explain:	☒	☐	☐
Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐
The objective(s) of the study?	☒	☐	☐
The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐
Which hypothesis(-es) is (are) to be tested?	☒	☐	☐
If applicable, that there is no *a priori* hypothesis?	☐	☐	☒

2. Methodology

2.1. Setting

	Yes	No	N/A
Does the protocol describe the data source(s) used in the study for the ascertainment of:			
Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐
Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐
Covariates?	☒	☐	☐
Does the protocol describe the information available from the data source(s) on:			
Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐
Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐
Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐
Is a coding system described for:			
Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐
Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒
Covariates?	☐	☐	☒
Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒

2.2. Source and Study Population

	Yes	No	N/A
Is the source population described?	☒	☐	☐
Is the planned study population defined in terms of:			
Study time period?	☒	☐	☐
Age and sex?	☒	☐	☐
Country of origin?	☒	☐	☐
Disease/indication?	☒	☐	☐
Duration of follow-up?	☒	☐	☐
Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐

2.3. Study Design

	Yes	No	N/A
Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐
Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐
Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐
Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐
Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒

2.4. Outcome definition and measures

	Yes	No	N/A
Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐
Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐
Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒

Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒

2.5. Exposure definition and measures

	Yes	No	N/A
Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐
Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒
Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐
Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒

2.6. Covariate definition and measures

	Yes	No	N/A
Does the protocol describe how the study covariates are defined and measured? (e.g. operational details for defining and categorising covariates)	☒	☐	☐
Does the protocol address the validity of the covariate measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒
Are covariates classified according to time windows? (e.g. current user, former user, non-use or diagnosis ever before or within certain time window)	☐	☐	☒

2.7. Data collection and management

	Yes	No	N/A
Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐
Are methods of quality assurance described?	☒	☐	☐
Is there a system in place for independent review of study results?	☒	☐	☐

2.8. Validation procedures

	Yes	No	N/A
Does the protocol provide information on any validation procedures performed?	☐	☒	☐

2.9. Data analysis

	Yes	No	N/A
Is the choice of statistical techniques described?	☒	☐	☐
Are descriptive analyses included?	☒	☐	☐
Are stratified analyses included?	☒	☐	☐
Does the plan describe methods for adjusting for confounding?	☒	☐	☐
Does the plan describe methods for handling missing data?	☒	☐	☐
Does the protocol address confounding by indication if applicable?	☐	☐	☒

2.10. Sample size and power calculations

	Yes	No	N/A
Is sample size and/or statistical power estimated?	☒	☐	☐

2.11. Study strength and limitations

Study strengths

	Yes	No	N/A
Are strong points of the study described?	☒	☐	☐

Study limitations

	Yes	No	N/A
Does the protocol discuss the impact on the study results of:			
Selection bias? (e.g. healthy user bias)	☒	☐	☐
Information bias? (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐
Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐

3. Study Management

3.1. Ethical approval and subject consent

	Yes	No	N/A
Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐
Has any outcome of an ethical review procedure been addressed?	☒	☐	☐
Have data protection requirements been described?	☒	☐	☐

3.2. Study milestones

	Yes	No	N/A
Does the protocol specify timelines for			
1.1.1 Start of data collection[1]	☒	☐	☐
1.1.2 End of data collection[2]	☒	☐	☐
1.1.3 Study progress report(s)	☒	☐	☐
1.1.4 Interim progress report(s)	☐	☒	☐
1.1.5 Registration in the EU PAS register	☒	☐	☐
1.1.6 Final report of study results.	☒	☐	☐

3.3. Study reporting and publications

	Yes	No	N/A
Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐
Are plans described for disseminating study results externally, including publication?	☒	☐	☐

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.