Influence of the Month of Birth and Persistence of ADHD in Prospective Studies:
Protocol for an Individual Patient Data Meta-Analysis

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S1. Supplemental Text: Search strategy
S2. Supplemental Table: PRISMA-P checklist

**Abstract**

*Introduction.* Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with symptoms, especially the hyperactive ones, that tend to decrease in severity with age. Interestingly, children born just before the school-entry cut-off date (*i.e.,* the youngest pupils of a classroom) are at higher risk of being diagnosed with ADHD compared to children born just after the cut-off date. Noteworthy, this *month-of-birth* effect tends to disappear with increasing absolute age. Therefore, it is possible that young children erroneously diagnosed with ADHD due to their month of birth present a lower chance to have their diagnosis confirmed at later age, artificially reinforcing the low persistence of ADHD across the lifespan. This protocol outlines an individual patient data (IPD) meta-analysis of prospective observational studies to explore the role of month of birth in the low persistence of ADHD across the lifespan. *Methods and analysis.* Five databases will be systematically searched in order to find prospective observational studies where the presence of ADHD is assessed both at baseline and at a follow-up of at least four years. We will use a two-stage IPD meta-analytic approach to estimate the role of month of birth in the persistence of ADHD. Various sensitivity analyses will be performed to assess the robustness of the results. *Ethics and dissemination.* No additional data will be collected and no deidentified raw data will be used. Ethics approval is thus not required for the present study. Results of this IPD meta-analysis will be submitted for publication in a peer-reviewed journal.

*Keywords:* ADHD; persistence; month of birth; meta-analysis

**Strength and limitations of this study**

* A systematic review of prospective observational studies assessing the persistence of attention-deficit/hyperactivity disorder (ADHD) will be performed.
* Based upon studies retrieved in the systematic review, we will conduct the first individual patient data (IPD) meta-analysis assessing the role of month of birth in the persistence of ADHD
* Limitations of this study include both the potential difficulty in acquiring some IPD and the potential heterogeneity in ADHD diagnosis procedures.

**Influence of the Month of Birth and Persistence of ADHD in Prospective Studies:
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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impairing and developmentally inappropriate levels of attention and/or hyperactivity/impulsivity.[1] Contrary to other neurodevelopmental disorders which have a relatively stable course across the lifespan,[2-5] ADHD symptoms - at least those of the hyperactive domain - tend to fade with increasing age. A review of follow-up studies assessing the long-term stability of ADHD diagnoses revealed that only one in six children with ADHD continue to meet the full criteria for ADHD into adulthood, even though impairing symptoms not meeting the threshold persist in about 70% of the childhood cases.[6] Given the widespread burden caused by ADHD on adults’ quality of life,[7] identifying the mechanisms underlying the persistence of ADHD through the lifespan remains one of the main issues in the field.

Along with its particular developmental course, another peculiarity of ADHD lies in its close association with birthdate.[8, 9] As shown in a very comprehensive study, including approximatively one million participants recruited over a period of 11 years, children born in the last months of the civil year have a higher risk of being diagnosed with ADHD compared to children born in the first months of the year (this increase in risk is substantial, of about 40%).[10] Since the school-entry cut-off date is the 31st of December in most countries (i.e., all children born between January 1st and December 31st start school the same year), children born at the end of the civil year may present with a higher level of cognitive and behavioral immaturity relative to their older classmates. This relative developmental bias could mimic some of the ADHD symptoms and could lead to inappropriate ADHD diagnoses in the youngest children. This interpretation has been reinforced by results showing that the month-of-birth effect can be reversed in some places. Children born in the last months of the civil year have a lower chance to be diagnosed with ADHD in regions where school-entry cut-off date is in late August (i.e., where children born from September to December are the oldest pupils in the classroom).[11]

Several studies have revealed that a key moderator of this month-of-birth effect on ADHD diagnosis is the absolute age of the children. As the age of the children increases, most studies show that the impact of month of birth on ADHD diagnosis tends to decrease.[12] To our knowledge, the mediator of this effect has not been explained empirically. Nevertheless, a common interpretation proposes that the effect of absolute age is most likely caused by the fact that a developmental difference of up to twelve months results in a more pronounced relative immaturity in young children than in adolescents or adults.[13]

In summary, compared to other neurodevelopmental disorders, ADHD presents two critical features: its developmental course, with severity and number of symptoms decreasing through the lifespan, and its high sensitivity to the month of birth, which gradually decreases with age. Taken together, these findings suggest that inappropriate diagnoses of ADHD due to the month of birth may contribute to the apparent low persistence of ADHD through the lifespan. Indeed, if the relative immaturity of a young child leads to an inappropriate diagnosis of ADHD, a reassessment of the original diagnosis several years later will most likely be associated with a reduction in ADHD symptoms. The aim of the present study will be to quantify the role of month of birth as a possible factor contributing to the low persistence of ADHD throughout the lifespan. To this end, we will perform a systematic review of prospective observational studies assessing the persistence of ADHD with increased age and, through an individual patient data (IPD) meta-analysis, we will quantify the magnitude of the month-of-birth effect on the persistence of ADHD.

**METHOD**

The present IPD meta-analysis will be conducted in accordance with standard methods for IPD meta-analysis and reporting will conform to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA)-IPD checklist.[14, 15]

**Eligibility Criteria**

*Study design.* We will consider only prospective studies in which ADHD was diagnosed both at baseline and follow-up. A mean follow-up duration of 4 years after the initial diagnosis will be required (this criterion also applies to the participant-level).

*Participants*. We will consider children with either a categorical diagnosis of ADHD in accordance with DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, or a categorical diagnosis of hyperkinetic disorder in accordance with ICD-9 or ICD-10. This diagnosis should have been established using either a clinical interview or a validated questionnaire. Moreover, the participants should have received the initial (baseline) diagnosis before the age of 10 and the final (follow-up) diagnosis after the age of 10. Studies in which ADHD is a comorbid disorder secondary to a genetic syndrome will be excluded. Moreover, only participants living in a country/region in which a school-entry cut-off date is applied (e.g., a country in which all children born between January 1st and December 31st of a same civil year start school during the same school year) will be included in our main analyses. Participants living in a country/region with no school-entry cut-off date will be included in a moderation analysis (dichotomous moderator = school-entry cut-off date: present *vs.* absent).

*Outcome.* The primary and the only outcome of the present study will be a categorical diagnosis of ADHD in accordance with standard classifications (as defined above). This diagnosis at follow-up should be performed at least four years after the diagnosis at baseline.

**Search methods for identification of studies**

In order to identify relevant studies, we will search five main databases (MEDLINE, Embase, CINAHL, PsycInfo and PubPsych). The search will be from inception up to August 2020. We will use controlled vocabulary (when available) and free text to search for two constructs, namely, ‘ADHD’ and ‘prospective studies’ (see Supplemental Text 1). No date, publication type or language restriction will be applied.

All reference lists of included studies and relevant reviews will be screened to identify potentially eligible studies not found by the electronic searches. Moreover, authors of all included studies will be contacted to ask for published or unpublished data that could have been missed (see the Data Collection and Transfer section for details on the contact procedure).

**Data extraction**

Two review authors will independently screen the titles and abstracts to identify potential eligible studies from the results of the searches. All disagreements will be resolved by discussion or, if impossible, the article will be processed to the next stage. Full texts of all reports selected on the basis of their title and/or abstract will be obtained and will be assessed against our inclusion criteria. Again, disagreements will be discussed and a senior author will be consulted if agreement is not reached. All studies excluded after full-text reading will be recorded, along with the reason for their exclusion, in the Supplementary Materials.

Two review authors will independently extract the following study-level data: Name of first author and year of publication, publication type, name of the cohort, country in which the study took place, school-entry cut-off date, participation rate, percentage of attrition, sampling method (e.g., cluster random sampling), mean follow up duration, number of participants, mean age at baseline and at follow up, diagnostic procedure used at baseline and at follow up, diagnosis classification used at baseline and at follow up, comorbidities. Authors of included studies will then be invited to confirmed the accuracy of these data and then to access to the following participant-level data: month of birth, diagnosis status at follow-up, age at baseline and follow up, follow up duration, psychiatric comorbidity and diagnosis procedure used at baseline and follow up.

If the school-entry cut-off date cannot be obtained by the authors of primary studies, we will contact governmental administration of the country in which the study took place to obtain this cut-off date. Then, all months of birth will be recoded depending on the school-entry cut-off date (i.e., month 1 will indicate the first month after the school-entry cut-off date). For example, a child born in January will be coded as born in month 1 if born in a region where the school-entry cut-off date is 31st December but will be coded as born in month 5 if born in a region where the school entry cut-off date is 31st August. The participants in studies conducted in a region where no strict school-entry cut-off date is applied will be coded with a “non-applicable” month of birth and will be analyzed separately.

**Risk of bias**

The risk of bias of the included studies will be assessed based upon the Newcastle Ottawa Scale – cohort studies by two reviewers.[16]

**Data collection and transfer**

Because we anticipate that authors of included studies have not routinely reported the association between the month of birth and the persistence of ADHD, we plan to contact the authors of each included study. Corresponding authors of these included studies will be invited to collaborate with our team by e-mail. A maximum of two reminders will be sent. If we do not achieve to contact a corresponding author, the same procedure will be applied for the first and/or last author, if different from the corresponding author.

The month of birth is a possible deidentifying information and the diagnosis status is a sensible data. Therefore, it is likely that participants of included studies had not given their approval for sharing this information. We believe that requesting raw data would increase the likelihood that study authors may decline the invitation to participate in our project, increasing the bias in our final analyses. Therefore, authors will be invited to perform the analyses on their raw data and to share only the results of these analyses. Authors will be sent an R code to obtain the results automatically and homogeneously across studies.

**Statistical analysis**

All statistical analyses will be performed in R environment. No quantitative analysis will be performed for individual studies including less than 10 participants (and no sensitivity analysis will be performed for conditions including less than 10 participants). Meta-analysis will be performed for synthesizing data from, at least, 5 studies (Jackson et al., 2017). If data are acquired for less studies, they will be described qualitatively. No moderation analysis or publication bias analysis will be performed for less than 10 studies (Higgins, 2011). We anticipate that a number of studies will meet inclusion criteria but will not be included in quantitative analysis (for example, because the month of birth will not be recorded, because we will not be able to obtain response from study authors, because the sample size was too small, etc…). Characteristics of eligible studies included in quantitative analysis will be compared to those not included in quantitative analysis.

We will perform IPD meta-analysis using only the two-stage approach.[17] The choice to rely on the two-stage approach is based on a number of considerations. First, as stated earlier, we believe that requesting to share raw data (which is needed in the one-stage approach but not in the two-stage) may decrease the rate of data inclusion. Second, a major drawback of the one-stage approach lies in its convergence issues, which can be reinforced by the use of a fully specified model and a binary dependent variable (ADHD diagnosis at follow up confirmed or not confirmed).[18] Taken together, and because one-stage and two-stage approaches generally produce similar results,[20] we chose to rely only on the two-stage approach.

For each study, we will fit a logistic regression model assessing the linear effect of month of birth (predictor) on the persistence of ADHD at follow up (dependent variable). Any participant with a missing month of birth or ADHD diagnosis at follow up will be excluded from this main analysis. Then, the pooled estimate will be obtained by random-effects meta-analysis (using the restricted maximum likelihood estimator in ‘metafor’ package in R). Heterogeneity will be assessed using the Cochran’s Q and I² statistics. Heterogeneity source and robustness of our findings will be assessed in several sensitivity and moderation analyses. In the sensitivity analyses, we will reassess our primary analysis (i) on participants with a follow up duration superior to 10 years, (ii) on participants with a baseline diagnosis performed before the age of 8 and after the age of 16, (iii) on participants with identical diagnosis procedure at baseline and at follow up, (iv) on participants with no comorbid psychiatric disorder, (v) on studies with a low percentage of attrition (inferior or equal to 20%), (vi) when effect sizes of individual studies are obtained using a robust logistic regression (using the ‘robustbase’ package in R), (vii) when influential studies (identified using Cook’s distance) are removed and (viii) when missing values are handled using multiple imputations (using the ‘mice’ package in R). For imputation models, we will fit a model with no auxiliary variables and a model with all recorded variable as auxiliary variables. In the moderation analyses, we will investigate the role of two study-level moderators and one patient-level moderator. For study-level moderation analysis, we will start by investigating the influence of the presence of a school-entry cut-off in the region/country in which primary studies took place on the association between month of birth and ADHD persistence. This moderator is thus a study-level binary moderator (presence *vs.* absence of a school-entry cut-off). To ensure homogeneous comparisons across the two groups, only countries in which the school-entry cut-off is the 31st December will be included in the presence group. This methodological precaution will allow to compare data for which the month of birth has the same scoring (i.e., month 1 refers to January for both groups). Then, we will explore the influence of the diagnosis procedure (questionnaires *vs.* clinical interview) on the association between month of birth and ADHD persistence. This moderator is also a study-level binary moderator. For the patient-level moderation analysis, we will explore the influence of ADHD subtypes on the association of month of birth with ADHD persistence. To do so, we will assess the influence of month of birth on ADHD persistence for each ADHD subtypes in individual studies. Then, a moderation analysis and an average estimate effect for each subtype will be obtained using a two-stage meta-analysis without model intercept. Last, publication bias will be acknowledged if the p-value of the Egger test is strictly inferior to .10.

**Ethics and dissemination**

No raw data will be transferred for this IPD meta-analysis and thus does not require any supplemental ethics committee approval – as any standard meta-analysis. Findings of this study are planned to be disseminated through peer-reviewed publications and/or conference presentations.

**Patient and public involvement**

There have been no patient and/or public involvement in the design of this IPD meta-analysis.

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