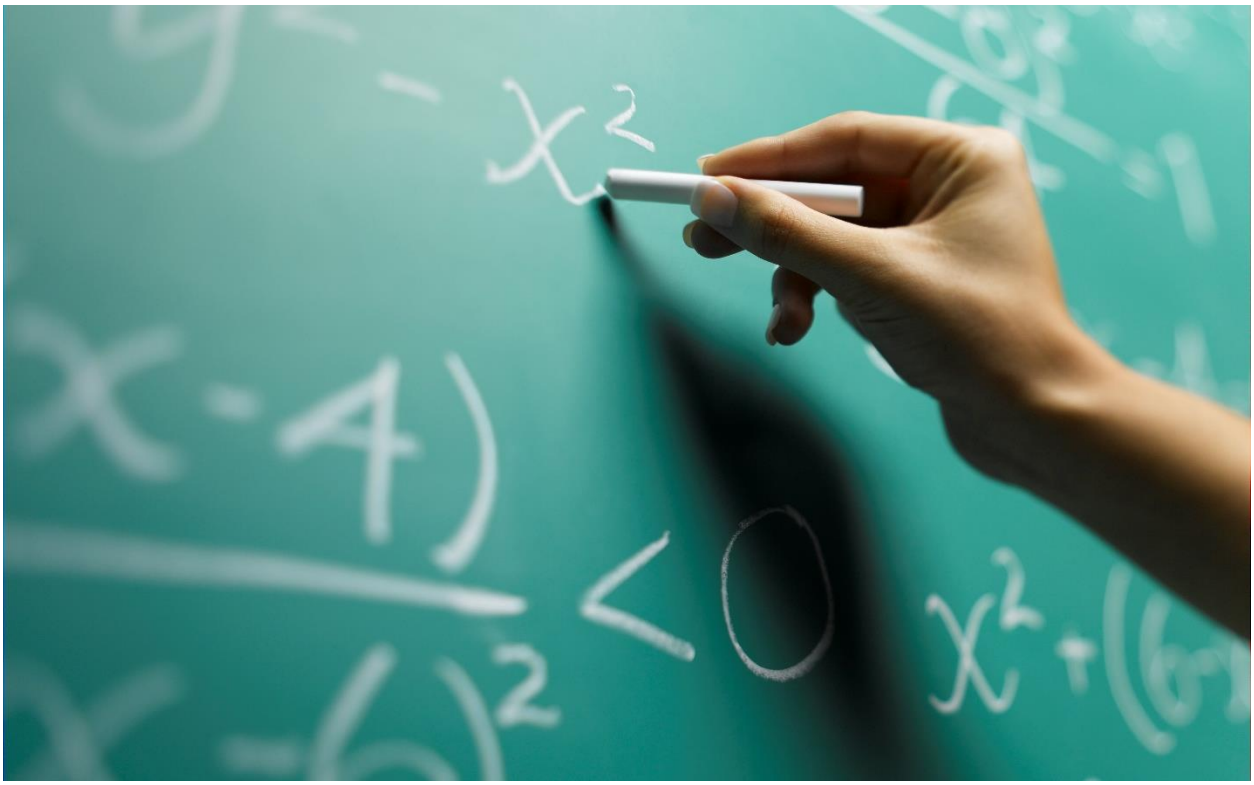
Academic, health and healthcare utilization outcomes in New Brunswick grade school students prescribed long-acting stimulants for the management of ADHD: An administrative data study



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Project Title

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Project Data

Research analytic outputs were produced using platform data accessed through NB-IRDT.

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Executive Summary

Attention-deficit/hyperactivity disorder, also known as ADHD, is a common neurodevelopmental disorder that interferes with individual functioning or development and is often characterized by an ongoing pattern of three particular symptoms: inactivity, hyperactivity and impulsivity [1]. ADHD is the most commonly diagnosed mental disorder among children and youth [2]. Research shows that school-aged children and youth are being diagnosed with ADHD with increasing frequency [3], and with this rise in diagnoses comes an increase in prescription medications used to treat the symptoms of this disorder [4]. To help alleviate symptoms, many families turn to long-acting stimulants as a prescribed treatment method.

Unlike short-acting stimulants, which typically start working within 30-45 minutes and wear off in 3-6 hours, long-acting stimulants are designed to work in phases, through an extended release into the bloodstream throughout the day [5]. Long-acting stimulants have been the topic of extensive research, and studies show they improve core symptoms of ADHD [6] – such as inattention and hyperactivity – making them the gold standard for medical treatment of ADHD [7]. However, their ability to improve functional outcomes associated with ADHD – such as reduced academic achievement or increased risk of injury – is less well understood.

Children and youth with ADHD face challenges that could inhibit their ability to excel academically or make them more likely to be hospitalized. To help measure the impacts of ADHD and of treatment with long-acting stimulants, this study uses linked administrative data records to examine academic, health and healthcare utilization outcomes in New Brunswick grade school students (Kindergarten through Grade 12) with ADHD. It compares outcomes between students with ADHD who are being treated with long-acting stimulants, students with ADHD who are not being treated and students without ADHD.

Highlight of Findings

Overall, our results suggest that, for grade school students with ADHD, treatment with long-acting stimulants has a positive impact on students' academic performance (primarily in high school) and may lower risk of injury, based on the following outcomes:

Report card scores

> High school students with ADHD who were taking long-acting stimulants received higher report card scores and failed courses less often than their untreated counterparts – and in some cases, their outcomes were similar to those of students without ADHD.

Performance on standardized provincial assessment exams

> Although K-12 students with ADHD scored lower on standardized provincial assessment exams than students without ADHD, high school students with ADHD who were taking long-acting stimulants scored higher on math exams than their untreated counterparts.

Graduation from high school

ADHD is associated with a lower likelihood of students graduating from high school on their first attempt. However, students with ADHD who were taking long-acting stimulants were as likely as students without ADHD to graduate on their first try.

Transition to post-secondary education

While untreated students with ADHD were less likely to transition to post-secondary education than those without ADHD, students with ADHD taking long-acting stimulants were more likely to enrol in post-secondary education than both untreated students and those without ADHD.

School attendance

Untreated students with ADHD were absent from school more frequently than those without ADHD, while students with ADHD taking long-acting stimulants were absent less frequently than both untreated students and those without ADHD.

Frequency of general practitioner and specialist physician visits

Both general practitioner and specialist physician visits were significantly more frequent among students with ADHD, and they were significantly more frequent among students taking long-acting stimulants than their untreated counterparts.

Frequency of hospitalization due to injury or stimulant and other drug toxicity

Hospitalization due to injury or stimulant and other drug toxicity was more frequent among untreated students with ADHD than among those without ADHD. Among students treated with long-acting stimulants, hospitalization rates for injury were similar to those among students without ADHD, and hospitalization rates for stimulant and other drug toxicity were lower than those among students without ADHD.

These findings may help inform ADHD management practices and policies in New Brunswick and elsewhere. By examining markers of academic achievement, attendance rates and healthcare utilization patterns, they offer insights into the potential functional benefits and limitations of long-acting stimulant drug therapy – evidence that may be used to help inform clinical practices, educational interventions and healthcare policies with the potential to positively impact the lives of individuals with ADHD and those who are invested in their success.

Notably, this is one of the first population-level administrative data studies on this topic in Canada and represents the first of its kind within the New Brunswick context. This type of 'big picture' research provides valuable, comprehensive evidence that captures outcomes reflective of a whole population, rather than a limited sample. For decision makers and service providers operating at the provincial level, the results of this study are particularly relevant as they are specific to New Brunswick's population and its education and healthcare systems.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in school-aged individuals. It is estimated that 3.4% of children and adolescents around the world have ADHD [8].

Quality of life is significantly impaired among those with ADHD as the impacts on self-esteem and functionality span across multiple domains of life [9]. Data consistently demonstrate the negative consequences of ADHD on individuals, particularly during the formative years. ADHD is shown to increase risks for mental health disorders, motor vehicle accidents, injuries, suicidality, criminality and adverse educational outcomes [9,10]. In the educational realm, ADHD is shown to negatively impact academic achievement as measured through teacher/parent rating, grade point averages, grade retention, high school graduation and transition to post-secondary education [11,12].

Stimulant medications, particularly long-acting stimulants, are considered the gold standard for medical treatment of ADHD [7]. However, while long-acting stimulants have been shown to improve the core symptoms of ADHD [6], such as inattention and hyperactivity, their effects on functional outcomes like healthcare use and educational achievements are less well-defined.

> **An estimated 3.4% of children and adolescents have ADHD, which increases their risk for negative health and educational outcomes. Long-acting stimulants are shown to improve symptoms of ADHD, but less is known about their impact on functional outcomes.**

In a 2013 review and meta-analysis of 43 randomized controlled trials of stimulant medications [13], most of the reviewed studies found that stimulants were associated with significant improvements in academic productivity and on-task behaviour in students with ADHD, although some studies reported no such benefit. Substantially fewer reviewed studies showed improvement in accuracy of academic work associated with stimulant medications. A more recent 2019 review and meta-analysis of 34 placebo-controlled studies [14] found that methylphenidate treatment of students with ADHD significantly improved math productivity and to a lesser extent accuracy, significantly improved reading productivity but not accuracy, and did not conclusively improve outcomes related to spelling.

Another frequently studied functional outcome of ADHD pharmacotherapy is its impact on the risk of accidents and injuries, which was examined in 14 studies identified in a 2020 review and meta-analysis [15]. Of these, eight found that ADHD medications (predominantly stimulants) were associated with a significant reduction in risk, two found non-statistically significant reductions and four found no association with risk of accidents and injuries.

Most studies on academic outcomes associated with stimulant drug therapy have examined relatively small sample sizes in controlled experiments; however, a smaller number of studies has used administrative data to examine drug effects on a much larger scale in a real-world setting. A recent review and meta-analysis [15] examined eight studies that used large databases to

investigate the impact of stimulant medications on academic outcomes. Five of these eight studies reported that stimulant medications were associated with significantly higher test scores and grade point averages and reduced school absence; however, one study [16] showed no relationship between stimulants and academic outcomes, and two studies [17,18] showed that stimulants were associated with a decline in academic performance.

Administrative databases are a valuable tool for studying functional outcomes associated with ADHD drug therapy. These databases generally include a broad sample universe and are linkable at the individual level across a variety of administrative data resources, permitting longitudinal, often population-level, studies that are capable of assessing relationships with, and adjusting for, a broad spectrum of covariates that include health, demographic and socioeconomic data.

A key advantage of this approach is its potential for efficient generation of real-world evidence, which can provide a novel perspective that may help to improve our understanding of the impact of stimulant medications on academic outcomes. Since relatively few large-scale administrative data studies have addressed this topic, and those that have offer seemingly conflicting evidence [15], further studies using this approach are warranted.

> **Administrative data allow researchers to study the impact of long-acting stimulants across large populations and over long periods of time, and linkage of records across multiple databases permits adjustment for a wide variety of covariates.**

The present study uses administrative data to examine the relationship between long-acting stimulant pharmacotherapy and functional outcomes in New Brunswick grade school students with ADHD.

A variety of academic outcomes are assessed, including report card and provincial assessment exam scores, high school graduation, transition to post-secondary education and attendance. Additional functional outcomes including hospitalization for injury and drug toxicity and physician and specialist visit frequency are also examined.

It is anticipated that the results of this study will improve understanding of the broader impact of long-acting stimulant therapy beyond symptom reduction and provide insights to support evidence-informed policy and practice decisions surrounding the management of ADHD.

Study Overview

This study examines the impact of long-acting stimulants (LAS) on academic, health and healthcare utilization outcomes in New Brunswick grade school students with ADHD.

Using administrative data, students were classified according to ADHD diagnosis and LAS treatment history into three groups:

Treated	Untreated	No ADHD
Individuals with ADHD who were treated with long-acting stimulants	*Individuals with ADHD who were not treated with long-acting stimulants*	*Individuals who do not have ADHD*

Administrative data were then used to examine the following outcomes in each group:

Academic outcomes:

- Report card scores
- Performance on standardized provincial assessment exams
- Graduation from high school
- Transition to post-secondary education
- School attendance

Health and healthcare utilization outcomes:

- Frequency of general practitioner and specialist physician visits
- Frequency of hospitalization due to injury or stimulant and other drug toxicity

Some details of the analysis for each outcome (e.g., study period, sample size) vary according to data availability and are described in outcome-specific sections of this report.

Data Sources

This study was conducted using a variety of administrative data sets accessed via the New Brunswick Institute for Research, Data and Training (NB-IRDT).

Located at the University of New Brunswick, NB-IRDT is the sole administrative data repository for the province of New Brunswick. Defined in legislation to receive data from government, private sector and not-for-profit organizations, NB-IRDT serves as a data custodian for over 100 linkable data sets, which are made accessible to researchers through a rigorous application process.

Administrative data resources can be linked at the individual level across multiple data sets through the use of a scrambled unique identifier. When individual-level administrative data were not available for a variable of interest, an area-level proxy was created instead. To create the proxy, Statistics Canada data were used to determine the average value for a given variable (e.g., income quintile) in a Dissemination Area (DA; a small geographic area comprising ~200-300 people), and then every individual who resides in that DA (determined by their postal code) was assigned that value for the variable.

A summary of the administrative data sets used in this study is provided in Supplementary Table 1.

General Methods

This section describes methods that apply to all outcomes included in the study.

Definition of ADHD diagnosis

ADHD diagnosis was defined using administrative data records. The first criterion for establishing diagnosis was identification of a 'sign of ADHD' in the data. Timing of ADHD diagnosis was then determined based on the 'sign of ADHD' as described below.

Signs of ADHD

Three data sources were used to define a 'sign of ADHD': Physician notes in NB Physician Billing data (which contain records of physician services billed to the provincial Medicare plan), prescription drug records and the Students Diagnosed with ADHD data set, which identifies students who have an academic medical plan in place for the management of ADHD in school.

Individuals meeting one or more of the following criteria were considered to have a 'sign of ADHD':

1) **Criteria in the NB Physician Billing records**
   Based on a keyword search of free text physician notes found in NB Physician Billing records spanning April 1, 2008 – November 17, 2021, individuals with at least one record containing any occurrence of at least one of the keyword terms summarized in Supplementary Table 2 were considered to have a 'sign of ADHD,' with one exception: Keyword search results using the 'ADD' keyword were subjected to an additional review step to assess the relevance of the result to ADHD, since the letters 'ADD' are likely to appear in other contexts unrelated to ADHD.

   Search results (short text strings) found using the 'ADD' keyword were reviewed and classified as either unrelated to ADHD (Flag 0), possibly representing an ADHD diagnosis (Flag 1) or likely representing an ADHD diagnosis (Flag 2) based on reviewer impressions. Criteria for classification of keyword screening results as unrelated/possible/likely ADHD are outlined in Supplementary Table 3.

   Only 'likely' (Flag 2) results for the 'ADD' keyword were considered to represent a 'sign of ADHD.'

2) **Criteria in prescription drug records**
   Individuals with any history of treatment with long-acting central nervous system stimulants (summarized along with corresponding Anatomical Therapeutic Chemical (ATC) codes in Supplementary Table 4) were considered to have a 'sign of ADHD.' Drug treatment information was derived from two data sources containing records of prescription drugs dispensed in NB community pharmacies:

1) The New Brunswick (NB) Drug Plan data set, which includes prescription records for individuals covered by NB's Prescription Drug Program (PDP) (about 14% of NB residents). Records spanning April 1, 2008 – March 31, 2018 were examined for LAS prescription history.

2) The NB Drug Information System (DIS), which contains prescription dispensing records for all study subjects regardless of drug plan coverage. Records spanning January 1, 2015 - December 31, 2021 were examined for LAS prescription history.

3) **Criteria in the Students diagnosed with ADHD data set**
Individuals whose school records indicate an academic medical plan in place for the management of ADHD (as per the Students Diagnosed with ADHD data set, spanning July 1, 2019 – June 30, 2021) were considered to have a 'sign of ADHD.' Medical plans for ADHD in academic records outline the health support services required at school to accommodate the needs of students with ADHD (e.g., administration of medication during school hours). These plans typically require a physician diagnosis of ADHD in order to be established. It is noted, however, that not all students with ADHD will have a medical plan in place.

Timing of ADHD diagnosis

The entire available date range of the NB Physician Billing, NB Drug Plan, NB Drug Information System and Students Diagnosed with ADHD data sets were screened for 'signs of ADHD.' The date of a 'sign of ADHD' was taken as the date associated with the sign-defining record (i.e., the date the physician service was billed or the prescription was dispensed).

For 'signs of ADHD' coming from medical plan records in the Students Diagnosed with ADHD data set, the date of the sign was taken as September 1 of the academic year in which the medical plan occurred.

An ADHD 'start date' (the earliest known date on which an individual is assumed to have symptoms of ADHD) was defined for each individual based on the 'signs of ADHD' identified in the data.

The ADHD 'start date' was defined as the date 180 days before the earliest 'sign of ADHD' across all data sources, as ADHD diagnostic criteria require that symptoms are present for at least six months before a diagnosis is rendered [19]. However, if an individual's earliest 'sign of ADHD' occurred after their twelfth birthday, their ADHD 'start date' was defined as the date of their twelfth birthday, since diagnostic criteria require that symptoms have been present since before age 12 [19]. In cases where an individual had a Flag 1 result (i.e., those *possibly* representing an ADHD diagnosis) from NB Physician Billing data that occurred earlier than a 'sign of ADHD,' the Flag 1 result was considered to be the earliest 'sign of ADHD.'

Definition of the ADHD diagnosis

> **Students were assumed to have ADHD if physician notes suggested they likely had ADHD, if they had a history of prescribed long-acting stimulants or if they had an academic plan for managing ADHD.**

In general, an individual was considered to have ADHD as of their ADHD 'start date' and was considered to have ADHD during a given observation period only if their ADHD 'start date' was earlier than the beginning of that observation period.

Definition of diagnosis/treatment groups

As mentioned in the Study Overview, this study examined outcomes across three groups:

Treated	Untreated	No ADHD
Individuals with ADHD who were treated with long-acting stimulants	*Individuals with ADHD who were not treated with long-acting stimulants*	*Individuals who do not have ADHD*

These groups were defined as follows:

Treated group

The treated group was defined based on the concept of continuous treatment.

Continuous treatment was defined as the period beginning with the fourth consecutive prescription for any LAS (considering all available prescription records, i.e., the full available date range of NB Drug Plan and NB Drug Information System data) and continuing for as long as prescriptions for LAS were dispensed regularly with no gaps between consecutive dispensing dates longer than 180 days (a threshold that has been used previously in studies of this nature [20-23]).

This approach ensures a lead-in period of three consecutive prescriptions for LAS (regardless of dose and dispensed days supply, with gaps no greater than 180 days between lead-in prescriptions), with the fourth prescription being taken as the beginning of continuous treatment. The initial four prescriptions need not all be for the same LAS.

The lead-in requirement was intended to exclude from analysis the initial drug trials and dose titration common in treatment-naïve individuals, with the intent of increasing the likelihood of the period of continuous treatment to reflect stable, effective drug therapy.

Following the lead-in period, switching between LAS or changing doses within the stated time constraints was not considered an interruption to continuous treatment. If continuous treatment was interrupted due to a gap between prescriptions of greater than 180 days, continuous treatment was considered to resume starting with the next LAS prescription. No lead-in period was required to meet the definition of continuous treatment when resuming continuous treatment after an interruption.

For most outcomes, the study period was divided into academic years (September 1 through June 30), and members of the study population (defined for each outcome) were considered to have ADHD in a given academic year if their ADHD 'start date' was earlier than the start of that academic year. Members of the study population with ADHD were included in the Treated group for a given academic year if they had at least 150 days of continuous treatment with LAS in that academic year.

Definition of the Treated group varied for some outcomes; these variations are described in the Methods section for each outcome.

Untreated group

For most outcomes, members of the study population with ADHD were included in the Untreated group for a given academic year if they had **no** prescriptions for LAS dispensed in that academic year **and** in the 180 days ***before*** the start of that academic year.

Definition of the Untreated group varied for some outcomes; these variations are described in the Methods section for each outcome.

No ADHD group

For most outcomes, members of the study population were included in the No ADHD group only if they had no 'signs of ADHD' and no Flag 1 results from an NB Physician Billing ADHD keyword search at any time across the full date range of all data sources used in defining ADHD diagnosis.

Definition of the No ADHD group varied for some outcomes; these variations are described in the Methods section for each outcome.

Exclusions

For most outcomes (i.e., those with study periods divided into academic years), individuals with one or more dispensed prescriptions from among those listed in the Excluded Medications Table (Supplementary Table 5) during or 180 days before an academic year were excluded from analysis for that academic year.

Individuals were excluded from analysis for a given academic year if they died or left NB during that academic year. Additionally, any individual enrolled (as per student enrolment data) in

grade school (grades K-12[1]) at age 22 years or older was excluded from analysis (this would likely be a data error as public funding for school stops at age 21 in NB). Exclusion criteria varied for some outcomes; these variations are described in the Methods section for each outcome.

Sources of prescription drug data: Prescription Drug Program (PDP) and Drug Information System (DIS) analyses

This study used two sources of prescription drug data:

- NB Drug Plan (Prescription Drug Program) data
- NB Drug Information System data

NB Drug Plan data include prescription records of individuals covered by the **NB Prescription Drug Program (PDP)** and are available from April 1, 2008 to March 31, 2018. The NB PDP covers approximately 14% of the province's population, including Social Development clients with low income, low-income seniors, residents of nursing and special care homes, individuals with certain chronic diseases and children with special needs or who are under care of the Minister of Social Development.

The **NB Drug Information System (DIS)** contains records of all prescription drugs dispensed in NB pharmacies regardless of drug plan coverage. This study used a custom extract of the NB DIS covering a date range of January 1, 2015 to December 31, 2021, which includes only a subset of drugs related to the treatment of ADHD (ATC codes included in the extract are summarized in Supplementary Table 6). NB pharmacies gradually began reporting data to the DIS following its launch in 2014, and all pharmacies were connected to the DIS as of January 1, 2017. For this reason, DIS data were only used for analysis from January 1, 2017 onwards (although DIS records back to January 1, 2015 were screened for LAS prescriptions as signs of ADHD, as described above under Definition of ADHD diagnosis).

Due to date range limitations, analysis of an unrestricted population was only possible during the available DIS date range (January 1, 2017 - December 31, 2021), while analyses prior to January 1, 2017 necessarily relied on NB Drug Plan data and were therefore limited to individuals covered by the NB PDP.

Table 1: Date ranges of prescription drug data used for analysis

Prescription Drug Program (PDP)	Drug Information System (DIS)	Pooled (PDP + DIS)
2008-2018 *(Apr 1, 2008 - Mar 31, 2018)*	**2017-2021** *(Jan 1, 2017 - Dec 31, 2021)*	**2008-2021** *(Apr 1, 2008 - Dec 31, 2021)*

[1] Grade K refers to Kindergarten throughout this report.

For outcomes whose study periods included both the PDP and DIS date ranges, two separate analyses were performed:

- A 'PDP' analysis spanning the PDP date range and using PDP data as the exclusive source of prescription drug data.

- A 'DIS' analysis spanning the DIS date range and using DIS data as the exclusive source of prescription drug data.

Pooled analyses (PDP + DIS) were also conducted.

Due to its exclusive use of PDP data to define diagnosis/treatment groups, the PDP analysis focused on a lower-income study population compared to the unrestricted study population defined in the DIS analysis.

NB Drug Plan data only reflect dispensed prescriptions covered by the Provincial Drug Program. The plan coverage of study subjects included in the PDP analysis was confirmed to ensure that their prescription history could be observed over the course of the study period (acknowledging the limitation that only those prescriptions paid by the Provincial Drug Plan are observable). NB Drug Plan coverage was confirmed using NB Social Assistance Data, which permitted confirmation of coverage for low-income social development clients. The study population for the PDP analysis was therefore limited to low-income social development clients (a population which would encompass the majority provincial drug plan-covered school-aged children).

Only those individuals with confirmed provincial plan coverage over the entirety of a given observation period (e.g., academic year) and for 180 days before that observation period were eligible for inclusion in the Untreated and No ADHD groups for that observation period. Plan coverage for any portion of an observation period was sufficient for eligibility for inclusion in the Treated group for that observation period.

Since NB Drug Plan data were only available up to March 31, 2018, PDP analyses of academic year 2017 (September 1, 2017 - June 30, 2018) were missing prescription drug data for the period of April through June 2018. In these cases, DIS records were used to fill in missing prescription records for April through June 2018 for individuals already included in the study population (no new individuals were added to the analysis based on DIS data alone).

Although all NB pharmacies were connected to the DIS as of January 1, 2017, overall annual prescription volume captured in the data in 2017 was lower than in later years. This suggests that some pharmacies may not have been reporting to the DIS for at least part of 2017. A non-reporting pharmacy presents the possibility that some LAS prescriptions may not be observable in the DIS data, which creates a risk of misclassifying treated individuals into the Untreated or No ADHD groups.

To mitigate this risk, only individuals with one or more prescriptions (for any drug) present in the study-specific DIS extract during the first six months of 2017 were eligible for inclusion in the Untreated or No ADHD groups for any observation period of a DIS analysis that included any

portion of 2017. This approach assumes that a pharmacy reporting to DIS within the first six months of 2017 was reporting for the entirety of 2017, and that individuals did not switch pharmacies in 2017.

Independent variables in regression models and variables for descriptive statistics

All regression models included the same set of independent variables, defined using linked administrative data:

- Mean age (continuous)
- Health zone of residence[2]
- Program of study
- Immigration status
- Select medications
- Indicators from the Canadian Index of Multiple Deprivation (CIMD)
- Sex
- District of school attended
- Household composition
- Comorbid conditions
- Household income quintile
- History of social assistance use

Diagnosis/treatment group assignment (Treated, Untreated, No ADHD) was also included in the models as an independent variable.

The same variables were generally included in descriptive tables of each analysis cohort, except where prohibited due to low category counts (see Management of small cell counts below).

Values of time-varying covariates (e.g., age, area of residence) were taken at the midpoint of the unit observation period used in the analysis (usually academic year).

Individual-level data (i.e., unique value for each individual obtained from the data) were used for variables wherever possible, but in cases where individual-level data were not available (noted below), area-level data were used instead to assign values to individuals.

Detailed descriptions of select variables are provided below:

School district: NB has four Anglophone and three Francophone school districts. These were condensed to form two categories – Anglophone and Francophone.

Program of study: In the NB education system, program of study refers to the language focus of the student's school programming. The most common programs include core study in English ('English Prime'), core study in French ('Regular/Régulier') and French immersion with early or late program

[2] Among NB's seven designated geographic health zones

entry. Program types were condensed to form three categories: English prime, Regular/Régulier and French Immersion/Other.

Household composition: Household composition refers to the group of individuals residing in the same household as the student included in the analysis. Two dimensions of household composition were reported: co-habitation with adults and co-habitation with children. The categories for co-habitation with adults include: no one residing with the student is older than 21 years; exactly 1 person residing with the student is older than 21 years; more than 1 person residing with the student is older than 21 years. The categories for co-habitation with children include: no one residing with the student is aged 21 years or younger; one or more than one person residing with the student is aged 21 years or younger.

Immigration status: Categories include 'recent immigrant' and 'other' (i.e., does not meet the definition of recent immigrant). Recent immigrant was defined as someone who immigrated to Canada from another country within the past five years (counting from the midpoint of the unit observation period).

Comorbid conditions: Comorbid conditions were identified using Canadian Chronic Disease Surveillance System (CCDSS) data, which identify individuals with chronic conditions based on hospitalization and physician service records. Comorbid conditions examined include asthma, diabetes, epilepsy, mood and anxiety disorders and schizophrenia. Generally, mood and anxiety disorders were reported separately, while asthma, diabetes, epilepsy and schizophrenia were grouped together as a separate dimension of comorbidity to mitigate low cell counts (see Management of small cell counts below). For each dimension of comorbidity, students were categorized as either having or not having one or more of the conditions included in that dimension.

Select medications: Select medications include second generation antipsychotics, clonidine, modafinil and guanfacine. A full list (with corresponding ATC codes) is provided in Supplementary Table 7. Individuals were categorized as either having or not having one or more prescriptions for one or more select medications during the unit observation period.

Income quintile: In this area-level variable, individuals were categorized by area-level before-tax income quintile (QABTIPPE), with quintile 1 representing the lowest and quintile 5 representing the highest level of income.

Canadian Index of Material Deprivation (CIMD): This area-level variable was defined using the CIMD based on 2016 Census data. The CIMD includes four indicators of material deprivation: Residential Instability, Economic Dependency, Ethno-Cultural Composition and Situational Vulnerability. Individuals were categorized on each

	indicator by quintile, with quintile 1 representing the lowest and quintile 5 representing the highest level of deprivation.
Social assistance use:	Categories include 'any' and 'none,' where 'any' refers to one or more social assistance payments received during the unit observation period or within five years before its midpoint, and 'none' refers to no social assistance payments received during that timeframe.

Management of small cell counts

Minimum release requirements specify that frequency counts of less than five cannot be released from the NB-IRDT secure data facility in order to minimize risk of disclosure of identifying information. To permit disclosure of all results values, categories having low cell counts were combined with other categories to yield cell counts of five or greater. Variables were omitted from tables when combining categories was not feasible (for example, when a variable had only two categories, one of which had a cell count below the minimum threshold). In some cases, certain portions of unadjusted tables, or combinations of unadjusted results, were not releasable due to actual or residual cell counts below the minimum release standard and were therefore omitted.

Statistical analysis

Statistical analysis was conducted using SAS 9.4. Mean estimates were generated using the proc_means function to generate mean, median and 95% confidence intervals. Generalized linear model (GLM) and logistic regression estimates were generated using the proc_glm and proc_logistic functions, respectively. Reported p-values and confidence intervals associated with regression estimates were obtained from the output of these functions. Regression estimates were deemed to be statistically significant if the associated p-value was less than or equal to 0.05.

All regression estimates shown for the Treated and Untreated groups used the No ADHD group as the reference category. Separate regression models (not shown) directly compared the Treated and Untreated groups. A significant difference relative to the No ADHD group is denoted by highlighting of the relevant row(s) in the results figures. A significant difference between Treated and Untreated groups on direct comparison is denoted by an asterisk (*) next to the row in the results figure with the higher estimate.

Reported n values refer to the number of observation periods for which an individual contributed data to a given regression model or descriptive table. As described below, the same individual may contribute data from each of several observation periods, resulting in multiple observation periods contributed by the same individual to a given model/table.

Outcome-Specific Methods

Report card scores

This outcome assesses academic performance using scores on grade school report cards.

New Brunswick is a bilingual province containing both Anglophone and Francophone school districts serving students in grades K-12. Report card grading systems vary in some cases by school and by district and have changed over time. Additionally, some students with specialized needs follow modified course plans which use different grading systems. Generally, however, most grade K-8 students are graded on a 1-4 scale, and most grade 9-12 students are graded on a standard percentage scale.

For students in grades K-8, the 1-4 scale assigns a whole number value from 1-4 to each of several grade-specific competencies based on student performance, with a grade of 3 representing achievement of the minimal acceptable standard of success.

Students in grades 9-12 are enrolled in a variety of courses, and a final percentage grade reflecting student performance is assigned to each course. For grade 9-12 students, our analysis considered a grade of 60% to represent achievement of the minimal acceptable standard of success and a grade of lower than 60% to represent course failure.

Two different methods were used in analyzing report card scores:

- A **Between-Student** method comparing academic performance between students classified in different diagnosis/treatment groups (i.e. Treated, Untreated, No ADHD).

- A **Within-Student** method comparing student performance in a given academic year to their own performance in a preceding academic year, noting which diagnosis/treatment group the student belonged to in each year.

Between-Student method

Report card performance was examined using three different approaches:

- Mean report card score
- Achievement of minimum acceptable standard
- Course failure

For each approach, separate PDP and DIS analyses, as well as a pooled analysis, were conducted as described under General Methods. Additionally, each analysis examined overall performance, as well as subject-specific performance in math, STEM (science, technology, engineering and math), and language.

For students in grades K-8, only scores using the 1-4 scale were included in the analysis. For students in grades 9-12, only scores using the percentage scale were included in the analysis. Scores of 0% (approximately 0.3% of total recorded scores) were excluded as these were assumed to represent instances where course work was not completed and therefore no true score was generated. A sensitivity analysis showed that retention of 0% scores did not affect outcomes.

Table 2: Study period (academic years) for report card scores: Between-Student method

	PDP	DIS	Pooled
Years of data availability	2016 - 2017	2017 - 2020	2016 - 2020

**Note: Academic years run from September 1 until June 30 the following year.*

The study period, determined by data availability, included academic years 2016 and 2017 for each PDP analysis, academic years 2017-2020 for each DIS analysis and academic years 2016-2020 for each pooled analysis.

Analysis cohorts included the entire NB population enrolled in the included grade range (K-8 and/or 9-12, as indicated below) for at least one full academic year of the study period, with exclusions and limitations as described under General Methods.

Between-Student method: Mean report card score

Separate analyses were conducted for students in grades K-8 and 9-12.

In each academic year, students were categorized as Treated, Untreated or No ADHD as described under General Methods. Descriptive statistics for the PDP and DIS cohorts in each grade range, overall and for each diagnosis/treatment group were derived from linked administrative data records, with each student contributing a data point for each year they were observed. A single mean overall report card score was calculated for each student in each observed year by averaging the student's scores across all competencies (K-8) or courses (9-12) graded in a given year.

Subject-specific mean scores were also calculated for each student in each year by averaging grades within the same subject area. Overall and subject-specific mean scores for each student-year were used in multivariate GLM regression models to estimate a mean report card score for each diagnosis/treatment group, adjusting for independent variables as described under General Methods.

Separate estimates were conducted for grades K-8 (PDP, DIS and pooled) and 9-12 (PDP, DIS and pooled), further separating overall and subject-specific estimates within each of these six analyses. Unadjusted mean scores for each diagnosis/treatment group were also calculated by averaging mean scores for each student-year included in each diagnosis/treatment group.

Between-Student method: Achievement of minimum acceptable standard

Only students in grades K-8 were included in this analysis, using the same cohort that was defined for the *Mean report card score* analysis.

In each academic year, students were categorized as Treated, Untreated or No ADHD as described under General Methods. For each student in each academic year, the proportion of that student's total number of competency scores that were 3 or higher was calculated. Similar calculations were performed for subject-specific competency scores. Calculated overall and subject-specific proportions were used in multivariate GLM regression models to estimate the proportion of scores 3 or higher (i.e., frequency of achieving minimum acceptable standard of performance) for each diagnosis/treatment group, adjusting for independent variables as described under General Methods.

Separate estimates were conducted for PDP, DIS and pooled cohorts, further separating overall and subject-specific estimates within each of these three analyses. Unadjusted mean proportions of scores 3 or higher for each diagnosis/treatment group were also calculated by averaging proportions for each student-year included in each diagnosis/treatment group.

Between-Student method: Course failure

Only students in grades 9-12 were included in this analysis, using the same cohort that was defined for the *Mean report card score* analysis.

In each academic year, students were categorized as Treated, Untreated or No ADHD as described under General Methods. For each student in each academic year, the proportion of that student's total number of course scores that were lower than 60% (i.e., course failure) was calculated. Similar calculations were performed for subject-specific course scores. Calculated overall and subject-specific proportions were used in multivariate GLM regression models to estimate proportion of scores lower than 60% (i.e., frequency of course failure) for each diagnosis/treatment group, adjusting for independent variables as described under General Methods.

Separate estimates were conducted for PDP, DIS and pooled cohorts, further separating overall and subject-specific estimates within each of these three analyses. Unadjusted mean proportions of scores lower than 60% for each diagnosis/treatment group were also calculated by averaging proportions for each student-year included in each diagnosis/treatment group.

Within-Student method

Report card performance was examined using two different approaches:

- Mean report card score
- Achievement of minimum acceptable standard

For each approach, separate PDP and DIS analyses, as well as a pooled analysis, were conducted as described under General Methods. Additionally, each analysis examined overall performance, as well as subject-specific performance in math, STEM, and language. As described under the Between-Student method, only scores using the 1-4 scale were included in analysis of grade K-8 students, and only scores using the percentage scale were included in analysis of grade 9-12 students, with scores of 0% excluded.

Table 3: Study period (academic years) for report card scores: Within-Student method

	PDP	DIS	Pooled
Years of data availability	2016 - 2017	2017 - 2020	2016 - 2020

**Note: Academic years run from September 1 until June 30 the following year.*

The study period, determined by data availability, included academic years 2016 and 2017 for each PDP analysis, academic years 2017-2020 for each DIS analysis, and academic years 2016-2020 for each pooled analysis.

Analysis cohorts included the entire NB population enrolled in one of the included grade ranges (K-8 and/or 9-12, as indicated below) for at least two consecutive academic years of the study period, with exclusions and limitations as described under General Methods. Students could not be included in the Within-Student analysis during the pair of academic years they were enrolled in grades 8 and 9, as these two grades utilize different report card scoring systems.

Within-Student method: Mean report card score

Separate analyses were conducted for students in grades K-8 and 9-12.

Students were categorized as Treated, Untreated or No ADHD in each observed academic year, and a single mean overall report card score was calculated for each student in each observed academic year, as described under the Between-Student method. A score difference was then calculated for each student in each consecutive pair of observed academic years within the study period (mean score in year 2 – mean score in year 1 of a consecutive pair of years).

Each score difference was then assigned to one of the following 'transition groups' based on diagnosis/treatment classification of the students in each of the two consecutive years:

- UnTx→Tx
  - (Untreated in year 1, Treated in year 2)
- Tx→UnTx
  - (Treated in year 1, Untreated in year 2)
- NoADHD→NoADHD
  - (No ADHD in years 1 and 2)
- UnTx→UnTx
  - (Untreated in years 1 and 2)

- Tx→Tx
    - (Treated in years 1 and 2)

The same process was used with subject-specific scores to generate subject-specific score differences.

Table 4: Consecutive academic years observed: Within-Student method

	PDP	DIS	Pooled
Consecutive years of data availability	2016 - 2017	2017 - 2018 2018 - 2019 2019 - 2020	2016 - 2017 2017 - 2018 2018 - 2019 2019 - 2020

**Note: Academic years run from September 1 until June 30 the following year.*

The pairs of consecutive academic years observed were 2016-2017 for the PDP analysis, 2017-2018, 2018-2019 and 2019-2020 for the DIS analysis and 2016-2017, 2017-2018, 2018-2019 and 2019-2020 for the pooled analysis.

Overall and subject-specific score differences for each student in each pair of consecutive years were used in multivariate GLM regression models to estimate a mean report card score difference for each transition group, adjusting for independent variables as described under General Methods.

Separate estimates were conducted for grades K-8 (PDP, DIS and pooled) and 9-12 (PDP, DIS and pooled), further separating overall and subject-specific estimates within each of these six analyses. Unadjusted mean overall score differences for each transition group were also calculated by averaging all individual mean score differences included in each transition group.

Within-Student method: Achievement of minimum acceptable standard

Only students in grades K-8 were included in this analysis, using the same cohort that was defined for the Within-Student *Mean report card score* analysis.

Students were categorized as Treated, Untreated or No ADHD in each observed academic year, and the proportion of total competency scores that were 3 or higher was calculated for each student in each observed academic year, as described under the Between-Student method. Differences in proportions between consecutive academic years for each student in each pair of observed years were then calculated and assigned to transition groups as described under *Mean report card score*. The same process was used with subject-specific scores to generate subject-specific differences in proportions. The pairs of consecutive academic years observed were the same as those described under *Mean report card score*.

Overall and subject-specific proportion differences for each student in each pair of consecutive years were used in multivariate GLM regression models to estimate proportion difference for

each transition group, adjusting for independent variables as described under General Methods. Separate estimates were conducted for PDP, DIS and pooled cohorts, further separating overall and subject-specific estimates within each of these three analyses.

Performance on standardized provincial assessment exams

This outcome assesses student performance on NB provincial assessment exams.

These standardized exams assess the performance of grade school students in a variety of subject areas including math, language and science. Different subject areas are evaluated at different grade levels each year. All NB students have the opportunity to participate in assessment exams, though exemptions are granted if necessary. Only exams scored on a percentage scale (the majority of exams) were included in the analysis. The list of included exams, by grade level and academic year, is summarized in Supplementary Table 8.

Some exams are scored using a 'true score,' which is a percentage score based on item response theory, which adjusts for relative difficulty of exam questions based on the examined cohort's performance on each question. True scores were used for this analysis where available; otherwise, raw percentage scores were used.

Table 5: Study period (academic years) for performance on standardized provincial assessment exams

	PDP	DIS	Pooled
Years of data availability	2015 - 2017	2017 - 2019	2015 - 2019

**Note: Academic years run from September 1 until June 30 the following year.*

The study period, determined by data availability, included academic years 2015-2017 for each PDP analysis, academic years 2017-2019 for each DIS analysis, and academic years 2015-2019 for each pooled analysis.

Analysis cohorts included the entire NB population enrolled in the included grade ranges (K-8 and/or 9-12, as indicated below) for at least one full academic year of the study period, with exclusions and limitations as described under General Methods.

Each exam score was categorized as Treated, Untreated or No ADHD based on the student's diagnosis/treatment status, as described under General Methods. The majority of included assessment exams were written in the latter half of the academic year. For these exams, diagnosis/treatment group categorization was based on the academic year during which the exam was written, as was verification of NB Drug Plan coverage for PDP analyses (as described under General Methods).

A minority of included exams were written in September, at the beginning of the academic year. For these exams, diagnosis/treatment group categorization and verification of NB Drug

Plan coverage were based on the academic year prior to the one in which the exam was written, with the rationale that categorization would reflect diagnosis/treatment status during a substantial period of instruction that most closely preceded the exam date.

Descriptive statistics for the overall PDP and DIS cohorts (grades K-12) and each diagnosis/treatment group within each cohort were derived from linked administrative data records, with each student contributing a data point for each year they were observed. Each included exam score was converted to a percentile rank among students who wrote the same exam in the same year. The percentile rank therefore reflects the performance of each student relative to their peers who wrote the same exam at the same time.

Overall and subject-specific (math, language, STEM) percentile ranks were used in multivariate GLM regression models to estimate percentile rank for each diagnosis/treatment group, adjusting for independent variables as described under General Methods. Separate estimates were conducted for grades K-8 (PDP, DIS and pooled), 9-12 (PDP, DIS and pooled) and K-12 (PDP, DIS and pooled), further separating overall and subject-specific estimates within each of these nine analyses. Unadjusted mean percentile ranks for each diagnosis/treatment group were also calculated by averaging percentile ranks for each exam result included in each diagnosis/treatment group.

Graduation from high school

This outcome examines the likelihood of failure of grade 12 students to graduate from high school on their first attempt.

Table 6: Study period (academic years) for graduation from high school

	PDP	DIS	Pooled
Years of data availability	2010 - 2017	2017 - 2019	2010 - 2019

**Note: Academic years run from September 1 until June 30 the following year.*

The study period, determined by data availability, included academic years 2010-2017 for the PDP analysis, academic years 2017-2019 for the DIS analysis and academic years 2010-2019 for the pooled analysis.

Analysis cohorts included the entire NB population enrolled in grade 12 for the first time during one of the academic years included in the study period, with exclusions and limitations as described under General Methods.

Students were categorized as Treated, Untreated or No ADHD based on their diagnosis/treatment status during their grade 12 academic year, as was verification of NB Drug Plan coverage for PDP analysis (as described under General Methods). Descriptive statistics for the overall PDP and DIS cohorts and each diagnosis/treatment group within each cohort were derived from linked administrative data records. The outcome of each student's grade 12 year

(graduation or failure to graduate) was obtained from administrative data records and used in multivariate logistic regression models to estimate likelihood of not graduating for each diagnosis/treatment group, adjusting for independent variables as described under General Methods.

Separate estimates were conducted for PDP, DIS and pooled cohorts. Unadjusted failure rates (failures to graduate divided by total enrolled students) were also calculated for each diagnosis/treatment group within each cohort.

Transition to post-secondary education

This outcome examines the likelihood of students not transitioning to post-secondary education in NB following graduation from high school.

Administrative data permit examination of enrolment in NB's major post-secondary education institutions, which include the province's four public universities and three of its four public colleges.[3] Enrolment at institutions outside NB is not observable using NB administrative data and was not examined in this study.

Analysis cohorts were determined by data availability and included the entire NB population graduating from high school at the conclusion of the 2014-2017 academic years (i.e., graduation in June 2015, 2016, 2017 or 2018), with exclusions and limitations as described under General Methods.

Two separate outcomes were examined:

- Enrolment at one of the seven observable NB post-secondary education institutions within the first six months of the academic year following graduation.

- Enrolment within the first two academic years following graduation.

For example, for a student graduating in June 2015, post-secondary enrolment within six months was checked for the period of September 1, 2015 - February 28, 2016, and enrolment within two years was checked for the period of September 1, 2015 - April 30, 2017.

[3] NB's four public universities include Mount Allison University, St. Thomas University, Université de Moncton and the University of New Brunswick. The three colleges include the New Brunswick Community College, the Collège Communautaire du Nouveau-Brunswick and the New Brunswick College of Craft and Design.

Table 7: Study period (by date of graduation) for transition to post-secondary education

	PDP	DIS	Pooled
6-month enrolment study period	Sept 2015 - Feb 2016 Sept 2016 - Feb 2017 Sept 2017 - Feb 2018 Sept 2018 - Feb 2019	Sept 2018 - Feb 2019	Sept 2015 - Feb 2016 Sept 2016 - Feb 2017 Sept 2017 - Feb 2018 Sept 2018 - Feb 2019
2-year enrolment study period	Sept 2015 - Apr 2017 Sept 2016 - Apr 2018 Sept 2017 - Apr 2019	-	-

The PDP analysis examined enrolment within six months for students who graduated in June 2015, 2016, 2017 and 2018, and enrolment within two years for students who graduated in June 2015, 2016 and 2017. The DIS analysis examined enrolment within six months for students who graduated in June 2018. The pooled (PDP + DIS) analysis examined enrolment within six months for students who graduated in June 2015, 2016, 2017 and 2018.

Each analysis included only those graduates who maintained NB Medicare eligibility (as verified via administrative data records) throughout the entire duration of the respective observation window (six months or two years).

Students were categorized as Treated, Untreated or No ADHD based on their diagnosis/treatment status during their grade 12 academic year, as was verification of NB Drug Plan coverage for PDP analysis (as described under General Methods). Descriptive statistics for the overall 6-month PDP and DIS cohorts and each diagnosis/treatment group within each cohort were derived from linked administrative data records. The outcome for each graduate (enrolment or lack of enrolment within the observed timeframe) was obtained from administrative data records and used in multivariate logistic regression models to estimate likelihood of lack of 6-month and 2-year enrolment for each diagnosis/treatment group, adjusting for independent variables as described under General Methods.

Separate estimates were conducted for PDP (6-month and 2-year), DIS (6-month) and pooled (6-month) cohorts. Unadjusted estimates of the proportion of students transitioning to post-secondary education for each diagnosis/treatment group were also calculated for the PDP (6-month) and DIS (6-month) cohorts. Unadjusted estimates for the PDP (2-year) and pooled (6-month) cohorts were not releasable due to risk of residual disclosure (residual counts compared to the released PDP (6-month) and DIS (6-month) estimates were below the required minimum).

School attendance

This outcome examines the frequency of student absence from school.

Administrative education data permit examination of absences, including reason for absence and duration of absence.

Table 8: Study period (academic years) for school attendance

	PDP	DIS	Pooled
Years of data availability	-	2018 – 2020*	-

** The 2019 academic year only includes an observation period of September 2019 - February 2020 due to pandemic-related school closures from March 2020 - June 2020.*

The study period, determined by data availability, included academic years 2018 - 2020. Analysis of absences used DIS as the sole source of prescription drug data as DIS data were available for all years of the study period. The observation period for the 2019 academic year included September 2019 through February 2020 only as schools were closed from March through June 2020 due to the COVID-19 pandemic.

Analysis cohorts included the entire NB population enrolled in grades K-12 during any portion of the study period. Students were categorized as No ADHD as described under General Methods. Students were considered to have ADHD as of their ADHD 'start date.' Students with ADHD were categorized as Treated during periods of continuous treatment during the study period, and as Untreated outside of periods of continuous treatment during the study period.

Each academic year of the study period constituted a distinct observation window. Additionally, each portion of an academic year during which a student was categorized as belonging to a different diagnosis/treatment group constituted a distinct observation window. The maximum duration of an observation window was therefore one academic year.

Unlike for previous outcomes, students were not excluded from analysis if they died or left NB partway through an academic year. Rather, students were observed during the time they were present in NB. Students were excluded from analysis for a given observation window if they had one or more dispensed prescriptions from among those listed in the Excluded Medications Table (Supplementary Table 5) at any time during that observation window. Otherwise, exclusions were as described under General Methods.

Descriptive statistics for each diagnosis/treatment group and the overall cohort (academic years 2018 - 2020 combined) were derived from linked administrative data records, with each student contributing a data point for each distinct observation window in which they were included. The value of time-varying characteristics (e.g., age, place of residence) was taken at the midpoint of each observation window.

Absences during each observation window were counted and attributed to the diagnosis/treatment group in which the student was categorized during that observation window. Overall absences (any reason/duration), as well as absences by reason (illness, medical appointment, out of school suspension, unknown) and absences by duration (one period, longer than one period) were counted. Absences due to bereavement or school sports were not included.

The observed numbers of absences per student per observation window were used in multivariate GLM regression models to estimate the number of absences per person for each diagnosis/treatment group, adjusting for independent variables as described under General Methods (with the value of time-varying covariates taken at the midpoint of each observation window). Models also included the duration of each observation window as an independent variable in order to adjust for differences in observation time.

Separate models were created for overall absences in each academic year of the study period, and for all years combined, as well as for absences by reason and duration. Unadjusted estimates of absences per person-month (overall, by reason and by duration) were also calculated for each diagnosis/treatment group and the overall cohort, for each academic year of the study period.

Frequency of general practitioner and specialist physician visits

This outcome examines frequency of generalist and specialist physician visits using NB Physician Billing data, which captures billing of physician services to provincial Medicare.

Table 9: Study period for frequency of general practitioner and specialist physician visits

	PDP	DIS	Pooled
Years of data availability	Oct 2008 - Mar 2018	Jul 2017 - Dec 2020	Oct 2008 - Dec 2020

The study period, determined by data availability, included October 1, 2008 through March 31, 2018 for the PDP analysis, July 1, 2017 through December 31, 2020 for the DIS analysis and October 1, 2008 through December 31, 2020 for the pooled analysis.

Analysis cohorts included the entire NB population aged 5-18 years who were residing in NB during any portion of the study period. Individuals were categorized as No ADHD as described under General Methods. Individuals were considered to have ADHD as of their ADHD 'start date.' Individuals with ADHD were categorized as Treated during periods of continuous treatment during the study period, and as Untreated outside of periods of continuous treatment during the study period.

Each portion of the study period during which an individual was categorized as belonging to a different diagnosis/treatment group constituted a distinct observation window, up to a maximum duration of one year. Uninterrupted observation periods longer than one year were broken into smaller observation windows such that no single observation window was longer than one year.

Unlike for previous outcomes, individuals were not excluded from analysis if they died or left NB partway through an academic year. Rather, individuals were observed during the time they were present in NB. Individuals who had dispensed prescriptions from among those listed in the Excluded Medications Table (Supplementary Table 5) were excluded from analysis for the 180

days following each such prescription, but they were eligible for inclusion if more than 180 days had passed since the most recently dispensed excluded medication. Otherwise, exclusions and limitations were as described under General Methods.

Descriptive statistics for the overall PDP and DIS cohorts and each diagnosis/treatment group within each cohort were derived from linked administrative data records, with each individual contributing a data point for each distinct observation window in which they were included. The value of time-varying characteristics (e.g., age, place of residence) was taken at the midpoint of each observation window.

Physician visits with general practitioners (GPs) (including nurse practitioners [NPs]), pediatricians and psychiatrists were identified using records of physician services billed to Medicare. One or more services billed by an individual provider on a given date was counted as a visit with that provider, with a maximum of one visit per provider per day.

All billed services were counted, with the following exceptions: hospital inpatient and emergency department services, extramural hospital services, nursing and special care home visits, medical laboratory services, detention fees and fees for consultation of other practitioners.

Services billed by different providers on the same date were counted as separate visits, with two exceptions:

- NB Physician Billing data do not permit distinction between individual NPs; therefore, all services billed by any NP on a given date were counted as a single visit.

- In cases where the provider ID is not known, all services billed by unknown providers on a given date were counted as a single visit (noting that services billed by NPs and unknown providers represent only a small proportion of total billed physician services).

Physician visits during each observation window were counted and attributed to the diagnosis/treatment group in which the individual was categorized during that observation window. Physician visits with GPs (including NPs), pediatricians and psychiatrists were counted, as were total physician visits (combining all three types).

The observed numbers of visits per observation window were used in multivariate GLM regression models to estimate the number of visits per person for each diagnosis/treatment group, adjusting for independent variables as described under General Methods (with the value of time-varying covariates taken at the midpoint of each observation window). Models also included the duration of each observation window as an independent variable in order to adjust for differences in observation time.

Separate estimates were conducted for each physician category (GP/NP, pediatrician, psychiatrist, total combined) for each of the PDP, DIS and pooled cohorts. Unadjusted estimates of visits per person-year (by physician type and for all types combined) were also calculated for each diagnosis/treatment group and the overall cohort, for the PDP and DIS analyses.

Frequency of hospitalization due to injury or stimulant and other drug toxicity

This outcome examines frequency of hospitalization due to injury or stimulant and other drug toxicity using NB Discharge Abstract Data (DAD), which captures records of services and diagnoses rendered during inpatient hospital stays in NB.

Table 10: Study period for frequency of hospitalization due to injury or stimulant and other drug toxicity

	PDP	DIS	Pooled
Years of data availability	Oct 2008 - Mar 2018	Jul 2017 - Mar 2021	Oct 2008 - Mar 2021

The study period, determined by data availability, included October 1, 2008 through March 31, 2018 for the PDP analysis, July 1, 2017 through March 31, 2021 for the DIS analysis and October 1, 2008 through March 31, 2021 for the pooled analysis.

Analysis cohorts included the entire NB population aged 5-18 years who were residing in NB during any portion of the study period. Individuals were categorized as No ADHD as described under General Methods. Individuals were considered to have ADHD as of their ADHD 'start date.' Individuals with ADHD were categorized as Treated during periods of continuous treatment during the study period, and as Untreated outside of periods of continuous treatment during the study period.

Each portion of the study period during which an individual was categorized as belonging to a different diagnosis/treatment group constituted a distinct observation window, up to a maximum duration of one year. Uninterrupted observation periods longer than one year were broken into smaller observation windows such that no single observation window was longer than one year.

Unlike for previous outcomes, individuals were not excluded from analysis if they died or left NB partway through an academic year. Rather, individuals were observed during the time they were present in NB. Individuals who had dispensed prescriptions from among those listed in the Excluded Medications Table (Supplementary Table 5) were excluded from analysis for the 180 days following each such prescription, but they were eligible for inclusion if more than 180 days had passed since the most recently dispensed excluded medication. Otherwise, exclusions and limitations were as described under General Methods.

Descriptive statistics for the overall PDP and DIS cohorts and each diagnosis/treatment group within each cohort were derived from linked administrative data records, with each individual contributing a data point for each distinct observation window in which they were included. The value of time-varying characteristics (e.g., age, place of residence) was taken at the midpoint of each observation window.

Hospitalizations due to injury and stimulant and other drug toxicity were identified based on diagnostic information in DAD records. Individual hospitalization events were defined using the

Canadian Institute for Health Information's (CIHI) method for identifying 'episodes of care' [24] in order to avoid counting inter-institutional transfers (which are common in NB) as multiple distinct hospitalizations. Cause-specific hospitalizations were then identified as episodes of care in which one or more than one discharge record meets cause-specific criteria, as described below.

Hospitalizations due to injury were defined using ICD-10-CA (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada) codes specified by CIHI as defining injury hospitalizations, modified to exclude injury due to assault or when the injured party was the passenger of a vehicle. The complete method and list of ICD-10-CA codes used to identify hospitalizations due to injury are detailed in Supplementary Table 9.

Hospitalizations due to stimulant and other drug toxicity were defined using ICD-10-CA codes specifying poisoning by psychostimulants with abuse potential, excluding methamphetamine; acute intoxication due to stimulants, excluding methamphetamine; and poisoning by antiepileptic, sedative-hypnotic, anti-parkinsonism and psychotropic drugs, including psychostimulants (accidental, intentional and undetermined intent).

The definition excludes hospitalization due to known/expected adverse effects of psychostimulants and mental/behavioural disorders due to psychostimulant abuse (i.e., harmful use pattern, dependence, withdrawal). The complete method and list of ICD-10-CA codes used to identify hospitalizations due to stimulant and other drug toxicity are detailed in Supplementary Table 9.

Hospitalizations during each observation window were counted and attributed to the diagnosis/treatment group in which the individual was categorized during that observation window. The observed numbers of hospitalizations per observation window were used in multivariate GLM regression models to estimate the number of hospitalizations per person for each diagnosis/treatment group, adjusting for independent variables as described under General Methods (with the value of time-varying covariates taken at the midpoint of each observation window). Models also included the duration of each observation window as an independent variable in order to adjust for differences in observation time.

Separate estimates were conducted for hospitalizations due to injury or stimulant and other drug toxicity, and for each of the PDP, DIS and pooled cohorts. Unadjusted estimates of hospitalizations per person-year, by type, were also calculated for each diagnosis/treatment group and the overall cohort, for the PDP and DIS analyses.

Results

Report card scores

Between-Student method

> **K-8 students with ADHD had lower report card scores and were more frequently below the minimum acceptable standard than students without ADHD. Scores were similar between students with ADHD being treated with long-acting stimulants and those who were not.**
>
> **Among students in grades 9-12, those with ADHD had lower report card scores and failed more courses than those without ADHD. Among grade 9-12 students with ADHD, those treated with long-acting stimulants had higher report card scores and failed fewer courses than their untreated counterparts.**

Mean report card score

Among grade K-8 students in the PDP analysis (n = 2416) (Figure 1), regression estimates for mean overall report card score were significantly lower among both Treated and Untreated students with ADHD, compared to the reference category of students in the No ADHD group. Estimates for the Treated and Untreated groups were not significantly different from one another. The same pattern was evident across all subject-specific score estimates, and in the DIS (n = 159,778) (Figure 2) and pooled (n = 161,511) (Figure 3) analyses.

Among grade 9-12 students in the PDP analysis (n=2361) (Figure 4), the mean overall report card score estimate was significantly lower in the Untreated group compared to the No ADHD group, while the estimate for the Treated group was not significantly different from that for the No ADHD group. The same pattern was observed across all subject-specific estimates. Direct comparison of Treated and Untreated estimates showed that mean score estimates were significantly higher for the Treated group for overall scores. Math, language and STEM score estimates also trended higher in the Treated group compared to the Untreated group, though these differences were not statistically significant.

Among grade 9-12 students in the DIS analysis (n = 88,152) (Figure 5), the mean overall report card score estimates were significantly lower in both the Treated and Untreated groups compared to the No ADHD group. The same pattern was observed across all subject-specific estimates. Direct comparison of Treated and Untreated estimates showed that mean score estimates were significantly higher for the Treated group for overall, STEM and language scores. Math score estimates also trended higher in the Treated group compared to the Untreated group, though this difference was not statistically significant. The same patterns observed in the DIS analysis were also evident in the pooled analysis (n = 89,959) (Figure 6).[4]

[4] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheets 1-6, available upon request.*

Achievement of minimum acceptable standard

Among grade K-8 students in the PDP analysis (n = 2416) (Figure 7), regression estimates for the overall proportion of scores at or above minimum standard were significantly lower among both Treated and Untreated students with ADHD, compared to the reference category of students in the No ADHD group. Estimates for the Treated and Untreated groups were not significantly different from one another. The same pattern was evident across all subject-specific estimates, and in the DIS (n = 159,778) (Figure 8) and pooled (n = 161,511) (Figure 9) analyses.[5]

Course failure

Among grade 9-12 students in the PDP analysis (n=2361) (Figure 10), the overall estimate of the proportion of courses failed was significantly higher in the Untreated group compared to the No ADHD group, while the estimate for the Treated group was not significantly different from that for the No ADHD group. The same pattern was observed across all subject-specific estimates. Direct comparison of Treated and Untreated estimates showed that the estimate for the proportion of language course failed was significantly lower for the Treated group. Overall, math and STEM score estimates also trended lower in the Treated group compared to the Untreated group, though these differences were not statistically significant.

Among grade 9-12 students in the DIS analysis (n = 88,152) (Figure 11), the overall estimates of the proportions of courses failed were significantly higher in both the Treated and Untreated groups compared to the No ADHD group. The same pattern was observed across all subject-specific estimates. Direct comparison of Treated and Untreated estimates showed that that the estimate for the proportion of overall courses failed was significantly lower for the Treated group, and the same pattern was observed for all subject-specific estimates. Moreover, the same patterns (overall and subject-specific) observed in the DIS analysis were also evident in the pooled analysis (n = 89,959) (Figure 12).[6]

Within-Student method

> **In general, the within-student analysis did not show a strong association between treatment with long-acting stimulants and improved academic performance.**

Mean report card score

Among grade K-8 students in the PDP analysis (n = 502) (Figure 13), estimates of mean score differences for STEM courses showed that scores decreased significantly in the Tx→UnTx transition group relative to the reference transition group (NoADHD→NoADHD). No other mean score differences in the grade K-8 PDP analysis differed significantly from reference.

[5] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheets 7-9, available upon request.*

[6] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheet 10, available upon request.*

Among grade K-8 students in the DIS analysis (n = 75,682) (Figure 14), estimates of mean score differences for math, language and STEM courses showed that scores increased significantly in the UnTx→Tx transition groups relative to reference. Overall mean score differences, however, did not differ significantly from reference. It was also noted that language score difference estimates in the Tx→Tx and UnTx→UnTx transition groups differed significantly (increased) from reference. Patterns observed in the DIS analysis were mirrored in the pooled analysis (n = 76,184) (Figure 15).

Among grade 9-12 students in the PDP analysis (n=635) (Figure 16), estimates of mean score differences for language courses showed that scores decreased significantly in the UnTx→Tx transition group relative to reference. No other mean score differences in the grade 9-12 PDP analysis differed significantly from reference.

Among grade 9-12 students in the DIS analysis (n = 43,143) (Figure 17), estimates of mean score differences for language courses showed that scores decreased significantly in the Tx→UnTx transition group relative to reference. No other mean score differences among Tx→UnTx and UnTx→Tx transition groups differed significantly from reference, although it was noted that math and STEM score difference estimates for the UnTx→UnTx groups differed significantly from reference (i.e., scores decreased less, relative to reference).

Among grade 9-12 students in the pooled analysis (n = 43,778) (Figure 18), estimates of mean score differences showed that scores overall and for language courses decreased significantly in the Tx→UnTx transition groups relative to reference, while scores for math courses increased significantly in the Tx→UnTx transition group relative to reference. No other mean score differences among Tx→UnTx and UnTx→Tx transition groups differed significantly from reference, although it was noted that, as in the DIS analysis, math and STEM score difference estimates for the UnTx→UnTx groups differed significantly (increased) from reference.[7]

Achievement of minimum acceptable standard

Among grade K-8 students in the PDP analysis (n = 502) (Figure 19), estimates of the difference in proportion of scores at or above minimum standard showed that no transition groups differed significantly from the reference transition group (NoADHD→NoADHD), overall and across all subject areas.

Among grade K-8 students in the DIS analysis (n = 75,682) (Figure 20), estimates showed that the proportion of scores at or above minimum standard was significantly increased in the Tx→UnTx transition group relative to reference. No other differences in proportion among Tx→UnTx and UnTx→Tx transition groups differed significantly from reference, although it was noted that overall, language, and STEM estimates for the Tx→Tx groups differed significantly (increased) from reference, as did the language estimate for the UnTx→UnTx group.

[7] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheets 11-16, available upon request.*

Among grade K-8 students in the pooled analysis (n = 76,184) (Figure 21), no differences in proportion of scores at or above minimum standard among Tx→UnTx and UnTx→Tx transition groups differed significantly from reference. As in the DIS analysis, however, overall, language, and STEM estimates for the Tx→Tx groups differed significantly (increased) from reference, as did the language estimate for the UnTx→UnTx group.[8]

Performance on standardized provincial assessment exams

Across grades K-12, students with ADHD scored lower on standardized provincial assessment exams than students without ADHD. Students in grades 9-12 with ADHD taking long-acting stimulants scored higher on math assessments than their untreated counterparts.

Among grade K-8 students in the PDP analysis (n = 1193) (Figure 22), estimates of percentile rank were significantly lower in Treated and Untreated groups compared to the No ADHD group, overall and across all subject areas. Treated and Untreated estimates did not differ significantly from one another on direct comparison. The same patterns observed in the PDP analysis were mirrored in the DIS (n = 18,628) (Figure 23) and pooled (n = 19,562) (Figure 24) analyses.

Among grade 9-12 students in the PDP analysis (n = 673) (Figure 25), estimates for the Treated and Untreated groups did not differ significantly from the No ADHD or from one another, overall and across all subject areas. In the grade 9-12 DIS analysis (n = 16,932) (Figure 26), estimates for the Treated and Untreated groups were significantly lower compared to the No ADHD group, overall and across all subject areas. Direct comparison of Treated and Untreated estimates showed that the estimate for math assessments was significantly higher for the Treated group. The patterns observed in the DIS analysis were mirrored in the pooled analysis (n = 17,456) (Figure 27).

For the combined group of students in grades K-12, estimates for the Treated and Untreated groups were significantly lower compared to the No ADHD groups in the PDP (n = 1866) (Figure 28), DIS (n = 35,560) (Figure 29) and pooled (n = 37,018) (Figure 30) analyses, overall and across all subject areas. Direct comparison of Treated and Untreated estimates showed a significant difference only in the pooled analysis for math assessments, in which the Treated estimate was significantly higher.[9]

Graduation from high school

Untreated students with ADHD were more likely to fail to graduate from high school than students without ADHD, while the likelihood of graduation among students with ADHD treated with long-acting stimulants was similar to that of students without ADHD.

[8] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheets 17-19, available upon request.*

[9] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheets 20-22, available upon request.*

Regression estimates in the PDP (n = 2055), DIS (n = 14,710) and pooled (n = 16,651) analyses (Figure 31) showed that the likelihood of not graduating from high school on the first attempt was significantly higher in the Untreated group compared to the No ADHD group, while the likelihood in the Treated group did not differ significantly from that in the No ADHD group. On direct comparison of the Treated and Untreated estimates, the Untreated group had a significantly higher likelihood of failure to graduate in the DIS and pooled analyses.[10]

Transition to post-secondary education

> **Untreated students with ADHD were less likely to transition to post-secondary education in New Brunswick than students without ADHD. Students with ADHD treated with long-acting stimulants were more likely to transition to post-secondary education than both untreated students and those without ADHD.**

Regression estimates in the PDP analysis (n = 808 for 6 months cohort; n = 694 for 2 years cohort) (Figure 32) showed no significant difference in the likelihood of not transitioning to post-secondary education in NB within six months or two years of high school graduation in the Treated or Untreated groups compared to the No ADHD group and to one another.

The DIS analysis (n = 1299) (Figure 33) showed that the Untreated group had a significantly higher likelihood of not transitioning to post-secondary education within six months of graduation compared to both the No ADHD and Treated groups, and the Treated group had a significantly lower likelihood of not transitioning compared to the No ADHD group. These same patterns were evident in the pooled analysis (n = 2027) (Figure 34).[11]

School attendance

> **Among students in grades K-12, school absences were more frequent among untreated students with ADHD than among those without ADHD. Students with ADHD treated with long-acting stimulants were absent less frequently than both untreated students and those without ADHD.**

For absences by reason and duration, figures only show regression estimates for academic years 2018-2020 combined. Estimates for individual academic years are shown in the full regression tables.

Regression estimates showed that the frequency of any absence among students in grades K-12 was significantly higher in the Untreated group, and significantly lower in the Treated group, compared to the No ADHD group in all academic years studied (2018: n = 92,016, 2019: n =

[10] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheet 23, available upon request.*

[11] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheet 24, available upon request.*

91,862, 2020: n = 93,768, 2018-2020 combined: n = 277,990) (Figure 35). On direct comparison of Treated and Untreated groups, the Untreated group had significantly higher frequency of any absence across all academic years.

Regression estimates for absences by reason for absence showed that frequency of absence for all reasons (illness, medical appointment, out-of-school suspension and unknown reasons) was significantly higher in the Untreated group compared to the No ADHD group for the period combining academic years 2018-2020 (Figure 36). Frequencies of absence due to illness or unknown reasons in the Treated group during this period were significantly lower compared to the No ADHD group, while frequencies of absence due to medical appointment or suspension in the Treated group did not differ significantly from those in the No ADHD group. On direct comparison of Treated and Untreated groups, the Untreated group had significantly higher frequencies of absence due to illness or unknown reasons compared to the Treated group.

Regression estimates for absences by duration of absence showed that frequency of absence with a duration of one period was significantly higher in the Treated and Untreated groups compared to the No ADHD group, while frequency of absence for longer than one period was significantly higher in the Untreated group and significantly lower in the Treated group compared to the No ADHD group for the period combining academic years 2018-2020 (Figure 37). On direct comparison of Treated and Untreated groups, the Untreated group had significantly higher frequency of absence for longer than one period, while frequency of absence with a duration of one period did not differ significantly between Treated and Untreated groups.[12]

Frequency of general practitioner and specialist physician visits

Students with ADHD (treated and untreated) visited general practitioners and specialist physicians more frequently than students without ADHD. Among students with ADHD, those treated with long-acting stimulants visited general practitioners and specialists more frequently than their untreated counterparts.

Unadjusted estimates (Supplementary Data Sheet 26) showed that, across all diagnosis/treatment groups, general practitioners were the provider type most frequently visited, followed by pediatricians and then psychiatrists.

Unadjusted estimates also showed that physician visits of all types were more frequent in the PDP cohort compared to the DIS cohort. Regression estimates in the PDP (n = 60,348) (Figure 38), DIS (n = 294,751) (Figure 39) and pooled (n = 354,197) (Figure 40) analyses showed that the frequencies of all categories of physician visit (GP/NP, pediatrician, psychiatrist and all types combined) were significantly higher in the Treated and Untreated groups compared to the No ADHD group.

[12] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheet 25, available upon request.*

In the PDP analysis, direct comparison of Treated and Untreated estimates showed that the frequency of pediatrician visits was significantly higher in the Treated group, while the frequencies of GP/NP and combined-type physician visits were significantly higher in the Untreated group. In the DIS and pooled analyses, direct comparison of Treated and Untreated estimates showed that frequencies of all categories of physician visit were significantly higher in the Treated group.[13]

Frequency of hospitalization due to injury or stimulant and other drug toxicity

> **Hospitalization due to injury was more frequent among untreated students with ADHD than among those without ADHD, while students with ADHD treated with long-acting stimulants were hospitalized no more frequently than those without ADHD.**
>
> **Hospitalization due to stimulant and other drug toxicity was more frequent among untreated students, and less frequent among long-acting stimulant-treated students, compared to those without ADHD.**

Regression estimates in the PDP (n = 79,011) (Figure 41), DIS (n = 393,125) (Figure 42) and pooled (n = 471,028) (Figure 43) analyses showed that the frequencies of hospitalization due to injury were significantly higher in the Untreated groups compared to the No ADHD groups, while frequencies in the Treated groups did not differ significantly from the No ADHD groups. Direct comparison of Treated and Untreated estimates showed that frequencies of hospitalization due to injury were significantly higher in the Untreated group in the PDP and pooled analyses.

Frequency of hospitalization due to stimulant and other drug toxicity in the PDP analysis was significantly lower in the Treated group compared to the No ADHD group, while the Untreated estimate did not differ significantly from the estimate for the No ADHD group (Figure 41). In the DIS (Figure 42) and pooled (Figure 43) analyses, Treated estimates were significantly lower and Untreated estimates significantly higher than those for the No ADHD groups. Direct comparison of Treated and Untreated estimates showed that frequencies of hospitalization due to stimulant and other drug toxicity were significantly higher in the Untreated groups in the PDP and pooled analyses.[14]

[13] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheet 26, available upon request.*

[14] *Descriptive statistics, unadjusted results and full regression results for this section are found on Supplementary Data Sheet 27, available upon request.*

Discussion

Report card scores

Between-Student method

Among students in grades K-8, mean report card scores were significantly lower among students with ADHD compared to students without ADHD, regardless of treatment with LAS, across all analysis cohorts (PDP, DIS, pooled) and subject areas. Treated scores did not differ significantly from Untreated scores on direct comparison. These same patterns were evident when examining the proportion of report card scores meeting or exceeding the minimum acceptable performance standard. These observations suggest that grade K-8 students with ADHD experience a negative impact on academic performance compared to their peers without ADHD that does not appear to be mitigated by LAS drug therapy.

Report cards scores among both Treated and Untreated grade 9-12 students in the DIS and pooled cohorts were also significantly lower than those of their peers without ADHD across all subject areas. Treated scores, however, were significantly higher than Untreated scores overall and for language and STEM subjects but did not differ significantly from Untreated scores in math. Analysis based on frequency of course failure however suggested that course failure was significantly more common in Untreated (compared to Treated) grade 9-12 students in the DIS and pooled cohorts across all subject areas, math included.

> **These findings suggest that, in contrast with students in lower grade levels, long-acting stimulant pharmacotherapy prescribed to high school students (grades 9-12) with ADHD may attenuate aspects of negative academic performance, though the degree of impact may differ according to course subject area.**

Previous studies have also noted apparent subject-specific differences in the effects of LAS [14,25].

Results for the grade 9-12 PDP cohort differed somewhat from those for the DIS and pooled cohorts. Across all subject areas, Untreated mean report card scores were significantly lower, and frequency of course failure significantly higher, compared to students without ADHD, while mean report card scores and frequency of course failure among Treated students did not differ significantly from those among students without ADHD.

These results suggest a possible positive impact associated with LAS treatment. However, we also noted that upon direct comparison of Treated and Untreated groups, mean report card scores were only significantly higher in the Treated group for overall scores (subject-specific scores approached but did not reach significance), and frequency of course failure was only significantly lower in the Untreated group for language subjects. In general, fewer statistically significant differences were noted in the PDP cohort compared to the DIS and pooled cohorts, which may reflect the much smaller sample size of the PDP cohort.

It is also noted, however, that definition of the PDP cohort selects for socioeconomically disadvantaged individuals who receive means-tested provincial drug benefits, so it is possible that this underlying difference may be reflected in the results of the analysis.

Within-Student method

The within-student PDP analysis of grade K-8 students showed a statistically significant decrease in mean report card score for STEM subjects in the Tx→UnTx transition group (compared to the No ADHD→No ADHD group), suggesting a decrease in academic performance associated with cessation of LAS treatment; however, this effect was not replicated in the DIS and pooled cohorts with larger sample sizes.

The DIS and pooled analyses of grade K-8 students did show statistically significant increases in mean report cards scores for math, language and STEM subjects in the UnTx→Tx transition group, suggesting a positive impact on academic performance associated with starting or resuming LAS treatment in Untreated students. It is noted, however, that the magnitude of the observed score increases is small and similar to the magnitudes of statistically significant changes observed for transition groups whose treatment status did not change (i.e., the Tx→Tx and UnTx→UnTx groups for language scores in the DIS and pooled analyses, and the Tx→Tx group for overall scores in the pooled analysis).

Within-student analysis by achievement of minimum acceptable standard among grade K-8 students showed no significant differences in the PDP analysis, while in the DIS analysis we observed a significant increase in the proportion of STEM scores at or above minimum standard associated with cessation of LAS treatment (i.e., the Tx→UnTx transition group). This finding was unexpected, as it did not align with our within-student observations in grade K-8 students by mean report card score. It is noted, however, that although statistically significant, the magnitude of change in the Tx→UnTx transition group was small, and comparable to that seen in the Tx→Tx and UnTx→UnTx transition groups, whose treatment status did not change. No significant differences were observed in the Tx→UnTx and UnTx→Tx transition groups among grade K-8 students in the pooled analysis.

The within-student PDP analysis of grade 9-12 students showed a statistically significant decrease in mean language scores in the UnTx→Tx transition group, suggesting a decrease in academic performance associated with initiation of LAS treatment, which did not align with observations among grade K-8 students. This finding was not replicated in the DIS analysis, which had a much larger sample size. Rather, the DIS analysis showed a significant decrease in mean language scores in the Tx→UnTx transition group, suggesting a decline in performance associated with cessation of LAS treatment. As in previous analyses, however, the magnitude of difference is relatively small and is similar to that seen in the UnTx→UnTx transition group in the for math and STEM scores. Similarly, statistically significant but small magnitude changes were seen in the pooled analysis, with overall and language scores decreasing, and math scores increasing, in the Tx→UnTx transition group.

In general, a strong association between changes in treatment status and changes in academic performance was not evident in the within-student analyses.

Observed changes were not consistent across grade levels, subject areas or analysis cohorts, and magnitudes of change generally did not rise above background level variation evident in the Tx→Tx and UnTx→UnTx transition groups. The observed inconsistencies may be due in part to the inclusion criteria for this analysis, which resulted in a limited sample size, particularly in the UnTx→Tx and Tx→UnTx transition groups.

A possible reason for the low observed magnitudes of change could be that the design only examines adjacent academic years surrounding a change in treatment status, and meaningful changes in performance may take more time to develop. In other words, the design limits observation of change in performance to periods surrounding treatment transition, and these may not be the periods in which the most substantial changes occur. Furthermore, it may be unreasonable to expect a substantial change in performance in the Tx→UnTx transition group, as cessation of LAS therapy is likely motivated at least in some cases by a lack of discernable treatment benefit.

Performance on standardized provincial assessment exams

Both Treated and Untreated grade K-8 students with ADHD performed significantly worse on provincial assessment exams compared to their peers without ADHD, across all subject areas and analysis cohorts (PDP, DIS, pooled). No significant difference was observed between Treated and Untreated percentile rank, suggesting a lack of effect associated with LAS treatment.

Among grade 9-12 students, those with ADHD (both Treated and Untreated) performed significantly worse than their peers without ADHD across all subject areas in the DIS and pooled analyses, while no significant differences were observed in the PDP analysis. In the DIS and pooled analyses, percentile rank was significantly higher in the Treated group compared to the Untreated group for math exams only – a result that was replicated in the pooled analysis of all grades (K-12) combined.

> **Taken together, these findings suggest that ADHD negatively affects performance on standardized provincial assessment exams across all grade levels and subject areas, and that these performance deficits are potentially ameliorated by long-acting stimulant pharmacotherapy, specifically among high school students for math exams.**

Notably, the finding that the effect of LAS was apparently limited to math exams contrasted with results of the Between-Student mean report card score analysis for grades 9-12, which suggested a benefit of LAS in all subject areas *except* math. The report card analysis did suggest a benefit of LAS with respect to reduced frequency of failure of math courses among this student population, however.

Graduation from high school

Across all analysis cohorts (PDP, DIS, pooled), Untreated students were significantly more likely to fail to graduate on the first attempt compared to their peers with ADHD, while the likelihood of failure to graduate among Treated students did not differ significantly from that among those without ADHD.

> **These findings, consistent with findings from other studies, suggest that ADHD is associated with reduced likelihood of graduating from high school on the first attempt, and that long-acting stimulant drug therapy may mitigate this deficit, improving first attempt graduation rates among students with ADHD to a level comparable with that of students without ADHD.**

Transition to post-secondary education

The DIS and pooled analyses show that the Untreated group had a significantly higher likelihood of not transitioning to post-secondary education in NB within six months of graduating high school, compared with both the Treated group and the No ADHD group, and the Treated group had significantly lower likelihood of not transitioning compared to the No ADHD group.

> **These findings suggest that ADHD is associated with decreased likelihood of timely transition to post-secondary education, and that long-acting stimulant drug therapy may be associated with an increase in likelihood in the Treated group to a level comparable to that observed among students without ADHD.**

Some important limitations to this analysis must be acknowledged. First, not all post-secondary institutions in NB were accounted for as several private institutions exist in the province which could not be observed. Unobserved enrolments at the private institutions would be misclassified as non-enrolments in our analysis. If such misclassifications did not occur uniformly across diagnosis/treatment groups, the outcomes of the analysis would possibly be impacted. Private institutions generally enrol a smaller number of students than the public ones, however, which may mitigate to some extent the overall impact of private enrolment misclassifications.

Another notable limitation is that students who enrol in post-secondary education outside of NB generally still maintain an active NB Medicare status, which continues to provide coverage for health care received in NB as well as care received in the student's temporary province of residence if they remain in Canada. Since our analysis relies on active Medicare status to identify NB residents, and since we do not have access to records of post-secondary enrolment outside of NB, students enrolled in post-secondary institutions outside NB will be misclassified as being unenrolled in post-secondary education. If such misclassifications did not occur uniformly across diagnosis/treatment groups, the outcomes of the analysis would possibly be impacted. A possible mitigating factor, however, is that the majority of NB residents pursuing post-secondary education are expected to do so within NB. A previous study estimated that, among NB

residents who graduate from a publicly funded post-secondary institution in Canada, 80% graduate from an institution in NB [26].

School attendance

All-cause absences were significantly more frequent among students in the Untreated group, compared to both the No ADHD and Treated groups. Moreover, all-cause absences in the Treated group were significantly less frequent compared to the No ADHD group in all observed years.

It should be noted that results for the 2019 academic year may have been affected by reduced availability of attendance data owing to the COVID-19 pandemic, which resulted in closure of schools for the latter part of the 2019 academic year (March through June 2020). Similar results were noted for absence due to illness and for unknown reasons, and absences with a duration of longer than one period. Absences due to medical appointment or suspension were significantly more frequent in the Untreated group compared to the No ADHD group, but frequency did not differ significantly between the Treated and No ADHD group, nor between the Treated and Untreated groups.

> **Taken together, these findings suggest that ADHD is associated with increased frequency of absence from school for any reason, and that long-acting stimulant drug therapy may reduce absence rates to a level similar to that exhibited by students without ADHD.**

Reasons for increased absence associated with ADHD could include illness symptoms associated with ADHD or comorbidities, increased frequency of medical appointments associated with these conditions and suspension associated with ADHD-related behavioural issues. Illness and unknown reasons were the two most common reason categories for absence, which may explain in part why statistically significant differences associated with the Treated group were limited to these categories.

Frequency of general practitioner and specialist physician visits

> **The results of the DIS and pooled analyses show that both general and specialist physician visits are significantly more frequent among individuals with ADHD, and significantly more frequent among Treated than Untreated individuals.**

This finding is not unexpected as ADHD is a chronic health condition requiring routine follow-up, with Treated individuals requiring the most frequent follow-up due to the need for monitoring and adjustment of medications, and possibly due to increased disease severity within this population.

The results of the PDP analysis differed in that GP visits and visits with all observed provider types combined were significantly more frequent in the Untreated group than the Treated group (frequency of psychiatrist visits was not significantly different between the Treated and Untreated groups). The reason for this difference from the DIS and pooled results is not clear, but it may be related to the lower socioeconomic status inherent to the PDP cohort.

Frequency of hospitalization due to injury or stimulant and other drug toxicity

Hospitalizations due to injury were significantly more frequent among Untreated individuals with ADHD compared to those without ADHD across all analysis cohorts (PDP, DIS, pooled), which is consistent with the results of previous studies showing an association between ADHD and risk of injury [27,28]. Frequency of hospitalizations due to injury among Treated individuals were not significantly different that among individuals without ADHD, and Treated frequency was significantly lower than Untreated frequency in the PDP and pooled analyses.

> **This suggests that long-acting stimulant drug therapy may the reduce risk of injury-associated hospitalizations among individuals with ADHD to a level comparable to that among individuals without ADHD.**

The lack of significant difference between the Treated and Untreated groups in the DIS analysis may relate to the lower number of observations in that cohort. Unadjusted estimates showed that frequency of hospitalizations due to injury was higher in that PDP cohort than the DIS cohort for the Untreated and No ADHD groups (data for the Treated group in the PDP analysis was not reportable as the number of observations was below the minimum reporting standard), which may explain why significant differences between Treated and Untreated groups were limited to the PDP and pooled analyses.

The Treated group showed a significantly lower frequency of hospitalization due to stimulant and other drug toxicity compared to the No ADHD group across all analysis cohorts (PDP, DIS, pooled), and compared to the Untreated group in the PDP and pooled cohorts. Additionally, the Untreated group showed a significantly higher frequency of hospitalization than the No ADHD group in the DIS and pooled analyses.

> **Taken together, these findings suggest a possible association between ADHD and increased risk of hospitalization due to stimulant and other drug toxicity.**

This is consistent with literature suggesting increased risk of poisoning among individuals with ADHD [29].

> **Furthermore, these findings suggest a potential positive effect of long-acting stimulant drug therapy in reducing the risk of hospitalization due to stimulant and other drug toxicity among individuals with ADHD, even with the Treated group presumably having a higher degree of exposure to stimulant drugs.**

This finding is consistent with literature suggesting a reduced risk of all-cause poisoning associated with methylphenidate treatment of adolescents and children with ADHD [30]. It is noted that, due to limitations of the ICD-10-CA codes available to describe reasons for hospitalization, the hospitalizations due to drug toxicity we observed could have been attributable to stimulants or to other drug classes including antiepileptic, sedative-hypnotic, anti-parkinsonism and other psychotropic drugs.

A significant difference in frequency of hospitalization due to drug toxicity was observed between the Treated and Untreated groups in the PDP analysis but not the DIS analysis. This finding may suggest that the potential effect of LAS pharmacotherapy in reducing hospitalizations due to drug toxicity is more pronounced among individuals with lower socioeconomic status (i.e., the PDP cohort), although the underlying reason for this is not clear.

The lack of statistically significant difference in the DIS analysis may also be related to the lower number of observations in that cohort. As explained above for hospitalization due to injury, unadjusted estimates showed hospitalizations due to drug toxicity were less frequent in the DIS compared to the PDP cohort.

It is noted that, in general, hospitalizations due to injury or drug toxicity in the study population were relatively uncommon, and observed magnitudes of difference were small, so results should be interpreted with caution.

Limitations

In interpreting the results of this study, a number of limitations must be acknowledged.

Limitations associated with identification of ADHD cases and classification of diagnosis/treatment groups

ADHD cases were defined based on prescription drug records for LAS, physician notes related to ADHD in physician billing records and academic records indicating a medical plan in place for the management of ADHD in school. Individuals with ADHD were categorized as treated or untreated based on prescription drug records in NB Drug Plan and DIS data.

In theory it is possible that an individual with ADHD is not flagged in any of the data sources used to identify cases (i.e., no prescription drug records, physician notes, or medical plan), resulting in misclassification of a case as a non-case. This is expected to be unlikely, however, given the breadth of data and time horizon examined.

Limitations associated with prescription drug records

A fundamental limitation associated with use of prescription drug records is that a prescription history for LAS was assumed to be indicative of ADHD diagnosis, though it is possible some individuals were prescribed LAS for other reasons (e.g., off-label use). Additionally, LAS were the

only class of drugs used to flag ADHD diagnosis, which could result in individuals with ADHD treated exclusively with non-LAS agents being misclassified as No ADHD or Untreated. The most likely scenario would presumably be individuals treated exclusively with second-line agents being misclassified.

Misclassification as No ADHD is assumed to be unlikely, as it would require no other signs of ADHD in the data, and most individuals are likely to have had a trial of LAS at some point since LAS constitute first-line pharmacotherapy. Misclassification of exclusively second-line treated individuals as Untreated is mitigated by the exclusion of most second-line agents (guanfacine excepted) from analysis. Individuals treated with guanfacine in the absence of LAS or any excluded medications would be classified as Untreated, however, so this should be taken into consideration when interpreting results. Such individuals would be expected to represent a minority of cases, however. Furthermore, regression models include adjustment for treatment with guanfacine and several adjunctive/third-line medications (i.e., Select Medications, summarized in Supplementary Table 7).

A further limitation associated with prescription drug data is that, during study periods which relied on the NB Drug Plan as the sole source of prescription data, any drugs paid for outside of plan coverage would not have been visible in the data. This may have resulted in individuals with ADHD being misclassified as not having ADHD, LAS-treated individuals being misclassified as Untreated or individuals taking excluded medications being included in the analysis.

The available date range of prescription drug data presents another potential limitation. Namely, inclusion in the No ADHD group required no 'sign of ADHD' at any time across all available data records, but our lookback window for 'signs of ADHD' is limited by available date ranges of relevant data resources.

If an individual's only sign of ADHD existed outside of the available date range (a scenario that is probably unlikely), the individual would be misclassified as No ADHD. This risk of misclassification is enhanced in the PDP analyses because inclusion in PDP analysis for a given observation period (e.g., academic year) only required confirmation of NB Drug Plan coverage for the duration of that observation period and 180 days prior (a concession to allow for inclusion of an adequate sample size). This means that the lookback window for signs of ADHD in prescription drug records may be limited to as little as 180 days prior to the observation period for PDP analyses (i.e., if drug plan coverage was not active prior to that verified period). This may in theory increase the risk of misclassification of ADHD cases as No ADHD in the PDP analyses, although such misclassification would only occur if an individual had no other 'signs of ADHD' in the data, which is likely a rare occurrence. We also note that the DIS analyses, which accounted for the majority of our study population for each outcome, would be unaffected by this risk of misclassification.

There are also limitations associated with specification of the Treated group using prescription drug records. Inclusion in the Treated group of a PDP analysis for a given observation period required only that an individual otherwise met criteria for inclusion in the Treated group (i.e., evidence of a sufficient period of continuous LAS treatment during the observation period, as outlined in the Methods section); confirmation of NB Drug Plan coverage for the *entirety* of that

observation period or 180 days prior was not required as it was for inclusion in the Untreated and No ADHD groups.

The rationale for this approach was that the prescription data used to otherwise satisfy Treated group inclusion criteria in the PDP analysis would have by necessity come from NB Drug Plan records and would therefore itself constitute sufficient evidence of NB Drug Plan coverage. This approach represented a concession to boost sample size as the number of individuals eligible for inclusion in the Treated group would have been reduced if the requirement for confirmation of a longer NB Drug Plan coverage window were imposed as it was for the Untreated and No ADHD groups.

A limitation of this approach, however, is that it may result in a higher risk of individuals with unobserved prescription records for excluded medications being included in the Treated group. Since coverage was not confirmed over the entirety of the observation period and 180 days prior in the Treated group (as it was for the Untreated and No ADHD groups), it is possible that coverage was inactive during some portions of the Treated observation period during which coverage was not confirmed. If excluded medications were dispensed for Treated individuals during these periods of inactive coverage, they would go unobserved, and these would therefore remain eligible for inclusion in the Treated group (assuming excluded medications were not dispensed at any time during the covered portion of the outcome-specific lookback window for excluded medications).

This scenario is expected to be relatively uncommon, however, as most individuals in the PDP Treated groups likely had coverage for all or most of the observation period, and it is assumed to be relatively uncommon that an individual's sole prescription for excluded medication would occur during the inactive coverage 'blind spot' of the excluded medication lookback window. We also note that the DIS analyses, which accounted for the majority of our study population for each outcome, would be unaffected by this scenario.

Limitations associated with NB Physician Billing records

Diagnosis of ADHD was assumed based on presence of ADHD-related keywords in NB physician billing notes. Unlike in other Canadian provinces, diagnoses are not recorded in NB physician billing data using ICD codes, so diagnosis must be inferred based on a keyword search of freeform physician notes. Although our methods were designed to minimize uncertainty associated with this approach, it is possible that the approach yielded both false positive and false negative ADHD diagnoses.

For example, a physician record in which ADHD was discussed in the differential diagnosis but ultimately ruled out may be flagged as a case if keyword terms are found in the physician notes, since the context surrounding the keywords is not provided in the data (with the exception of the ADD keyword, as noted under General Methods). Alternatively, if a physician does not take notes referencing ADHD during a visit with a diagnosed patient, the case would be missed by the keyword screening approach. The possibility of false positives and negatives stemming from physician billing notes is significant, as a substantial proportion of the cases in the study population were identified using this approach.

Limitations associated with academic medical plan data

Academic medical plans are expected to provide the most reliable source of case identification, but these ultimately accounted for a minority of the cases identified due to the limited window of data available.

Other sources of limitations

Another potentially significant limitation is that the analysis did not account for many potential sources of inter-individual variation in disease and disease management. These include severity of symptoms, time since diagnosis, exposure to non-drug therapies, differences in supports provided by family or caregivers and use of academic accommodations in school. Factors related to drug therapy that were not accounted for include differences in actual drug entity and brand (all LAS were grouped together), dosage, adherence, adverse effects and cumulative time on drug therapy.

A further limitation is that most of the study periods included portions of the COVID-19 pandemic that at various times included closure of schools and/or substantial interruptions to or alterations of academic programming and assessment. The pandemic is also known to have impacted healthcare, social services, family dynamics and personal health, both physical and mental. The effects of the pandemic were not accounted for in our analyses.

The pandemic affected data availability for some of our analyses. For example, attendance data were not available during the later part of the 2019 academic year due to school closures, and fewer report card scores per student (about half as many as in other years) were available during the same period for the same reason. The results of our study may in some cases reflect the impact of the pandemic, which may in turn affect their generalizability to periods outside of the pandemic.

It is also possible that some aspects of the pandemic differently impacted the three diagnosis/treatment groups included in the study. For example, several studies have suggested that ADHD symptoms were increased during the pandemic [31], which may have influenced the conclusions of our analyses. This possibility should be noted when interpreting results and comparing to those of other studies conducted during non-pandemic periods.

Summary and Conclusion

This study used administrative data resources to examine the impact of long-acting stimulant drug therapy on a variety of academic and related outcomes among a large sample of grade school students with ADHD drawn from the entire New Brunswick population.

ADHD was associated with decreased academic performance reflected in report card results and provincial assessment exam scores, increased frequency of course failure and increased frequency of school absence among grades K-12 and reduced likelihood of high school graduation and transition to post-secondary education. ADHD was also associated with increased frequency of general and specialist physician visits, and increased frequency of hospitalization due to injury or stimulant and other drug toxicity among school-aged children.

> **Long-acting stimulant drug therapy was associated with improvement in report card and provincial assessment exam performance and reduction in the frequency of course failure among grades 9-12, increase in the likelihood of high school graduation and transition to post-secondary education and reduction in the frequency of school absence among grades K-12.**
>
> **Long-acting stimulant therapy was also associated with an increase in the frequency of physician visits and a decrease in the frequency of hospitalizations due to injury or stimulant and other drug toxicity.**

Our results suggest that among school-aged children with ADHD, treatment with long-acting stimulants positively impacts several measures of academic success, a finding that is consistent with many but not all previous studies on the topic [15]. Notably, the academic benefits we observed were mostly limited to high school aged students. Our results also suggest a protective effect of long-acting stimulants on the risk of injury, a finding that is strongly reflected in the existing literature [15].

Taken together, these findings contribute to our understanding of the impact of long-acting stimulant drug therapy on a range of functional outcomes associated with ADHD. Future work aimed at assessing the robustness of these findings would be beneficial and may include sensitivity analyses trialing different approaches to defining ADHD diagnosis and treatment groups in administrative data, measures to address the known methodological limitations of the study, such as accounting for non-drug therapy and academic accommodations, and larger sample sizes and longer observation windows as data availability improves.

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Appendices

Appendix 1: List of Supplementary Tables

Table Number	Description
1	Data sources
2	ADHD keywords
3	Classification criteria for ADD keyword
4	Long-acting stimulants
5	Excluded medications
6	Drug Information System extract
7	Select medications
8	Provincial assessment exams
9	Definition of cause-specific hospitalizations

Appendix 2: List of Supplementary Data Sheets[15]

Sheet Number	Description
1	Report Card, Between-Student, Mean Score, Grades K-8, PDP
2	Report Card, Between-Student, Mean Score, Grades K-8, DIS
3	Report Card, Between-Student, Mean Score, Grades K-8, Pooled
4	Report Card, Between-Student, Mean Score, Grades 9-12, PDP
5	Report Card, Between-Student, Mean Score, Grades 9-12, DIS
6	Report Card, Between-Student, Mean Score, Grades 9-12, Pooled
7	Report Card, Between-Student, Minimum Standard, Grades K-8, PDP
8	Report Card, Between-Student, Minimum Standard, Grades K-8, DIS
9	Report Card, Between-Student, Minimum Standard, Grades K-8, Pooled
10	Report Card, Course Failure, Grades 9-12
11	Report Card, Within-Student, Mean Score, Grades K-8, PDP

[15] Data sheets are available upon request.

12	Report Card, Within-Student, Mean Score, Grades K-8, DIS
13	Report Card, Within-Student, Mean Score, Grades K-8, Pooled
14	Report Card, Within-Student, Mean Score, Grades 9-12, PDP
15	Report Card, Within-Student, Mean Score, Grades 9-12, DIS
16	Report Card, Within-Student, Mean Score, Grades 9-12, Pooled
17	Report Card, Within-Student, Minimum Standard, Grades K-8, PDP
18	Report Card, Within-Student, Minimum Standard, Grades K-8, DIS
19	Report Card, Within-Student, Minimum Standard, Grades K-8, Pooled
20	Provincial Assessments, Grades K-8
21	Provincial Assessments, Grades 9-12
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23	Graduation from High School
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26	Physician Visits
27	Hospitalizations