OVERVIEW: Significance, Rationale & Impact

Autism is a neurodevelopmental disorder occurring in ~1.5% of the Canadian population[1], characterized by early-onset difficulties with social communication and restricted, repetitive patterns of behaviour[2]. The male-to-female prevalence ratio in clinically ascertained autism samples approximates 4-5:1[3], but population-based studies with active case ascertainment demonstrate a ratio closer to 3:1[4]. This would suggest that current standard clinical practice may have a bias towards recognizing autism more readily in boys/men than in girls/women. Emerging data from outside Canada indicate that, compared to boys/men, girls/women with autism tend to be diagnosed at a later age[5–8]. These differences highlight sex and gender impacts on the *recognition and diagnostic process* of autism in real-life clinical practice, above and beyond biological sex-related etiological vulnerability (i.e., higher vulnerability in males).

Recent qualitative studies with autistic adults, from our group in Canada[9,10] and others in the US and Europe[11–13], suggest that girls/women tend to be diagnosed with multiple other psychiatric disorders (e.g., anxiety disorders, attention-deficit/hyperactivity disorder [ADHD]) *prior to* receiving an autism diagnosis. Based on these accounts, *diagnostic overshadowing* (i.e., misattributing autism characteristics to previously diagnosed psychiatric disorders) may contribute to later identification of autism and may be particularly exacerbated in girls/women[14]. Sociodemographic and medical factors may further influence autism diagnosis timing[6,15]. Qualitative data also show that late identification of autism has negative repercussions for wellbeing for all autistic people[11,12] and may be one factor associated with elevated rates of health problems and service use, especially in girls/women. Overall, compared to boys/men, girls/women may be at elevated risk of having their autism overshadowed or overlooked[16–19]. This creates an important yet under-addressed health inequity.

Despite emerging clinical descriptions and qualitative findings, there remain critical **knowledge gaps** regarding this health inequity. There has been an **absence of population-based research** examining factors contributing to autism diagnosis patterns (including testing the hypothesis of diagnostic overshadowing) and health service utilization differences in girls/women compared to boys/men, in relation to when an autism diagnosis is made. Population-based health administrative data provide a unique opportunity to address these knowledge gaps. Our team is best positioned to conduct this research based on (i) our expertise in studying the impacts of sex and gender in autism[14,20,21]; (ii) our prior and ongoing qualitative studies on the diagnosis journey of autistic girls/women, which have guided the formulation of our quantitative research hypotheses[9,10]; and (iii) our extensive expertise analysing health administrative data, including health service use in populations with autism and other developmental disabilities, mental health care, and women's health[22–32].

By leveraging Ontario population-based health administrative datasets to create a cohort of *all* girls/women and boys/men with autism born in Ontario between 1988 and 2013, our **objectives** are to:

(1) Compare the age at which the first health claim for autism diagnosis is recorded among girls/women versus boys/men;

(2) Examine the sociodemographic, medical, and psychiatric characteristics associated with the timing of first recorded autism diagnosis, in girls/women versus boys/men;

(3) Explore patterns of pre- and post-autism-diagnosis health service use based on timing of first recorded autism diagnosis, in girls/women versus boys/men.

This project will provide key information about when and in what context autism is recognized and diagnosed in Ontario, which will critically **impact the effective matching of services to the needs of autistic individuals across sexes and genders**. Findings will contribute to an improved, sex/gender-informed assessment strategy for autism by raising awareness of diagnostic overshadowing, including the patterns of medical and psychiatric conditions that commonly precede a later autism diagnosis. Our established integrated knowledge translation (iKT) approach brings together autistic individuals, their families, and health care providers. Our high level of engagement with these diverse knowledge users has shaped the development of the current project goals, and will continue to guide our analytic plan, interpretation of findings, and end-of-grant dissemination activities.

BACKGROUND

1. Timing of autism diagnosis in girls/women versus boys/men

Autism is diagnosed based on behavioural features of social communication difficulties and restricted, repetitive patterns of behaviour, and is recognized more frequently in boys/men than in girls/women[2,4]. Diagnoses are made based on clinical judgements of health care professionals (e.g., paediatricians, psychiatrists, neurologists, clinical psychologists). Autism can be diagnosed at as young as 2 years of age[33], and the mean age of diagnosis is 4-5 years old, with large variations across service settings[34,35]. In the past two decades, owing to increased stakeholder advocacy, empirical research, and clinical awareness, there is increasing recognition of autism across the lifespan, leading to more people receiving initial autism diagnoses in adolescence and adulthood[14]. However, clinical data suggest the age at which autism is diagnosed in girls/women tends to be older than in boys/men[5–8]. Current practices have a bias towards identifying autism more readily in boys/men than in girls/women[4], likely due to a combination of subtle differences in behaviours in girls/women (e.g., greater social attention and less overt narrow interests) and clinicians' recognition biases (e.g., more easily attributing autism symptoms to other diagnoses such as anxiety in girls/women than boys/men)[20]. A recent analysis of clinical and community samples estimated that up to 39% more girls/women should have been diagnosed with autism when they were not[36], demonstrating that there is substantial room for improvement of earlier recognition. Earlier recognition of autism across sexes (i.e., biological males and females) and genders (e.g., boys/men, girls/women, transgender, non-binary) is crucial for accessing appropriate services and supports because nearly all Canadian provinces and territories (except Nunavut) require an autism diagnosis in order to access autism-specific interventions (e.g., early intervention, social skills group)[37].

2. Characteristics associated with age of autism diagnosis in girls/women versus boys/men

Past clinical, surveillance, and registry studies outside Canada have highlighted potential sociodemographic, medical, and psychiatric factors associated with age of autism diagnosis in children. Higher socioeconomic status, specifically greater household income and higher parental education, are most often associated with earlier diagnosis[38–43]. In the US, children living in urban areas are also likely to receive a diagnosis at an earlier age compared to children living in semi-urban or rural settings[38,39,43,44]. In terms of medical factors, the presence of intellectual disability and epilepsy tends to be associated with increased identification of autism especially in girls/women[4,6,45–47], perhaps because these co-occurring conditions indicate a more severe form of neurodevelopmental anomaly that may trigger more in-depth assessments. Conversely, psychiatric conditions (e.g., ADHD, anxiety) can impede the identification of autism and may be associated with later identification[16,34,38,48,49], particularly among girls/women[16]. Indeed, clinical cohort studies indicate that girls/women tend to present with more concurrent cognitive and psychiatric difficulties than boys/men when they are clinically diagnosed with autism[45,50].

There are several factors that may explain why autistic girls/women often "fly under the radar" or encounter difficulties obtaining an autism diagnosis. Prevailing gendered role expectations and gender stereotypes may impact referral sources' (e.g., parents, teachers) interpretation of behaviours and obscure the recognition of autism characteristics when they present in girls/women[51]. For example, social withdrawal may be disproportionately interpreted as "shyness" in girls compared to "unresponsiveness" in boys, the latter being more readily considered a red flag for autism. In clinical assessment, operational diagnostic criteria of autism and widely used diagnostic instruments are largely based on research with boys/men[21], and may overlook autistic girls/women who can present differently[52,53]. When using "gold standard" semi-structured instruments for the diagnosis of autism, autistic girls/women, on average, score lower on restricted and repetitive behaviours compared to boys/men[54]. However, lower scores on measures of restricted and repetitive behaviours may be reflective of more gender-normative restricted interests among autistic girls/women (e.g., dolls, animals, makeup) that go undetected on current instruments[55,56]. Additionally, there may be a general expectancy bias among clinicians since autism is frequently cited and believed to occur more in boys/men[17,56].

The bias against detecting autism in girls/women may be aggravated by *diagnostic overshadowing*. For instance, because rates of anxiety in the general population are higher in girls/women than in boys/men from early childhood onwards[57], clinicians may fail to explore characteristics and underlying sources of anxiety symptoms (e.g., sensory concerns, difficulties with transitions, intolerance of uncertainty) when present in autistic girls/women and simply diagnose them as anxious. Other diagnoses, in addition to anxiety, that might overshadow and delay autism diagnosis in girls/women might include ADHD, eating disorders, obsessive-compulsive disorder, and personality disorders[11,14,18,58,59]. In each case, observable behaviours may seemingly match common symptoms (e.g., restricted food intake in eating disorders), but a closer look is required to identify what drives these behaviours (e.g., sensory sensitivity in swallowing certain foods with no concern about weight or shape) among autistic girls/women.

3. Impact of autism diagnosis timing on health service use in girls/women versus boys/men

Survey and registry data outside Canada show that autistic girls/women experience more physical and mental health problems and have higher rates of health service use than boys/men[60,61], including disproportionately high use of psychiatric and emergency services, which translate into high system costs[62,63]. These studies, however, have failed to consider timing of autism diagnosis and its impact on broader health care use patterns. Could some of this increased health service use be mitigated by earlier autism diagnosis and hence appropriate services and support? Indeed, diagnostic overshadowing and missed/mis-diagnosis, which delays autism diagnosis, can hinder timely and adequate support tailored to the needs of autistic individuals and may even lead to mis-treatment due to incorrect diagnostic formulations, especially in girls/women[18]. Recent qualitative research implies that late autism diagnoses are associated with negative repercussions for women's health, with many women diagnosed in adulthood recalling stressful life experiences resulting in social alienation and negative self-identity that impeded their mental health[11,12,64]. As such, receiving an autism diagnosis in adulthood is often recounted as a positive reframing experience[11–13], which might lead to positive changes in health service use patterns, such as reduced acute service use for crisis (e.g., emergency department visits) and a proactive shift towards receiving care from specialists who can provide adequate support tailored to the needs of autistic individuals. Nevertheless, there is a lack of population-based data to illustrate whether a later autism diagnosis is associated with higher pre-autism-diagnosis health service use, how the autism diagnosis might change the patterns of health service use, and most importantly, how health service use patterns pre- and post-diagnosis vary in girls/women in contrast to boys/men.

Knowledge gaps: Administrative data research informed by qualitative studies

Our team has carried out key qualitative studies addressing autism diagnosis and health service use in girls/women in the Canadian context[9,10]. Autistic girls/women and their parents identified several "roadblocks" for their (child's) autism to be diagnosed as well as barriers to effective care provision (e.g., service providers' misperceptions regarding autism presentation)[9,10]. Our ongoing study with front-line clinicians further corroborates these lived experiences, with healthcare providers reporting a lack of knowledge and familiarity with potential sex and gender impacts on autism diagnosis. This qualitative research provides important insight into lived experiences. However, there has been no systematic investigation at the whole-population level in Canada on whether autism tends to be recognized later in girls/women compared to boys/men; the sociodemographic, medical, and psychiatric characteristics associated with diagnosis timing; and the impact of diagnosis timing on health service use patterns.

Researchers often use physician billing data to ascertain autism cases in the absence of prospectively collected clinical data on autism diagnoses[22,49,60,63,65–67]. While these administrative data are not as reliable and nuanced as clinical data (e.g., some autism diagnoses can be missed), administrative data capture the overall picture in a given health service system with reduced bias compared to focusing on smaller, selected cohorts recruited in local communities or tertiary clinical services, and is therefore frequently used to study autism health service use[22,60,63,68–73]. Yet, to our knowledge, no study to date has examined autism diagnosis timing and associated sociodemographic, medical, and psychiatric characteristics across sexes/genders, and only 3 administrative data studies have explored health service

use patterns in autistic women compared to men, but without consideration of autism diagnosis timing on these patterns[60,63,71]. In this project, we will identify a population-based cohort of individuals with autism in Ontario using ICES administrative data[22,66,74]. We will use the first health care claim of autism diagnosis in these administrative datasets as a proxy for timing of first autism diagnosis. Our team has carried out research using administrative data to study health service patterns in autistic young adults[22] and autistic women of childbearing age[74]. Our autism algorithm in both studies led to cohorts with similar health profiles and health service use as research from other jurisdictions[60,63]. The combination of administrative data, clinical expertise, and qualitative knowledge shared by our research team will provide a thorough understanding of what is currently occurring at the whole-population level.

OBJECTIVES & HYPOTHESES

Building on our health service research using the ICES data on developmental disabilities including autism[22–25,27–32,66,74,75] and qualitative research on autistic girls/women's experiences with diagnosis and health care[9–13,62,76], this project will use Ontario population-based health administrative data to create a birth cohort of individuals with autism to address the following **objectives** and *hypotheses*:

(1) **Compare the age at which the first health claim for autism diagnosis is recorded among girls/women versus boys/men.** *Hypothesis: Initial health claims for autism diagnosis are, on average, later among girls/women than boys/men.*

(2) **Examine the sociodemographic, medical, and psychiatric characteristics associated with the timing of first recorded autism diagnosis, in girls/women versus boys/men.** *Hypotheses: (i) Variables associated with an autism diagnosis recorded at a later age include more sociodemographic barriers (e.g., lower neighbourhood income, living in rural area), a lack of developmental disabilities other than autism, a lack of epilepsy, and presence of previous psychiatric diagnoses (i.e., those recorded prior to autism, implying diagnostic overshadowing); and (ii) The strength of association of these factors with autism diagnosis timing is stronger in girls/women than in boys/men.*

(3) **Explore patterns of pre- and post-autism-diagnosis health service use based on timing of first recorded autism diagnosis, in girls/women versus boys/men.** *Hypotheses: (i) Individuals whose autism is diagnosed later have a higher rate of pre-autism-diagnosis acute health service use (i.e., emergency department visits and hospitalization) than those diagnosed earlier; (ii) Autism diagnosis is associated with reduced acute health care use post-diagnosis relative to pre-diagnosis; and (iii) The strength of these changes is stronger in girls/women than in boys/men.*

APPROACH & METHOD

Overall Framework

Our project will use the unique Ontario population-based health administrative datasets hosted at ICES to identify proxy indices of autism diagnosis timing (i.e., first health claim for autism diagnosis), sociodemographic variables, medical and psychiatric conditions, and health service use that are influenced by sex and gender. Sex (biological attributes) and gender (social, psychological, and cultural attributes) are separate constructs and may have shared as well as specific influences on autism diagnosis timing and service use; however, Ontario health administrative data so far do not capture gender, but only sex assigned at birth based on an individual's health card, which, when used as an index variable, encompasses influences from both sex and gender that are difficult to disentangle. Hereafter, we use "sex" when referring to ICES data, to be consistent with how data are coded and described in previous ICES studies[77,78], acknowledging the limitations in making inferences based on gender identities and separating sex-specific versus gender-specific influences.

Data Sources

ICES is a prescribed entity under Section 45(1) of the 2004 Personal Health Information Privacy Act of Ontario. As such, policies, practices, and procedures are reviewed and approved by the Ontario Information & Privacy Commissioner. We will access the data through team members who are ICES-

affiliated scientists (Lunsky, Brown, Vigod). We will use (i) physician billing claims from the Ontario Health Insurance Plan database (OHIP, since 1991), (ii) hospitalization diagnoses from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD, since 1988) and Ontario Mental Health Reporting System (OMHRS, since 2006), and emergency department visit diagnoses from the National Ambulatory Care Reporting System (NACRS, since 2002). Date of birth, health card-recorded sex, residential postal code, and date of death will come from the Registered Persons Database (RPDB, since 1990). Social disparity data will come from the Census, which is linked with the RPDB by postal code. Health records are linkable at the individual level across databases and across time using a unique encoded identification number, allowing identification of diagnoses made in both childhood and adulthood and all health service use covered by Ontario's universal health care system. ICES quality assessments demonstrate the validity of primary hospital diagnoses and physician billing claims[79].

Cohort

We will create a birth cohort that includes all Ontario residents who were born in Ontario between April 1, 1988 (the inception of ICES databases) and March 31, 2013, who have been diagnosed with autism (see below), excluding those without an identified sex on their health card and those without a valid health card number. Autism diagnosis will be defined by: (i) ≥ 2 outpatient physician visits (i.e., with a family physician, paediatrician, or psychiatrist) with an autism diagnostic code (OHIP 299); or (ii) ≥ 1 hospital admissions (CIHI-DAD and OMHRS) or emergency department visits (NACRS) with an autism diagnostic code (ICD-9 299 or ICD-10 F84), between July 1, 1991 (the inception of the OHIP database) and March 31, 2016, so that we will include all autism diagnoses between a minimum of 3 and maximum of 29 years of age. For each person, a 3-year follow-up period (until a maximum of March 31, 2019) anchored on the first health claim for autism diagnosis, will then be created to capture post-autism-diagnosis service use, while a 3-year look-back period, again anchored on first health claim for autism diagnosis, will capture pre-autism-diagnosis service use and medical and psychiatric comorbidities. Our autism algorithm is informed by our prior research using ICES data[22,66,74,80] and a validation study conducted in Nova Scotia[67]. It is also consistent with research completed in other jurisdictions[81,82]. The benefits of using a birth cohort for this study are: (i) we have confidence that no health claims for autism diagnosis will be missed (e.g., prior to cohort entry or prior to inception of ICES databases), and (ii) we are able to take a longitudinal view of the data to investigate factors associated with later autism diagnosis and the impact of later autism diagnosis on health service use. Clarification of such temporal associations is novel and unique in the current autism research literature and is core to our research questions.

Variables

Age at first health claim for autism diagnosis will be defined based on the initial autism diagnosis recorded in health administrative data, which is a proxy for autism diagnosis timing. Age at first diagnosis will be treated as a continuous variable (in years) for Objective 1 analyses, and as an ordinal variable for Objectives 2 and 3. Therein, all individuals will be grouped into three categories by age of initial autism diagnosis claim: early childhood (<6 years), middle childhood and adolescence (6-17 years), and emerging adulthood (18-29 years). These age-bands are defined based on recent population-based data showing gender-differential changes in social challenges in adolescence (i.e., greater increase in challenges in girls than in boys)[83] and on Ontario's age-based policies for how autism services are provided. For example, publicly funded diagnostic services through the health care system are usually provided by paediatricians and child psychiatrists at ≤17 years of age (with different levels of provision before and after 6 years), whereas publicly funded diagnostic services are more limited for those ≥18 years and are provided mostly by psychiatrists. The Ontario Autism Program also only provides intervention services for those ≤17 years, and the services accessed often differ between early childhood and middle childhood/adolescence[84].

Sex will be operationalized as the sex recorded on an individual's health card at birth in the RPBD.

Sociodemographic characteristics at the first autism diagnosis claim will include the following: (i) *Neighbourhood income quintiles* will be derived by linking Canadian Census data to residential postal codes. Income data are adjusted for household and community size, so that each community would have

20% of its population in each quintile, ranked from poorest (quintile 1) to wealthiest (quintile 5). (ii) *Material deprivation quintiles* and (iii) *residential instability quintiles* will be measured using the Ontario Marginalization Index[85] representing area-level concentrations of individuals, respectively, unable to access basic material needs (6 indicators, e.g., proportion of households residing in dwellings in need of major repair) or experiencing housing or family instability (7 indicators, e.g., proportion of households who moved in the past 5 years), ranked from lowest (quintile 1) to highest (quintile 5). (iv) *Rurality* will be classified using the Rurality Index of Ontario, which includes 10 indicators (e.g., travel time to different care levels), with scores 0-44 classified as urban and ≥45 as rural[86].

Other diagnoses and timing of their first health care claim will be medical and psychiatric diagnoses. Medical diagnoses will be developmental disabilities (other than autism) and epilepsy[87–89]. Developmental disabilities other than autism will include intellectual disability, fetal alcohol syndrome, Down syndrome, and congenital anomalies, defined using algorithms (e.g., ≥ 2 physician visits or ≥ 1 emergency department visits or hospitalizations including specified codes) from a previous ICES study[80]. Epilepsy will also be defined using a validated and widely used algorithm (OHIP 345, ICD-9 345, ICD-10 G40)[89]. Psychiatric diagnoses will comprise psychotic mental illness[87], mood or anxiety disorder[87], substance use disorder[24], and "disturbance of emotions specific to childhood and adolescence" (OHIP 313, ICD-9 313). The variable for each disorder type will be defined as a binary variable (present or absent) and will be further coded as first recorded in a health claim prior to versus after the first autism diagnosis claim.

Health service use will be estimated separately for periods prior to first autism diagnosis claim in the 3-year look-back period, and after first autism diagnosis claim in the 3-year follow-up period. The indices include yearly acute service use: (i) *emergency department visits (psychiatric and non-psychiatric)* measured in NACRS, and (ii) *hospitalizations (psychiatric and non-psychiatric)* measured in CIHI-DAD and/or OMHRS; and other service use: (iii) *total number of physician visits overall and by specialties (primary care family physician, paediatrician, psychiatrist, and other specialists)* measured in OHIP.

Statistical Analysis

Objective 1: Compare the age at which the first health claim for autism diagnosis is recorded among girls/women versus boys/men. We will use Kaplan-Meier survival curves for girls/women and boys/men to estimate the cumulative probability of reaching a given age without an autism diagnosis, by sex. The resulting median age of diagnosis will be the age by which 50% of cases in each sex are identified as having autism. We will use the Tarone-Ware Chi-squared test to test whether the survival curves are different by sex[90]. This longitudinal analysis will account for cohort attrition via death or moving out of Ontario. We will also measure age at diagnosis as a categorical variable (i.e., early childhood, middle childhood and adolescence, and emerging adulthood), with the statistical significance of differences between sexes tested using a Chi-squared test.

Objective 2: Examine the sociodemographic, medical, and psychiatric characteristics associated with the timing of first recorded autism diagnosis, in girls/women versus boys/men. (i) We will use nominal logistic regression to assess if sociodemographic (i.e., neighbourhood income, material deprivation, residential instability, rurality), medical (i.e., a lack of other developmental disabilities or epilepsy), and psychiatric characteristics (i.e., presence of psychotic mental illness, mood or anxiety disorder, substance use disorder, and disturbance of emotions specific to childhood and adolescence) prior to the first autism diagnosis claim are associated with later autism diagnosis (as measured by an polytomous variable, as above: early childhood, middle childhood and adolescence, and emerging adulthood). We will generate unadjusted and adjusted models. Since all covariates have theoretical importance, we will include all in the adjusted model. (ii) Sex will be added to the model as a moderator of interest to examine any predictor-by-sex interactions on autism diagnosis timing. Statistically significant interaction terms will be followed by analyses stratified by sex to examine how the strength of the association between each predictor and autism diagnosis timing differs by sex.

Objective 3: Explore patterns of pre- and post-autism-diagnosis health service use based on timing of first recorded autism diagnosis, in girls/women versus boys/men. (i) We will use negative binomial

regression models to examine the association between autism diagnosis timing (i.e., middle childhood and adolescence, and emerging adulthood, each compared to early childhood) and pre-autism-diagnosis rates of acute health service use (i.e., emergency department visits and hospitalizations). Multivariable models will control for neighbourhood income, material deprivation, residential instability, rurality, developmental disability other than autism, epilepsy, and other psychiatric diagnoses. We will also use the same approach to explore three other health service use (i.e., psychiatrist visits, other specialist visits, and primary care family physician or paediatrician visits). (ii) We will use a segmented regression analysis of an interrupted time series to determine the extent to which autism diagnosis results in reduced emergency department visits and hospitalizations post- versus pre-autism-diagnosis; we will also explore changes in psychiatrist, other specialist, and primary care visits. The 3-year periods before and after autism diagnosis will be divided into months, for a total of 36 periods before and 36 after diagnosis. For each outcome, we will first plot the monthly number of emergency department visits, hospitalizations, psychiatrist visits, other specialist visits, and primary care family physician or paediatrician visits. We will then fit segmented regression models using a negative binomial distribution (assuming overdispersion is observed) to the monthly series, with parameters for the intercept, pre-diagnosis trend, and changes in level and trend after diagnosis. We will test for autocorrelation using the Durbin Watson statistic[91]. We will then estimate the difference between observed and expected rates of health service use post-diagnosis. The models will control for time-varying confounding, which is expected to be limited to diagnoses of developmental disabilities other than autism, epilepsy, and psychiatric disorders, which may be made after autism diagnosis. (iii) To test whether these patterns are different in girls/women compared to boys/men, in analysis (i) sex will be added into the model as a sex*age-at-diagnosis interaction term, followed by analyses where models are stratified by sex for statistically significant interaction terms, and analysis (ii) will be stratified by sex.

Implementation and Timeline

Table 1. Study timeline: We require three years of funding to accomplish our goals, defined below.

	Y1Q1	Y1Q2	Y1Q3	Y1Q4	Y2Q1	Y2Q2	Y2Q3	Y2Q4	Y3Q1	Y3Q2	Y3Q3	Y3Q4
Objective 1												
Cohort creation												
Analysis												
Objective 2												
Analysis												
Objective 3												
Analysis												
iKT												
Advisory meetings												
Present findings & manuscript writing												
End-of-grant KT meeting & products												

Study Power and Feasibility

We expect a sample size of at least *n*=31,000 individuals with autism, based on our unpublished work on the number of youth (11-20 years) and young women (20-29 years) with autism in Ontario[74], ascertained using a similar algorithm as the one to be used herein. Of these, we expect *n*=7,750 to be girls/women, based on the male:female ratio of 3:1 observed in our prior population-based research[22]. For Objective 1, we have the power to detect a small effect size (*E*=.10) for the difference in age at diagnosis between girls/women and boys/men. For Objective 2, with 11 predictors, and using a conservative requirement of 20 outcome events per predictor in the smallest outcome category[92,93], we require ≥ 220 individuals diagnosed in emerging adulthood. In our related work on the health of reproductive-aged women with autism, 15% were diagnosed during this period, suggesting our sample size will be more than adequate for the overall analysis (4,650 outcome events expected) and that stratified by sex (1,162 outcome events in girls/women expected). For Objective 3i, with 11 predictors and 20 outcome events per predictor, we

require at least 220 outcome events. We have previously shown that 26% of young adults with autism had an emergency department visit and 7% were hospitalized in a 1-year period[22] (equal to 4,940 and 1,330 expected outcome events, respectively, in the full sample and 1,235 and 333 outcome events in girls/women). We will therefore be powered for this analysis. Finally, for Objective 3ii, power calculations for interrupted time series are based on the number of pre- and post-"intervention" time periods available, with a minimum of 12 for each as widely cited[94]. Given that we have 36 months of pre- and 36 months of post-diagnosis data, our analyses should be adequately powered.

CHALLENGES & MITIGATION STRATEGIES

Limitation of identifying autism diagnoses. The absence of a diagnosis in ICES data does not guarantee a lack of diagnosis entirely, and the age at which a first diagnosis appears in ICES data may not be the first time autism was diagnosed. Initial diagnosis could have been recorded by a non-physician diagnostician (i.e., clinical or school psychologists) and if subsequent to that, an individual had no health care interaction in which autism was recorded within the list of billed diagnoses, said autism diagnosis would go unrecorded, the pattern of which may differ between sexes. In addition, the databases used to identify autism diagnosis start by different years, e.g., 1991 for OHIP and 2002 for NACRS. Further, our birth cohort design will only capture people born in Ontario but not immigrants or refugees with autism, so the generalizability of findings to the newcomer population will be limited. While a community-based, clinically ascertained cohort may allow for greater completeness of autism ascertainment, it has limited sample size and may introduce other biases (e.g., better access to care and earlier diagnosis due to selection bias towards more affluent families). Linkages with other databases (e.g., education) would be preferable, but are not currently available in Ontario. ***Mitigation*:** As a crucial step towards understanding health inequities for autistic girls/women, we will create a population-based birth cohort to understand diagnosis timing and patterns of health service use, which provides data in the context of the publicly funded health care system *accessible to all Ontarians*. Our prior work shows that the vast majority of autism diagnoses were identified via OHIP[22]. Our main analyses prioritize specificity of autism diagnosis; as a subsidiary analysis to increase sensitivity, we will broaden the inclusion to those with ≥ 1 physician visits with an autism diagnostic code, and examine the consistency of findings, acknowledging that the specificity of autism diagnosis may decrease in this scenario[67]. Our results will lead to further research with administrative data in other jurisdictions where educational diagnostic information is available (e.g., Manitoba). Finally, our findings can serve as the basis for future work focusing on autism service access in newcomers[31].

Limitation of addressing age-of-diagnosis effect versus cohort effect. Our longitudinal design spans nearly three decades and therefore the patterns revealed when contrasting those diagnosed with autism in younger versus older ages will include influences not only from age-of-diagnosis but also cohort effects (e.g., differences in autism diagnostic practice patterns over time). ***Mitigation*:** The benefits of using a birth cohort to ensure that we are capturing *first* health claims for autism diagnosis outweigh the limitations of a cohort effect. In sensitivity analyses, we will explore the use of hierarchical age-period-cohort effects models to disentangle these factors, as in prior research with similar designs[95].

Limitation of identifying sex versus gender impacts. ICES data have unique strengths to address our research questions at the population level. However, there are two important considerations related to sex and gender. First, one can only identify sex assigned at birth as recorded in the Registered Persons Database (not on karyotyping) and we will not be able to analyze data by gender owing to a lack of data; yet factors contributing to autism diagnosis timing and diagnostic overshadowing are related to *both sex and gender*. Second, binary sex as recorded in ICES does not capture individuals who identify as transgender or nonbinary, which might occur more frequently in people with autism[96–98]. This data limitation will inevitably confine our inferences of the findings in that (i) sex-specific and gender-specific effects are unable to be teased apart; and (ii) interpretations will be based on a binary male-female framework, missing the unique information relevant to the transgender or nonbinary population.

***Mitigation*:** We will work closely with our advisors (autistic adults, family members, and clinicians) to apply a gender-informed lens to the interpretation of results and to contextualize the findings in light of our qualitative work with autistic girls/women which addresses gender effects. Further, although we cannot measure self-identified gender, we will examine the effects of sociodemographic disparities that disproportionately affect the female gender, including poverty and marginalization. We also plan to collaborate with colleagues on a related study of autism rates in a cohort of ~2000 transgender individuals through ICES. We will integrate findings from that related study into our end-of-grant KT planning.

KNOWLEDGE TRANSLATION PLAN

Integrated KT (iKT): This project will be carried out in partnership with health care providers, autistic individuals, and families who have participated in work with us leading up to the current proposal, to ensure meaningful investigation and interpretation of findings. We will hold bi-monthly investigative team meetings with scientists and knowledge users and biannual meetings with our Advisory Committee, which will also include our Partners, collaborators, advocates, and policy-makers tied to the Health Care Access Research and Developmental Disabilities Program (H-CARDD) (led by Lunsky), either in person or by videoconference. We will also hold regular smaller meetings with autistic advisors and parent advisors over the course of the study to facilitate and support their involvement in the Advisory Committee.

End-of-grant KT: Our team is involved in autism research and service provision in a range of provincial, national, and international capacities (e.g., ongoing collaborations with Autism Ontario, Canadian Autism Spectrum Disorder Alliance, University of Cambridge, and consultation to the Ontario Autism Program). We will leverage these connections to disseminate our findings as widely as possible to ensure maximum reach and uptake of end-of-grant KT. We will hold a half day end-of-grant meeting with our advisory and additional stakeholders, which will also be live-streamed. We will develop H-CARDD research "snapshots" and videos summarizing study findings together with our autistic advisors and *Asperfemme*, a peer support group for autistic women, for the autism community, integrating lessons learned in this administrative data study and our prior qualitative work. With Autism Ontario, we will hold a "talk show" type webinar targeting families. Through our roles as Extension of Community Healthcare Outcomes (ECHO) leads (Penner, Lunsky), we will integrate findings from this research into the didactic training for clinicians on diagnosing and treating autism across Ontario. To further build our capacity, we will avail ourselves of supports that specialize in KT affiliated with the team (at CAMH, H-CARDD, ICES Communications Department). Our previous research projects and collective expertise provide evidence of the successful implementation and impact of this work in this timeframe and proposed budget.

EXPERTISE, EXPERIENCES & RESOURCES

We have assembled a team of investigators with expertise in autism, sex and gender, health services, and KT, representing psychiatry, paediatrics, psychology, epidemiology, and biostatistics, several of whom have worked on ICES studies leading to this proposal[22-32,66,74,75,77]. The investigators work in facilities with libraries, research support, media and communications support, and can support trainees.

NPA: **Dr. Meng-Chuan Lai** (8 hours/week) is an early career investigator, psychiatrist and clinician scientist at the Centre for Addiction and Mental Health (CAMH) and the Hospital for Sick Children, and Assistant Professor at the Department of Psychiatry, Institute of Medical Science, and Department of Psychology, University of Toronto (UofT). With extensive collaborations, >30 publications on autism, sex and gender[21] (among >100 peer-reviewed publications), and an international reputation on the study of sex, gender and autism, he is the Honorary Director of Gender Research in Autism at the Autism Research Centre, University of Cambridge. He is an expert in the clinical science and neuroscience of autism, especially on sex and gender impacts across behaviour, diagnosis, neurobiology, and service utilization. He is also a member of the Ontario Autism Program's Implementation Working Group. He will lead the research design, management, data analysis and interpretation, and KT, with input from the whole study team.

PAs: **Dr. Hilary Brown** (4 hours/week) is an Assistant Professor in the Interdisciplinary Centre for Health & Society at UofT Scarborough and the Dalla Lana School of Public Health at UofT, Adjunct Scientist at ICES, and Tier 2 Canada Research Chair in Disability & Reproductive Health. She is an epidemiologist with expertise in disability and women's health, with >20 publications on developmental disabilities including autism[75]. She will share responsibility for the research design, data analysis, and interpretation. **Dr. Yona Lunsky** (4 hours/week) is a psychologist, senior scientist and Director of the Azrieli Adult Neurodevelopmental Centre at CAMH, Professor in the Department of Psychiatry at UofT, and Adjunct Scientist at ICES. Since 2010, she has directed a research program on developmental disabilities and health service access (H-CARDD) using ICES data, leading to >50 publications[26] and a suite of KT products. She is a member of the Provincial Health Care Standards Committee focused on accessibility in health care across disabilities, co-directs the Adult Developmental Disabilities ECHO Mental Health training platform, and has contributed to the Canadian Primary Care Guidelines in Developmental Disabilities[99]. She will lead iKT and share responsibility for data analysis and interpretation.
Co-As: **Dr. Simone Vigod** (1 hour/week) is a clinician scientist and Psychiatrist-in-Chief at Women's College Hospital and Associate Professor and Director of the Division of Equity, Gender and Population at the Department of Psychiatry, UofT. She holds the Shirley A. Brown Memorial Chair in Women's Mental Health Research and is Adjunct Scientist at ICES. She is an expert in women's mental health and has led research on ICES studies regarding sex and gender differences in adults with developmental disabilities including autism and antipsychotic medication[29]. She will contribute to sex and gender considerations and conceptualization of psychiatric diagnoses and service use variables. **Dr. Melanie Penner** (1 hour/week) holds a Chair in Developmental Paediatrics at Holland Bloorview Kids Rehabilitation Hospital and leads Project ECHO Ontario Autism, a training platform to improve community care for autistic children/youth. She is the President of the Canadian Paediatric Society's Developmental Paediatrics section, a member of the Ontario Autism Program's Implementation Working Group, and has contributed to the Canadian Paediatric Society Autism Guidelines[100]. She will contribute to interpretation of findings and KT, especially with community health care providers. **Dr. Ami Tint** (8 hours/week) is a psychologist and postdoctoral trainee who published the first Canadian studies on the health care experiences of autistic girls and women[9,62]. She will co-lead iKT, lead regular advisory meetings and support autistic and parent advisors, and be closely involved in all research activities.

The research will be supported by advisors from the National Developmental Disabilities Primary Care Program responsible for national guidelines for family physicians (Knowledge User: **B. Sullivan**), Autism Ontario (Partner: **M. Spoelstra**) and Canadian Autism Spectrum Disorder Alliance (Partner and Knowledge User: **J. Lai**) who have provincial and national reach to clinicians and decision makers, leader in medical education in psychiatry (Collaborator: **P. Szatmari**), autistic women (representative Knowledge User: **G. Pineda-Aguirre**), parents of autistic people (representative Knowledge User: **L. Goldsmith**), and *Asperfemme* (Collaborators: **D. Zener** & **B. S. Tomas**). The advisors have all worked closely with the research team and have contributed to the concepts targeted in this proposal.

IMPACT

This project will provide critical new knowledge about current sex and gender inequities in health care for autistic people. Findings will inform the development of sex- and gender-informed assessment strategies and service pathways for autism by raising awareness about diagnostic overshadowing, including the potential patterns of previous co-occurring conditions preceding an autism diagnosis. Findings will also lead to future research on health care cost implications associated with autism diagnosis timing by sex and gender, and will inform the creation of training materials, tools and guidelines to assist clinicians in better identifying autistic girls/women and providing timely and tailored health care and support. At the service level, we will use the findings to work with systems partners to inform policy making and new strategies, to develop accessible pathways for autism diagnosis in girls/women and boys/men across the lifespan.