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Morbidity and mortality of women and men with intellectual and developmental disabilities newly initiating antipsychotic drugs

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Background
While up to 45% of individuals with intellectual and developmental disabilities (IDD) have a comorbid psychiatric disorder, and antipsychotics are commonly prescribed, gender differences in the safety of antipsychotics have rarely been studied in this population.

Aims
To compare men and women with IDD on medical outcomes after antipsychotic initiation.

Method
Our population-based study in Ontario, Canada, compared 1457 women and 1951 men with IDD newly initiating antipsychotic medication on risk for diabetes mellitus, hypertension, venous thromboembolism, myocardial infarction, stroke and death, with up to 4 years of follow-up.

Results
Women were older and more medically complex at baseline. Women had higher risks for venous thromboembolism (HR 1.72, 95% CI 1.15–2.59) and death (HR 1.46, 95% CI 1.02–2.10) in crude analyses; but only thromboembolism risk was greater for women after covariate adjustment (aHR 1.58, 95% CI 1.05–2.38).

Conclusions
Gender should be considered in decision-making around antipsychotic medications for individuals with IDD.

Declaration of interest
None.

Intellectual and developmental disabilities (IDD), affecting about 1 in 100 individuals, are neurodevelopmental disorders characterised by limitations in the intellectual and adaptive functioning leading to difficulties to cope with everyday life in areas such as communication, social and self-management skills.[1] Antipsychotic medication is one of the most commonly prescribed medications for individuals with IDD,[2] partly because of the high risk for comorbid psychiatric disorders such as psychosis, bipolar and even major depressive disorder and anxiety disorders in this group,[3,4] but also because antipsychotics are prescribed in an 'off-label' manner for the challenging and aggressive behaviours that often accompany IDD, despite evidence demonstrating that the effectiveness of antipsychotic medication in this situation is fairly equivocal.[5,6] A significant amount of research suggests that individuals with IDD are susceptible to the metabolic side effects of atypical antipsychotics, including weight gain, metabolic syndrome and its resultant cardiovascular effects.[7,8] However, research in IDD populations has been limited in its consideration of the impact of gender on the development of antipsychotic-related side effects. In non-IDD populations, gender differences have been observed in relation to antipsychotic side-effects, with some evidence suggesting greater susceptibility among women to weight gain, thromboembolic disease and QT interval prolongation that can trigger a potentially fatal arrhythmia.[9,10] This has allowed for more personalised counselling for patients and providers around antipsychotic use generally. However, it is not known whether similar gender differences exist among individuals with IDD as previous studies have been in small clinical populations (mostly $N<30$) and with short follow-up periods of less than 1 year.[8,11,12] Therefore, we undertook a population-based study among adults aged 18–64 with IDD in Ontario, Canada, who were newly prescribed antipsychotic medication between 1 April 2009 and 31 March 2012. Our objective was to compare men and women newly starting antipsychotic medication with respect to the incidence of metabolic and cardiovascular adverse events that have been previously associated with antipsychotic medications – including diabetes mellitus, hypertension, venous thromboembolism, acute myocardial infarction, stroke and death.

Method

Study design

This was a population-based cohort study comparing men and women with IDD newly prescribed antipsychotic medication on their risk for adverse metabolic and cardiovascular events between 1 April 2009 and 31 March 2012. Participants were followed up until 31 March 2013, allowing a minimum of 365 days of follow-up data to capture outcomes for each individual in the cohort, with a maximum follow-up of 4 years.

Data sources

Data were analysed at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario, Canada. ICES is a non-profit research organisation where patient-level records from health administrative data sources are linked using encoded identifiers derived from the health card number of every resident of Ontario. Individuals without health card numbers or for whom health card numbers were invalid could not be linked, but comprise a very small minority of Ontarians. For the current study, ICES health datasets were additionally linked with data from the Ontario Ministry of Community and Social Services to allow for more complete identification of individuals with IDD compared with health data alone.[13] At ICES, we used the Ontario Drug Benefit (ODB) programme database to capture information on prescription of antipsychotic drugs and other medications.[14] This publicly funded drug programme provides prescription coverage to individuals who are eligible because of factors such as unemployment, disability, high prescription drug costs relative to net household income and/or receipt of home care services in Ontario. The ODB captures more than two-thirds of individuals with IDD in the

province.[1] The Registered Persons Database (RPDB) that consists of date of birth, gender, postal code and date of death (where applicable) was used to define exposure groups, mortality outcomes and provided participant demographic information. Hospitalisation diagnoses were obtained from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), to which all hospitals in Ontario submit demographic and clinical information about all admissions and discharges using standard diagnostic (*International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, Canadian version, or ICD-10-CA) and procedural/interventional codes (Canadian Classification of Health Interventions, CCI);[15] and the Ontario Mental Health Reporting System (OMHRS), which contains mental health clinical and administrative data on adult patients, collected in all facilities in the province of Ontario with designated in-patient mental health beds.[16,17] Out-patient diagnoses and utilisation was obtained from the Ontario Health Insurance Plan (OHIP) database, which collects out-patient physician service information from Ontario physicians who are reimbursed after submitting claims to OHIP for each service provided.

Participants

Participants were drawn from a larger cohort of 66 484 adults with IDD aged 18–64 as of 1 April 2009.[13] We used a conceptual definition of IDD aligned with Canadian legislation and with commonly used international clinical definitions.[18,19] The conditions covered are characterised by lifelong limitations in cognitive and adaptive functioning that originate before age 18 and impact on activities of daily living. The definition therefore includes a broad range of conditions, neither based on aetiology nor an overall IQ score. The definition included autosomal and chromosomal anomalies, fetal alcohol syndrome, autism and pervasive developmental disorders, and intellectual disability (formerly labelled 'mental retardation'). A complete list of ICD-9, ICD-10 and DSM diagnostic codes used to capture these diagnoses is available in our manuscript describing cohort creation.[13] Individuals were considered to have an intellectual and/or developmental disability if they had any of these diagnostic codes recorded in health administrative data since database inception (≥2 physician visits or ≥1 emergency department visit or hospitalisation since 1992, 2000 and 1988, respectively) or in documentation for the Ontario Disability Support Program.

In our sample, we considered all those from the larger cohort who were eligible for publicly funded drug coverage under the ODB programme and who were aged 19–64 so as to allow for a minimum of 1 year look back to collect information on prescribed medications. We identified those who were newly prescribed at least one antipsychotic medication between 1 April 2009 and 31 March 2012 in order to compare outcomes between men and women. Antipsychotic medications available for prescription from the ODB during the time period under study are in Table 1. A prescription was considered new when there was no prescription for any antipsychotic medication in the year preceding initiation. Gender was determined from the ICES RPDB according to the information provided for each individual's provincial health card registration. For analyses related to incident diagnoses of diabetes mellitus and hypertension, those who were previously diagnosed with these diseases were excluded given that they were not at risk for the outcome (i.e. because they were already prevalent cases).

Outcomes

Study outcomes were metabolic and cardiovascular complications known to be associated with antipsychotic use: hypertension, diabetes mellitus, venous thromboembolic disease, acute myocardial infarction and stroke. We used validated algorithms to identify chronic hypertension (sensitivity 0.72, specificity 0.95),[20] diabetes mellitus (sensitivity 0.86, specificity 0.97)[21] and thromboembolic disease (specifically deep vein thrombosis or pulmonary embolism; sensitivity 0.87, specificity 0.78) using hospital-based diagnoses and out-patient fee claims.[22] Acute myocardial infarction and stroke were identified using hospital-based diagnoses only because these conditions primarily present in hospital and the validity of the primary diagnostic field in Ontario hospital databases is good.[15] All-cause mortality, or death, was also evaluated as an outcome variable determined from the ICES RPDB.

Table 1 List of antipsychotic medications used in the cohort

Oral and injectable antipsychotic medications	Database source	Drug names
First-generation ('typical')	ODB	Haloperidol, fluphenazine, trifluoperazine, zuclopenthixol, perphenazine, prochlorperazine, thiothixene, pimozide, chlorazepate, pipotiazine, loxapine, mesoridazine, thioridazine, chlorpromazine, methotrimeprazine, pericyazine
Second-generation ('atypical')	ODB	Risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, aripiprazole

ODB, Ontario Drug Benefit.

Covariates

We captured sociodemographic information including age, place of residence (urban/rural) and socioeconomic status using neighbourhood income quintile based on information from the ICES RPDB. Information on medical and psychiatric diagnoses and health service use in the 2 years prior to cohort entry was derived from in-patient and out-patient databases. The Resource Utilization Band (RUB) was used as a summary measure of healthcare resource intensity. It is a value between 0 and 5 that is used to classify persons based on predicted use of healthcare resources (0 = lowest expected healthcare utilisation; 5=highest expected healthcare utilisation). The RUB is established using a validated method, which considers information including age, gender, and diagnoses.[23] We also determined the type of antipsychotic medication used, and whether the index antipsychotic prescription led to continuous use, with continuity defined as filling at least two prescriptions in succession with no more than 1.5 times the number of days specified on the first prescription elapsing between prescriptions.

Statistical analysis

We compared the baseline characteristics of men and women using standardised differences, with differences of >10% indicating significant differences between groups. We reported the time to the development of each outcome using cumulative incidence of the outcome within these two strata. Cox's proportional hazards models were created to first determine the crude hazard ratio (HR) and 95% confidence interval associated with antipsychotic use and each outcome. Covariates were then added to these outcome specific models to arrive at adjusted hazard ratios (aHR) and 95% CI comparing women with men as the referent group using Cox's proportional hazards regression. Hazard ratios were adjusted for covariates where the standard difference between groups was >0.10. While consensus is not absolute as to what value of a standardised difference denotes important residual imbalance, it has been proposed that a standardised difference of 0.1 (10%) denotes meaningful imbalance in the baseline covariate.[24] In all Cox's proportional hazards models, the time to the first occurrence of

each outcome was used to determine the time to event. Individuals were censored either at the time of death or at the end of the follow-up time period. We conducted sub-analyses by the specific type of antipsychotic medication when sample size allowed.

For all outcomes (except mortality), death presented a possible competing risk where individuals who died before development of the outcome of interest would have been considered event free in a standard proportional hazards regression.[25] If the pre-event mortality rate differs between the two groups, this could confound the estimate of the outcome risk. As such, in sensitivity analyses for all outcomes except death, we conducted a competing-risks analysis using the Fine & Grey model that extends the Cox proportional hazards model to competing-risks data by considering the sub-distribution hazard.[26] In this analysis, individuals who die prior to the development of the outcome of interest are left uncensored in the risk set to generate a more direct cumulative incidence of the outcome, and then appropriately accounted for by weighting in the bivariable analysis. The competing-risks approach can allow for a more realistic representation of the relationship between covariates and specific outcomes in the setting of competing risks.[26] We obtained cumulative incidence function curves to describe the time to event after accounting for the competing risk of death for each of the other outcomes.

Analyses were performed at ICES using SAS 9.3 for Unix.[27] Permission to complete this study was granted by the Centre for Addiction and Mental Health and Sunnybrook Health Sciences Centre Research Ethics Boards in Toronto, Ontario, Canada.

Results

We identified 1457 women and 1951 men with IDD who newly started an antipsychotic medication between 1 April 2009 and 1 March 2010. Nearly, 90% of these were prescribed second-generation, or atypical, antipsychotic drugs, with the most commonly prescribed being quetiapine, risperidone and olanzapine (Table 2). Quetiapine was more commonly prescribed for women than for men. Olanzapine and risperidone were more commonly prescribed for men than for women. Women newly starting antipsychotic drugs were slightly older than men, had higher healthcare utilisation overall (46.3% *v.* 38.2% in the two highest utilisation brackets) and were more like to have diabetes mellitus prior to starting antipsychotic medication (15.4% *v.* 11.1%). Almost 80% of women and men had received at least one psychiatric diagnosis in the 2 years prior to starting antipsychotic medication. Diagnoses were similar between groups, except for alcohol and substance use disorders that were more common in men than in women (14.7% *v.* 10.5%). While both groups had high numbers of concomitant prescription medications, women were taking more unique medications overall and were more likely to be taking antidepressant drugs compared with men (52.8% *v.* 41.0%).

Women had slightly higher cumulative incidence of all outcomes, except for hypertension, over the study period (Table 3). However, there were only two significant differences between groups. Women had higher incidence of venous thromboembolism compared with men (cumulative incidence 10.5% *v.* 2.7%) before and after adjustment for confounding factors. Women also had a higher cumulative incidence of death compared with men (4.8% *v.* 3.2%) before, but not after, adjustment for confounders. We were able to perform sub-analyses by type of antipsychotic drug for quetiapine, olanzapine and risperidone (Fig. 1). There were no significant differences between men and women in risk for any of the outcomes in either crude or adjusted analyses.

Sensitivity analyses for a competing risk for death revealed that the pre-outcome risk for death did not differ between groups except for diabetes mellitus where 45 women (3.6%) and 37 men (2.1%) died before developing diabetes mellitus (HR 1.75, 95% CI 1.12–2.70). However, the competing risk analysis did not measurably change the relationship between gender and development of diabetes (aHR 1.10, 95% CI 0.75–1.61) (Fig. 2).

Discussion

This is the first population-based study to explore differences in medical outcomes between men and women among adults with IDD newly initiating antipsychotic medication. The women in our cohort were older and appeared to be more complex medically than the men overall, with greater healthcare use and more prescribed medications at baseline. Although the baseline rate of metabolic problems even prior to the initiation of antipsychotic medication was high in both groups, women had higher rates of metabolic problems such as diabetes mellitus than their male counterparts at baseline. Once antipsychotic medication was initiated, women appeared to be at higher risk than men for serious outcomes including venous thromboembolism and death. Some of this increased risk, at least for mortality, was explained by the older age, higher baseline medical morbidity and a greater number of concomitant medications among women. Interestingly, men and women appeared to be at equal risk for some of the other side-effects traditionally associated with the metabolic syndrome such as diabetes and hypertension. The type of antipsychotic medication initiated tended to be different in men *v.* women, but sub-analyses by type of antipsychotic did not reveal differences between groups on medical outcomes.

The slightly older average age of women *v.* men and their greater medical complexity are of some interest. The higher medical complexity that we observed among women compared with men is consistent with previous literature demonstrating higher healthcare utilisation, higher rates of prescriptions for antidepressant and other medications, and higher rates of medical morbidity, including diabetes mellitus among women *v.* men with IDD.[28,29] However, this does not explain why women were older at baseline. It is possible that there is a higher threshold for prescribing to women, either because of their higher medical morbidity, or because women tend to be perceived as less threatening when agitated than men with IDD,[30] and therefore providers may be more apt to attempt behavioural rather than pharmacological strategies until later in the course of an individual's illness. It is possible that the prescribing patterns that we observed to some extent support such a hypothesis. About 90% of individuals in our cohort were using atypical antipsychotic medications. This is consistent with literature reporting that second-generation antipsychotics are now the primary type of antipsychotic medication being prescribed to individuals with IDD, mainly because of the severe side-effect profile related to extrapyramidal side-effects and movement disorders of the older, typical or first-generation antipsychotic medications.[2,31,32] However, women were more commonly prescribed quetiapine, a sedating antipsychotic that can be prescribed initially in a very low dose that is often sufficient for behavioural management, and often takes weeks to titrate to an antipsychotic dosage. In contrast, men were more commonly prescribed risperidone or olanzapine, medications that can be titrated more quickly and may be more readily used in the setting of aggression.

Once antipsychotic medication was initiated, we found that there were relatively high rates of several of the adverse outcomes for both men and women. For example, depending on gender, the cumulative incidence was 4–5% for diabetes, 5–6% for hypertension, and there was a cumulative incidence of 3–4% for death over

Table 2 Baseline characteristics of 1457 women and 1951 men with an intellectual disability newly prescribed antipsychotic medication. Data are presented as *n* (%) unless otherwise specified

	Women (*n*=1457)	Men (*n*=1951)	s.d.
Sociodemographics			
Age in years, median (range)	40.5 (19–67)	38.4 (19–67)	0.16
Income quintile, Q1 (lowest)	505 (34.7)	611 (31.3)	0.10
Place of residence (urban, >10 000)	1224 (84.1)	1630 (83.5)	0.03
Medical morbidity and service use			
Diabetes mellitus	224 (15.4)	217 (11.1)	0.13
Chronic hypertension	260 (17.9)	310 (15.9)	0.05
Thromboembolic disease in past 2 years	20 (1.4)	20 (1.0)	0.03
Stroke in past 2 years	40 (2.8)	44 (2.3)	0.03
Acute myocardial infarction in past 2 years	≤6	16 (0.8)	0.07
Mean (range) no. hospitalisations in past 2 years	0.40 (0–13)	0.32 (0–23)	0.08
Mean (range) no. primary care provider visits in past 2 years	14.3 (0–228)	11.9 (0–214)	0.13
Mean (range) no. specialty medical visits in past 2 years	4.25 (0–131)	2.93 (0–240)	0.18
Resource Utilization Band (4 or 5) in past 2 years	673 (46.3)	746 (38.2)	0.20
Psychiatric morbidity and service use			
Any psychiatric diagnosis	1157 (79.5)	1506 (77.2)	0.06
Psychotic disorder	265 (18.2)	401 (20.6)	0.06
Non-psychotic disorder	947 (65.0)	1173 (60.1)	0.10
Alcohol and/or substance use disorder	153 (10.5)	286 (14.7)	0.13
Mean (range) no. hospitalisations in past 2 years	0.39 (0–20)	0.38 (0–10)	0.01
Mean (range) no. emergency department visits in past 2 years	0.61 (0–90)	0.52 (0–60)	0.04
Mean (range) no. outpatient psychiatry visits in past 2 years	2.53 (0–144)	3.01 (0–118)	0.06
Concomitant medications			
Number of unique medications, mean (range)	7.00 (1–50)	5.69 (1–40)	0.24
Number of additional psychotropics, mean (range)	1.07 (0–4)	0.91 (0–4)	0.18
Antidepressant medication	768 (52.8)	800 (41.0)	0.24
Antiepileptic medication	291 (20.0)	386 (19.8)	0.01
Lithium	38 (2.6)	49 (2.5)	0.01
Benzodiazepine	456 (31.3)	538 (27.6)	0.08
Oral steroid	115 (7.9)	152 (7.8)	<0.01
Type of antipsychotic medication			
Atypical antipsychotic medication only	1282 (88.0)	1711 (87.7)	
Typical antipsychotic medication only	160 (11.0)	209 (10.7)	
Atypical and typical together	14 (1.0)	31 (1.6)	
Specific drug (presented when >10 users in one group):			
Quetiapine	666 (45.7)	767 (39.3)	0.22
Risperidone	365 (25.1)	536 (27.5)	
Olanzapine	212 (14.6)	364 (18.7)	
Chlorpromazine	15 (1.0)	33 (1.7)	
Haloperidol	55 (3.8)	90 (4.6)	
Loxapine	21 (1.4)	21 (1.1)	
Methotrimeprazine	34 (2.3)	44 (2.3)	
Paliperidone	25 (1.7)	28 (1.4)	
Prochlorperazine	22 (1.5)	10 (0.5)	
Ziprasidone	15 (1.0)	16 (0.8)	
2+ consecutive antipsychotic prescriptions	973 (66.8)	1295 (66.4)	0.01

Table 3 Comparison of women and men with respect to the risk for selected adverse outcomes after initiation of a new antipsychotic medication

Outcome	Exposure group	Cumulative incidence (%)	Hazard ratio (95% CI)	Adjusted HR (95% CI)[a]
Diabetes mellitus	Men (*n*=1734)	4.46	1.00 (referent)	1.00 (referent)
	Women (*n*=1232)	5.46	1.24 (0.85–1.80)	1.09 (0.75–1.60)
Hypertension	Men (*n*=1641)	6.80	1.00 (referent)	1.00 (referent)
	Women (*n*=1196)	5.83	0.98 (0.66–1.45)	0.83 (0.56–1.24)
Thromboembolism	Men (*n*=1951)	2.74	1.00 (referent)	1.00 (referent)
	Women (*n*=1457)	10.5	**1.72 (1.15–2.59)**	**1.58 (1.05–2.38)**
Acute myocardial infarction	Men (*n*=1951)	0.43	1.00 (referent)	1.00 (referent)
	Women (*n*=1457)	0.99	1.19 (0.40–3.13)	0.92 (0.31–2.80)
Stroke	Men (*n*=1951)	1.63	1.00 (referent)	1.00 (referent)
	Women (*n*=1457)	2.48	1.27 (0.72–2.24)	1.10 (0.62–1.95)
Death	Men (*n*=1951)	3.17	1.00 (referent)	1.00 (referent)
	Women (*n*=1457)	4.83	1.46 (1.02–2.10)	1.27 (0.88–1.83)

Statistically significant results shown in bold.
a. Adjusted for age (continuous), Resource Utilization Band and total number of medications (continuous). Thromboembolism estimates additionally adjusted for previous venous thromboembolism.

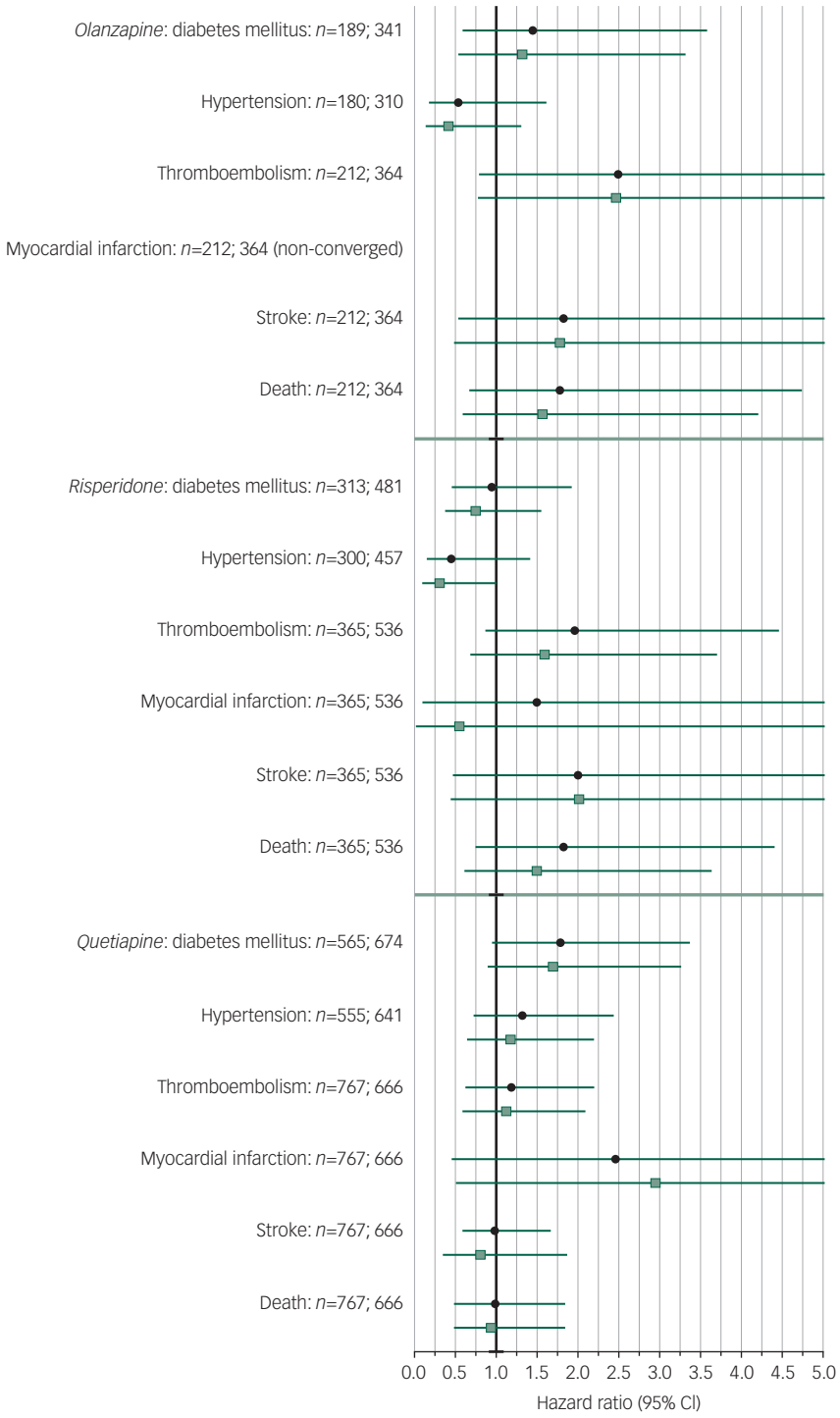

Fig. 1 Comparison of outcomes in women *v.* men by antipsychotic subtype, presented with number in the sample (*n*=women; men), and with crude (black circle) and adjusted (green square) hazard ratios and 95% confidence intervals. Hazard ratios adjusted for age (continuous), Resource Utilization Band and total number of medications (continuous). Thromboembolism estimates additionally adjusted for previous venous thromboembolism.

the study period. In general, these cumulative incidence estimates for the development of the stated medical outcomes are fairly conservative compared with previous literature on this topic for individuals with IDD demonstrating high risk for weight gain and the metabolic syndrome.[11,33–37] However, most previous studies have been clinical, rather than population-based, and tended to focus on weight gain and obesity but not diagnoses of diabetes and hypertension *per se*.[8,12,38] The fact that we observed such a high cumulative incidence of death over the study period for relatively young individuals (i.e. average age of 38 for men and 40 for women at antipsychotic initiation) suggests that, in fact, this is a very high-risk population in general.

Our findings of an increased risk for venous thromboembolism among women are consistent with research conducted in populations with psychosis who initiate antipsychotics,[10] where it is thought that women are more highly susceptible to antipsychotic induced activity in the coagulation system[39] and may also be at higher risk compared with men because of the addition of gender-specific risk factors such as hormonal oral contraceptive use and pregnancy.[40,41] However, we did not observe statistically increased

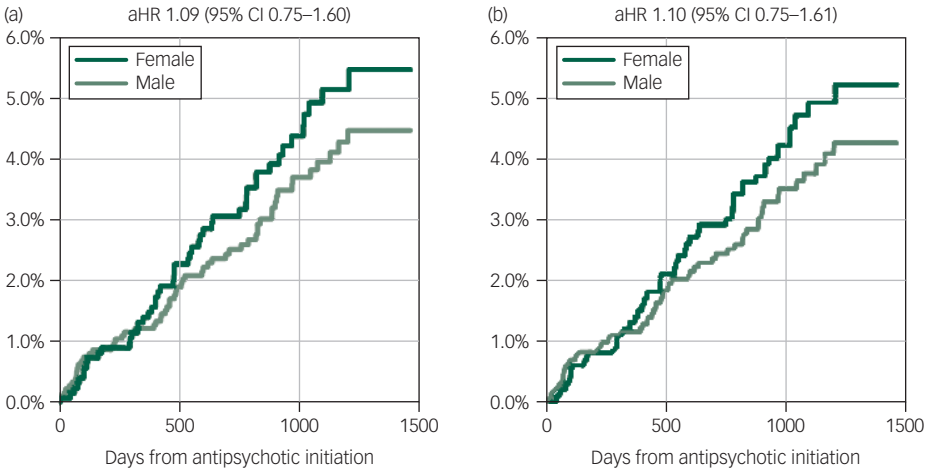

Fig. 2 Cumulative incidence of diabetes mellitus for 1232 women and 1734 men newly starting an antipsychotic drug, (a) without accounting for competing risk for death, and (b) accounting for competing risk for death.

risk for other medical outcomes, nor for death after adjusting for baseline medical morbidity. This is inconsistent with the evidence from studies comparing men and women with schizophrenia showing that women may be at greater risk of developing some of the metabolic side-effects associated with use of atypical antipsychotic medication, and at higher risk for QTc interval prolongation, which can lead to fatal arrhythmias and death.[10] The reasons for this require some consideration, especially in light of the results of previous work on gender differences in certain metabolic symptoms conducted among individuals with IDD.[42] One clinical study found that, among participants who had used antipsychotic medication for a year or more, female gender was associated with high waist circumference, and predicted higher scores on measures of body mass index after taking antipsychotic medication.[42] However, female gender was also associated with high HDL-cholesterol level at baseline and after antipsychotic initiation, a favourable sign with respect to the metabolic syndrome. Our study is not directly comparable as we considered medical diagnoses, not metabolic symptoms, and so perhaps there are subtle gender differences in metabolic parameters that are simply not borne out in hard outcomes such as diabetes, hypertension, myocardial infarction and stroke. Alternatively, it may be that gender differences observed in first-episode psychosis populations newly starting antipsychotics where most individuals are initially medically healthy are attenuated in a population like ours where the average age and baseline medical morbidity is already so high.

Strengths of this study are that it is large, population-based, and provides comprehensive coverage of individuals with IDD with ability to report on important health outcomes that have been validated for use in administrative data. We were also able to incorporate the concept of death as a competing risk for our outcomes to assure the most accurate cumulative incidence estimates. While health administrative data provide information only on dispensed medications (i.e. not on whether the medications were taken), the ODB prescription data have been shown to be accurate and reliable in validation studies.[14] We were limited in our inability to measure more clinical outcomes such as weight gain, laboratory measures of metabolic markers and cardiac changes through electrocardiograms; and we did not measure the impact of antipsychotic dosage in the current analysis. In addition, we only conducted our investigation in adults aged 19–64, and so the study findings cannot necessarily be generalised for children, or for elderly individuals with IDD. Common to all observational studies, and most using population-based data, the possibility remains that some of the observed effects could be explained by residual confounding.

Our study is situated in literature that is beginning to pay significant attention to concern over high rates of antipsychotic prescriptions in those with IDD.[2,6,43] Our findings go a step further by taking gender into account as it pertains to medical outcomes in a population-based sample of new antipsychotic users. Our results speak to the importance of careful consideration of the risks and benefits of prescribing antipsychotic medication to women and men with IDD; and illustrate that gender should be considered in the risk–benefit discussions about prescribing. They underscore the need to attend to the metabolic health of individuals with IDD prior to initiating antipsychotic medications, and to initiating interventions proactively to prevent the development of or manage the complications of pre-existing diabetes and heart disease. This may include behavioural interventions such as smoking cessation and diet management, and/or preventive medical interventions as needed to optimise glucose control, blood pressure and/or cholesterol levels as indicated. They also serve as a reminder of how important it is to monitor for metabolic and cardiac side-effects among both men and women with IDD newly starting antipsychotic medication, particularly in the context of some studies that show a lack of consistent monitoring of metabolic changes in patients with IDD.[7,11,44] Women may be at particularly high risk for venous thromboembolic disease after new initiation of antipsychotic medication and this should be considered in the clinical care of women newly starting antipsychotic medication.

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References

1 Lunsky Y, Klein-Geltink JE, Yates EA (eds). *Atlas on the Primary Care of Adults with Developmental Disabilities in Ontario.* Institute for Clinical Evaluative Sciences & Centre for Addiction and Mental Health, 2013.

2 Sheehan R, Hassiotis A, Walters K, Osborn D, Strydom A, Horsfall L. Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study. *BMJ* 2015; **351**: h4326.

3 Cooper S-A, Smiley E, Morrison J, Williamson A, Allan L. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. *Br J Psychiatry* 2007; **190**: 27–35.

4 Morgan VA, Leonard H, Bourke J, Jablensky A. Intellectual disability co-occurring with schizophrenia and other psychiatric illness: population-based study. *Br J Psychiatry* 2008; **193**: 364–72.

5 Brylewski J, Duggan L. Antipsychotic medication for challenging behaviour in people with learning disability. *Cochrane Database Syst Rev* 2004; **3**: CD000377.

6 Glover G, Bernard S, Branford D, Holland A, Strydom A. Use of medication for challenging behaviour in people with intellectual disability. *Br J Psychiatry* 2014; **205**: 6–7.

7 Teeluckdharry S, Sharma S, O'Rourke E, Tharian P, Gondalekar A, Nainar F, et al. Monitoring metabolic side effects of atypical antipsychotics in people with an intellectual disability. *J Intellect Disabil* 2013; **17**: 223–35.

8 Frighi V, Stephenson MT, Morovat A, Jolley IE, Trivella M, Dudley CA, et al. Safety of antipsychotics in people with intellectual disability. *Br J Psychiatry* 2011; **199**: 289–95.

9 Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry* 2007; **68**(Suppl 1): 20–7.

10 Nasrallah HA. The roles of efficacy, safety, and tolerability in antipsychotic effectiveness: practical implications of the CATIE schizophrenia trial. *J Clin Psychiatry* 2007; **68**(Suppl 1): 5–11.

11 Azimi K, Raina P, Lunsky Y. Brief report: occurrence of metabolic syndrome in patients with intellectual disability treated with atypical antipsychotics. *J Dev Disabil* 2011; **17**: 47–50.

12 Gazizova D, Puri BK, Singh I, Dhaliwal R. The overweight: obesity and plasma lipids in adults with intellectual disability and mental illness. *J Intellect Disabil Res* 2012; **56**: 895–901.

13 Lin E, Balogh R, Cobigo V, Ouellette-Kuntz H, Wilton AS, Lunsky Y. Using administrative health data to identify individuals with intellectual and developmental disabilities: a comparison of algorithms. *J Intellect Disabil Res* 2013; **57**: 462–77.

14 Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003; **10**: 67–71.

15 Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, et al. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. Canadian Institute for Health Information, 2006.

16 Hirdes JP, Smith TF, Rabinowitz T, Yamauchi K, Perez E, Telegdi NC, et al. The Resident Assessment Instrument-Mental Health (RAI-MH): inter-rater reliability and convergent validity. *J Behav Health Serv Res* 2002; **29**: 419–32.

17 Urbanoski KA, Mulsant BH, Willett P, Ehtesham S, Rush B. Real-world evaluation of the Resident Assessment Instrument-Mental Health assessment system. *Can J Psychiatry* 2012; **57**: 687–95.

18 Government of Ontario. *Services and Supports to Promote the Social Inclusion of Persons with Developmental Disabilities Act*, 2008 (https://www.ontario.ca/laws/statute/08s14). Government of Ontario, 2008.

19 American Association on Intellectual & Developmental Disabilities. *Intellectual Disability: Definition, Classification, and Systems of Supports*, 11th ed. American Association on Intellectual & Developmental Disabilities, 2011.

20 Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, et al. Validation of a case definition to define hypertension using administrative data. *Hypertension* 2009; **54**: 1423–8.

21 Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002; **25**: 512–6.

22 Tagalakis V, Kahn SR. Determining the test characteristics of claims-based diagnostic codes for the diagnosis of venous thromboembolism in a medical service claims database. *Pharmacoepidemiol Drug Saf* 2011; **20**: 304–7.

23 The Johns Hopkins ACG System. *Technical Reference Guide Version 9.0.* Health Services Research & Development Center, Johns Hopkins University, Bloomberg School of Public Health, 2009.

24 Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001; **54**: 387–98.

25 Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. *J Am Geriatr Soc* 2010; **58**: 783–7.

26 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496–509.

27 SAS Software. Version 9.3 of the SAS System for Unix. SAS Institute Incorporated, 2012.

28 Tsakanikos E, Bouras N, Sturmey P, Holt G. Psychiatric co-morbidity and gender differences in intellectual disability. *J Intellect Disabil Res* 2006; **50**: 582–7.

29 Balogh RS, Lake JK, Lin E, Wilton A, Lunsky Y. Disparities in diabetes prevalence and preventable hospitalizations in people with intellectual and developmental disability: a population-based study. *Diabet Med* 2015; **32**: 235–42.

30 Lunsky Y, Bradley EA, Gracey CD, Durbin J, Koegl C. Gender differences in psychiatric diagnoses among inpatients with and without intellectual disabilities. *Am J Intellect Dev Disabil* 2009; **114**: 52–60.

31 Matson JL, Neal D. Psychotropic medication use for challenging behaviors in persons with intellectual disabilities: an overview. *Res Dev Disabil* 2009; **30**: 572–86.

32 Leucht S, Bradley EA, Gracey CD, Durbin J, Koegl C. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; **373**: 31–41.

33 Merriman S, Haw C, Kirk J, Stubbs J. Risk factors for coronary heart disease among inpatients who have mild intellectual disability and mental illness. *J Intellect Disabil Res* 2005; **49**: 309–16.

34 Valdovinos M, Parsa R, Alexander M. Results of a Nation-Wide survey evaluating psychotropic medication use in Fragile X Syndrome. *J Dev Phys Disabil* 2009; **21**: 23–37.

35 Bhaumik S, Watson JM, Thorp CF, Tyrer F, McGrother CW. Body mass index in adults with intellectual disability: distribution, associations and service implications: a population-based prevalence study. *J Intellect Disabil Res* 2008; **52**: 287–98.

36 Tenenbaum A, Chavkin M, Wexler ID, Korem M, Merrick J. Morbidity and hospitalizations of adults with Down syndrome. *Res Dev Disabil* 2012; **33**: 435–41.

37 Humphries K, Traci MA, Seekins T. Nutrition and adults with intellectual or developmental disabilities: systematic literature review results. *Intellect Dev Disabil* 2009; **47**: 163–85.

38 de Winter CF, Bastiaanse LP, Hilgenkamp TI, Evenhuis HM, Echteld MA. Cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia and metabolic syndrome) in older people with intellectual disability: results of the HA-ID study. *Res Dev Disabil* 2012; **33**: 1722–31.

39 Hagg S, Spigset O. Antipsychotic-induced venous thromboembolism: a review of the evidence. *CNS Drugs* 2002; **16**: 765–76.

40 Moores L, Bilello KL, Murin S. Sex and gender issues and venous thromboembolism. *Clin Chest Med* 2004; **25**: 281–97.

41 Aichhorn W, Whitworth AB, Weiss EM, Marksteiner J. Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? *Drug Saf* 2006; **29**: 587–98.

42 de Kuijper G, Mulder H, Evenhuis H, Scholte F, Visser F, Hoekstra PJ. Determinants of physical health parameters in individuals with intellectual disability who use long-term antipsychotics. *Res Dev Disabil* 2013; **34**: 2799–809.

43 Tyrer P, Cooper SA, Hassiotis A. Drug treatments in people with intellectual disability and challenging behaviour. *BMJ* 2014; **349**: g4323.

44 Baburaj R, El Tahir M. *Monitoring for Metabolic Syndrome in People with Intellectual Disability on Antipsychotic Medication*. Advances in Mental Health and Intellectual Disabilities, 2011.