Title

Risk of anticholinergic burden in adults with intellectual disabilities: A Scottish retrospective cohort study of n = 17,220

Running Title

Anticholinergic burden & intellectual disabilities

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Conflict of interest

No conflict of interest has been declared by the authors

Abstract

Background: Several drugs have anticholinergic side effects which are associated with adverse health outcomes. Anticholinergic burden studies in adults with intellectual disabilities (ID) have focused exclusively on older adults. This study investigates anticholinergic burden and its associations in adults with ID of all ages (17-94 years).

Method: Adults with ID (n=4,305), each with three general population age-sex-neighbourhood matched controls (n=12,915), were linked to their prescribed medications with anticholinergic effects between 2009-2017. Analyses were undertaken using logistic regression models.

Results: Adults with ID were more likely to be prescribed any anticholinergic medicines: OR=1.49 (1.38-1.59); especially 'very strong' risk medicines: OR=2.59 (2.39-2.81). 48.5% had very high total anticholinergic burden (3+) compared to 35.4% of the general population; OR=1.77 (1.64-1.90). This group difference was greater for males; OR=2.02 (1.84-2.22), than females; OR=1.48 (1.33-1.65). Adults with ID had significantly higher odds of having very high total anticholinergic burden up to 75 years old, with the greatest group effect occurring in younger ages, 17-24 year olds; OR=3.05 (2.39-3.89), and the extent of the difference decreased as age increased. The main effect of neighbourhood deprivation showed greater group differences with increasing affluence of neighbourhood. Results examining only the ID group showed that very high total anticholinergic burden was greatest for females OR=1.21 (1.07-1.37) and those over age 55, and extent of neighbourhood deprivation was not significant.

Discussion: Adults with ID are at higher risk of anticholinergic burden than the general population, especially young adults. Overall anticholinergic burden increased with age, but burden was high across all ages in the ID group. Very high total anticholinergic burden is prevalent across all types of neighbourhoods for the adults with ID, in contrast to the steeper gradient seen in the general population. Adults with ID have increased likelihood of unintended adverse effects, regardless of potential confounds, so clinicians undertaking medication reviews need to consider anticholinergic side effects and cumulative burden across concomitant medications, including in young adults with ID, not just older adults, and particularly women.

Keywords: Intellectual disabilities, learning disabilities, anticholinergic burden, drugs, data linkage

Background

Several drugs have anticholinergic properties, and there is a cumulative effect of using multiple medications with anticholinergic effects concomitantly, referred to as anticholinergic burden. Drugs with anticholinergic properties inhibit nerve impulses in both the central and peripheral nervous systems due to selective binding to the neurotransmitter acetylcholine. Whilst medicines may have an intended therapeutic effect via blocking muscarinic (i.e. acetylcholine) receptors, e.g. antiparkinsonians, many

medications have unintended anticholinergic side effects, e.g. antipsychotics (Gray *et al.*, 2015). Individual drug anticholinergic effects vary, and in some cases may be small, but are additive, so can constitute significant anticholinergic burden.

Scientific literature has focused almost exclusively on older aged samples from the general population, with evidence of harmful central effects such as cognitive impairment, episodic memory decline, delirium, confusion and dementia (Hilmer *et al.*, 2007; Boustani *et al.*, 2008; Ruxton, Woodman and Mangoni, 2015; Crispo *et al.*, 2016; Pfistermeister *et al.*, 2017; Pieper *et al.*, 2020); the latter being associated with high anticholinergic burden 15-20 years before diagnosis (Richardson *et al.*, 2018). There is also evidence of peripheral effects such as dry mouth (Cockburn *et al.*, 2017; Tiisanoja *et al.*, 2018), urinary retention, constipation (Boustani *et al.*, 2008), impairments in physical mobility (Hilmer *et al.*, 2007), fall risk (Ruxton, Woodman and Mangoni, 2015; Crispo *et al.*, 2016), impaired ability to perform activities of daily living (Wouters, van der Meer and Taxis, 2017; Mur *et al.*, 2020) and all-cause mortality (Fox *et al.*, 2011; Ruxton, Woodman and Mangoni, 2015; Corsonello *et al.*, 2019; Ali *et al.*, 2020; Hanlon *et al.*, 2020). The cumulative impact of anticholinergic medications across years therefore cannot be underestimated.

Current evidence shows that the risk of anticholinergic burden is associated with older adults (65+ years old), multimorbidity (two or more long-term health conditions), polypharmacy (five or more medications), social deprivation, those living in care homes and women (Boustani *et al.*, 2008; Fox *et al.*, 2011; Sumukadas *et al.*, 2014; Rhee *et al.*, 2018; Mur *et al.*, 2020). Scientific literature has previously focused on older adults from the general population, given the patient group's vulnerability to polypharmacy due to multimorbidity (Molokhia and Majeed, 2017).

Many of the pharmacotherapy issues associated with anticholinergic burden are present in the lives of those with Intellectual Disabilities (ID) at much younger ages (<65 years old) (Zaal *et al.*, 2013; Haider *et al.*, 2014; Scheifes *et al.*, 2016; Peklar *et al.*, 2017). Compared to the general population, people with ID have greater and different patterns of multimorbidity, beginning earlier in life, with poorer health outcomes (Cooper *et al.*, 2015; Glover *et al.*, 2017; Kinnear *et al.*, 2018). Hence their pharmacotherapy is often multiple and complex (O'Connell *et al.*, 2018) from an early age. One study revealed that the extent of multimorbidity in people with ID aged 20-25 years was similar to that in the general population aged 50-55 years (Cooper *et al.*, 2015), suggesting that anticholinergic burden may be a problem for young adults with ID much more than for the general population. People with ID may have 'idiosyncratic responses to drugs' (O'Dwyer *et al.*, 2018), and a higher risk of side effects as drug pharmacokinetics may differ. Anticholinergic side effects of cognitive impairment and constipation can overlap with ID and be

difficult to detect, leading to further health problems (Axmon *et al.*, 2017). Additionally, there may be delays in detecting anticholinergic side effects due to communication issues (O'Dwyer *et al.*, 2018). Given that adults with ID die approximately 20 years earlier than the general population (O'Leary *et al.*, 2018), and the known relationship between anticholinergic burden and mortality, it is clear that anticholinergic burden is pertinent to all people with ID.

There are few studies investigating anticholinergic burden in adults with ID, and those that have, have focused on older adults (40+ years old). The Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing (IDS-TILDA) found 753 adults with ID (40 – 90 years old) were frequently exposed to polypharmacy (5+ medicines) and reported 'excessive polypharmacy' (10+ medicines) in over a fifth of the sample (O'Dwyer, Peklar, *et al.*, 2016; O'Connell *et al.*, 2018). The authors highlight this polypharmacy is due to treatment of multiple morbidities, particularly mental health conditions and epilepsy (O'Dwyer, Peklar, *et al.*, 2016). The adults with ID over the age of 65 were more likely to have mental health conditions and high anticholinergic burden compared with the same-aged general population (O'Dwyer, Maidment, *et al.*, 2016). An Italian cohort of 276 adults with ID over the age of 40 were described as having high anticholinergic load, and this was associated with having mental health conditions and neurological comorbidity (De Vreese *et al.*, 2018). Antipsychotics accounted for 86% of the cumulative anticholinergic burden. A Swedish cohort of 7,936 adults with ID over the age of 55, found from self/proxy report that older adults with ID had double the relative risk compared to the general population to be prescribed any anticholinergic medications (Axmon *et al.*, 2017). Additionally, these medications were more likely to be prescribed for longer periods and at higher dosages (Axmon *et al.*, 2017).

The aim of this research was to quantify anticholinergic burden in adults of all ages with ID compared with the general population, and its demographic associations.

Methods

Approval

Approval for this research was granted by Scotland's Public Benefit and Privacy Panel for Health and Social Care (reference 1516-0281).

Sample and Data Linkage

Routinely collected health administrative data from 2009–2017 were used to investigate prescribing patterns in our two groups: adults with ID and matched controls from the general population. NHS Greater Glasgow & Clyde (GG&C) is the largest health board in Scotland and serves a population of 1.2 million. The Primary Care Intellectual Disabilities Register of 2014 from NHS GG&C was used to identify

adults aged 17+ years with ID in its geographical area. All people identified as of 2014 were included. The register was established in 2000-2001 from multiple sources including the ID health service, social work services for people with ID, social services funding to people with ID, day centres, and General Practitioners (GPs). GPs were financially incentivised to identify their adult population with ID, and 100% of them did so. All adults identified were checked by an ID nurse to confirm they had ID and were removed from the register if they did not. The register was then updated annually, jointly by the GPs and ID service. In 2014, 73% of the GP practices consented to data on their patients on the Intellectual Disabilities Register to be deposited in NHS GG&C's Safe Haven (Pavis and Morris, 2015), for use in approved research. Following ethical approval, this register held at the Safe Haven was disclosed to NHS Scotland's Information Services Division (ISD) to create a matched control cohort from the general population (3:1) based on age (year of birth), sex, and postcode area (Scottish Index of Multiple Deprivation: SIMD2016) as of 2017. Using the matching algorithm for record linkage meant that each control could only be matched to data on one person with ID.

In Scotland, the Community Health Index (CHI) number is a unique identifier for each patient used in health records in administrative databases. The CHI database enabled patient records to be linked across different health datasets by NHS ISD. After the probabilistic matching was run, personal identifiers were removed (including CHI number) to ensure patient confidentiality, and access to the pseudonymised linked dataset was given to our research team via the Safe Haven. The process was in accordance with algorithms and decision rules by NHS ISD for routine linkage of health records (Clark *et al.*, 2017). Following receipt of the pseudonymised linked dataset, it was observed that two controls were identified as having ID, therefore, all participants from their matched clusters were excluded (n=8).

Data Sources

The Prescribing Information System (PIS) was used to identify medication use between January 2009 and August 2017 for everybody included in the analysis. This database records all community prescriptions prescribed and dispensed; recording has been robust since 2009 (inclusion of the CHI) (Alvarez-Madrazo *et al.*, 2016). Drugs with anticholinergic burden were identified using the modified Anticholinergic Risk Scale (ARS) (Rudolph *et al.*, 2008; Sumukadas *et al.*, 2014) a validated and pharmacist-developed list of prescribed medications with anticholinergic risk. This list was reviewed and refined by the authors (S.A-C., C.P., J.G., D.K.); a dentist with specialist interest, a psychiatrist and a pharmacist specialising in ID (Appendix 1). The ARS list classifies the anticholinergic effect of medicines as moderate (risk category 1), strong (risk category 2), and very strong (risk category 3).

Statistical Analysis

Data were summarised descriptively for each group (ID group and general population controls), using counts and percentages for categorical variables and mean, standard deviation (SD), or median, 25th and 75th percentiles (Q1, Q3 respectively), depending on the distribution of the data. Group comparisons were made using generalised linear models and linear mixed models, specifically binary logistic regression. All models included a fixed effect for group. Models (except from the temporal trends analysis) were then extended to include the additional main effect for each of age category, sex and SIMD, before including the two-way interactions between group and each of the other main effects. Finally, the group effect from subgroup analyses, when the two-way interactions were significant, were explored whilst adjusting for other main effects, e.g. when exploring age subgroups, sex and SIMD were adjusted for. A further subgroup analysis was then performed to explore the main effects of age category, sex and SIMD in the ID group. To explore temporal trends between 2009 and 2017, generalised linear mixed effects models were used adjusting for the random subject effect and fixed effects for group and year. The group effect from subgroup analyses by year were then explored and models were extended to adjust for the additional main effects of age category, sex and SIMD. Odds Ratios (OR), 95% Confidence Intervals (CI) and p-values for the group effect are reported.

Exposure to anticholinergic burden was calculated in 3 ways: (a) binary for any anticholinergic burden, identified as any prescription of anticholinergic drugs in the period 2009-2017; (b) binary for each individual ARS risk category, identified as any prescription of anticholinergic drugs in the period 2009-2017 listed as each of ARS 1 (moderate), ARS 2 (strong), and ARS 3 (very strong); and (c) ordinal for summed ARS scores during the period 2009-2017 for individual drugs: 0 (no exposure), 1-2 (moderate), or 3+ (very high). Summed ARS scores quantifies the total anticholinergic burden for each participant across 2009-2017, e.g. if an individual received 3 different risk category 1 drugs, and 1 category 2 drug, they scored 5. Group differences in these anticholinergic burden outcomes were explored as described above using binary and ordinal logistic regression models. Statistical analyses were conducted using SAS version 9.4 and R version 3.5.0.

Results

General Demographics

The final dataset of n=17,220 included 4,305 adults with ID and 12,915 adults from the general population. As expected, there were more men than women (Females=41.8%). Age ranges for the groups in 2014 were 17–94 years, with a mean age of 47.0 years (SD=16.0). A higher proportion of adults lived in more deprived areas (Table 1).

Table 1. Group characteristics in 2014.

		Intellectual Disabilities	General Population
Total	n (17,220)	4,305	12,915
Sex	Female	1,801 (41.8%)	5,403 (41.8%)
	Male	2,504 (58.2%)	7,512 (58.2%)
Age	17-24	403 (9.4%)	1,209 (9.4%)
	25-34	811 (18.8%)	2,433 (18.8%)
	35-44	673 (15.6%)	2,019 (15.6%)
	45-54	965 (22.4%)	2,895 (22.4%)
	55-64	794 (18.4%)	2,382 (18.4%)
	65-74	464 (10.8%)	1,392 (10.8%)
	75+	195 (4.5%)	585 (4.5%)
SIMD (2016)	1-most deprived	2,293 (53.3%)	6,879 (53.3%)
	2	848 (19.7%)	2,544 (19.7%)
	3	545 (12.6%)	1,635 (12.6%)
	4	349 (8.1%)	1,047 (8.1%)
	5-least deprived	270 (6.3%)	810 (6.3%)

Exposure to anticholinergic medicines

In the total sample of 17,220, more adults with ID were prescribed anticholinergic medication compared to the general population (57.9% (n=2,493), 48.3% (n=6,235) respectively, OR=1.49 [1.38-1.59], p<0.001). This observed result was similar when we analysed each of the individual anticholinergic drug risk categories, with a larger group difference occurring in the drugs with the greatest anticholinergic burden, OR=2.59 (2.39-2.81) (Table 2). 48.5% (n=2,088) of adults with ID had a very high total anticholinergic burden score (3+), 13.1% more than the general population (35.4%, n=4,577). Total anticholinergic burden scores were higher for the adults with ID with a median of 2 (Q1=0; Q3=8) and a median for the general population of 0 (Q1=0; Q3=5).

Table 2. Group differences for prescribed anticholinergic medications between 2009-2017

Anticholinergic burden outcome		Intellectual disabilities	General population	OR [95% CI]	p-value
Any anticholinergic medication		2,493 (57.9%)	6,235 (48.3%)	1.49 [1.38-1.59][1]	p<0.001
Individual drug anticholinergic risk	Moderate (ARS=1)	2,104 (48.9%)	5,211 (40.3%)	1.44 [1.34-1.54] [1]	p<0.001
	Strong (ARS=2)	1,830 (42.5%)	4,241 (32.8%)	1.53 [1.42-1.64] [1]	p<0.001
	Very strong (ARS=3)	1,431 (33.2%)	2,118 (16.4%)	2.59 [2.39-2.81] [1]	p<0.001
Total anticholinergic burden	None (0)	1,812 (42.1%)	6,680 (51.7%)		
	Moderate (1-2)	405 (9.4%)	1,658 (12.8%)	1.61 [1.51-1.72][2]	p<0.001
	Very high (3+)	2,088 (48.5%)	4,577 (35.4%)		

ARS= modified Anticholinergic Risk Scale, OR= Odds Ratio, CI= Confidence Interval, [1] Binary logistic regression model outcome, [2] Ordinal logistic regression model outcome

Examining the temporal trends revealed that more adults with ID were prescribed any anticholinergic medication compared to the general population for every year between 2009-2017 ($p<0.001$). Adults with ID were more likely to be prescribed any anticholinergic medication, the unadjusted group effect OR=25.68 (19.01-35.05), $p<0.001$, and for each 1-year increase the main effects OR=1.14 (1.13-1.15), $p<0.001$. The significant interaction between group and year ($p<0.001$) revealed a group difference in 2009 OR=2.33 [2.15-2.51], $p<0.001$, decreasing gradually through to 2017 OR=1.90 [1.77-2.05], $p<0.001$. In 2009 the group difference was 16.5% which dropped to 13.4% by 2017. The decrease in OR over time was due to a greater increase in prescriptions of any anticholinergic medications in the general population (from 23.6% in 2009 to 29.1% in 2017) compared with the ID group (from 40.1% in 2009 to 42.5% in 2017).

Regardless of which anticholinergic burden outcome was used (listed in Table 2), results from the regression analyses indicated that adults with ID presented with a higher risk of anticholinergic burden. Each analyses were qualitatively similar with consistent main effects of slightly different magnitude. In line with previous literature (e.g. Sumukadas *et al*., 2014) we focus current results on the total anticholinergic burden scores, specifically, on those categorized as having very high anticholinergic burden (ACB 3+) in comparison to either none/moderate burden (ACB <3). Demographics for those adults with very high anticholinergic burden (ACB 3+) can be seen in Table 3.

Table 3. Group descriptives for those adults with very high total anticholinergic burden (ACB 3+) n=6,665/ 17,220

Variable	Category	Total	Intellectual Disabilities	General Population
Population	Total n	6,665	2,088	4,577
Sex	Male	3,451	1,158 (55.5%)	2,293 (50.1%)
	Female	3,214	930 (44.5%)	2,284 (49.9%)
Age	17-24	411	172 (8.2%)	239 (5.2%)
	25-34	929	341 (16.3%)	588 (12.8%)
	35-44	893	302 (14.5%)	591 (12.9%)
	45-54	1,580	456 (21.8%)	1,124 (24.6%)
	55-64	1,438	425 (20.4%)	1,013 (22.1%)
	65-74	950	265 (12.7%)	685 (15.0%)
	75+	464	127 (6.1%)	337 (7.4%)
SIMD (2016)	1-most deprived	3,739	1,091 (52.3%)	2,648 (57.9%)
	2	1,343	427 (20.5%)	916 (20.0%)
	3	816	292 (14.0%)	524 (11.4%)
	4	469	171 (8.2%)	298 (6.5%)
	5-least deprived	298	107 (5.1%)	191 (4.2%)

Demographic factors associated with very high anticholinergic burden

Overall, adults with ID had greater odds of having very high total anticholinergic burden (ACB 3+) OR=1.77 (1.64-1.90), p<0.001 (Supplementary Table 1). The overall model showed each of sex (female), age (older age groups) and neighbourhood deprivation (most deprived SIMD quintile) were significantly associated with having very high total anticholinergic burden (p<0.001). Extending the model to further include two-way interactions between group and each of sex, age category and SIMD, indicated that these were also statistically significant (p<0.001), hence subgroup analyses for the group effect in each were explored (Table 4). As there are 3 controls for each person with ID, in these regressions, adults from the general population contribute more to the findings on sex, age, and SIMD. The interaction subgroup analysis for sex showed that adults with ID had significantly higher odds of having very high anticholinergic burden compared to the general population controls: males OR=2.02 (1.84-2.22), and females; OR=1.48 (1.33-1.65), p<0.001 (Table 4). Adults with ID had significantly higher odds of having very high anticholinergic burden in every age category up to 75, with the greatest group effect occurring in younger ages, 17-24 year olds; OR=3.05 (2.39-3.89) p<0.001 (Table 4) and the extent of the difference decreasing as age increases. This reflects the age-related increase in anticholinergic burden in the general population group, whereas burden is high across all age categories in the intellectual disabilities group. Group differences were present for all neighbourhood deprivation areas, with the extent of the difference widening with increasing affluence of neighbourhood. This shows that very high total anticholinergic burden is prevalent across all neighbourhoods for the adults with ID, whereas there is a steeper gradient for very high total anticholinergic burden in more deprived neighbourhoods for the general population. Group differences were greatest in the SIMD 4 neighbourhood areas; OR=2.62 (2.01-3.40), p<0.001 (Table 4).

Table 4. Subgroup analyses for the effect of group differences within demographic subpopulations for the outcome very high total anticholinergic burden (ACB 3+).

Demographic factor	Model Subpopulation	ID Group Effect OR [95% CI]	p-value
Sex	Males	2.02 [1.84-2.22]	p<0.001
	Females	1.48 [1.33-1.65]	p<0.001
Age category	17-24	3.05 [2.39-3.89]	p<0.001
	25-34	2.33 [1.97-2.77]	p<0.001
	35-44	1.99 [1.66-2.38]	p<0.001
	45-54	1.42 [1.23-1.65]	p<0.001
	55-64	1.56 [1.33-1.84]	p<0.001
	65-74	1.38 [1.11-1.70]	p=0.003
	75+	1.38 [0.98-1.94]	p=0.063
SIMD	SIMD 1–most deprived	1.47 [1.34-1.62]	p<0.001
	2	1.86 [1.58-2.19]	p<0.001
	3	2.59 [2.11-3.18]	p<0.001
	4	2.62 [2.01-3.40]	p<0.001
	SIMD 5–least deprived	2.20 [1.63-2.97]	p<0.001

Models are restricted to only the statistically significant two-way interactions between group and each demographic factor, and are adjusted for other demographic factors with the Odds Ratio (OR) and Confidence Interval (CI) presented for the ID group with general population as the reference group.

Intellectual Disabilities and very high anticholinergic burden

Here we provide novel results examining the association of demographic factors (sex, age, deprivation) with very high anticholinergic burden within the ID group. Females with ID had significantly higher odds of having very high anticholinergic burden compared to males, OR=1.21 (1.07-1.37), p=0.003 (Table 5). Very high burden was associated with older ages, specifically 55-64 OR=1.51 (1.18-1.92), 65-74 OR=1.74 (1.33-2.29) and 75+ OR=2.41 (1.69-3.45), p≤0.001, though notably, this increase with age was much less than that seen in the supplementary table which reflects predominantly the findings in the general population. A gradient was not found across extent of neighbourhood deprivation levels; only the adults with ID living in SIMD 3 had greater odds of having very high anticholinergic burden compared to SIMD 1, OR=1.29 [1.06-1.55], p=0.009.

Table 5. Multivariable analysis of within-group differences in demographic factors associated with very high total anticholinergic burden (ACB 3+) for the intellectual disabilities group only. Overall significance of demographic factors assessed using the Likelihood Ratio test.

Model effect	Overall significance	Variable level	OR [95% CI]	p-value
Sex (ref: Males)	p<0.001	Female	1.21 [1.07-1.37]	p=0.003
Age category (ref: 17-24)	p<0.001	25-34	0.97 [0.76-1.23]	p=0.777
		35-44	1.08 [0.84-1.39]	p=0.532
		45-54	1.17 [0.93-1.49]	p=0.181
		55-64	1.51 [1.18-1.92]	p=0.001
		65-74	1.74 [1.33-2.29]	p<0.001
		75+	2.41 [1.69-3.45]	p<0.001
SIMD (ref: SIMD 1–most deprived)	p=0.010	2	1.11 [0.95-1.31]	p=0.186
		3	1.29 [1.06-1.55]	p=0.009
		4	1.07 [0.85-1.34]	p=0.580
		SIMD 5–least deprived	0.78 [0.60-1.01]	p=0.060

Discussion

As far as we are aware, our study is the first to report on anticholinergic burden in adults with ID of all ages, in comparison with the matched general population. In 2017, adults with ID were almost twice as likely to be prescribed any anticholinergic medication compared to controls from the general population. This was consistently true for medicines of each level of risk category, and for total anticholinergic burden, regardless of sex, age, or extent of neighbourhood deprivation. The adults with ID were frequently prescribed medicines with 'very strong' risk of anticholinergic burden, at more than twice the amount compared to the general population (OR=2.59 [2.39-2.81], p<0.001). Almost half of the adults with ID had very high anticholinergic burden (48.5% compared to 35.4%). Compared to the general population, both sexes with ID were more likely to have very high total anticholinergic burden, with the extent of the difference greater in males OR=2.02 (1.84-2.22), than in females OR=1.48 (1.33-1.65). As expected, total anticholinergic burden increased with age, but to a lesser extent for the ID group, who experienced very high burden at all ages. The level of anticholinergic burden experienced by the youngest adults (17-24 years) was over three times as much as the burden in the general population. This novel and important finding was irrespective of sex or neighbourhood deprivation.

Living in more deprived neighbourhoods was associated with a higher proportion with very high anticholinergic burden for the general population group, but less so for the adults with ID, hence a greater difference is seen between the two groups the more affluent the area. Few people lived in the most affluent area (SIMD 5) and in these most affluent areas the housing stock for people with ID tends to be converted large houses which provide care along the lines of congregate care/group homes rather than

the small supported living (2 or 3 adults with intellectual disabilities sharing a tenancy) which is typical elsewhere in NHS Greater Glasgow & Clyde for adults who have left their parental homes.

Between 2009–2017 more adults with ID were prescribed (any) anticholinergic medication compared to the general population (57.9%, 48.3% respectively). This group difference reduced over the study period, due to a slightly greater rise in anticholinergic prescribing in the general population compared with the adults with ID, but was prominent throughout. This general population increase in anticholinergic prescribing has been reported in both older adults (Sumukadas *et al.*, 2014; Grossi *et al.*, 2020) and more recently in middle-age to older adults (Mur *et al.*, 2020). There are various UK campaigns aimed to optimise pharmacotherapy and to reduce the over-medication of people with ID, advocating systematic medication reviews/deprescribing, particularly for the over-prescription of antipsychotic drugs (which have anticholinergic properties) for problem behaviour (NICE, 2015; Scottish Government Model of Care Polypharmacy Working Group, 2015; Sheehan *et al.*, 2015; National Institute for Clinical Excellence (NICE), 2017; Nabhanizadeh *et al.*, 2019; NHS England, 2019). Despite this, our study shows that adults with ID had 1.14 odds of being prescribed anticholinergic medication in each study year. We are not aware of other studies that have examined such temporal trends.

These results support and extend previous findings from smaller samples of older adults with ID (aged 40+) (O'Dwyer, Maidment, *et al.*, 2016; Axmon *et al.*, 2017; De Vreese *et al.*, 2018). O'Dwyer et al. (2016) reported n=214/736 (29%) and De Vreese et al. (2018) report n=31/276 (11%) adults with ID with very high anticholinergic burden. Combining our older age categories, n=1,273/ 2,418 (53%) had a very high anticholinergic burden, much higher than both these previous studies. However, O'Dwyer categorizes very high anticholinergic burden as 5+, and De Vreese 3+, both with smaller samples in different countries.

Within the ID population, women were 21% more likely than men to experience very high anticholinergic burden regardless of age or deprivation circumstances. Adults with ID aged over 55 years were more likely to have very high anticholinergic burden, but the slope of the gradient is less than that seen in the general population. Extent of neighbourhood deprivation was not associated with very high anticholinergic burden within the ID group, showing that this risk of having high anticholinergic burden is regardless of neighborhood. Regarding sex, whilst our findings support previous evidence from the general population (Sumukadas *et al.*, 2014; Mur *et al.*, 2020), the available ID literature differs. Two previous smaller studies of older populations with ID report no association (O'Dwyer, Maidment, *et al.*, 2016; De Vreese *et al.*, 2018), and Axmon et al. (2017) reports that over the age of 55 years, males were more likely than females with ID to be prescribed anticholinergic medication. Our findings on age are

similar to those in the ID literature, albeit in older populations only (O'Dwyer, Maidment, *et al.*, 2016; Axmon *et al.*, 2017), and in the general population but notably, to a lesser extent (Hanlon *et al*., 2020). Findings on neighbourhood deprivation differ to those seen in the general population; people with ID have high rates of very high total anticholinergic burden regardless of neighbourhood deprivation.

Adults with ID are being exposed to a greater risk of very high anticholinergic burden and the subsequent detrimental effects this can have on their health. The unintended effects of anticholinergic medicines need to be addressed, with individual patient reviews including consideration of anticholinergic burden (Zaal *et al.*, 2016), alternative medications (Hanlon *et al.*, 2015), the role of other alternative interventions such as psychosocial/behavioural interventions for problem behaviours (Hassiotis *et al.*, 2011; Koch, Dobrindt and Schützwohl, 2021), and sleep hygiene for sleep problems (Hanlon *et al*., 2015).

The main strength of this study is the large representative cohort of adults with ID in NHS Greater Glasgow & Clyde of n=4,305, drawn from 73% of all general practices in the area. The use of participant's linked health records provides robust and accurate prescription data for use of medicines with anticholinergic risk. Moreover, we included all ages of adults and, for the first time, have an insight into the anticholinergic medications taken in the younger adult population with ID. A limitation is that the study was conducted in only one part of Scotland and the PIS database does not include those prescriptions dispensed within hospital settings, e.g. the use of clozapine. Additionally, we did not have access to information about the health conditions of people with ID or the general population, and therefore cannot provide detail on the level of multimorbidity in both groups. Undoubtedly, information on multimorbidity, and possibly polypharmacy, would further inform these results on why adults with ID experience such high anticholinergic burden. Finally, there lacks a 'gold standard' for capturing anticholinergic burden and though there is a significant overlap between the various lists used, discrepancies remain. There have been 2 studies assessing up to 10 different anticholinergic burden scales in both middle-aged and older-aged general populations of over 500,000 (Hanlon *et al*., 2020; Salahudeen *et al*., 2015). Each study investigated anticholinergic burden and the associated adverse health outcomes as defined by either hospital admissions, length of stay, and visits to the general practitioner, and a composite score for all-cause mortality and major adverse cardiovascular event. Scores varied between scales used, though all scores derived from each scale was related to adverse health outcomes (Hanlon *et al*., 2020; Salahudeen et al., 2015). The UK Biobank results indicated that the ARS scale (used in the current study) identified approximately 8% of participants as taking any anticholinergic medication, compared to the Anticholinergic Loading Scale which reported 17.6% (Hanlon *et al*., 2020).

In conclusion, younger adults with ID face a threefold difference in their likelihood of experiencing very high anticholinergic burden compared to the general population. Prescriptions of anticholinergic drugs from an early age increases the likelihood of burden across the lifespan, increasing the likelihood of adverse effects on health and reduced quality of life in an already vulnerable cohort. Many of these drugs, particularly psychotropics, are prescibed long-term, so causing chronic anticholinergic effects. There is robust evidence correlating anticholinergic burden to poor health outcomes, with recommendations of avoiding strong anticholinergic medication long-term use in older adults (Samuel, 2015; Grossi *et al.*, 2019), a recommendation which should arguably be in place for those with ID also. Results examining just the ID group showed that women with ID were 21% more likely than men with ID to have very high anticholinergic burden, regardless of age and deprivation. There was no statistically significant effect of neighbourhood deprivation within the ID group, showing that adults with ID face a strong risk of having high anticholinergic burden regardless of their deprivation circumstances. Clinicians undertaking medication reviews need to consider anticholinergic side effects and cumulative burden across concomitant medications, including in young adults with ID, not just older adults, and particularly women. There is greater multimorbidity in adults with ID, but excessive polypharmacy should be kept to a minimum to avoid more cognitive decline, increased risk of mortality, greater dependence for activities of daily living, somnolence and constipation (O'Dwyer, Maidment, *et al.*, 2016), and other anticholinergic side effects. A diagnosed health disorder may require treatment; however, it is important to not cause further impairment and function. Careful prescribing and regular multidisciplinary medication reviews could minimise the adverse effects experienced by adults with ID and reduce anticholinergic burden.

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