Supplementary materials for

Cumulative incidence and severity of adverse drug reactions and associated patient characteristics in older community-dwelling adults attending general practice – a six year prospective cohort study.

The following information supplements that presented in the manuscript main text and is presented as follows: Supplementary Appendix S1) further detail on the study methods; Supplementary Tables S1–S3) further detail on those participants excluded from the study; and Supplementary Tables S4–S6) sensitivity analysis results.

Appendix S1: Methods

The Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) guidelines were adhered to in the conduct and reporting of this study. [27]

Study design and setting

This six-year prospective cohort study was established in 2010 to examine the association between potentially inappropriate prescribing (PIP), patient reported outcomes such as adverse drug reactions (ADRs), and health related quality of life. [28, 29] The cohort includes older (aged ≥70 years) community-dwelling people recruited from 15 general practices in Leinster, Republic of Ireland. Baseline data collection took place in 2010 and subsequent follow-up data collection was conducted in 2012 and 2016. Ethical approval for this study was obtained from the institution's Human Research Ethics Committee (REC) in 2009 under approval reference REC462b. Ethical approval for follow up data collection was granted in 2012 (Wave 2: REC462bb and REC462bbb) and in 2016 (Wave 3: REC1277, REC1277b and REC1277bbb). All participants provided informed consent prior to participating and consented to their data being linked to the national Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) database of dispensed medicines.

Participants

A proportionate stratified random sampling approach was used to recruit patients for participation in this study. [30, 31] Participants were recruited from 15 general practices in the Republic of Ireland, with a total of 4573 patients aged ≥70 years across the 15 practices. From this a proportionate random sample (n=1764) were selected to participate. Following the application of study inclusion criteria a total of 1487 eligible patients were invited to participate. A total of 904 (61% response rate) consented to participate. The study inclusion criteria were (i) aged ≥70 years on 1st January 2010; (ii) in receipt of a valid General Medical Services (GMS) card; and (iii) in receipt of at least one drug. Over 90% of people aged ≥70 years in the Republic of Ireland are in receipt of a

GMS card, which entitles the holder to free public health services (including GP visits) and prescriptions, subject to a maximum co-payment of €15 monthly. At baseline, patients were excluded from this study if they met any of the following criteria (i) receiving palliative care; (ii) cognitive impairment at the level that would impact their ability to complete the outcome measure (defined as Mini Mental State Exam (MMSE) ≤20); (iii) significant hearing/speech/visual impairment; (iv) currently experiencing a psychotic episode; (v) hospitalised long-term, in a nursing home, homeless or in sheltered accommodation; and (vi) recent (<one month) bereavement. Each participant'sGPappliedtheexclusioncriteriaatbaseline to assess eligibility for participation in this cohort study. At baseline, a total of 904 participants met the inclusion criteria and consented to take part in the study. A total of 592 participants completed three waves of data collection. Losses to follow-up are presented in Figure 1 (main text). Those who did not complete three data collection waves were older and prescribed more drug classes. Descriptive statistics for those who completed study follow-up and those excluded are reported in Table S1.

Data collection

Baseline data collection took place in 2010 and subsequent follow-up data collection was conducted in 2012 and 2016. Datacollectioninvolvedreviewoftheparticipant'sGPelectronicmedicalrecord and a detailed self-report patient postal questionnaire completed at baseline that included measures of self-rated health, health-related quality of life, function, mental health and social support. Consent was obtained from participants to link their medical record and questionnaire data with their prescription dispensing information from the national Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) database which contains records of dispensed prescription medications.

Primary outcome

The primary outcomes were ADR occurrence and ADR severity. An ADR is defined by the World Health Organization (WHO) as any noxious, unintended and undesired effect of a drug, excluding

therapeutic failures, intentional and accidental poisoning, and drug abuse. [8] ADRs were recorded over a six-year period by manual review of the GP electronic medical record. Manual chart review is the methodology known as the gold standard for the detection of adverse drug events. [32] Detecting ADRs using this method involved reviewing each participant's individual GP consultations and hospital and other correspondence over the outcome measurement period. An ADR was deemed to have occurred based on the treating GP's record of the ADR with the following documented; drug or drugs implicated, the adverse drug reaction experienced, any outpatient or inpatient hospital treatment or follow-up required, and the action taken by the GP. Drugs associated with each ADR category were classified according to the WHO-ATC classification system, including anatomical main groups (first level) and therapeutic subgroups (second level).

ADR causality was assessed using the following classification system for causality as proposed by the EU pharmacovigilance working parties. [33] All ADRs recorded in this study were
Category A: 'Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable'. ADR severity was assessed using a previously validated classification system as defined by Bates et al. with severity categorised as i) mild (laboratory abnormality or symptom not requiring treatment), ii) moderate (laboratory abnormality or symptom requiring treatment with GP/hospital outpatients or emergency admission to hospital or ADRs resulting in non-permanent disability or iii) severe (laboratory abnormality or symptom that was life-threatening or resulted in permanent disability or death). [34] ADRs were independently rated in terms of severity by an academic pharmacist (AD) and an academic GP (EW). Disagreements in ratings were resolved by discussion of the ratings and consensus.

Explanatory variables / Patient characteristics

Patient characteristics were selected a priori for inclusion in this study based on their inclusion in prior research on this subject. [54, 55] Patient characteristics were recorded at baseline from the GP

electronic medical record (age, sex, deprivation, multimorbidity using the Charlson comorbidity index); through linkage to the HSE-PCRS national database of pharmacy claims for dispensed medicines prescribed by GPs (number of drug classes and medication adherence using the medication possession ratio [MPR]); and from the patient questionnaire (marital status, private health insurance, instrumental activities of daily living using the Vulnerable Elders Survey-13). The Vulnerable Elder's Survey (VES) is a 13 item questionnaire which incorporates patient age, self-rated health, the ability to perform six physical tasks (e.g. handling small objects) and five instrumental activities of daily living (e.g. light housework, managing finances etc.). A VES score ≥3 indicates a higher likelihood of experiencing functional decline in over the next two years compared with those who score ≤2. [35]

Age, deprivation and number of drug classes were examined as continuous variables. Categorical variables were sex (male/female), private health insurance (no/yes), marital status (married / separated or divorced / widowed / never married or single), multimorbidity (Charlson index score=0/ Charlson index score=1/ Charlson index score ≥2), medication adherence (MPR <80%/≥80%), VES (score <3/ score ≥3) and polypharmacy (0-4 drug classes/5-9 drug classes/≥10 drug classes).

Statistical analysis

Descriptive statistics were utilised to describe the study population and the primary outcomes. The cumulative incidence of ADRs was expressed as the proportion of participants who experienced at least one ADR over the six year study period (2010-2016). Differences in participant characteristics at baseline were explored using Mann-Whitney U test for non-normally distributed continuous variables and the Chi-square test of independence for categorical variables. Unadjusted and adjusted logistic regression analyses were utilised to investigate the association between patient characteristics at baseline and the primary outcome ADR occurrence (any ADR versus none over six years follow-up 2010-2016). Unadjusted and adjusted odds ratios (ORs), 95% confidence intervals [CIs] and p-values were calculated and reported. Correlations between patient characteristics were

assessed to ensure that correlated characteristics were not both included in the multivariable model. Complete cases were included for all analyses. Stata version 15 (Stata Corporation, College Station, Texas, USA) was utilised for all analyses.

Sensitivity analysis

A sensitivity analysis was conducted by examining the ADR occurrence between 2010 and 2016 among those participants with at least two years of follow-up data (n=816). For the sensitivity analysis 168 participants had a minimum of two years of follow-up data but less than six years of follow up data and 592 participants had six years of follow-up data. A follow up duration of two years was imputed for an additional 56 cases known to have dropped out at Wave 3 but had data missing for exact date of loss to follow-up. As the follow-up duration varied for participants in the sensitivity sample the cumulative incidence of ADRs over six years could not be determined. For the sensitivity sample the proportion of participants who experienced at least one ADR using the total number of participants in the sensitivity sample (n=816) as the denominator is reported. Both the unadjusted and adjusted logistic regression models controlled for length of follow-up (years).

Participants excluded from the primary analyses (2010-2016)

As indicated in Figure 1 (main text) a total of 312 participants were excluded between 2010 and 2016. Eighty-eight participants were excluded at Wave 2 and 224 participants were excluded at Wave 3. Descriptive statistics for those who completed the study and those excluded are presented in Table S1. Those who were excluded were older and prescribed more drug classes. A greater proportion of those excluded reported ≥2 comorbidities, as calculated using the Charlson comorbidity index and more likely to experience functional decline (VES≥3) compared with those who completed the study.

Table S1. Descriptive characteristics at baseline for those who completed the study and those excluded.

	Study completion n=592	Excluded n=312	Full cohort n=904	
	median (IQR)	**median (IQR)**	**median (IQR)**	***p***
Age (years)	75 (73, 79)	80 (76, 84)	77 (73, 81)	<0.001 **
Deprivation – patient	1.37 (-0.64, 2.88)	1.75 (-0.57, 3.38)	1.49 (-0.64, 3.04)	0.15
Number of drug classes	5 (3, 7)	6 (4, 9)	6 (3, 8)	<0.001 **
	n (%)	**n (%)**	**n (%)**	***p***
Sex, female	322 (54.4)	167 (53.5)	489 (54.1)	0.80
Male	270 (45.6)	145 (46.5)	415 (45.9)	
Private health insurance	276 (46.6)	119 (38.1)	395 (43.7)	0.01*
Marital status[‡], married	292 (49.3)	111 (35.6)	403 (44.6)	<0.001 **
separated and/or divorced	30 (5.1)	15 (4.8)	45 (5.0)	
Widowed	175 (29.6)	118 (37.8)	293 (32.4)	
never married and/or single	94 (15.9)	68 (21.8)	162 (17.9)	
Charlson comorbidity index[†], 0	315 (53.2)	132 (42.3)	447 (49.4)	0.001*
1	151 (25.5)	82 (26.3)	233 (25.8)	

≥2	125 (21.1)	97 (31.1)	222 (24.6)	
Medication adherence, MPR ≥80%^	374 (63.2)	218 (69.9)	592 (65.5)	0.07
VES ≥3	172 (29.1)	179 (57.4)	351 (38.8)	<0.001 **
Polypharmacy, 0-4 drugs classes	252 (42.6)	94 (30.1)	346 (38.3)	<0.001 **
5-9 drug classes	287 (48.5)	143 (45.8)	430 (47.6)	
≥10 drug classes	53 (9.0)	75 (24.0)	128 (14.2)	

Note. IQR= inter-quartile range; MPR=medication possession ratio; VES= Vulnerable Elders Survey; ‡= missing data (n=1); †= missing data (n=2); ^= missing data (n=49); *p <0.05; **p <0.001; p values obtained from Mann-Whitney U test (continuous variables with non-normal distribution) and Chi-square tests of independence for categorical variables

Among the 312 excluded participants, a total of 54 ADRs were recorded for 45 study participants. Six ADRs were recorded for five participants at Wave 2 and 48 ADRs were recorded for 40 participants at Wave 3. A total of 37 participants reported one ADR, seven participants experienced two ADRs and one participant experienced three ADRs. The drug classes most commonly implicated in ADRs among excluded participants included drugs for the cardiovascular system, drugs for the nervous system and drugs for the alimentary tract and metabolism (Table S2).

Table S2. Drug classes implicated in ADRs experienced by excluded participants according to the WHO-ATC classification system (n=45 study participants).

	WHO-ATC classes implicated in ADRs	Number of ADRs	% all ADRs
A	**Alimentary tract and metabolism**	**9**	**16.67**
A02	Drugs for acid related disorders	5	9.26
A03	Drugs for functional gastrointestinal disorders	1	1.85
A10	Drugs used in diabetes	3	5.56
B	**Blood and blood forming organs**	**4**	**7.41**
B01	Antithrombotic agents	3	5.56
B03	Antianaemic preparations	1	1.85
C	**Cardiovascular system**	**11**	**20.37**
C01	Cardiac therapy	1	1.85

C02	Antihypertensives	2	3.70
C08	Calcium channel blockers	3	5.56
C09	Agents acting on the renin-angiotensin system	3	5.56
C10	Lipid modifying agents	2	3.70
G	**Genito urinary system and sex hormones**	**1**	**1.85**
G04	Urologicals	1	1.85
H	**Systemic hormonal preparations, excl. sex hormones and insulins**	**1**	**1.85**
H03	Thyroid therapy	1	1.85
J	**Antiinfectives for systemic use**	**7**	**12.96**
J01	Antibacterials for systemic use	7	12.96
L	**Antineoplastic and immunomodulating agents**	**3**	**5.56**
L01	Antineoplastic agents	3	5.56
M	**Musculo-skeletal system**	**6**	**11.11**
M01	Antiinflammatory and antirheumatic products	3	5.56
M05	Drugs for treatment of bone diseases	3	5.56
N	**Nervous system**	**9**	**16.67**
N02	Analgesics	4	7.41
N03	Antiepileptics	1	1.85
N05	Psycholeptics	1	1.85
N06	Psychoanaleptics	3	5.56
P	**Antiparasitic products, insecticides and repellents**	**1**	**1.85**
P01	Antiprotozoals	1	1.85
R	**Respiratory system**	**2**	**3.70**
R03	Drugs for obstructive airways disease	1	1.85
R06	Cough and cold preparations	1	1.85

Regarding ADR severity among those excluded, 36 ADRs (66.6%) were classified as mild, 11 (20.4%) as moderate, and 7 (13%) as severe. One ADR, classified as moderate, resulted in an outpatient appointment and 17 ADRs (four mild, six moderate and seven severe) resulted in an emergency hospital admission. No ADRs resulting in death were detected. The breakdown of ADR severity by reason for exclusion is presented in Table S3.

Table S3. ADR severity categorised by reason for exclusion.

Severity	Death	Moved GP	Nursing home admission	Long stay inpatient
Mild	27	4	4	0
Moderate	7	2	1	1
Severe	5	0	2	0

Note. One ADR classified as mild recorded for one participant who had missing data for reason for loss to follow-up.

Those who were excluded from the main analysis (n=312) were less likely to experience an ADR over the six year period than those that completed to follow-up (OR= 0.46, 95% CI 0.32 to 0.66, p<0.001). Of the 312 participants excluded from the main analysis, 45 participants (14.4%) experienced an ADR over 1-5 years follow-up, compared with 26.9% of the main sample (n= 592) over six years.

Sensitivity analysis results

Sensitivity analysis was conducted by examining ADR occurrence between 2010 and 2016 among those not excluded at Wave 2 (n=816; an additional 224 participants) and who thus provided at least two years of follow-up data (See Figure 1, main text). Descriptive statistics for those participants who were excluded at Wave 2 and those included in the sensitivity analyses are presented in Table S4. The median number of drug classes prescribed in the sensitivity sample was 6 (Interquartile range [IQR] 3 to 8). A total of 501 (61.4%) participants experienced polypharmacy (≥5 drug classes) and 108 (13.2%) experienced major polypharmacy (≥10 drug classes).

Table S4. Descriptive characteristics at baseline for the sensitivity analysis sample and those excluded.

	Sensitivity analysis sample n=816	Excluded at Wave 2 n=88	Full cohort n=904	
	median (IQR)	**median (IQR)**	**median (IQR)**	***p***
Age (years)	76 (73, 80)	80 (76, 85)	77 (73, 81)	<0.001**
Deprivation – patient	1.46 (-0.64, 3.04)	1.72 (-0.68, 3.31)	1.49 (-0.64, 3.04)	0.97
Number of drug classes	6 (3, 8)	6 (4, 9)	6 (3, 8)	0.05
	n (%)	**n (%)**	**n (%)**	***p***
Sex, female	445 (54.5)	44 (50.0)	489 (54.1)	0.42
Male	371 (45.5)	44 (50.0)	415 (45.9)	
Private health insurance	365 (44.7)	30 (34.1)	395 (43.7)	0.06
Marital status[‡], married	373 (45.7)	30 (34.1)	403 (44.6)	0.15
separated and/or divorced	41 (5.0)	4 (4.5)	45 (5.0)	
Widowed	256 (31.4)	37 (42.0)	293 (32.4)	
never married and/or single	145 (17.8)	17 (19.3)	162 (17.9)	
Charlson comorbidity index[†], 0	413 (50.6)	34 (38.6)	447 (49.4)	<0.001*
1	216 (26.5)	17 (19.3)	233 (25.8)	

≥2	186 (22.8)	36 (40.9)	222 (24.6)	
Medication adherence^, MPR ≥80%	527 (64.6)	65 (73.9)	592 (65.5)	0.13
VES ≥3	301 (36.9)	50 (56.8)	351 (38.8)	<0.001**
Polypharmacy, 0-4 drug classes	315 (38.6)	31 (35.2)	346 (38.3)	0.05
5-9 drug classes	393 (48.2)	37 (42.0)	430 (47.6)	
≥10 drug classes	108 (13.2)	22 (22.7)	128 (14.2)	

Note: IQR= inter-quartile range; MPR=medication possession ratio; VES= Vulnerable Elders Survey; ‡= missing data (n=1); †= missing data (n=2); ^= missing data(n=49); *p <0.05; **p <0.001; p values obtained from Mann-Whitney U test (continuous variables with non-normal distribution) and Chi-square tests of independence for categorical variables

Those who dropped out at Wave 2 (n=88) were less likely to experience an ADR compared with those retained in the sensitivity sample (n=816), OR=0.19, 95%CI 0.08, 0.47, p=0.001.

Baseline descriptive statistics are presented for those with and without the primary outcome of ADR within the sensitivity sample in Table S5. Those who experienced at least one ADR were prescribed more drug classes. Sex differences were also observed with more females than males experiencing at least one ADR.

Table S5. Descriptive characteristics at baseline for those with and without an ADR in the sensitivity analysis sample (n=816).

	Without ADR n=617	With ADR n=199	Full sensitivity sample n=816	
	median (IQR)	**median (IQR)**	**median (IQR)**	***p***
Age (years)	76 (73, 80)	76 (73, 80)	76 (73, 80)	0.62
Deprivation – patient	1.36 (-0.65, 2.88)	1.75 (-0.20, 3.31)	1.46 (-.064, 3.04)	0.04*
Number of drug classes	5 (3, 8)	7 (4, 9)	6 (3, 8)	<0.001**
	n (%)	**n (%)**	**n (%)**	***p***
Sex, female	311 (50.4)	134 (67.3)	445 (54.5)	<0.001**

male	306 (49.6)	65 (32.7)	371 (45.5)	
Private health insurance	279 (45.2)	86 (43.2)	365 (44.7)	0.62
Marital status[†], married	292 (47.3)	81 (40.7)	373 (45.7)	0.02*
separated and/or divorced	33 (5.3)	8 (4.0)	41 (5.0)	
widowed	176 (28.5)	80 (40.2)	256 (31.4)	
never married and/or single	115 (18.6)	30 (15.1)	145 (17.8)	
Charlson comorbidity index[†], 0	321 (52.0)	92 (46.2)	413 (50.6)	0.35
1	158 (25.6)	58 (29.1)	216 (26.5)	
≥2	137 (22.2)	49 (24.6)	186 (22.8)	
Medication adherence[^], MPR ≥80%	397 (64.3)	130 (65.3)	527 (64.6)	0.54
VES ≥3	214 (34.7)	87 (43.7)	301 (36.9)	0.02*
Polypharmacy, 0-4 drug classes	265 (42.9)	50 (25.1)	315 (38.6)	<0.001**
5-9 drug classes	284 (46.0)	109 (54.8)	393 (48.2)	
≥10 drug classes	68 (11.0)	40 (20.1)	108 (13.2)	

Note: IQR= inter-quartile range; MPR=medication possession ratio; VES= Vulnerable Elders Survey; [†]= missing data (n=1); [^]= missing data(n=46); *p <0.05; **p <0.001; p values obtained from Mann-Whitney U test (continuous variables with non-normal distribution) and Chi-square tests of independence for categorical variables

A total of 259 ADRs were recorded for 199 participants in the sensitivity sample, thus 24.4% of participants experienced at least one ADR between 2010 and 2016. A total of 43 (5.3%) participants experienced more than one ADR as follows: n=31 experienced two ADRs, n=8 experienced three ADRs, n=3 experienced four ADRs, and n=1 experienced five ADRs. The breakdown of ADRs by severity in the sensitivity analysis sample was as follows: n=224 (86.5%) classified as mild, n=31 (12%) as moderate, and n=4 (1.5%) as severe. No ADRs resulting in death were recorded. Four ADRs resulted in an outpatient appointment (two mild and two moderate) and 19 ADRs resulted in a hospital admission (four mild, eleven moderate and four severe).

Unadjusted and adjusted logistic regression analysis results are presented in Table S6. Both the unadjusted and adjusted logistic regression models controlled for length of follow-up (years). Unadjusted associations were observed for sex, marital status, deprivation, Charlson comorbidity score, VES score, and polypharmacy. In the adjusted model female sex (OR=1.68, 95% CI 1.14, 2.47, *p*=0.009) and deprivation (OR=1.09, 95% CI 1.01, 1.17, *p*=0.03) were associated with an increased likelihood of experiencing an ADR. Those with polypharmacy (5-9 drug classes: OR=1.87, 95% CI 1.24, 2.82, *p*=0.003) and major polypharmacy (≥10 drug classes: OR=2.72, 95% CI 1.50, 4.93, *p*=0.001) also had an increased likelihood of experiencing an ADR.

Table S6. Unadjusted (N=816) and adjusted (N=768) logistic regression for at least one ADR in the sensitivity analysis sample (2010-2016).

Characteristics	Unadjusted[¶]		Adjusted[¶]	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	1.01 (0.98, 1.05)	0.47	0.98 (0.94, 1.02)	0.26
Deprivation	1.07 (1.01, 1.14)	0.03*	1.09 (1.01, 1.17)	0.03*
Female sex	2.06 (1.47, 2.89)	<0.001**	1.68 (1.14, 2.47)	0.009*
Private health insurance	0.90 (0.65, 1.24)	0.52	1.30 (0.88, 1.91)	0.19
Medication adherence, MPR ≥80%[^]	0.91 (0.64, 1.28)	0.58	0.82 (0.57, 1.18)	0.28
Marital status[†]		<0.002**		
Separated/divorced	0.92 (0.41, 2.09)	0.84	0.73 (0.31, 1.70)	0.46
Widowed	1.74 (1.21, 2.51)	0.003*	1.36 (0.88, 2.08)	0.16
Never married/single	1.03 (0.64, 1.65)	0.92	0.97 (0.58, 1.62)	0.90
Charlson comorbidity[‡]		0.002*		
1	1.34 (0.91, 1.97)	0.13	1.12 (0.74, 1.70)	0.59
≥2	1.31 (0.88, 1.97)	0.19	1.13 (0.72, 1.78)	0.59
VES ≥3	1.75 (1.25, 2.46)	0.001*	1.31 (0.87, 1.97)	0.20
Polypharmacy[§]		<0.001**		
5-9 drug classes	2.15 (1.48, 3.14)	<0.001**	1.87 (1.24, 2.82)	0.003*
≥10 drug classes	3.98 (2.38, 6.67)	<0.001**	2.72 (1.50, 4.93)	0.001*

Note. [^]missing data for 46 cases; [†]referent married, missing data for one case; [‡] referent 0, missing data for one case ; [§] referent 0-4 drug classes; [¶] model controlled for number of years of follow-up; *p <0.05; **p <0.001