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ORIGINAL RESEARCH ARTICLE

Prevalence and Factors Associated with Potential Drug-Drug Interactions in Older Community-Dwelling Adults: A Prospective Cohort Study

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Abstract

Background Older patients are at increased risk of drug-drug interactions (DDIs) due to polypharmacy. Cardiovascular and central nervous system (CNS) drugs are commonly implicated in serious DDIs.

Objectives This study aimed to determine the prevalence and factors associated with potential 'severe' cardiovascular and CNS DDIs among older (≥ 70 years) community-dwellers.

Methods This was a prospective cohort study using linked data from a national pharmacy claims database and waves 1 and 2 of The Irish LongituDinal study on Ageing (TILDA). 'Severe' cardiovascular and CNS DDIs were identified using the British National Formulary 77 and Stockley's Drug Interactions. The prevalence of 'severe' DDIs (any DDI vs. none) was calculated. Logistic regression was used to examine the association between sociodemographic, functional ability, and medication-related factors and the risk of DDI exposure between waves 1 and 2.

Results A total of 1466 patients were included [mean age (standard deviation) = 78 (5.5) years; female $n = 795$, 54.2%]. In total, 332 community-dwellers aged ≥ 70 years [22.65%, 95% confidence interval (CI) 20.58–24.86] were potentially exposed to at least one 'severe' cardiovascular or CNS DDI, with more than half (54.82%) of this cohort dispensed the same DDI for a prolonged time (≥ 3 consecutive claims). Aspirin-warfarin was the most frequently dispensed (co-prescribed) DDI ($n = 34$, 10.24%, 95% CI 7.39–14.00), followed by atorvastatin-clarithromycin ($n = 19$, 5.72%, 95% CI 3.64–8.81). Polypharmacy [≥ 10 vs. < 5 drugs, odds ratio (OR) 13.40, 95% CI 8.22–21.85] and depression (depressed vs. not, OR 2.12, 95% CI 1.34–3.34) were significantly associated with these DDIs, after multivariable adjustment.

Conclusion 'Severe' cardiovascular and CNS DDIs are prevalent in older community-dwellers in Ireland, and those with polypharmacy and depression are at a significantly increased risk.

1 Introduction

Ageing populations lead to an increased burden of chronic diseases and rising polypharmacy (five or more regular medicines prescribed) associated with an increased risk of medication-related harm amongst older people [1–3]. In Ireland, the proportion of adults aged ≥ 65 years with polypharmacy increased from 17.8% to 60.4% between 1997 and 2012 [4]. Studies in Europe, the USA, and New Zealand, all report similar trends, with the prevalence of polypharmacy in older people increasing over time [3]. Although polypharmacy may be required to manage some patients' morbidity, the use of multiple medications increases an individual's risk of potential adverse effects of medicines, including drug-drug interactions (DDIs) [2, 5]. A DDI is said to occur when the effect of one drug is altered by the use of another

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Key Points

We present a novel, evidence-based methodology to identify 'severe' drug-drug interactions (DDIs) that may result in adverse health outcomes.

In our study, approximately one-quarter of older (≥ 70 years) participants were potentially exposed to at least one 'severe' cardiovascular or central nervous system DDI. Polypharmacy and depression were significantly associated with potential exposure to these DDIs.

Older adults dispensed warfarin, escitalopram, atorvastatin, furosemide, or clarithromycin had the highest burden of potential exposure to multiple DDIs examined. These older patients should be the focus of medication review/optimisation interventions.

drug [6]. DDIs are an example of an avoidable cause of patient harm, and older patients are particularly vulnerable to potential DDIs due to age-related physiological changes in pharmacokinetic and pharmacodynamic parameters [7, 8]. Cardiovascular and central nervous system (CNS) drugs are reported to be commonly implicated in potentially serious DDIs [9].

The prevalence of potential DDIs in older populations has been shown to vary widely across different settings, ranging from 1.5% to 47.4% in population-based studies [10]. A study of 1601 older outpatients from six European countries found that 46% of patients had at least one potential DDI, and almost 10% of these interactions were classified as combinations that should be avoided [11]. Another study, including 287,074 Australian veterans, found that 1.5% of patients were dispensed potentially hazardous DDIs [12]. The large variation in the prevalence of DDIs is due in part to the range of methods used to define a DDI, the classification of DDIs (i.e. potential, clinically significant, etc.), and the databases and information sources used [7, 13]. Some studies have used lists of all potentially clinically relevant DDIs [14, 15], whereas others have used interaction databases relevant to their specific country [16–18], DDI software [12, 19], or have applied explicit measures of potentially inappropriate prescribing (PIP) such as Beers criteria, which only measures a limited number of specific DDIs [20]. In order to be able to measure and compare rates of DDIs accurately, studies need to reach consensus on measures of DDIs that are clinically significant and relevant to practice.

Investigating factors associated with DDIs in older populations will help inform healthcare professionals in clinical practice and will identify older people at risk of medication-related harm. A number of studies have reported increasing age, multimorbidity, and polypharmacy as potential risk factors for DDIs [9, 18, 21, 22]. Other age-related factors may also contribute to this risk, including sociodemographic factors (e.g. gender and ethnicity), clinical and treatment factors, prescriber factors, and healthcare system factors [7, 20]. However, further research is required to understand the relationship between these factors and the risk of DDIs. The aim of this study is to determine the prevalence of and factors associated with potential 'severe' cardiovascular and CNS DDIs in a cohort of community-dwelling older adults aged ≥ 70 years in Ireland.

2 Methods

The STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the reporting of this study [23].

2.1 Study Population

This was a prospective population-based cohort study using data from a national pharmacy claims database, the Health Service Executive–Primary Care Reimbursement Service (HSE-PCRS) General Medical Services (GMS) scheme, linked to waves 1 and 2 of The Irish LongituDinal study on Ageing (TILDA). TILDA is a nationally representative sample of community-dwelling individuals aged ≥ 50 years in Ireland. Wave 1 (October 2009–February 2011) and wave 2 (April 2012–January 2013) data were collected using computer-aided personal interviews, self-completed questionnaires, and nurse-led health assessments measuring participants' health, economic, and social circumstances (N = 8175 participants aged ≥ 50 years). The sampling framework is described in detail elsewhere [24].

The HSE-PCRS GMS scheme provides free health services, including subsidised medications, to eligible persons in Ireland (~ 40% of the population) [25]. Automatic entitlement for those aged ≥ 70 years occurred between July 2001 and December 2008; however, in January 2009, means testing was introduced, but with a higher income threshold than that required for the population < 70 years. As of 2013, 90% of men and 94% of women in the general population aged ≥ 70 years were eligible, representing a unique population-based resource [25]. Within the HSE-PCRS GMS pharmacy claims database, prescriptions are coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, and prescriber information, defined daily doses, strength, quantity, and the method and unit of administration of each drug dispensed are all available. TILDA participants with GMS eligibility were asked to provide consent to link their pharmacy claims data to study data. Pharmacy claims data were extracted for TILDA participants aged ≥ 70 years

with GMS eligibility for the period between wave 1 and wave 2 interview dates. To be included in this study, participants were required to have at least two medicines (distinct ATC codes) on any pharmacy claim during the time period. Ethical approval for TILDA was granted by the Faculty of Health Sciences Ethics Committee, Trinity College Dublin.

2.2 Identification of Potential DDIs

Two pharmaceutical references commonly used in current practice, the British National Formulary (BNF) and Stockley's Drug Interactions [6, 26], were used to identify DDIs that could potentially cause an adverse event for the cardiovascular system and CNS. These two physiological systems were considered as they have been shown to have the highest prevalence of potential DDIs in older people [9]. A list of all the cardiovascular and CNS drugs within chapters 2 and 4, respectively, of the BNF 77 was developed by consensus between two pharmacists (JH and VR) (see the electronic supplementary material, Supplementary file 1). 'Severe' cardiovascular and CNS DDIs were identified using the BNF 77 and cross-referenced with Stockley's Drug Interactions (online database). 'Severe' cardiovascular and CNS DDIs were DDIs classified as being both 'severe' (i.e. the result may be a life-threatening event or have a permanent detrimental effect) per the BNF 77 and also as being 'a life-threatening or contraindicated combination' (red warning) or 'dosage adjustment or close monitoring is needed' (orange warning) per Stockley's. All other DDIs were excluded (Fig. 1). A similar method of identifying DDIs by comparing internationally recognised criteria has been used in previous research [12]. The final list of 'severe' cardiovascular and CNS DDIs contained details of the cardiovascular and CNS drug names, corresponding ATC codes, and the interacting drugs and their ATC codes (Supplementary file 2). Using this list, medication dispensing data for all TILDA participants aged ≥ 70 years with GMS eligibility for the period between wave 1 and wave 2 interview dates were examined for potential 'severe' cardiovascular and CNS DDIs.

2.3 Factors Associated with Potentially 'Severe' DDIs

A number of factors associated with DDIs were identified from previous studies and included the following: (1) sociodemographic-related factors; (2) functional ability-related factors (geriatric syndromes); and (3) medication-related factors [9, 18, 20–22, 27, 28]. Sociodemographic factors included age and gender, marital status (currently married/cohabiting vs. not), education, and smoking status. Education was stratified into primary/none, secondary, and third/higher level education. Smoking status was stratified as never smoked, past smoker, and current smoker. Functional ability-related factors (geriatric syndromes) included the

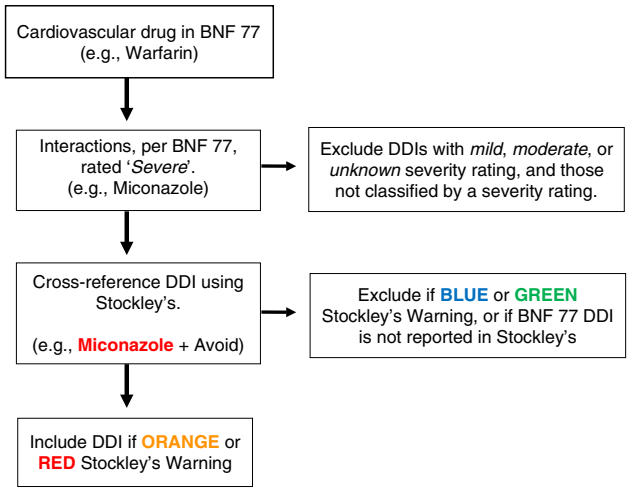

Fig. 1 Identification of 'severe' DDIs using BNF 77 and Stockley's Drug Interactions. *Red DDIs*: a life-threatening or contraindicated combination; *orange DDIs*: dosage adjustment or close monitoring is needed; *blue DDIs*: give guidance about possible adverse effects and/or consider some monitoring; *green DDIs*: no interactions or no interaction of clinical significance. *BNF* British National Formulary, *DDI* drug-drug interaction

number of chronic conditions, frailty, depression, and poor delayed recall [27]. Number of chronic conditions was determined using participant's self-reported doctor-diagnosed chronic diseases (categorised as 0, 1, 2, or ≥ 3) from TILDA data. Frailty was measured using a frailty index adapted to the TILDA cohort, which classifies participants as robust, pre-frail, or frail [29, 30]. Depression was defined as scoring 16 or greater on the Centre for Epidemiologic Studies Depression Scale (CES-D) [31]. Delayed recall (none vs. poor), based on participants being presented with ten words during the interview and being later asked to recall as many as possible, was defined as poor where participants recalled three or fewer words. Medication-related risk factors included polypharmacy [14, 28], which was defined as the number of regular medicines at ATC level 3 dispensed in at least 3 consecutive months, per participant during the study period. It was stratified into three levels: no polypharmacy (0–4 drugs), polypharmacy (5–9 drugs), and excessive polypharmacy (≥ 10 drugs) [32].

2.4 Statistical Methods

2.4.1 Prevalence of 'Severe' DDIs

The frequency and prevalence of 'severe' DDIs (any DDI vs. none) was calculated for TILDA participants aged ≥ 70 years with GMS eligibility for the period between wave 1 and wave 2. 95% confidence intervals (CIs) for DDI prevalence, estimated using the Agresti-Coull method, are presented. Two different dispensing patterns were used to define

DDIs: (1) drug combinations dispensed on the same day (same date of claim, i.e. co-prescribed); and (2) drug combinations dispensed within 7 days of each other (± 7 days of date of claim). The number of acute DDIs (DDI occurred for a period of less than three consecutive prescription claims) and chronic DDIs (same DDI continued for three or more consecutive prescription claims) were also calculated per number of TILDA participants [33]. The drug combinations involved in the most frequently reported DDIs per dispensing pattern (co-prescribed, ± 7 days of date of claim, acute/chronic) and the potential effect and action required per the BNF 77 and Stockley's are presented. The drugs that were most frequently implicated in the 'severe' DDIs examined in this study were also identified, and the proportion of participants who experienced DDIs with these drugs was calculated per individual drug combination.

2.4.2 Factors Associated with 'Severe' DDIs

Baseline risk factors from wave 1 of TILDA were used to predict an individual's risk of exposure to a 'severe' cardiovascular and/or CNS DDI. Descriptive statistics including means [standard deviation (SD)], medians [inter-quartile range (IQR)], and proportions were calculated for all factors. Univariate and multivariate logistic regression was used to examine the association between the factors identified in wave 1 interviews and the risk of any DDI during the time period between wave 1 and wave 2 of TILDA (approximately 2 years). Unadjusted and adjusted odds ratios (ORs) and 95% CIs are presented. Multivariable negative binomial regression was also used to investigate the association between the factors and the number of DDIs experienced by participants during the time period between wave 1 and wave 2 of TILDA. Incidence rate ratios (IRRs) and 95% CIs are presented. The data were analysed using SAS version v9.4 statistical package and Stata version 14.0 (StataCorp, College Station, TX, USA).

3 Results

3.1 Study Population

We identified $n = 1506$ TILDA participants aged ≥ 70 years with GMS eligibility. In total, following exclusion of ineligible participants, $n = 1466$ participants aged ≥ 70 years were included in this cohort study. The mean age was 78 years (SD = 5.53), and $n = 849$ (57.91%) were aged ≥ 75 years. The majority of participants were female ($n = 795$, 54.23%) and married ($n = 805$, 54.91%). On average each participant had 23 (median = 25, IQR 17–30) claims over the period between wave 1 and wave 2.

3.2 Prevalence of 'Severe' DDIs per Number of TILDA Participants

3.2.1 DDIs: Medications Co-prescribed (Same Claim Date)

The overall prevalence of co-prescribed 'severe' cardiovascular and CNS DDIs in the cohort of 1466 participants was 22.65% (95% CI 20.58–24.86) ($n = 332$); 222 participants (15.14%) had one DDI co-prescribed, 67 (4.57%) had two or more DDIs co-prescribed, and 43 (2.93%) had three or more DDIs co-prescribed. Of the cohort exposed to one or more 'severe' DDIs, this included 176 (87.6%) 'orange' co-prescribed DDIs and 25 (12.4%) 'red' co-prescribed DDIs. Table 1 describes the prevalence and interaction effect for the top ten most frequently dispensed (co-prescribed) 'severe' DDIs per participant. Aspirin-warfarin was the most frequently dispensed DDI per participant ($n = 34$, 10.24%), followed by atorvastatin-clarithromycin ($n = 19$, 5.72%) and aspirin-nicorandil ($n = 15$, 4.52%).

3.2.2 DDIs: Medications Dispensed Within 7 Days of Each Other

The overall prevalence of DDIs in the cohort per medications dispensed within 7 days of each other was 25.92% (95% CI 23.74–28.23) ($n = 380$); 242 participants (16.51%) had one DDI, 75 (5.12%) had two or more DDIs, and 63 (4.30%) had three or more DDIs. Among the cohort exposed to one or more 'severe' DDIs involving medications dispensed within 7 days of each other, this included 189 (86.3%)'orange' DDIs and 30 (13.7%)'red' DDIs. The ten most frequently dispensed 'severe' DDIs involving medications dispensed within 7 days of each other per participant were similar to the drug combinations for co-prescribed DDIs, but also included the medications furosemide, pravastatin, and lercanidipine, each potentially interacting with clarithromycin (Table 2).

3.2.3 Acute and Chronic DDIs: Medications Co-prescribed (Same Claim Date)

Of the 332 participants co-prescribed a DDI, 182 participants (54.82%) were dispensed the same DDI for three or more consecutive claims (chronic DDI), while 150 participants (45.18%) were dispensed the same DDI for fewer than three consecutive claims (acute DDIs). Aspirin-warfarin was again the most frequently dispensed co-prescribed chronic ($n = 14$, 7.69%) and acute ($n = 20$, 13.33%) DDI per participant. The prevalence of all 'severe' cardiovascular and CNS *chronic* DDIs dispensed (*co-prescribed*) is presented in Supplementary Table S1.

Table 1 A description of the prevalence and interaction effect for the 10 most frequently dispensed (co-prescribed) 'severe' DDIs per number of TILDA participants

DDI	Prevalence per TILDA participants ($N = 332$)		BNF 77		Stockley's Drug Interactions			
	N (%)	95% CI	Interaction effect	Evidence	Interaction effect	Evidence	Action	Warning
Aspirin and warfarin[†]	34 (10.24)	[7.39–14.00]	Warfarin is predicted to increase the risk of bleeding events when given with aspirin. Manufacturer advises use with caution or avoid	Theoretical	Low-dose aspirin (75–325 mg daily) increases the risk of bleeding when given with warfarin. High doses of aspirin (4 g daily or more) can also increase prothrombin times in patients taking warfarin	Extensive	Avoid high-dose aspirin. If low-dose aspirin is indicated, monitor for signs of bleeding. Consider giving gastroprotection (e.g. a proton pump inhibitor) to at-risk patients	
Atorvastatin and clarithromycin	19 (5.72)	[3.64–8.81]	Clarithromycin is predicted to increase the exposure to atorvastatin. Manufacturer advises avoid or adjust dose and monitor rhabdomyolysis	Study	Clarithromycin moderately increases atorvastatin exposure. Rhabdomyolysis has been reported in patients taking atorvastatin with a macrolide	Study	Temporarily withhold the statin or, if necessary, give the lowest possible statin dose. Warn patients to report any unexplained muscle pain or weakness. Caution with atorvastatin dosages greater than 20 mg daily (UK). Maximum atorvastatin dosage of 20 mg daily (US)	
Aspirin and nicorandil	15 (4.52)	[2.70–7.38]	Aspirin is predicted to increase the risk of gastrointestinal perforation when given with nicorandil. Manufacturer advises caution	Theoretical	The manufacturer of nicorandil notes that there might be an increased risk of gastrointestinal ulceration, perforation, and haemorrhage on current use of aspirin and nicorandil	Theoretical	Caution is advised, and it would seem prudent to monitor for adverse gastrointestinal effects on concurrent use	
Warfarin and rosuvastatin	15 (4.52)	[2.70–7.38]	Rosuvastatin increases the anticoagulant effect of warfarin. Manufacturer advises monitor INR and adjust dose	Study	Rosuvastatin causes a clinically significant increase in the INR of patients taking warfarin, and cases of bleeding have been reported	Study	Increased INR monitoring is required when starting or stopping the statin, or changing the dose	
Escitalopram and omeprazole	14 (4.22)	[2.47–7.01]	Omeprazole slightly to moderately increases the exposure to escitalopram. Manufacturer advises monitor and adjust dose	Study	Omeprazole slightly to moderately increases the exposure to escitalopram, which might increase the risk of QT-interval prolongation	Study	Until more is known, be alert for an increase in escitalopram adverse effects (such as nausea, diarrhoea, dry mouth, palpitations), decreasing the dose of escitalopram if these become troublesome. Increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation	
Amiodarone hydrochloride and warfarin	13 (3.92)	[2.24–6.65]	Amiodarone increases the anticoagulant effect of warfarin. Manufacturer advises monitor INR	Study	Amiodarone increases the anticoagulant effects of warfarin, and bleeding might occur. The interaction is dose-dependent, with higher amiodarone doses having a greater effect. Onset occurs within a few days, is maximal within 2–7 weeks, and might persist for several months after the amiodarone has been withdrawn	Extensive	Monitor INR at least weekly, until a new steady state is achieved, and for several weeks after amiodarone is stopped. Warfarin dose reductions of up to about 60% have been required	
Diltiazem hydrochloride and bisoprolol	13 (3.92)	[2.24–6.65]	Diltiazem is predicted to increase the risk of cardiodepression when given with bisoprolol. Manufacturer advises monitor	Study	The cardiac depressant effects of diltiazem and beta-blockers are additive, and although concurrent use can be beneficial, close monitoring is recommended. A number of patients, (usually those with pre-existing ventricular failure or conduction abnormalities) have developed serious and potentially life-threatening bradycardia	Theoretical	Monitor the outcome of concurrent use for additive haemodynamic effects (e.g. bradycardia or heart failure). Note that an interaction has been reported to occur from within a few hours of starting treatment to after 2 years of concurrent use	
Escitalopram and domperidone	12 (3.61)	[2.01–6.28]	Domperidone increases the risk of QT-prolongation when given with escitalopram. Manufacturer advises avoid	Theoretical	Escitalopram has some risk of prolonging the QT interval. Dangerous QT prolongation might occur if it is given with domperidone	Theoretical	Concurrent use is contraindicated (UK)	
Escitalopram and esomeprazole	12 (3.61)	[2.01–6.28]	Esomeprazole is predicted to slightly to moderately increase the exposure to escitalopram. Manufacturer advises monitor and adjust dose	Theoretical	The concentration of escitalopram has been shown to be higher in patients also taking esomeprazole. This might increase the risk of QT-interval prolongation with escitalopram. Concurrent use of escitalopram and esomeprazole resulted in serotonin syndrome in one case	Study	Until more is known, be alert for an increase in escitalopram adverse effects (such as nausea, diarrhoea, dry mouth, palpitations), decreasing the dose of escitalopram if these become troublesome. If symptoms of serotonin syndrome (such as fever, tremors, diarrhoea, and agitation) occur, concurrent treatment should be stopped. Increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation	
Escitalopram and furosemide	12 (3.61)	[2.01–6.28]	Furosemide is predicted to cause hypokalaemia (potentially increasing the risk of torsade de pointes) when given with escitalopram. Manufacturer makes no recommendation	Theoretical	Furosemide can cause hypokalaemia, increasing the risk of torsade de pointes, which might be additive with the effects of escitalopram	Theoretical	Monitor potassium concentrations closely	

Red Stockley's warning: a life-threatening or contraindicated combination; *orange Stockley's warning*: dosage adjustment or close monitoring is needed

BNF British National Formulary, *CI* confidence interval, *DDI* drug-drug interaction, *INR* international normalised ratio, *TILDA* The Irish Longitudinal study on Ageing

[†] $n < 5$ TILDA participants still receiving this DDI 12 months after first receipt

Table 2 A description of the prevalence and interaction effect for the 10 most frequent 'severe' DDIs (involving medications dispensed ± 7 days of each other) per number of TILDA participants

DDI	Prevalence per medications dispensed ± 7 days of each other (N = 380)		BNF 77		Stockley's Drug Interactions			
	N (%)	95% CI	Interaction effect	Evidence	Interaction effect	Evidence	Action	Warning
Atorvastatin and clarithromycin	41 (10.79)	[8.03–14.33]	Clarithromycin is predicted to increase the exposure to atorvastatin. Manufacturer advises avoid or adjust dose and monitor rhabdomyolysis	Study	Clarithromycin moderately increases atorvastatin exposure. Rhabdomyolysis has been reported in patients taking atorvastatin with a macrolide	Study	Temporarily withhold the statin or, if necessary, give the lowest possible statin dose. Warn patients to report any unexplained muscle pain or weakness. Caution with atorvastatin dosages greater than 20 mg daily (UK). Maximum atorvastatin dosage of 20 mg daily (US)	
Aspirin and warfarin[†]	37 (9.74)	[7.12–13.16]	Warfarin is predicted to increase the risk of bleeding events when given with aspirin. Manufacturer advises use with caution or avoid	Theoretical	Low-dose aspirin (75–325 mg daily) increases the risk of bleeding when given with warfarin. High doses of aspirin (4 g daily or more) can also increase prothrombin times in patients taking warfarin	Extensive	Avoid high-dose aspirin. If low-dose aspirin is indicated, monitor for signs of bleeding. Consider giving gastroprotection (e.g. a proton pump inhibitor) to at-risk patients	
Furosemide and Clarithromycin	23 (6.05)	[4.03–8.96]	Furosemide is predicted to cause hypokalaemia (potentially increasing the risk of torsade de pointes) when given with clarithromycin. Manufacturer makes no recommendation	Theoretical	Furosemide can cause hypokalaemia, increasing the risk of torsade de pointes, which might be additive with the effects of clarithromycin	Theoretical	Monitor potassium concentrations closely	
Pravastatin and clarithromycin	16 (4.21)	[2.56–6.78]	Clarithromycin moderately increases the exposure to pravastatin. Manufacturer advises caution	Study	Clarithromycin moderately increases pravastatin exposure. Rhabdomyolysis has been seen with pravastatin and macrolides	Study	Limit the pravastatin dosage to 40 mg daily (US). Warn patients to report signs of myopathy (e.g. muscle pain or weakness)	
Escitalopram and omeprazole	15 (3.95)	[2.35–6.46]	Omeprazole slightly to moderately increases the exposure to escitalopram. Manufacturer advises monitor and adjust dose	Study	Omeprazole slightly to moderately increases the exposure to escitalopram, which might increase the risk of QT-interval prolongation	Study	Until more is known, be alert for an increase in escitalopram adverse effects (such as nausea, diarrhoea, dry mouth, palpitations), decreasing the dose of escitalopram if these become troublesome. Increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation	
Escitalopram and esomeprazole	15 (3.95)	[2.35–6.46]	Esomeprazole is predicted to slightly to moderately increase the exposure to escitalopram. Manufacturer advises monitor and adjust dose	Theoretical	The concentration of escitalopram has been shown to be higher in patients also taking esomeprazole. This might increase the risk of QT-interval prolongation with escitalopram. Concurrent use of escitalopram and esomeprazole resulted in serotonin syndrome in one case	Study	Until more is known, be alert for an increase in escitalopram adverse effects (such as nausea, diarrhoea, dry mouth, palpitations), decreasing the dose of escitalopram if these become troublesome. If symptoms of serotonin syndrome (such as fever, tremors, diarrhoea, and agitation) occur, concurrent treatment should be stopped. Increasing age, female sex, cardiac disease, and some metabolic disturbances (notably hypokalaemia) predispose to QT prolongation	
Aspirin and nicorandil	15 (3.95)	[2.35–6.46]	Aspirin is predicted to increase the risk of gastrointestinal perforation when given with nicorandil. Manufacturer advises caution	Theoretical	The manufacturer of nicorandil notes that there might be an increased risk of gastrointestinal ulceration, perforation, and haemorrhage on current use of aspirin and nicorandil	Theoretical	Caution is advised, and it would seem prudent to monitor for adverse gastrointestinal effects on concurrent use	
Warfarin and rosuvastatin	15 (3.95)	[2.35–6.46]	Rosuvastatin increases the anticoagulant effect of warfarin. Manufacturer advises monitor INR and adjust dose	Study	Rosuvastatin causes a clinically significant increase in the INR of patients taking warfarin, and cases of bleeding have been reported	Study	Increased INR monitoring is required when starting or stopping the statin, or changing the dose	
Amiodarone hydrochloride and warfarin	14 (3.68)	[2.15–6.14]	Amiodarone increases the anticoagulant effect of warfarin. Manufacturer advises monitor INR	Study	Amiodarone increases the anticoagulant effects of warfarin and bleeding might occur. The interaction is dose-dependent, with higher amiodarone doses having a greater effect. Onset occurs within a few days, is maximal within 2–7 weeks, and might persist for several months after the amiodarone has been withdrawn	Extensive	Monitor INR at least weekly, until a new steady state is achieved, and for several weeks after amiodarone is stopped. Warfarin dose reductions of up to about 60% have been required	
Lercanidipine and clarithromycin	14 (3.68)	[2.15–6.14]	Clarithromycin is predicted to markedly increase the exposure to lercanidipine. Manufacturer advises avoid	Study	Clarithromycin is predicted to increase calcium-channel blocker exposure: lercanidipine seems likely to be markedly affected	Theoretical	Concurrent use is contraindicated (UK). If both drugs are given, monitor for calcium-channel blocker adverse effects (e.g. hypotension, headache, oedema) and reduce the calcium-channel blocker dose as necessary	

Orange Stockley's warning: dosage adjustment or close monitoring is needed

BNF British National Formulary, *CI* confidence interval, *DDI* drug-drug interaction, *INR* international normalised ratio, *TILDA* The Irish LongituDinal study on Ageing

[†] $n < 5$ TILDA participants still receiving this DDI 12months after first receipt

3.2.4 Acute and Chronic DDIs: Medications Dispensed Within 7 Days of Each Other

Of the 380 participants dispensed DDIs involving medications dispensed within 7 days of each other, 181 participants (47.63%) were dispensed the same DDI for three or more consecutive claims (chronic DDI), while 199 participants (52.37%) were dispensed the same DDI for fewer than three consecutive claims (acute DDIs). Aspirin-warfarin was the most frequent chronic DDI involving medications dispensed within 7 days of each other (n = 13, 7.18%), while atorvastatin-clarithromycin was the

most frequent acute DDI involving medications dispensed within 7 days of each other ($n = 41$, 20.60%). The prevalence of all 'severe' cardiovascular and CNS *chronic* DDIs dispensed *within 7 days* of each other is presented in Supplementary Table S2.

3.3 Drugs Most Frequently Involved in Potentially 'Severe' DDIs

Figure 2 presents the drugs most frequently implicated in 'severe' co-prescribed DDIs. In total, out of 332 participants potentially exposed to one of the 'severe' co-prescribed DDIs examined, warfarin was the drug most commonly implicated, where 75 TILDA participants (22.59%) dispensed warfarin were found to have been dispensed a total of five interacting drugs, the most frequent being aspirin (10.2%). This was closely followed by escitalopram ($n = 67$, 20.18%) and atorvastatin ($n = 66$, 19.88%) (Fig. 2). Figure 3 presents the drugs most frequently implicated in 'severe' DDIs involving drugs dispensed within 7 days of each other. There were 380 TILDA participants potentially exposed to one of the 'severe' DDIs examined, and clarithromycin was found to be the drug most commonly implicated, where 128 TILDA participants (33.7%) dispensed clarithromycin were found to have been dispensed eight interacting drugs within 7 days of clarithromycin. This was closely followed by warfarin ($n = 107$, 28.2%), atorvastatin ($n = 94$, 24.7%), and furosemide ($n = 78$, 20.5%) (Fig. 3).

3.4 Factors Associated with DDI

Table 3 presents the association between participant sociodemographic, functional ability (geriatric syndrome), and medication-related factors associated with the risk of any potential 'severe' cardiovascular or CNS DDI. In the unadjusted analysis, older age, being a past or current smoker, having three or more chronic conditions, being classified as pre-frail or frail, having depression, poor delayed recall, and polypharmacy were all significantly associated with being potentially exposed to a 'severe' DDI. Participants with third level education were less likely to be exposed to one of these 'severe' DDIs. In the adjusted analysis, participants with polypharmacy (5–9 medications, OR 4.81, 95% CI 3.16–7.33; ≥ 10 medications, OR 13.40, 95% CI 8.22–21.85), compared to those in receipt of fewer than five medications, and those with depression (OR 2.12, 95% CI 1.34–3.34) were significantly more likely to be exposed to a 'severe' cardiovascular and/or CNS DDI, after adjusting for sociodemographic, functional ability (geriatric syndrome), and medication-related factors. Of the 119 study participants with a self-reported depression diagnosis, 56 (47%) were dispensed antidepressants (N06A) during the study observation period. Including those dispensed multiple antidepressants, most ($n = 37$) received a selective serotonin reuptake inhibitor (SSRI), few ($n = 12$) received a tricyclic antidepressant (TCA), and $n = 21$ received either a non-selective monoamine oxidase inhibitor (N06AF04) or other antidepressant (N06AX). Among those dispensed any

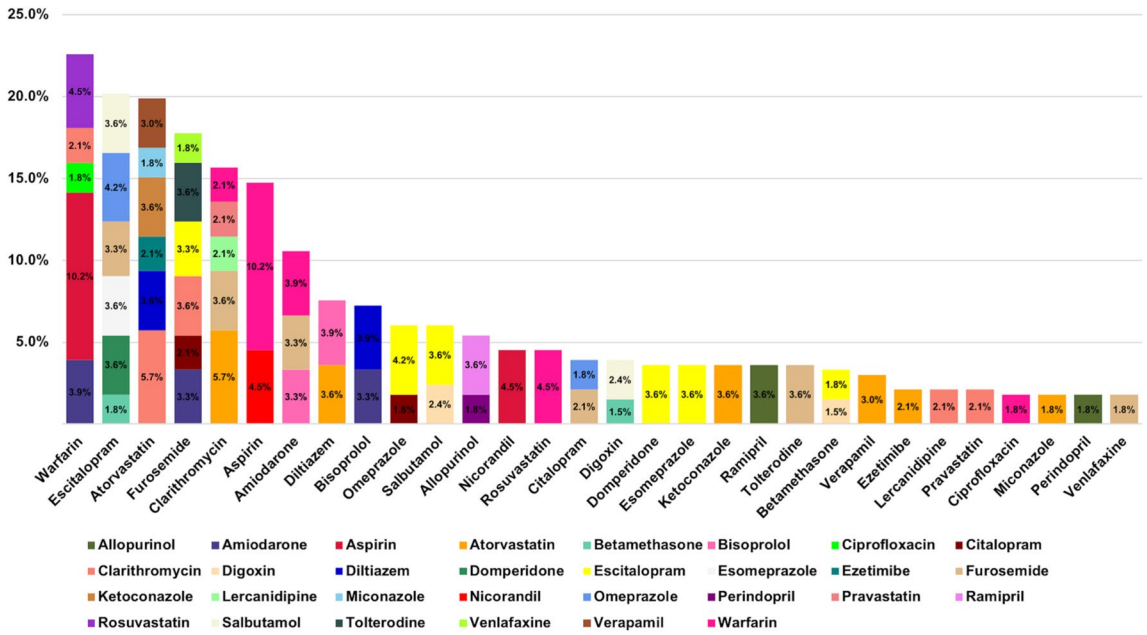

Fig. 2 Drugs most frequently involved in co-prescribed (same prescription claim date) 'severe' cardiovascular or CNS DDIs. *CNS* central nervous system, *DDI* drug-drug interaction

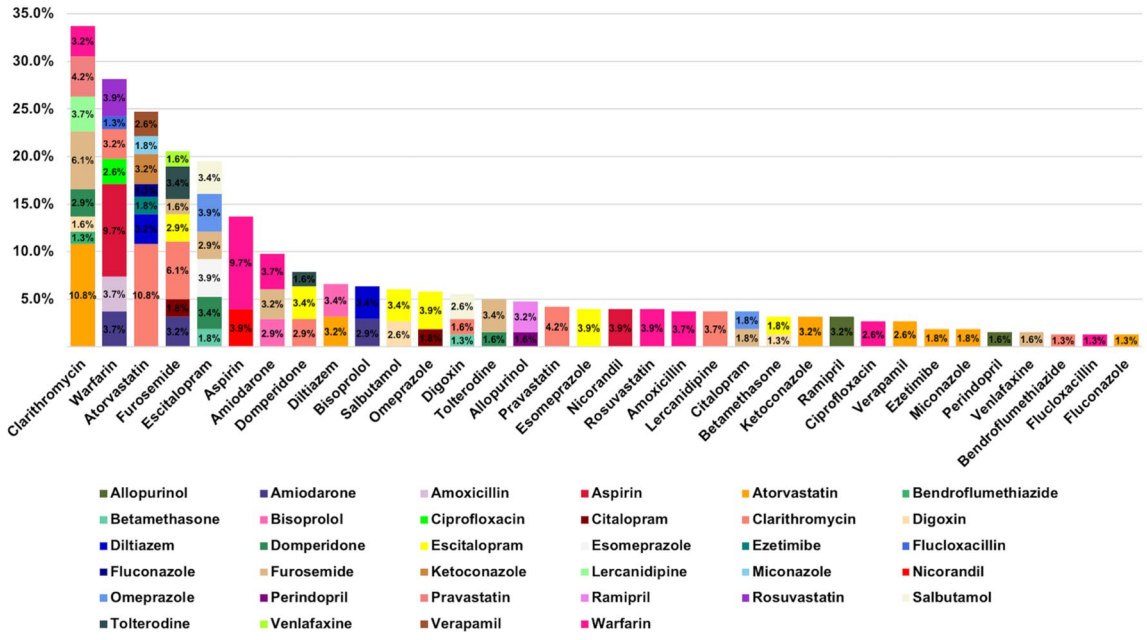

Fig. 3 Drugs most frequently involved in 'severe' cardiovascular or CNS DDIs dispensed within 7 days of any claim. *CNS* central nervous system, *DDI* drug-drug interaction

antidepressant, 50% ($n = 28$) were potentially exposed to a DDI, and 46% ($n = 13$) of these TILDA participants were dispensed a DDI that involved the drug escitalopram.

In multivariable negative binomial regression, the number of DDIs also significantly increased for participants with polypharmacy (5–9 medications, IRR 4.79, 95% CI 3.18–7.22; ≥ 10 medications, IRR 11.78, 95% CI 7.48–18.55), compared with those in receipt of fewer than five medications, and also for those with depression versus without depression (IRR 1.45, 95% CI 1.05–2.01) after adjusting for sociodemographic, functional ability (geriatric syndrome), and medication-related factors (Table 3).

4 Discussion

In a representative population-based study of ageing in Ireland, we found that almost a quarter (22.65%) of community-dwelling adults aged ≥ 70 years were potentially exposed to at least one 'severe' cardiovascular or CNS DDI, with more than half (54.82%) of this cohort found to have been dispensed the same DDI for a prolonged period of time (≥ 3 consecutive claims). The majority were potentially exposed to 'orange' co-prescribed DDIs, requiring dosage adjustment or close monitoring; however, we found that potential exposure to 'red' contraindicated DDIs was greater where medications were dispensed within 7 days of each other. Polypharmacy and depression were significantly associated with potential exposure to these DDIs.

Compared with previous population-based studies [19, 27], we report a higher prevalence of community-dwelling older adults potentially exposed to aspirin-warfarin and amiodarone-warfarin DDIs. These findings are potentially concerning, especially since the increased bleeding risk associated with these DDIs is well-established in the literature [34, 35]. Indeed, with the advent of novel oral anticoagulants (NOACs), it is important to consider the consequent decline in warfarin use in current clinical practice in Ireland [36]. However, it should be noted that previous studies have reported the combined use of NOACs and antiplatelet drugs [37] and NOACs and amiodarone [38] to similarly be associated with an increased risk of major bleeding. In addition, it should also be noted that warfarin may be the most suitable anticoagulant for some patients (e.g. an atrial fibrillation patient with a mechanical heart valve or mitral stenosis) [39]. Previous research has highlighted that the older patient is at increased risk of drug-induced QT prolongation, which may contribute to serious adverse outcomes, including torsade de pointes [40, 41]. Our study reports a relatively high prevalence of older community-dwelling adults potentially exposed to DDIs associated with QT prolongation, including the contraindicated DDI escitalopram-domperidone. These drug combinations may confer serious risks to the older patient and should, therefore, be avoided. Our study also reveals some important insights at the individual drug level,

Table 3 Sociodemographic, functional ability, and medication-related factors associated with any potential 'severe' cardiovascular or CNS DDI between wave 1 and 2 ($N = 1466$)

	DDI	No DDI	Unadjusted ORs (CI)	Adjusted ORs (CI)
Sociodemographic factors				
Age, mean (SD)	78.69 (5.63)	77.40 (5.47)	1.04 (1.02–1.06)*	1.02 (0.99–1.05)
Age < 80 years, *n* (%)	192 (57.83)	777 (68.52)		
Age ≥ 80 years, *n* (%)	140 (42.17)	357 (31.48)	1.58 (1.23–2.04)*	-
Gender, *n* (%)				
Male	161 (48.49)	510 (44.97)	1.0	1.0
Female	171 (51.51)	624 (55.03)	0.87 (0.68–1.11)	0.75 (0.55–1.02)
Marital status, *n* (%)				
Not married/cohabiting	152 (45.78)	509 (44.89)	1.0	1.0
Currently married/cohabiting	180 (54.22)	625 (55.11)	0.96 (0.75–1.23)	1.33 (0.97–1.81)
Education[#], *n* (%)				
Primary/none	185 (55.72)	533 (47.04)	1.0	1.0
Secondary	101 (30.42)	378 (33.36)	0.77 (0.58–1.01)	0.97 (0.70–1.33)
Third/higher	46 (13.86)	222 (19.59)	0.60 (0.42–0.85)*	0.76 (0.50–1.16)
Smoker, *n* (%)				
Never smoked	121 (36.45)	527 (46.47)	1.0	1.0
Past smoker	163 (49.10)	482 (42.50)	1.47 (1.13–1.92)*	1.23 (0.90–1.69)
Current smoker	48 (14.46)	125 (11.02)	1.67 (1.14–2.46)*	1.50 (0.95–2.36)
Functional ability-related factors (geriatric syndromes)				
No. of self-reported chronic conditions, *n* (%)				
0	16 (4.82)	119 (10.49)	1.0	1.0
1	52 (15.66)	246 (21.69)	1.57 (0.86–2.87)	1.44 (0.72–2.90)
2	68 (20.48)	285 (25.13)	1.77 (0.99–3.19)	1.23 (0.60–2.50)
≥ 3	196 (59.04)	484 (42.68)	3.01 (1.74–5.21)*	1.17 (0.56–2.43)
Frailty, *n* (%)				
Robust	56 (16.87)	379 (33.42)	1.0	1.0
Pre-frail	130 (39.16)	487 (42.95)	1.81 (1.28–2.54)*	1.14 (0.74–1.76)
Frail	146 (43.98)	268 (23.63)	3.69 (2.61–5.21)*	1.28 (0.77–2.14)
Depression[#], *n* (%)				
Not depressed	270 (83.59)	1048 (94.08)	1.0	1.0
Depressed	53 (16.41)	66 (5.92)	3.12 (2.12–4.58)*	2.12 (1.34–3.34)*
Poor delayed recall[#], *n* (%)				
None	196 (62.03)	785 (71.23)	1.0	1.0
Poor	120 (37.97)	317 (28.77)	1.52 (1.17–1.97)*	1.27 (0.94–1.72)
Medication-related factors				
Polypharmacy[#], *n* (%)				
≤ 4 medications	32 (9.64)	502 (44.31)	1.0	1.0
5–9 medications	179 (53.92)	512 (45.19)	5.48 (3.69–8.15)*	4.81 (3.16–7.33)*
≥ 10 medications	121 (36.45)	119 (10.50)	15.95 (10.30–24.71)*	13.40 (8.22–21.85)*

CI confidence interval, *CNS* central nervous system, *DDI* drug-drug interaction, *OR* odds ratio, *SD* standard deviation

*$P < 0.05$

[#]Missing data for 1 participant for education, 1 participant for polypharmacy, 29 participants for depression and 48 participants for poor delayed recall

including that the frequency of older adults co-prescribed a 'severe' DDI was highest for those prescribed the anticoagulant warfarin, while the antidepressant escitalopram was the second most frequently implicated drug in 'severe' co-prescribed DDIs. Anticoagulants and antidepressants are commonly used in the older population, and have been highlighted as a high-risk drug category for drug interactions in the older patient [13].

This study identified a slightly higher prevalence of older persons potentially exposed to a DDI involving medicines dispensed within 7 days of each other compared to medicines co-prescribed. One possible explanation for the difference observed here could be that these medicines were prescribed by different prescribers. Tamblyn et al. [42] have shown that an older patient's risk of receiving an inappropriate drug combination is directly related to the number of prescribers. In addition, a recent study conducted in a primary care setting in Sweden found that DDIs were more likely to occur as a result of prescriptions from multiple prescribers [16]. Among the medications dispensed within 7 days of each other, atorvastatin-clarithromycin was the most prevalent DDI, with almost one in ten TILDA participants ≥ 70 years potentially exposed. The adverse effects of this pharmacokinetic interaction are well-reported in the literature [43]. Moreover, at the individual drug level, for one third of older adults with any 'severe' cardiovascular or CNS DDI involving drugs dispensed within 7 days of each other, the macrolide antibiotic clarithromycin was most commonly implicated. Given the high prevalence of statin use among Ireland's older population [44], prescribers and pharmacists caring for these patients need to be aware of such interactions and intervene if appropriate.

The findings from this study also highlight that after adjusting for a wide range of sociodemographic and functional ability-related (geriatric syndrome) factors associated with DDIs in older community-dwelling adults, polypharmacy was significantly associated with DDIs. Previous studies have also reported an association between polypharmacy and DDIs, which persists over time [3, 7, 12, 14]. Moreover, while previous research has reported an association between depression and polypharmacy [45], to our knowledge, this is the first study to identify a positive association between depression and potential DDI exposure in the older population. This may be due to treatment-resistant depression, requiring multiple or older, more toxic antidepressants to manage symptoms [46]. However, other confounding factors contributing to this association cannot be excluded, and further research is therefore needed to validate our findings. Nonetheless, this is important information for healthcare professionals caring for older patients with cardiovascular disease, especially since antidepressants are frequently prescribed in this population [47].

4.1 Strengths and Limitations

To the authors' knowledge, this is the first study to investigate the prevalence and factors associated with potential DDIs in older community-dwelling adults in Ireland. Previous studies have reported DDI prevalence rates to vary considerably in this population due to the disparate methods used to identify and classify a DDI [7, 13]. To address this, we have developed a comprehensive, robust, and reproducible methodology that researchers in other countries can use—this will allow for direct comparison of DDI prevalence estimates between countries. This study used data from a prospective longitudinal cohort study and includes participants who are representative of the general population aged ≥ 70 years in Ireland. This study does have some limitations to consider. Firstly, we only examined cardiovascular and CNS DDIs, and while these have been shown to be the most commonly implicated drug groups involving potentially serious DDIs [9], other drug groups may also be important here (e.g. musculoskeletal and gastrointestinal drugs). In addition, as we only included DDIs with a 'severe' severity rating per the BNF 77, DDIs which contained no severity rating (e.g. opioids and gabapentin) were not included. Moreover, we do not know if some DDIs were prescribed intentionally—for example, aspirin-warfarin following acute coronary syndrome in patients with a pre-existing indication for anticoagulation, typically for no longer than 12 months and with regular monitoring and patient follow-up being undertaken [39]. Further, in the case of acute prescriptions, such as antibiotics, we do not know if the patient was advised by their pharmacist to hold potentially interacting drugs until completion of the antibiotic course. Some medications (e.g. hepatitis C and HIV medications) are not reimbursed under the GMS community drug scheme, and therefore our study does not capture the prevalence of DDIs involving these drugs. In addition, over-the-counter (OTC) products, including pain killers such as ibuprofen, are not routinely captured in pharmacy claims data, and the prevalence of DDIs may be underestimated—although this may not be a significant factor since GMS patients can get a prescription for an OTC item if the co-payment price is less and the drug is eligible for reimbursement. The data used in the present study were limited to older community-dwellers in Ireland; hence, the results reported may not be generalisable to other EU/developed nations. This study investigated a range of factors associated with DDIs, but there may be other relevant factors (e.g. prescribing habits and healthcare utilisation [16, 42]) associated with these DDIs. We only included those with a valid medical card, and this smaller sample size may have contributed to under-powered associations. Finally, our study used pharmacy refill claims data, and therefore assumes that all medicines dispensed for a patient were taken.

4.2 Implications

Our study findings suggest that greater attention is warranted for older adults prescribed warfarin, escitalopram, atorvastatin, furosemide, and clarithromycin. These drugs were found to be commonly implicated in potential exposure to multiple 'severe' cardiovascular and/or CNS DDIs, many of which

may have resulted in adverse health outcomes. In addition, our findings indicate that older adults with depression are at greater risk of potential exposure to cardiovascular and/or CNS DDIs, and prescribers and pharmacists should be mindful of these potential DDIs. In practice, DDI software is commonly employed when prescribing and dispensing medication for patients. However, this technology often has varying sensitivity and specificity [48], which results in multiple alerts, and consequently 'alert fatigue' [49]. Previous studies have reported the use of a clinical decision support system (CDSS) has a positive impact on reducing the rate of potentially important DDIs [50, 51].

Future research should extend the present study's methodology to examine 'severe' DDIs involving all physiological systems. Further research is needed to determine and validate the health outcomes/clinical consequences associated with these DDIs in this population to identify the more clinically significant DDIs. Validated tools such as the anticholinergic drug burden index have been applied to this same cohort [52, 53] and may provide some utility for this purpose. To facilitate improved comparability of DDI prevalence rates across studies/countries, future research could use the present study's methodology to determine and compare the rate of 'severe' cardiovascular and CNS DDIs in older community-dwellers. Research is also needed on methods and approaches to reduce DDIs in older populations. Older people with multimorbidity frequently have multiple care providers and often experience inappropriate polypharmacy. Polypharmacy has consistently been shown to be associated with DDIs, PIP, medication adherence problems, increased drug costs, and adverse drug events. A combination of computerised decision support systems, integrated medical record systems, and multidisciplinary approaches to prescribing may facilitate medication reviews and deprescribing, thereby reducing the risk of DDIs. A recent study that examined the effect of community pharmacist medication review on the quality of drug prescribing in elderly patients in Slovenia found that pharmacist-GP collaboration significantly improved prescribing quality and reduced potentially contraindicated DDIs by 42% [54]. A similar multidisciplinary initiative could be explored in Ireland.

5 Conclusion

In 2017, the third WHO global patient safety challenge was introduced that aims to reduce severe avoidable medication-related harm by 50% globally in the next 5 years [55]. The DDIs identified by this study have the potential to result in avoidable medication-related harm if not appropriately managed. With increased longevity, the prevalence of these DDIs, and the potential for adverse outcomes, is likely to increase. Older aged adults should be the focus of medication review/optimisation interventions to identify DDIs that have the potential to result in adverse outcomes.

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Declarations

Authors' contributions All authors were involved in the concept and design of the study. JH and VR developed the list of DDIs. JH, KB, and CC undertook the analysis and interpretation of the data. JH led on the write-up of the manuscript, and all authors reviewed and provided feedback on this. All authors read and approved the final manuscript.

Conflicts of interest None to declare.

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Availability of data The data that support the findings of this study are available from TILDA and the HSE-PCRS, but restrictions apply to the availability of these datasets, which were used under licence for the current study, and so are not publicly available. Researchers interested in using TILDA data may access the anonymised dataset for free from the following sites: Irish Social Science Data Archive (ISSDA) at University College Dublin http://www.ucd.ie/issda/data/tilda/ and Interuniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34315.

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