

Title	The impact of age, sex, and gender on polypharmacy and potential prescribing cascades: lessons from five databases
Authors	Rochon, Paula A.;Li, Joyce;O'Mahony, Denis;Onder, Graziano;Petrovic, Mirko;Sternberg, Shelley A.;Gurwitz, Jerry H.;Savage, Rachel D.;Wu, Wei;Giannakeas, Vasily;Kthupi, Altea;Dalton, Kieran;McCarthy, Lisa M.;Mason, Robin;Giancola, Amanda;Borhani, Parya;Cherubini, Antonio
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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Supplement. The Impact of Age, Sex, and Gender on Polypharmacy and Potential Prescribing Cascades:
Lessons from 5 databases

Table S1. Checklist of items that should be included in reports of descriptive studies

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Figure S1. Prevalence of calcium channel blocker to diuretic co-prescribing suggesting a prescribing cascade in older adults disaggregated by sex, age, socioeconomic status, and their intersections

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Table S1. Checklist of items that should be included in reports of descriptive studies¹

	Item No	Recommendation	Page No
Title and abstract	1	Explicitly state that this is a ‘descriptive study’ in the title or the abstract	4
		(b) Summarize the target population and provide an informative and balanced summary of estimated disease occurrence in the abstract.	4
Introduction			
Background/rationale	2	State the motivation for the study, including, where relevant, the action that might be informed by the results.	6
Objectives	3	State the descriptive estimate and, explicitly including: (a) The target population (who would be affected by any decisions made as a result of the study?) (b) The health state to be summarized; (c) The measure of occurrence; and (d) Any stratification variables, if applicable	6
Methods			
Study design	4	(a) State whether the study is cross-sectional or longitudinal (b) Restate the measure of occurrence being targeted (c) If the study is longitudinal, specify the time origin and follow-up period for the measure of occurrence; if the study is cross-sectional specify the time anchor at which the health state is summarized for individuals.	6,7
Setting	5	Describe any relevant features of the place and time in which the target population resides and across which data were collected.	7
Participants	6	(a) Describe the target population thoroughly in terms of person, place, and time. (b) Describe sampling into the study population (whether sampling was explicit or implicit, e.g., by inclusion in an administrative database); this includes eligibility criteria (see recommendations on data sources in item 9 below). (c) Describe any restrictions on the analytical sample.	7
Outcomes	7	(a) State when and how the outcome is measured. (b) Include estimates or discussion of the sensitivity and specificity of the study outcome definition relative to the gold standard. (c) List secondary outcomes or competing events of interest.	8
Covariates	8	Specify any stratification or adjustment variables—clearly define how variables were collected or constructed.	7,8
Data sources/ measurement	9*	Clearly delineate any inclusion/exclusion criteria for membership in the data source, including the original purpose for which the data were collected, if not for the study at hand	7
Bias	10	Describe any assumptions or methods used to extrapolate data from the analytical sample to the study population and from the study population to the target population	NA
Statistical methods	11	(a) Describe the primary statistical methods used to estimate the measure of disease occurrence being targeted; discuss assumptions of that method in light of data limitations (e.g., assumption of independent censoring for people lost to follow-up). (b) If any adjustment/standardization will be done, state the goal of such adjustment.	8,9

Results

Participants	12*	(a) Report numbers of individuals at each study stage (this is likely to be approximate for the target population); consider summarizing this information in a flow diagram	9
Descriptive data	13*	(a) Report on the characteristics of the analytical sample in a “Table 1.” (b) Indicate the number of participants with missing data for each variable used in the analysis. (c) If any weighting or imputation is done to reconstruct the study sample or target populations, include columns for those populations	9
Outcome data	14*	(a) Present an overall (unstratified) estimate of the measure of occurrence of interest. (b) Report “crude” (raw data in the analytical sample) and (if applicable) “corrected” (after any weighting or imputation) estimates.	9,10
Other analyses	15	Present prespecified stratum-specific or adjusted/standardized results.	9, 10
Discussion			
Key results	16	Summarise key results with reference to the study objectives	10,11
Limitations	17	Summarize potential sources of selection bias and measurement error and any attempts to mitigate these biases. Discuss both the direction and magnitude of any potential bias. Integrating quantitative bias analysis into the study to guide these discussions is encouraged.	11
Interpretation	18	(a) Avoid causal interpretations of descriptive results; avoid overinterpreting stratum-specific differences in measures of occurrence. (b) Describe how results of this study might inform or improve public health or clinical practice.	11,12

*Give information separately for exposed and unexposed groups.

Table S2 Description of the secondary databases providing drug prescribing data on adults 65 years of age or older

Data type	Population Level Data		Clinical Trial Data	Patient Registry Data	
Setting of care	Community and nursing home		Hospital	Geriatric Hospital	Nursing home
Database (Country/Countries)	ICES (Canada)	Maccabi (Israel)	SENATOR (IRL, ITA, BEL, ESP, SCT, ISL)	Report-AGE (Italy)	SHELTER (ITA, ISR, CZE, ENG, FIN, FRA, DEU, NLD)
Number of individuals included in database	2,377,885	289,994	1,537	6,737	3,966
Location and Description	Living in Ontario	Members of Maccabi Healthcare Services	3 chronic medical conditions Undergoing unscheduled hospital admission under the care of non-geriatricians	Older adults with multimorbidity and polypharmacy admitted to a geriatric hospital in Italy	Living in one of 57 nursing homes included in the registry
Primary Investigator	Dr. Paula Rochon	Dr. Shelley Sternberg	Dr. Denis O'Mahony	Dr. Antonio Cherubini	Dr. Graziano Onder
Index Date	January 1st, 2020	January 1st, 2020	Date of hospital admission (2016-2018)	Date of hospital admission (2011-2019)	Date of nursing home admission (2010-2012)
Ethics Approval	Use of ICES data was authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board.	Approved by the Helsinki Committee of Maccabi Healthcare Services.	Approved by The Clinical Research Ethics Committee of the Cork Teaching Hospitals, University College Cork.	Approved by the Ethical committee at IRCCS INRCA on 2-17-2011, code SC/10/272.	Ethics approval was obtained for all participating countries from the following ethics committees: METC VUmc Amsterdam, METC University, University Cattolica del Sacro Cuore Rome, METC National Committee, THL Helsinki, METC Hospital Saint Péline Paris, METC Haifa University, Kaplan Medical Center, The Schools Research Committee Ethical Panel, University of Kent Canterbury, METC University of Ulm, Multi-centric Ethics Committee, General Faculty Hospital Prague.

BEL Belgium; CAN Canada; CZE Czech Republic; DEU Germany; ENG England; ESP Spain; FIN Finland; FRA France; IRL: Ireland; ISL Iceland; ISR Israel; ITA Italy; NLD Netherlands; SCT Scotland.

Table S3 Description of the gender-related sociocultural variables from each secondary database using the Canadian Institutes of Health Research Framework²

Gender-related sociocultural Variable*	Category	Definition	Database Reporting Variable
Man, Woman, Non-binary	Gender Identity	Identifying as man, woman, non-binary	None
Socioeconomic Status	Institutionalized Gender	Lower socioeconomic status	
<i>Income Based</i>		Eligibility for a low-income subsidy from the Ontario Drug Benefit program, annual income of Canadian \$19,300 or less per individual or a combined annual income of Canadian \$32,300 or less per couple	
<i>Cluster Based</i>		Residences in clusters 1-3 (on a scale of 1-10 with 1 being the lowest socio-economic status)	
<i>Educational attainment Based</i>		Education level: no school, primary school education only, some secondary education, complete secondary education, some third level education at college/university, and complete third level education at college/university	SENATOR
Marital Status	Gender Roles and Relations	Married (married or common-law) Un-married (single, widowed or separated)	Report-AGE SHELTER

* These gender-related sociocultural variables were obtained from the Canadian Institutes of Health Research framework² and relevant articles^{3,4}

Table S4 Definition of the Medication Included in Each Database.

	ICES	Maccabi	SENATOR	Report-AGE	SHELTER
Time of medication use	January 1st, 2020	January 1st, 2020	Date of hospital admission (2016-2018)	Date of hospital admission (2011-2019)	Date of nursing home admission (2010-2012)
Collection of medication information	Medications were identified using the Ontario Drug Benefit (ODB). The ODB database contains prescription medication claims for those covered under the provincial drug program, mainly those aged 65 years and older. Drug identification number was used for specific medications.	Medications were identified using the Maccabi Healthcare Services database. All dispensed prescriptions covered under the National Drug Plan and prescribed by a Maccabi physician are included.	The list of medications prescribed in their hospital drug chart was collected by study researchers at the time of recruitment into the trial, which had to be within 60 hours of admission (but was mostly within 24 hours).	Medications assessment within 24 hours from admission. -commercial name -doses -units -route of administration -frequency -prescription yes/no	Direct assessment by study researchers
Concurrent medications	Unique prescription medications (count of drugs) at index date.	Unique generic components at index date	Unique generic components at multiple visits	Unique components at index date (count of every single medicine)	ATC codes at index date
Combination medication	Considered as one medication	Considered as multiple medications	Considered as multiple medications	Considered as multiple medications	Considered as multiple ATC
Calcium channel blockers	Amlodipine, Amlodipine Besylate, Besylatecleveldipine, Diltiazem, Diltiazem HCL, Erythryltetranitrate, Extemporaneous Mixture, Felodipine, Isradipine, Nicardipine HCL, Nifedipine, Nimodiine, Propiverine HCL, Verapamil HCL	Amlodipine, Diltiazem, Enalapril and Lercanidipine, Lercanidipine, Nifedipine, Valsartan and Amlodipine, Verapamil,	Amlodipine, Felodipine, Lacidipine, Lercanidipine, Nifedipine	Amlodipine, Barnidipine, Diltiazem, Felodipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nimodipine, Verapamil	Amlodipine, Felodipine, Isradipine, Nicardipine, Nifedipine, Nimodiine, Nisoldipine, Nitrendipine, Lacidipine, Nilvadipine, Barnidipine, Lercanidipine, Verapamil, Gallopamil, Diltiazem, Ramipril and felodipine, Trandolapril and verapamil, Atorvastatin and amlodipine
Diuretic drugs	Amiloride HCL, Amiloride HCL and Hydrochlorothiazide, Bumetanide, Chlorthalidone, Eperenone, Eplerenone, Ethacrynic Acid, Ethacrynic Acid Sodium, Furosemide, Hydrchlorthiazide,	Hydrochlorothiazide, Indapamide, Furosemide, Spironolactone, Eplerenone, Amiloride, Candesartan and Diuretics, Cilazapril and Diuretics,	Endroflumethiazide, Bumetanide, Furosemide, Hydrochlorothiazide, Indapamide, Metolazone, Spironolactone, Torasemide	Butizide and Potassium-Sparing Agent, Canrenone, Chlorthalidone, Furosemide, Furosemide and Potassium-Sparing Agents, Hydrochlorothiazide,	Bendroflumethiazide, Hydrochlorothiazide, Enalapril and diuretics, Lisinopril and diuretics, Perindopril and diuretics, Ramipril and diuretics, Quinapril and diuretics, Benazepril and diuretics, Fosinopril and diuretics, Delapril and diuretics, Losartan and diuretics,

	Hydrochlorothiazide and Spironolactone, Hydrochlorothiazide and Triamterene, Hydrochlorothiazide and Triamterene Hydroxyzine HCL, Inapamide, Mannitol, Methyclothiazide, Pamabrom, Polythazide, Potassium Nitrate, Potassium Nitrate Quinethazone, Spironolactone, Tolvaptan, Torsemide, Triamterene	Fosinopril and Diuretics, Hydrochlorothiazide and Potassium-Sparing Agent, Irbesartan and Diuretics, Losartan and Diuretics, Ramipril and Diuretics, Valsartan and Diuretics,		Hydrochlorothiazide and Potassium-Sparing Agents, Hydrochlorothiazide and Spironolactone, Indapamide, Spironolactone, Torasemide	Valsartan and diuretics, Irbesartan and diuretics, Candesartan and diuretics, Telmisartan and diuretics, Metoprolol and thiazides, Acebutolol, Metoprolol and other diuretics, Atenolol and other diuretics, Furosemide, Hydrochlorothiazide, Eptizide, Altizide, Chlortalidone
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ATC: Anatomical Therapeutic Chemical

Table S5 Description of the Age, Sex and Gender-related Sociocultural Factors among Older Adults in Five Secondary Databases by Sex

Characteristic	Community				Geriatric Hospital		Nursing Home						Hospital	
	ICES		Maccabi Healthcare		Report-AGE		ICES		Maccabi Healthcare		SHELTER		SENATOR	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Number	1,249,355	1,053,160	153,366	129,926	3,897	2,840	52,193	23,177	4,587	2,115	2,943	1,023	725	812
Age: Mean years	75.0*	74.2*	73	73	86.6*	84.9*	86.2*	82.5*	85*	82*	85.5*	82.1*	79.0*	77.4*
Mean number of medications	3.5	3.7	6	6	6.0	6.0	5.9	6.3	7	8	7.0	7.2	9.3	9.3
Gender-related Sociocultural Factors														
Socioeconomic status (SES)														
SES status (Income),%: Low	15.2 [†]	10.5 [†]	Data unavailable		Data unavailable		27.1 [†]	16.2 [†]	Data unavailable		Data unavailable			
SES status (Cluster), %: Low	Data unavailable		19.2 [†]	17.9 [†]	Data unavailable		Data unavailable		21.6	23.5	Data unavailable			
SES status (Educational attainment)	Data unavailable													
No more than primary, %													46.2 [†]	32.4 [†]
Secondary, %													42.6 [†]	51.7 [†]
Third level, %													11.2 [†]	15.9 [†]
Marital status														
Marital status: Data available, n	Data unavailable				3,194	2,505	Data unavailable				2,408	828	Data unavailable	
Unmarried, %					75.9 [†]	31.8 [†]					87.9 [†]	60.1 [†]		
Single, %					8.1	5.3					12.4	13.5		
Widowed, %					67.2	25.6					69.7	37.0		
Separated/ Divorced, %					0.6	0.9					5.7	9.7		
Married/ Common law, %					24.1 [†]	68.2 [†]					12.1 [†]	39.9 [†]		
Marital status not reported, n					703	335					535	195		

In the ICES database, lower socioeconomic status was identified by eligibility for a low-income subsidy from the Ontario Drug Benefit program⁵, defined as an annual income of \$19,300 (Canadian) or less per individual or a combined annual income of \$32,300 (Canadian) or less per couple.

In the Maccabi Healthcare Services database, socioeconomic status of the older adult was classified into clusters from 1–10, with 1 symbolizing a very low and 10 a very high socioeconomic status. Residences in clusters 1-3 were categorized as lower socioeconomic status.

In the Report-AGE and SHELTER databases, marital status was not reported by all older adults. These data were not reported for 15.3% of those in the Geriatric Hospital and 18.4% in the SHELTER database, primarily female older adults.

In the SENATOR database, no more than primary education was classified as lower socioeconomic status. Third level of educational attainment was university/college level education.

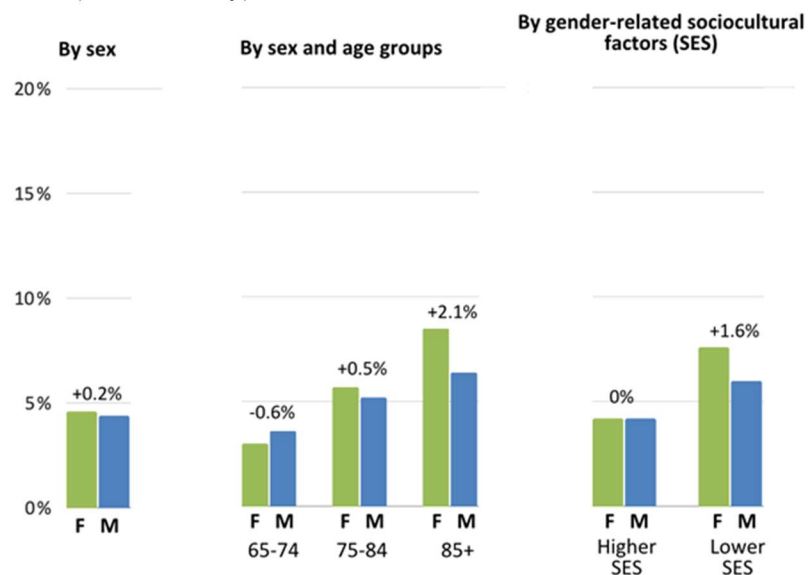
Data unavailable indicates that the data does not exist.

* p -value<0.05 with t test for the comparison between females and males

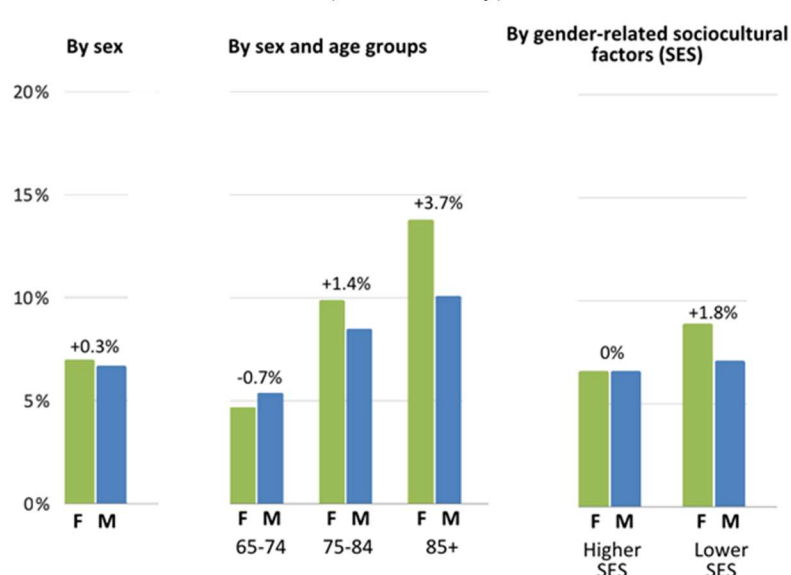
[†] p -value<0.05 with chi-square test for the comparison between females and males

Figure S1 Prevalence of calcium channel blocker to diuretic co-prescribing suggesting a prescribing cascade in older adults disaggregated by sex, age, socioeconomic status, and their intersections

ICES (Community)



Maccabi healthcare (Community)



The figure describes the calcium channel blocker and diuretic co-prescribing suggesting a prescribing cascade in older adults living in the community in Ontario, Canada and Maccabi Health System, Israel, on January 1st, 2020. This index date was selected because it precedes the presence of COVID-19. The percentage of potential prescribing cascade was provided by sex (female [F] or male [M]), age (65-74 years old, 75-84 years old, or 85 years of age and older), and the gender-related sociocultural factors of socioeconomic status (SES) that was available from this population-level data. The differential prevalence⁶ (the percent of the female population experiencing co-prescribing subtracting the corresponding percent within the male population) is provided between the bars representing the female and male older adults.

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