Received: 29 March 2019 | Accepted: 30 April 2019

DOI: 10.1111/jcpt.12854

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Clinically relevant drug-drug interactions and the risk for drug adverse effects among home-dwelling older persons with and without type 2 diabetes

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Funding information
M.K has received a personal grant from the North Savo Cultural Foundation.

Abstract

What is known and objective: Polypharmacy and age are known to increase the risk for potential drug interactions. Type 2 diabetes has been associated with polypharmacy and several comorbidities. Currently, there is no information on whether the frequency of clinically relevant drug-drug interactions and the risk for drug adverse effects differ between older persons with and without diabetes. The aim of this study was to investigate the frequency of drug-drug interactions and the risk for drug adverse effects in these two groups in primary care.

Methods: The basic study population consisted of Finnish home-dwelling primary care patients aged ≥ 65 years (N = 3039). For each person with diabetes, two controls were selected with adjusted age and gender. To collect data, electronic primary care patient records, a structured health questionnaire and a structured health examination conducted by a physician were utilized. Using the SFINX-PHARAO® database, drug-drug interactions and the risk for drug adverse effects were evaluated in 182 persons with type 2 diabetes and 176 persons without diabetes.

Results and discussion: There were no significant differences in the frequency of drug-drug interactions or the risk for drug adverse effects in persons with and without diabetes. At least one clinically relevant interaction was found in 81 (44.5%) persons with diabetes and 73 (41.5%) persons without diabetes. The most common drugs causing interactions included non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin.

What is new and conclusion: There is no difference in the frequency of drug-drug interactions or risk for drug adverse effects in older home-dwelling persons with and without diabetes. Due to common comorbidities and commonly used drugs among persons with diabetes, drug-drug interactions involving warfarin or NSAIDs in particular should be carefully monitored to avoid drug adverse effects.

KEYWORDS
adverse effect, diabetes, drug–drug interactions, elderly

1 | WHAT IS KNOWN AND OBJECTIVE

The number of the world's population aged over 60 years will reach 2 billion in 2050.[1] It is estimated that in 2014 there were 422 million adults with diabetes and the number is still increasing.[2] The ageing of the population will certainly increase the prevalence of diabetes in older adults.[3] Older persons with diabetes are known to have several comorbidities, for example coronary heart disease and stroke, more frequently than those without diabetes.[4]

Older age is associated with polypharmacy and multimorbidity as well as the risk for drug adverse effects.[5-7] Polypharmacy and age increase the risk for potential drug interactions.[8] Moreover, research has found an association between polypharmacy and type 2 diabetes, although polypharmacy is often justified due to the current guidelines for diabetes treatment.[9] Diabetes has been shown to increase the risk for admission to a medical emergency department due to drug adverse effects in older persons.[10]

There are only a few previous studies concerning drug-drug interactions among older persons with diabetes.[11,12] As far as we know, no study comparing drug-drug interactions and the risk for drug adverse effects between older persons with and without diabetes has been conducted. Therefore, the aim of this study was to investigate the frequency of drug-drug interactions and the risk for drug adverse effects among home-dwelling older persons with and without type 2 diabetes in primary care.

2 | METHODS

2.1 | Study population

This study is a part of the Inner Savo DM65+ (ISDM) study. The basic population of the ISDM study consisted of older home-dwelling persons (N = 3039) living in Inner Savo in Finland. The study population was gathered from primary care electronic patient records by identifying persons with diabetes (N = 540) according to diagnostic codes E10 and E11 of the International Classification of Diagnoses (ICD-10).[13] For each person with diabetes, two controls with adjusted age and gender were selected. Persons suffering from the terminal stages of cancer or other terminal illnesses were excluded, in addition to persons hospitalized or living permanently in institutional care. A structured health questionnaire was posted to 1,417 persons, 527 with diabetes and 890 without diabetes in August and September of 2015 (response rate 76.5%). After the questionnaire, 259 persons with diabetes and 259 persons without diabetes were invited to a health examination conducted by a physician. A complete set of data were available from 187 persons with diabetes and 176 persons without diabetes. To study drug-drug interactions (DDI) and the risk of drug adverse effects among persons with type 2 diabetes, persons with type 1 diabetes (N = 5) were excluded. Ultimately, drug-drug interactions and the risk for drug adverse effects were examined among 358 persons, of whom 182 had type 2 diabetes and 176 did not have diabetes.

2.2 | Measurements and tools

The risk for clinically significant drug-drug interactions and drug adverse effects were evaluated by using the SFINX-PHARAO® database (Medbase Ltd). The Swedish Finnish Interaction X-referencing (Sfinx®, currently INXBASE) database was developed in co-operation between Finnish and Swedish experts.[14] DDIs in the database are classified based on their severity (A-D) and the level of documentation (0-4). Class A interactions are minor interactions or clinically irrelevant interactions. The clinical outcome of class B interactions may vary and/or be uncertain. Class C interactions are clinically relevant but can be handled, for example by dose adjustments. Class D interactions include interactions that are best avoided. In this study, class C and class D interactions are regarded to be clinically relevant drug-drug interactions. The level of documentation is highest with number 4, when the interaction has been documented in controlled studies in relevant patient populations, and lowest with number 0, when the interaction has been documented from extrapolation from studies with similar drugs. The frequency of interactions in the study population and the total number of interactions were calculated.

The Pharmacological Risk Assessment Online System (Pharao®, currently RiskBase) database was used to investigate the risk for drug adverse effects. The database is developed by the Sfinx® working group.[15] There are nine different common and/or severe adverse effects in the database including bleeding, constipation, anticholinergic side effects, orthostatic hypotension, sedation, QT prolongation, seizures, serotonergic side effects and nephrotoxicity. The risk of an adverse effect is classified from A to D, class A meaning no increased risk and class D meaning high risk for an adverse effect. In addition, each drug in the database has been scaled from 0 to 3 based on the strength of the pharmacological effect to increase the risk. In this study, the frequency of having class D, that is high risk, for each adverse effect based on a person's medication was calculated.

Background variables (sex, age and education years), amount of exercise, ability to move without assistive aid, smoking, consumption of alcohol, depressive symptoms and health-related quality of life were determined using a structured health questionnaire. The Kasari's FIT index was used to evaluate the duration, efficiency and frequency of exercise.[16] Alcohol consumption and depressive symptoms were assessed using the Alcohol Use Disorders Identification Test (AUDIT-C) and Geriatric Depression Scale (GDS-15).[17,18] Quality of life was evaluated using the EuroQol EQ-5D questionnaire.[19] Cognitive functioning was assessed based on the Mini-Mental State Examination (MMSE).[20] The Lawton Instrumental Activities of Daily Living Scale (IADL) was used to evaluate a person's ability to function.[21] MMSE and IADL tests were part of the health examination.

The physical health examinations were standardized and conducted by MK. Blood pressure was determined from an orthostatic hypotension test. The test was made after 10 minutes of rest in a lying position, 1 minute at a time in a sitting position and 3 minutes at a time in a standing position. The measurement result of the sitting position (1 minute at a time) was used as a person's blood pressure. Body mass index (BMI) was determined from weight and height (kg/

m^2). Comorbidities were verified by MK from the electronic patient records, and ten different comorbidities were confirmed: heart diseases, cerebrovascular accident, peripheral arterial diseases, musculoskeletal diseases, pulmonary diseases, cancer, neurological diseases, gastrointestinal diseases, dementia and psychiatric diseases. A pharmacist reviewed the medication of each participant.

Laboratory tests were performed by Eastern Finland Laboratory Centre (ISLAB), which is licensed by the Finnish Accreditation Service. Total LDL and HDL cholesterol levels along with triglycerides (fP-Kol, fP-Kol-LDL, fP-Kol-HDL and fP-Trigly) were measured. The values are based on fasting samples.

2.3 | Ethical considerations

The ethical permission for the ISDM study protocol was granted by the Research Ethics Committee of Northern Savo Hospital District, Kuopio, Finland. The study was conducted in accordance with the Declaration of Helsinki. Each participant signed an informed consent form, and returning the health questionnaire was voluntary. Data were handled and analysed anonymously.

2.4 | Statistical analysis

IBM SPSS Statistics (25) for Windows was used for processing and analysing the data. The analysis included descriptive statistics, that is frequencies and cross-tabulations. Differences in frequencies between groups were tested using a chi-squared test. *P*-values of 0.05 or less were considered statistically significant.

3 | RESULTS AND DISCUSSION

Complete data were available from 358 patients, 182 (50.8%) of whom had type 2 diabetes and 176 (49.2%) who did not have diabetes. The characteristics of the study population are presented in Table 1. 91 (50%) of the persons with diabetes and 116 (66%) of the persons without diabetes were men. Persons with diabetes had a higher BMI, lower level of physical activity, were less frequently able to move without assistive aid and smoked less. Persons with diabetes had lower total LDL and HDL cholesterol levels, while their triglyceride levels were higher. Heart diseases were more common among persons with diabetes. Persons with diabetes had a lower mean AUDIT-C score, meaning less consumption of alcohol, a higher mean GDS-15 score, meaning more depressive symptoms and a lower mean EQ-5D score, indicating lower health-related quality of life. Persons with diabetes used more drugs on a regular basis and used more drugs as needed. Relative portions of drugs used in different ATC classes among persons with and without diabetes are shown in Figure 1. The number of persons with diabetes using the most commonly used drugs among persons with diabetes together with corresponding numbers of persons without diabetes using these drugs is shown in Table 2. The frequency of use differed to a great extent between persons with and without diabetes, especially for drugs used in cardiovascular diseases.

Seventy-five persons with diabetes (41.2%) and 69 persons without diabetes (39.2%) had at least one interaction classified as a class C interaction, meaning an interaction requiring, for example dose adjustments ($P = 0.699$). 13 (7.1%) persons with diabetes and 9 (5.1%) persons without diabetes had at least one interaction classified as a class D interaction, meaning an interaction to be best avoided ($P = 0.424$). When combined, 81 (44.5%) persons with diabetes and 73 (41.5%) persons without diabetes had at least one drug-drug interaction considered to be clinically relevant, that is a class C or class D interaction ($P = 0.563$). One person could have had more than one interaction, ranging from 1 to 7 interaction(s) per person with diabetes and from 1 to 9 interaction(s) per person without diabetes.

The number of times different drugs were involved in the clinically relevant drug-drug interactions is shown in Table 3. The most common drugs causing interactions are listed in the Table. The total number of clinically relevant interactions (class C or D interaction in Sfinx® database) was 183 in persons with diabetes and 150 in persons without diabetes. Of 183 interactions in persons with diabetes, 170 were class C and 13 were class D interactions. Of 150 interactions in persons without diabetes, 140 were class C and 10 were class D interactions. Most common were interactions with non-steroidal anti-inflammatory drugs (NSAIDs) along with interactions with warfarin. The most common interactions with warfarin were interactions with paracetamol and simvastatin. NSAID interactions consisted mostly of interactions with acetylsalicylic acid and drugs used in cardiovascular diseases (eg, ACE inhibitors, angiotensin II receptor blockers and β-blockers). Interactions with warfarin along with interactions with selective serotonin uptake inhibitors (SSRI) or serotonin and noradrenaline uptake inhibitors (SNRIs) were more common among persons with diabetes.

The frequency of high risk for drug adverse effects is shown in Table 4. Persons with diabetes had a high risk for constipation ($P = 0{,}039$) more frequently. The risk for bleeding, anticholinergic side effects, orthostatic hypotension, sedation, QT prolongation, seizures and serotonergic side effects were also more frequent among persons with diabetes, but these differences were statistically insignificant.

Our main findings are that there were no significant differences in the frequency of drug-drug interactions or high risk for drug adverse effects among persons with and without diabetes. However, drug use was more common among persons with diabetes compared to persons without diabetes and there were some differences in drugs with significantly increased risk for interactions.

Our study shows that potential drug-drug interactions are less frequent among home-dwelling persons with diabetes when compared to older persons with diabetes in home health care studied by Ibrahim et al,[12] where potentially moderate drug-drug interactions were recorded in 92.8% of patients and potentially severe drug-drug interactions were found in 38.8% of patients. However, it should be noted that the interaction database used was different, and therefore, the classification of interactions may not be equivalent. Clinically relevant interactions using the SFINX-PHARAO® database were found in 74% of the home care patients in a study conducted in Finland by Auvinen et al,[22] though the patients used more drugs and were older and more fragile than in our study. In

TABLE 1 Descriptive characteristics of the study population

	Diabetes mellitus		
	Diabetes N = 182	No diabetes N = 176	*P*-Value*
Men, n (%)	91 (50)	116 (66)	0.002
Age, mean (SD)	74 (7)	74 (6)	0.96
Education years, mean (SD)	9.5 (3.2)	9.8 (3.3)	0.38
Body mass index, kg/m^2, mean (SD)	31.2 (5.9)	27.6 (5.0)	<0.001
Physical activity, Kasari FIT index, mean (SD)	31 (20)	43 (22)	<0.001
Able to move without assistive aid, n (%)	124 (75)	147 (88)	0.002
Smoking n (%)	11 (6)	24 (14)	0.016
Blood pressure, mean (SD)			
Systolic	152 (22)	156 (22)	0.072
Diastolic	87 (11)	90 (12)	0.059
Total cholesterol, mmol/l, mean (SD)	4.60 (1.12)	4.91 (1.01)	0.006
LDL, mean (SD)	2.71 (0.99)	3.00 (0.84)	0.004
HDL, mean (SD)	1.38 (0.42)	1.56 (0.44)	<0.001
Triglycerides, mean (SD)	1.53 (0.66)	1.14 (0.51)	<0.001
Comorbidities n (%)			
Heart diseases	149 (82)	118 (67)	<0.001
Cerebrovascular accident	4 (2)	6 (3)	0.54
Peripheral arterial disease	5 (3)	6 (3)	0.72
Musculoskeletal diseases	70 (38)	64 (36)	0.68
Pulmonary diseases	19 (10)	17 (10)	0.81
Cancer	13 (7)	14 (8)	0.77
Neurological diseases	7 (4)	3 (2)	0.34
Gastrointestinal diseases	2 (1)	1 (1)	0.99
Dementia	8 (4)	2 (1)	0.11
Psychiatric diseases	8 (4)	3 (2)	0.22
AUDIT-C, mean (SD)	1.8 (1.9)	2.5 (2.4)	0.007
IADL, mean (SD)	10.8 (4.7)	10.9 (4.0)	0.90
MMSE, mean (SD)	26.9 (3.3)	27.4 (3.2)	0.18
GDS-15, mean (SD)	3.4 (3.1)	2.1 (2.4)	<0.001
EQ-5D, mean (SD)	0.758 (0.166)	0.829 (0.162)	<0.001
Drugs used on a regular basis, mean (SD)	7.1 (3.1)	4.2 (2.9)	<0.001
Drugs used as needed, mean (SD)	2.7 (2.5)	2.1 (2.0)	0.021

Abbreviations: EQ-5D, EuroQol Questionnaire; GDS-15, Geriatric Depression Scale; IADL, Lawton Instrumental Activities of Daily Living Scale; MMSE, Mini-Mental State Examination; SD, standard deviation.

the present study, the frequency of interactions to be best avoided (class D interactions) was slightly higher among persons with diabetes (7.1%) whereas the frequency among persons without diabetes (5.1%) was similar to the study conducted by Hosia-Randell et al,[23] which studied DDIs among nursing home residents (4.8%). The frequency of serious interactions (7.1%) among persons with diabetes was consistent with previous drug-drug interaction studies among persons with diabetes (5.1%-17.5%). However, a direct comparison is not possible since the classification and frequency of interactions were determined using different methods and the study populations differed from our study population.[11,24]

As for drug-drug interactions in different drug classes, interactions with warfarin were more common among persons with diabetes, which is probably related to the higher prevalence of heart diseases and use of antithrombotic agents among persons with diabetes. In our study population, 25.3% of persons with diabetes and 21.0% of persons without diabetes had a high risk for bleeding. A slightly higher frequency of risk for bleeding among persons with diabetes may be a consequence of higher frequency of warfarin interactions. Concurrent use of warfarin and warfarin-potentiating medication, for example antiplatelet or analgesic, has been associated with more haemorrhagic events and therefore higher treatment

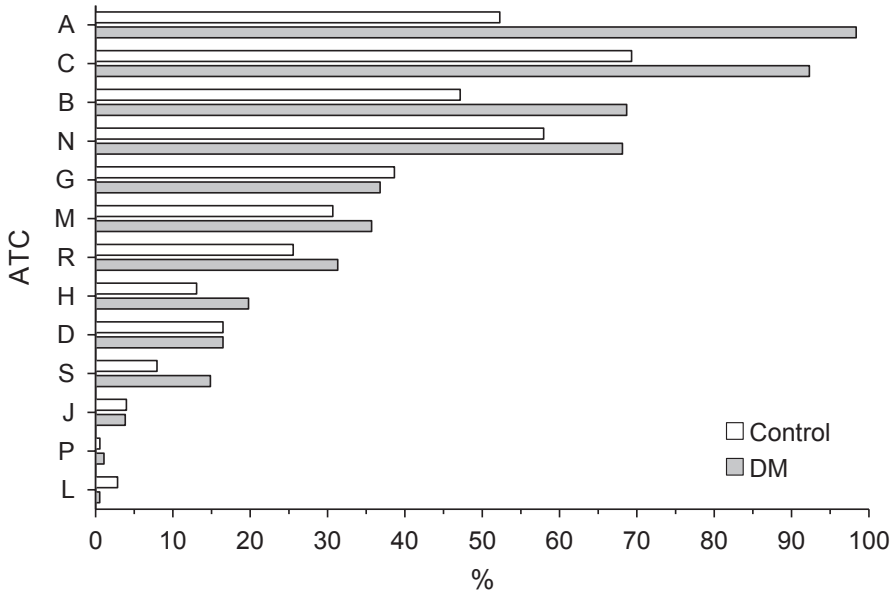

FIGURE 1 Relative portions of drugs used in different ATC classes among persons with and without diabetes. ATC, Anatomical Therapeutic Chemical

TABLE 2 Number of patients using the drugs most commonly used among persons with diabetes and corresponding numbers of patients without diabetes using these drugs

Number of patients using the most commonly used drugs, n (%)	Diabetes N = 182	No diabetes N = 176
A10 Drugs used in diabetes	167 (91.8)	0 (0)
B01 Antithrombotic agents	121 (66.5)	77 (43.8)
C09 Agents acting on the renin-angiotensin system	120 (65.9)	77 (43.8)
C10 Lipid-modifying agents	108 (59.3)	71 (40.3)
C07 Beta-blocking agents	107 (58.8)	68 (38.6)
N02 Analgesics	101 (55.5)	87 (49.4)
A12 Mineral supplements	62 (34.1)	54 (30.7)
C01 Cardiac therapy	55 (30.2)	38 (21.6)
A02 Drugs for acid related disorders	55 (30.2)	43 (24.4)
N05 Psycholeptics	50 (27.5)	31 (17.6)

costs.[25] In addition, Obreli-Neto et al[26] found that adverse drug effects related to warfarin (eg, gastrointestinal bleeding) are a common reason for hospital admissions. Ultimately, warfarin is highly noticed in The American Geriatrics Society Beers Criteria® updated in 2019 in potentially clinically important drug-drug interactions that should be avoided in older adults.[27] Therefore, drugs that interact with warfarin in particular should be considered carefully when prescribed to older persons with and without diabetes.

Interactions with NSAIDs were common in our study population in both persons with and without diabetes and NSAIDs interacted most commonly with antihypertensive drugs. Concurrent use of NSAIDs and antihypertensive drugs may diminish the antihypertensive effect.[28] Moreover, concurrent use of NSAIDs and ACE inhibitors has been associated with nephrotoxicity especially in elderly patients and the combination should therefore be carefully considered.[29] Interactions with SSRIs and with SNRIs were more common among persons with diabetes probably due to a slightly higher prevalence of depressive symptoms.

The strengths of this study include validated measurement tools (MMSE, AUDIT-C, IADL, GDS-15 and EQ-5D) and a standardized health examination conducted by one physician only. In addition, the diagnosis of diabetes was made according to the ICD-10 classification. Furthermore, the SFINX-PHARAO® database contains updated and evidence-based information of drugs used in Finland and the database is widely used as a support for clinical decision.

Our study has some limitations. First, this study was cross-sectional, and therefore, the interactions or changes in the medication in future cannot be determined. In addition, our study was conducted in only one primary care district, and therefore, the results cannot be generalized directly on the national level. Furthermore, the consequences of drug-drug interactions were not defined, that is the manifestations of the DDIs are uncertain. Finally, it should be noted that only a high risk for adverse effects was determined and a minor risk for adverse effects may exist.

4 | WHAT IS NEW AND CONCLUSION

In conclusion, clinically relevant drug-drug interactions among older persons with and without diabetes are common and should be

TABLE 3 Number of times different drugs were involved in clinically relevant drug-drug interactions. Clinically relevant interaction = class C or class D interaction in the Sfinx® database

	Number of times one drug was involved in a clinically relevant drug-drug interaction among persons with diabetes	Number of times one drug was involved in a clinically relevant drug-drug interaction among persons without diabetes
NSAIDs[a]	76	81
Warfarin	58	35
ACE inhibitors and angiotensin II receptor blockers[b]	33	30
Platelet aggregation inhibitors[c]	29	26
Paracetamol	23	19
β-blockers[d]	22	27
Diuretics[e]	22	17
Statins[f]	19	13
SSRIs and SNRIs[g]	18	7

ACE inhibitor, angiotensin-converting-enzyme inhibitor; NSAID, non-steroidal anti-inflammatory drug; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Ibuprofen, naproxen, meloxicam, ketoprofen, diclofenac, etoricoxib.
[b]Losartan, ramipril, valsartan, candesartan, enalapril, eprosartan, telmisartan, perindopril.
[c]Acetylsalicylic acid, clopidogrel, dipyridamole.
[d]Bisoprolol, metoprolol, betaxolol, celiprolol, propranolol, atenolol, nebivolol.
[e]Hydrochlorothiazide, amiloride, spironolactone, furosemide, indapamide.
[f]Simvastatin, fluvastatin, atorvastatin, rosuvastatin.
[g]Duloxetine, citalopram, fluoxetine, escitalopram, venlafaxine.

TABLE 4 Frequency of having a high risk for drug adverse effect among persons with diabetes and without diabetes

Adverse effect	Diabetes, n (%) (N = 182)	No diabetes, n (%) (N = 176)	*P*-Value
Bleeding	46 (25.3)	37 (21.0)	0.341
Constipation	35 (19.2)	20 (11.4)	0.039
Anticholinergic side effects	30 (16.5)	17 (9.7)	0.056
Orthostatic hypotension	23 (12.6)	14 (8.0)	0.146
Sedation	11 (6.0)	7 (4.0)	0.371
QT prolongation	3 (1.6)	1 (0.6)	0.331
Seizures	1 (0.5)	0 (0)	
Serotonergic side effects	1 (0.5)	0 (0)	
Nephrotoxicity	0 (0)	1 (0.6)	

monitored regularly. In particular, due to several comorbidities related to diabetes and commonly used drugs among persons with diabetes, interactions with NSAIDs, warfarin and drugs used in heart diseases should be carefully considered to avoid drug adverse effects.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (256/2015) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

The health questionnaire included an information letter explaining the use of the data and returning the questionnaire was voluntary. The autonomy of the research subjects was respected, and only anonymous data were analysed. No harm to the subjects was possible, and the confidentiality of the subjects and research data were protected.

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How to cite this article: Ikäheimo I, Karjalainen M, Tiihonen M, et al. Clinically relevant drug-drug interactions and the risk for drug adverse effects among home-dwelling older persons with and without type 2 diabetes. *J Clin Pharm Ther*. 2019;44:735–741. https://doi.org/10.1111/jcpt.12854