BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020852
Article Type:	Research
Date Submitted by the Author:	29-Nov-2017
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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Health services research, Pharmacology and therapeutics
Keywords:	DIABETES & ENDOCRINOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY

Polypharmacy Use among Patients with Diabetes: A Cross-Sectional Retrospective Study

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ABSTRACT

Objectives. Patients with diabetes are at high risk for polypharmacy (i.e. use of multiple classes of medications) for treatment of diabetes, associated comorbidities, and other co-existing conditions. This study aims to estimate the prevalence of polypharmacy and factors associated with polypharmacy among adult patients with diabetes.

Methods. A cross-sectional retrospective observational study of adults with diabetes, who visited the outpatient clinic of a tertiary teaching hospital in Saudi Arabia, was conducted. Data were extracted from the Electronic Health Record (EHR) database for a period of twelve-month (January to December 2016). Polypharmacy was defined as the cumulative use of five or more medication classes. Polypharmacy among adults with diabetes was measured by calculating the average number of medication classes prescribed per patient. A multivariable logistic regression model was used to examine the factors associated with polypharmacy after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions.

Results. A total of 8,932 adults with diabetes were included in this study. Of these, nearly 78 % had polypharmacy, which was more likely among women as compared to men and more likely among the elderly (age $\geq$ 60 years) as compared to the adults. Also, polypharmacy was two times as likely among patients with coexisting cardiovascular disease (AOR=2.89; 95% CI: 2.54-3.29), respiratory disease (AOR=2.42; 95% CI: 1.92-3.03), and mental health conditions (AOR=2.19; 95% CI: 1.74-2.76), and three times as likely among patients with co-existing musculoskeletal disease as compared to those without these co-existing chronic conditions categories.

Conclusions. Polypharmacy is common among patients with diabetes, with an even higher rate in the elderly patients. Health care providers can help in detecting polypharmacy and in providing recommendations for simplifying medication regimens and minimizing tablet-counts to enhance the outcome of diabetes care.

Keywords. Diabetes; Polypharmacy; Chronic conditions; Electronic health records.

Strengths and limitations of this study

- Findings from this study have identified the individuals who have a high risk of polypharmacy and added to the existing literature on the prevalence of polypharmacy among all age groups.
- The study results highlighted the need to routinely monitor high-risk individuals for drug-related problems.
- This study has used a large sample size, which allowed us to do a subgroup analysis to examine the polypharmacy use among the elderly population.
- This study have not controlled for the severity of diabetes using the Diabetes Complications Severity Index (DCSI) which may affect the rate of polypharmacy.
- It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not.

INTRODUCTION

Diabetes is a highly prevalent chronic condition among adults in Saudi Arabia; between 21-24% of adults are estimated to have diabetes.[1,2] It is projected that 27% of adults in Saudi Arabia will have diabetes by 2035.[3] Diabetes is one of the top ten causes of morbidity and mortality worldwide.[4] Patients with diabetes often have co-existing chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression and renal disease, which requires the use of multiple medications to treat those co-existing chronic conditions.[5] All of this put patients with diabetes at high risk of polypharmacy,[6,7] with an estimated prevalence of 57% to 84% of patients with diabetes using five or more medications.[8] In Saudi Arabia, a cross-sectional study among 766 adults who visited outpatient's clinic at a tertiary care center, reported that the prevalence of polypharmacy among patients with diabetes was 71%.[9]

An examination of polypharmacy among patients with diabetes is important because polypharmacy increases the probability of the adverse drug events, drug-drug interactions, duplication of therapy,[10] decrease compliance to antidiabetic medications,[11] and poor glycemic control.[12] The presence of polypharmacy is also associated with prescribing cascades, in which adverse drug events are misinterpreted as new medical conditions which can result in the prescription of new medications to treat those conditions.[13] Polypharmacy has other negative health consequences such as increased risk of hospitalization and medication error,[14,15] higher risk of fall,[16] poor functional status,[17] poor quality of life, and high healthcare cost.[18,19] Polypharmacy among diabetes patients is often associated with many factors. These include age,[9] sex,[20] co-existing conditions,[20] rurality, [21,9] diabetes complications, and aggressive diabetic treatment.[22,23]

To date, limited studies have examined the prevalence of polypharmacy among adults with diabetes living in Saudi Arabia on a large scale, and looking at specific factors that put patients at risk of polypharmacy. Identifying the prevalence and the subgroup of patients at high risk of polypharmacy will facilitate pharmacovigilance efforts in clinical practice settings. Therefore, the primary objective of this observational study is to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia and to identify the factors that are associated with polypharmacy, specifically the association between co-existing chronic conditions and polypharmacy.

METHODS

Study Design

A cross-sectional retrospective observational study was conducted in a tertiary teaching hospital in Saudi Arabia.

Data Source and Data Extraction

This study used data retrieved from the Electronic Health Record (EHR) database for the period from 1st January 2016, until 30th December 2016. Institutional review board (IRB) approval was obtained to conduct the study (IRB number: E-17-2601). Strict confidentiality of the data was maintained throughout the research process. The data from EHR were derived from demographics file, clinical diagnosis file, and prescription drug file. The demographics file contained information about the patients' date of birth, gender, marital status, nationality, and encounter type. The clinical diagnosis file provided information about the clinical diagnosis from inpatient and outpatient visits. Physicians reported clinical diagnosis using the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes, *International*

Classifications of Diseases – 10th edition, Clinical Modification (ICD-10-CM) codes, or the *Systematized Nomenclature of Medicine* (SNOMED) diagnosis codes. The prescription drug file contained information about the medications used. The demographics, clinical diagnosis, and prescription drug files were merged into one file using the encrypted patient medical record number. The completeness and the validity of the data from EHR in this tertiary teaching hospital in Saudi Arabia has not been studied before; however the researchers of this study examined the completeness of this data and found that 91.0% of the patients had a complete data (i.e., have information on the age, gender, marital status, nationality, encounter type, and clinical diagnosis) and 85.0% of the patients had complete medication-related information.

Study Population

The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary teaching hospital during a one-year period. No exclusion criteria were applied to the study population.

Measures

Dependent Variable

In our study, the dependent variable was "polypharmacy use". There are different approaches in the literature to measure polypharmacy such as simultaneous, cumulative and continuous. Also, there is no consensus on the thresholds regarding the number of medications above which we consider the existence of polypharmacy.[24] In the current study, we defined polypharmacy as the cumulative use of five or more medication classes during a one year period, this threshold has been used more than others.[21,24,25] Using this definition, the prevalence of polypharmacy among adults was measured by the sum of different medication classes

administered over a twelve-month period. There is no consensus on the medications that should be included in the measurements of the polypharmacy. We have included all medication classes, including topical agents and vitamins in our definition.

Independent Variables

Independent variables included were age groups in years (18-29, 30-39, 40-49, 50-59, ≥60), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into four categories (cardiovascular, musculoskeletal, respiratory, or mental health conditions) (Appendix I). Cardiovascular conditions composed of hypertension, ischemic heart disease, vascular heart disease, heart failure, hyperlipidemia, and stroke. Musculoskeletal conditions composed of osteoarthritis, and osteoporosis; respiratory conditions include asthma, and chronic obstructive pulmonary disease (COPD). Mental health conditions include dementia, depression, anxiety, and schizophrenia. These conditions have been selected because they are highly prevalent among patients with diabetes and some of them were associated with polypharmacy use.[5,26]

Statistical Analysis

Chi-square tests were used to examine the factors associated with polypharmacy use. A multivariable logistic regression was used to examine the factors associated with polypharmacy (i.e., use of $\geq$ 5 medication classes) after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions. All statistical analyses were carried out using the Statistical analysis software, version 9.2 (SAS® 9.2).

RESULTS

A total of 8,832 adults patients were identified during the twelve-month period. The majority were female (62.2%), and 43.3% of the study population were elderly (age ≥60 years). About half of the subjects (54.1%) had two or more diagnosed co-existing chronic health conditions. Hypertension, dyslipidemia were among the most common chronic conditions in our study population. Characteristics of the study population are presented in Table 1.

Polypharmacy Use among Patients with Diabetes

Overall 77.9 % of adults with diabetes were using five or more medication classes. The study population characteristics by polypharmacy status are summarized in Table 2. This study found a significantly higher percentage of polypharmacy among the elderly as compared to other age groups, for example, as compared to patients with age between 18-29 (84.8% vs 37.4%, P-value <0.001). Women with diabetes had a significantly higher percentage of polypharmacy as compared to men (81.7% vs. 71.6%, P-value <0.001). Moreover, polypharmacy was significantly higher among diabetes patients with two or more co-existing comorbid conditions versus those with no co-existing chronic conditions (89.6% vs. 48.6%, P-value <0.001). Looking at comorbid conditions closely, polypharmacy was significantly higher among patients with cardiovascular (54.7%), musculoskeletal (76.4%), respiratory (76.6%), and mental health conditions (77.2%) as compared to those without those co-existing chronic conditions.

Logistic Regression: Factors Associated with Polypharmacy

The adjusted odds ratios (AOR) and 95% confidence intervals (CI) from multivariable logistic regression on polypharmacy are displayed in Table 3. Several factors were identified: age, gender, and co-existing chronic conditions. Polypharmacy was less likely among young adults as compared to the elderly. Women were more likely to have polypharmacy compared to men (AOR=1.60; 95% CI: 1.43-1.79). Polypharmacy was two times as likely among patients with co-existing cardiovascular disease (AOR=2.89; 95% CI: 2.54-3.29), mental health conditions (AOR=2.19; 95% CI: 1.74-2.76), and respiratory diseases (AOR=2.42; 95% CI: 1.92-3.03), and three times as likely among those with musculoskeletal disease (AOR=3.16; 95% CI: 2.31-4.30) compared to adults with diabetes and without these co-existing chronic conditions.

DISCUSSION

Our study estimated the prevalence of polypharmacy among adults with diabetes in Saudi Arabia. In our study population, the rate of polypharmacy was high; nearly eighty percent of adults with diabetes used five or more medication classes. While this rate is within the documented rate in the literature among adults with diabetes 57% to 84%,[9,20] we could not find a study that reported the rate of polypharmacy among all age groups of adults with diabetes. We observed a higher rate of polypharmacy among the elderly as compared to all age groups. The very high rate of polypharmacy observed in our study population suggests that health care providers need to routinely monitor these individuals for potentially inappropriate medications, adverse drug events, and drug-drug interactions. Diabetes patients with polypharmacy may benefit from multidisciplinary collaborative care model that involves pharmacist follow up for the patients to assess the medication use. In an open-label, parallel-arm, randomized, controlled study, collaborative care has been associated with improvement in the management of diabetes

and reduction the healthcare cost.[27] Pharmacists can help other health care providers in detecting polypharmacy, drug interactions, and in providing recommendations for simplified medication regimens, and minimizing tablet-counts to enhance the outcome of diabetes care.

In our study population, co-existing chronic conditions were very common,[28] studies have shown that 90% of patients with diabetes had at least one additional chronic condition,[5] our study found that 86% of patients with diabetes had at least one co-existing chronic condition. It is plausible that we have very high rates of polypharmacy because 54% of adults in our study had multimorbidity (i.e. two or more co-existing chronic conditions). As a result, we found that polypharmacy rate was associated with the number of co-existing chronic conditions.[5] Although there is a well-documented literature on the relationship between the higher number of coexisting conditions and polypharmacy,[5,20,29] our study extended the literature by analyzing the association between type of chronic conditions and polypharmacy among patients with diabetes. We observed that the polypharmacy rates differed by the type of co-existing chronic conditions; with the highest use among those with musculoskeletal conditions.[9] This is not surprising because of the use of many vitamin supplements, and oral and topical medications to relieve the chronic pain. Further, we found a high rate of polypharmacy among adults with diabetes and co-existing cardiometabolic conditions as compared to adults without cardio-metabolic conditions which is consistent with the published literature among the elderly with cardiometabolic conditions cluster.[30,31]

Women were more likely to have a polypharmacy compared to men, this is consistent with the findings from studies among patients with diabetes.[20] In addition, studies have reported that women in the general population have a higher use of prescribed and non-prescribed medications, and higher healthcare utilization as compared to men.[32-35] This could be as a result

of that women tend to be more concerned about their health and seek health services more often than men.[36]

This study has some limitations; we used a 12-month period to measure multiple medications use, which is not concurrent use and may have resulted in a very high rate of multiple medications uses. We did not control for the severity of diabetes using the Diabetes Complications Severity Index (DCSI) which may affect the rate of polypharmacy. We have also only observed filled prescriptions and not actual use of the medications. By using the EHR data; so we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR. Due to the cross-sectional nature of the data; it is difficult to assess the causal relationship. People with the end of life care were included and this may have overestimated the rate of polypharmacy. Moreover, we have included all medication classes, including the topical agents, and vitamins in our definition, which may have overestimated the rate of polypharmacy. It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not.

Despite these limitations, this study has many advantages such as the use of large sample size, which allowed us to do a subgroup analysis to examine the polypharmacy use among the elderly population. Furthermore, findings from this study added to the existing literature on the prevalence of polypharmacy among all age groups and have identified the individuals who have a high risk of polypharmacy. In addition, our results highlighted the need to routinely monitor high-risk individuals for drug-related problems.

CONCLUSION

Polypharmacy is very common among adults with diabetes; particularly among individuals with multiple chronic conditions. Those individuals may benefit from collaborative

care model that follow up the patients to assess the medication use. Also, health care providers can help in reducing polypharmacy rate by providing recommendations to simplified treatment regimens; thereby enhance the health outcomes of patients with diabetes.

Ethics and Data Confidentiality

Confidentiality of the data was maintained throughout the research process. Retrieved data was stored and saved as coded excel files. A customized formula was used to generate study encrypted IDs assigned to each participant and replaced patients MRN's. Data extracted were stored at the Research Unit at the tertiary hospital on secured, password protected, and limited accessed computers.

Authors' contribution

Dr.Monira Alwhaibi, Dr.Bander Balkhi,Dr.Tariq Alhawassi,Dr.Hadeel Alkofide, Nouf Alduhaim, Rawan Alabdulali, Hadeel Drweesh and Prof.Usha Sambamoorthi have all participated in designing the study, drafting the manuscript, analysis, interpretation of the findings, revising the manuscript content and gave final approval of the final version of this manuscript.

Acknowledgement

This project was supported by King Saud University, Deanship of Scientific Research, Research Chair.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1
Characteristics of the Study Population
Adults with Diabetes
Electronic Health Records Database, 2016

	N	%
Total	8,932	100.0
Age Group		
18-29	198	2.2
30-39	463	5.2
40-49	1,226	13.7
50-59	3,176	35.6
=>60	3,869	43.3
Marital Status		
Single	957	11.6
Married	7,310	88.4
Gender		
Male	3,375	37.8
Female	5,557	62.2
Nationality		
Saudi	7,957	89.4
Non-Saudi	946	10.6
Cardiovascular		
Yes	7,209	80.7
No	1,723	19.3
Musculoskeletal		
Yes	787	8.8
No	8,145	91.2
Respiratory		
Yes	961	10.8
No	7,971	89.2
Mental		
Yes	766	8.6
No	8,166	91.4
# Chronic Conditions		
Without co-existing conditions	1250	14.0
Single co-existing condition	2849	31.9
≥2 co-existing conditions	4833	54.1

Note: Study population comprised of 8,932 diabetic adults
(Age ≥18year) who visited outpatient's clinics from a tertiary hospital in 2016

Table 2
Number and Row Percentage of Characteristics by Polypharmacy
Adults with Diabetes,
Electronic Health Records Database, 2016

	Polypharmacy		No Polypharmacy				
	N	%	N	%	Chisqval	chisqp	Sig
ALL	6,957	77.9	1,975	22.1			
Age Group					517.7	0.000	***
18-29	74	37.4	124	62.6			
30-39	253	54.6	210	45.4			
40-49	830	67.7	396	32.3			
50-59	2,521	79.4	655	20.6			
=>60	3,279	84.8	590	15.2			
Marital Status					76.5	0.000	***
Single	635	66.4	322	33.6			
Married	5,769	78.9	1,541	21.1			
Gender					122.8	0.000	***
Male	2,418	71.6	957	28.4			
Female	4,539	81.7	1,018	18.3			
Nationality					6.6	0.010	**
Saudi	6,167	77.5	1,790	22.5			
Non-Saudi	768	81.2	178	18.8			
Cardiovascular					668.1	0.000	***
Yes	6,015	83.4	1,194	16.6			
No	942	54.7	781	45.3			
Musculoskeletal					124.4	0.000	***
Yes	737	93.6	50	6.4			
No	6,220	76.4	1,925	23.6			
Respiratory					76.8	0.000	***
Yes	855	89.0	106	11.0			
No	6,102	76.6	1,869	23.4			
Mental					27.3	0.000	***
Yes	654	85.4	112	14.6			
No	6,303	77.2	1,863	22.8			
# Chronic Conditions					1093.807	0.000	***
Without co-existing condition	607	48.6	643	51.4			
Single co-existing condition	2,018	70.8	831	29.2			
≥2 co-existing conditions	4,332	89.6	501	10.4			

Note: Study population comprised of 8,932 adults with diabetes (age ≥18year) who visited outpatient's clinics from a tertiary hospital in 2016. Polypharmacy use was defined as the use of five or more medication classes during the one year period. Asterisks (*) represent significant differences in polypharmacy from chi-square tests
***P< .001

Table 3
Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CI)
Logistic Regression on Polypharmacy
Adults with Diabetes,
Electronic Health Records database, 2016

	AOR	95% CI	Sig.
Age Group			
18-29	0.18	[0.13 , 0.27]	***
30-39	0.31	[0.24 , 0.39]	***
40-49	0.45	[0.39 , 0.54]	***
50-59	0.73	[0.64 , 0.84]	***
≥60 (Ref.)			
Marital Status			
Single	1.16	[0.96 , 1.40]	
Married (Ref.)			
Gender			
Female	1.60	[1.43 , 1.79]	***
Male (Ref.)			
Nationality			
Non-Saudi	1.81	[1.50 , 2.19]	***
Saudi (Ref.)			
Cardiovascular			
Yes	2.89	[2.54 , 3.29]	***
No (Ref)			
Musculoskeletal			
Yes	3.16	[2.31 , 4.30]	***
No (Ref)			
Respiratory			
Yes	2.42	[1.92 , 3.03]	***
No (Ref)			
Mental			
Yes	2.19	[1.74 , 2.76]	***
No (Ref)			

Note: Based on 8,932 adults with diabetes, who visited outpatient's clinics from a tertiary hospital in 2016. Polypharmacy use was defined as the use of five or more medication classes during the one year period. Asterisks (*) represent significant differences on polypharmacy use compared to the reference group based on logistic regression.
***P< .001
Ref: Reference Group

Appendix I
Diagnoses codes used to identify the types of chronic conditions
Electronic Health Records database, 2016

Type of Chronic Conditions	ICD-9-CM Codes	ICD-10-CM Codes	SNOMED Codes
Cardiovascular Conditions			
Diabetes	250, 250.00	E11, E11.9, E14.9	121589010, 502372015
Hypertension	401.9	I10, 10	64176011, 2164904016
Ischemic heart disease		I25, I25.9	2534671011, 2537479013, 397667016, 2534663012
Vascular heart disease			1705016
Heart failure	428.0, 428.1	I50,I50.9	1234906013, 143156018, 251680018, 94251011, 2645367010, 18472010, 139475013, 2816764017, 493289014, 70653017, 80720010
Hyperlipidemia		E78.5	92826017, 1209706018
Musculoskeletal Conditions			
osteoarthritis			1776248011, 359420013, 359421012, 1785522017
Osteoporosis		M81.99	453855011, 107806013
Respiratory Conditions			
Asthma	493, 493.90	J45	301485011, 301480018
COPD		J44.1, J44.9	23290013, 23287019, 475431013, 475427019
Mental Health Conditions			
Dementia		F02	87274019
Depression	311	F31.3	486186018, 486187010, 110183011, 346973011, 346979010, 55208011, 454082014, 486187010, 124707013, 1208903011, 490537016, 346980013, 1228731019, 486184015
Anxiety		F41.8, F41.9	346980013, 369987018, 303689015, 481155011, 81133019
Schizophrenia		F20	114425016, 405368015, 294764011, 138883015, 96745016

ICD-9-CM codes: International Classifications of Diseases – 9th edition, Clinical Modification
ICD-10-CM codes: International Classifications of Diseases – 10th edition
SNOMED: Clinical Modification Systematized Nomenclature of Medicine
COPD: Chronic Obstructive Pulmonary Disease

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020852.R1
Article Type:	Research
Date Submitted by the Author:	27-Feb-2018
Complete List of Authors:	Alwhaibi, Monira; King Saud University College of Pharmacy, Clinical Pharmacy; King Saud University, Medication Safety Research Chair Balkhi, Bander; King Saud University College of Pharmacy, Clinical Pharmacy; King Saud University, Medication Safety Research Chair Alhawassi, Tariq ; King Saud University College of Pharmacy, Clinical Pharmacy; King Saud University, Medication Safety Research Chair Alkofide, Hadeel; King Saud University College of Pharmacy, Clinical Pharmacy Alduhaim, Nouf; King Saud University College of Pharmacy, Clinical Pharmacy Alabdulaali, Rawan; King Saud University College of Pharmacy, Clinical Pharmacy drweesh, hadeel ; King Saud University College of Pharmacy, Clinical Pharmacy Sambamoorthi, Usha; West Virginia University Health Sciences Center, Pharmaceutical Systems & Policy
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Health services research, Pharmacology and therapeutics
Keywords:	DIABETES & ENDOCRINOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY, Drug Use Evaluation

Polypharmacy among Patients with Diabetes: A Cross-Sectional Retrospective Study in a Tertiary Hospital in Saudi Arabia

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ABSTRACT

Objectives. Patients with diabetes are at high risk for polypharmacy (i.e. use of multiple medications) for treatment of diabetes, associated comorbidities, and other co-existing conditions. This study aims to estimate the prevalence of polypharmacy and factors associated with polypharmacy among adult patients with diabetes.

Methods. A cross-sectional retrospective observational study of adults with diabetes, who visited the outpatient clinic of a tertiary teaching hospital in Saudi Arabia, was conducted. Data were extracted from the Electronic Health Record (EHR) database for a period of twelve-month (January to December 2016). Polypharmacy was defined as the cumulative use of five or more medications. Polypharmacy among adults with diabetes was measured by calculating the average number of medications prescribed per patient. A multivariable logistic regression model was used to examine the factors associated with polypharmacy.

Results. A total of 8,932 adults with diabetes were included in this study. Of these, nearly 78 % had polypharmacy, which was more likely among women as compared to men and more likely among older adults (age $\geq$ 60 years) as compared to the adults. Also, polypharmacy was two times as likely among patients with coexisting cardiovascular conditions (AOR=2.89; 95% CI: 2.54-3.29), respiratory disease (AOR=2.42; 95% CI: 1.92-3.03), and mental health conditions (AOR=2.19; 95% CI: 1.74-2.76), and three times as likely among patients with co-existing musculoskeletal disease (AOR=3.16; 95% CI: 2.31-4.30) as compared to those without these co-existing chronic conditions categories.

Conclusions. Polypharmacy is common among patients with diabetes, with an even higher rate in older adults patients. Health care providers can help in detecting polypharmacy and in providing recommendations for simplifying medication regimens and minimizing medications to enhance the outcome of diabetes care.

Keywords. Diabetes; Polypharmacy; Chronic conditions; Electronic health records; Drug use evaluation.

Strengths and limitations of this study

- This study has provided a real insight into the current prevalence and predictors of polypharmacy among patients with diabetes in Saudi Arabia including a large study population of patients with diabetes.
- Around nine-thousand patients were included in this study, which allowed us to identify the prevalence of polypharmacy among a subgroup of patients.
- This study has not controlled for the severity of diabetes using the Diabetes Complications Severity Index (DCSI) which may affect the rate of polypharmacy.
- This study used a twelve-month period to measure multiple medications use, which is not concurrent use and may have resulted in a very high rate of multiple medications uses.
- By using the EHR data; so we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR.
- It has to be noticed that not all polypharmacy is harmful; however, future studies to assess inappropriate medications associated with polypharmacy is warranted

INTRODUCTION

Diabetes is a highly prevalent chronic condition among adults in Saudi Arabia; between 21-24% of adults are estimated to have diabetes.[1,2] It is projected that 27% of adults in Saudi Arabia will have diabetes by 2035.[3] Diabetes is one of the top ten causes of morbidity and mortality worldwide.[4] Patients with diabetes often have co-existing chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression and chronic kidney disease, which requires the use of multiple medications to treat those co-existing chronic conditions.[5] All of this put patients with diabetes at high risk of polypharmacy,[6,7] with an estimated prevalence of 57% to 84% of patients with diabetes using five or more medications.[8] A study among adults with diabetes in the US documented that the 54% of adults with diabetes have polypharmacy.[9] A multicenter cross-sectional survey conducted in Italy reported that 57% of patients with diabetes use five or more medications.[10] In addition, polypharmacy was reported among 84% older adults patients with diabetes.[8] In Saudi Arabia, a cross-sectional study among 766 adults who visited outpatient's clinic at a tertiary care center, reported that the prevalence of polypharmacy among patients with diabetes was 71%.[11]

An examination of polypharmacy among patients with diabetes is important because polypharmacy increases the probability of the adverse drug events[12,13], drug-drug interactions[14], duplication of therapy,[15] decreases compliance to antidiabetic medications,[16] and poor glycemic control.[17] The presence of polypharmacy is also associated with prescribing cascade, in which adverse drug events are misinterpreted as new medical conditions which can result in the prescription of new medications to treat those conditions.[18] Polypharmacy has other negative health consequences such as increased risk of

hospitalization and medication error,[19,20] higher risk of fall,[21] poor functional status,[22] poor quality of life, and high healthcare cost.[23,24] Polypharmacy among diabetes patients is often associated with many factors. These include age,[11] sex,[10] co-existing conditions,[10] rurality, [25,11] diabetes complications[10], and aggressive diabetes treatment.[26,27]

To date, limited studies have examined the prevalence of polypharmacy among adults with diabetes living in Saudi Arabia on a large scale, and assessed the specific factors that put patients at risk of polypharmacy. Identifying the prevalence and the subgroup of patients at high risk of polypharmacy will facilitate pharmacovigilance efforts in clinical practice settings. Therefore, the primary objective of this observational study is to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia and to identify the factors that are associated with polypharmacy, specifically the association between co-existing chronic conditions and polypharmacy.

METHODS

Study Design

A cross-sectional retrospective observational study was conducted in a tertiary teaching hospital in Saudi Arabia. This hospital is one of the largest tertiary teaching hospitals in Riyadh, Saudi Arabia, with a 1200-bed facility and all general and subspecialty medical services. The hospital provides primary, secondary, and tertiary care services. The patient population is composed predominantly of local citizens as well as residents, from northern region in Riyadh; the hospital also serves the entire country as a referral center.

Data Source and Data Extraction

This study used data retrieved from the Electronic Health Record (EHR) database for the period from 1st January 2016, until 30th December 2016. Institutional review board (IRB) at King Saud University Medical City approval was obtained to conduct the study (IRB number: E-17-2601). Strict confidentiality of the data was maintained throughout the research process. The data from EHR were derived from demographics file, clinical diagnosis file, and prescription drug file. The demographics file contained information about the patients' date of birth, gender, marital status, nationality, and encounter type. The clinical diagnosis file provided information about the clinical diagnosis from inpatient and outpatient visits. Physicians reported clinical diagnosis using the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes, *International Classifications of Diseases – 10th edition, Clinical Modification* (ICD-10-CM) codes, or the *Systematized Nomenclature of Medicine* (SNOMED) diagnosis codes. The prescription drug file contained information about the medications used. The demographics, clinical diagnosis, and prescription drug files were merged into one file using the encrypted patient medical record number. The completeness and the validity of the data from EHR in this tertiary teaching hospital in Saudi Arabia has not been studied before; however the researchers of this study examined the completeness of this data and found that 91.0% of the patients had a complete data (i.e., have information on the age, gender, marital status, nationality, encounter type, and clinical diagnosis) and 85.0% of the patients had complete medication-related information.

Study Population

The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary teaching hospital during a one-year period. No exclusion criteria were applied to the study population.

Patient and Public Involvement

This study used a retrospective data for patients who visited a tertiary hospital in Riyadh; therefore patients were not involved in the design of this study.

Measures

Dependent Variable

In our study, the dependent variable was "polypharmacy". There are different approaches in the literature to measure polypharmacy such as simultaneous, cumulative and continuous. Also, there is no consensus on the thresholds regarding the number of medications above which we consider the existence of polypharmacy.[28] In the current study, we defined polypharmacy as the cumulative use of five or more medications during a one year period, this threshold has been used more than others.[25,28,29] Using this definition, the prevalence of polypharmacy among adults was measured by the sum of unique therapeutic medication classes administered over a twelve-month period. There is no consensus on the medications that should be included in the measurements of the polypharmacy. Also, all the prescription and the non-prescription/Over the Counter (OTC) medications categories were included in our definition of polypharmacy.

Independent Variables

Independent variables included were age groups in years (18-29, 30-39, 40-49, 50-59, ≥60), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into five categories (cardiovascular, chronic kidney disease, musculoskeletal, respiratory, or mental health conditions) (Appendix I). Cardiovascular conditions composed of hypertension, ischemic heart disease, vascular heart disease, stroke, heart failure, and dyslipidemia. Musculoskeletal conditions composed of osteoarthritis, and osteoporosis; respiratory conditions include asthma, and chronic obstructive pulmonary disease (COPD). Mental health conditions include dementia, depression, anxiety, and schizophrenia. These conditions have been selected because they are highly prevalent among patients with diabetes and some of them were associated with polypharmacy.[5,30]

Statistical Analysis

Frequency and percentage were used to describe the categorical variables (age, sex, marital status, nationality, co-existing chronic conditions, and polypharmacy). Mean and Standard deviation were used to describe continuous variables. Chi-square tests were used to examine the factors associated with polypharmacy. A multivariable logistic regression was used to examine the factors associated with polypharmacy (i.e., use of ≥ 5 medications) after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions. All statistical analyses were carried out using the Statistical analysis software, version 9.2 (SAS® 9.2).

RESULTS

A total of 8,932 adult patients were identified during the twelve-month period. The majority were Saudi (89.4%), female (62.2%), and 43.3% of the study population were older

adults (age ≥60 years), the mean age of the study population was 57 years old. About half of the subjects (54.1%) had two or more diagnosed co-existing chronic health conditions. Hypertension, dyslipidemia, asthma, osteoarthritis, and anxiety were among the most common chronic conditions in our study population. Characteristics of the study population are presented in Table 1.

Polypharmacy among Patients with Diabetes

Overall 77.9 % of adults with diabetes were using five or more medications. Also, when we identified the rate of polypharmacy (i.e, taking 10 or more medications) we found that 17.2% of adults have a hyperpolypharmacy. The most commonly used medications in our study population were antidiabetic medications (81.4%), followed by nonsteroidal anti-inflammatory drugs (72.4%) and antihyperlipidemic agents (68.8%) (Table 2).

The study population characteristics by polypharmacy status are summarized in Table 1. This study found a significantly higher percentage of polypharmacy among older adults as compared to other age groups, for example, as compared to patients with age between 18-29 (84.8% vs 37.4%, P-value <0.001). Women with diabetes had a significantly higher percentage of polypharmacy as compared to men (81.7% vs. 71.6%, P-value <0.001). Moreover, polypharmacy was significantly higher among diabetes patients with two or more co-existing comorbid conditions versus those with no co-existing chronic conditions (89.6% vs. 48.6%, P-value <0.001). Looking at comorbid conditions closely, polypharmacy was significantly higher among patients with cardiovascular (83.4%, P-value <0.001), chronic kidney disease (95.2%, P-value <0.001), musculoskeletal (93.6%, P-value <0.001), respiratory (89.0%, P-value <0.001), and mental health conditions (85.4%, P-value <0.001) as compared to those without those co-existing chronic conditions.

Logistic Regression: Factors Associated with Polypharmacy

The adjusted odds ratios (AOR) and 95% confidence intervals (CI) from multivariable logistic regression on polypharmacy are displayed in Table 3. Several factors were identified: age, gender, and co-existing chronic conditions. Polypharmacy was less likely among young adults as compared to older adults. Women were more likely to have polypharmacy compared to men (AOR=1.60; 95% CI: 1.43-1.79). Patients with co-existing cardiovascular conditions were two times more likely to have polypharmacy (AOR=2.89; 95% CI: 2.54-3.29), those with mental health conditions were two times more likely to have polypharmacy (AOR=2.19; 95% CI: 1.74-2.76), patients with respiratory diseases were two times more likely to have polypharmacy (AOR=2.42; 95% CI: 1.92-3.03), and those with musculoskeletal disease were three times more likely to have polypharmacy (AOR=3.16; 95% CI: 2.31-4.30) as compared to adults with diabetes and without these co-existing chronic conditions.

DISCUSSION

Our study was set out to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia. In this large sample of subjects with diabetes, the rate of polypharmacy was high, as nearly four out of five adults with diabetes were prescribed five or more medications. Similar rates were reported in the literature among patients with diabetes 54-84%,[8-10] however, to our knowledge, no study has attempted to measure the rate of polypharmacy among all age groups of adults with diabetes, which is a major contribution of our study. A higher rate of polypharmacy among older individuals (age 60 and above) as compared to all age groups was also observed in this study. Studies among adults in the general population have reported that older adults (defined as age ≥60 or age ≥65 years) have a higher risk of

polypharmacy use as compared to adults.[31,32] One possible reason for the high rate of polypharmacy among this population is the coexistence of other chronic conditions.

Furthermore, a noteworthy finding of the current study is the high prevalence of chronic conditions and the higher rate of polypharmacy among diabetic individuals with co-existing chronic conditions. Previous studies have shown that 90% of patients with diabetes had at least one co-existing chronic condition,[5] our study found that 86% of patients with diabetes had at least one co-existing chronic condition. It is plausible that the high rate of polypharmacy in this study is potentially associated with the number of comorbidities among the study population. The finding of this study support that diabetic patients with multiple chronic conditions were at higher risk of polypharmacy.[5,33] Although there is a well-documented literature on the relationship between the higher number of coexisting conditions and polypharmacy,[5,10,34] our study extended the literature by analyzing the association between the type of chronic conditions and polypharmacy. We observed that the polypharmacy rates differed by the type of co-existing chronic conditions; with the highest use among those with musculoskeletal conditions. This is not surprising because individuals with musculoskeletal conditions such as osteoarthritis use analgesic and non-steroidal anti-inflammatory drugs (NSAIDs) to relieve the chronic pain. We also observed that patients with cluster of diseases (diabetes and cardiovascular conditions) have a higher rate of polypharmacy as compared to adults without the cluster of diseases which is consistent with the published literature.[31,35] Patients with diabetes and mental health conditions have also a high rate of polypharmacy as compared to those without mental health conditions. Further studies are required to explore the contributing factors, as there is no supporting evidence in the literature. Polypharmacy was also highly prevalent among diabetic patients with respiratory conditions, which is consistent with data from previous studies, which showed higher

rates of medication use in patients with COPD. [36]

Accordingly, health care providers need to routinely monitor these individuals for potentially inappropriate medications, adverse drug events, and drug-drug interactions. For instance, in older individuals, comprehensive geriatric assessment has shown effective impact in decreasing the number of medications prescribed.[37] Further, patients with diabetes and polypharmacy may benefit from multidisciplinary collaborative care model that involves pharmacist follow up for the patients to assess the medication use and minimize polypharmacy. In an open-label, parallel-arm, randomized, controlled study, collaborative care has been associated with improvement in the management of diabetes and reduction the healthcare cost.[38] Pharmacists can help other healthcare providers in detecting polypharmacy, drug interactions, and in providing recommendations for simplified medication regimens and minimizing medications to positively impact health outcomes of diabetes care. [39,40]

We also looked at other related factors for polypharmacy, and we observed that women were more likely to have a polypharmacy compared to men, this is consistent with the findings from data among patients with diabetes.[10] In addition, studies have reported that women in the general population have a higher use of prescribed and non-prescribed medications, and higher healthcare utilization as compared to men.[41-44] This could be because women tend to be more concerned about their health and seek health services more often than men.[45]

Strengths and limitations

This study has some limitations; we used a twelve-month period to measure multiple medications use, which is not concurrent use and may have resulted in a very high rate of multiple medications uses. We did not control for the severity of diabetes using the Diabetes Complications Severity Index (DCSI), which may affect the rate of polypharmacy. We have also

only observed filled prescriptions and not actual use of the medications. By using the EHR data, we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR. Due to the cross-sectional nature of the data, it is difficult to assess any causal relationships. People with the end of life care were included in the study, which may have also overestimated the rate of polypharmacy.[46] Moreover, we have included all therapeutic medication classes, including over the counter medications and vitamins in our definition, which may have overestimated the rate of polypharmacy. It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not. This study was conducted in a tertiary hospital in Riyadh; therefore, the findings from this study cannot be generalized to primary care settings or to other regions in Saudi Arabia. In addition, we cannot exclude selection-bias; patients included in this study may be sicker, have sever diabetes, and higher rates of comorbidities as compared to individuals seen in primary care settings.

Despite these limitations, this study has many advantages such as the use of large sample size, which allowed us to identify the prevalence of polypharmacy among a subgroup of patients. Furthermore, findings from this study added to the existing literature on the prevalence of polypharmacy among all age groups and identified the individuals who have a high risk of polypharmacy based on their comorbidities. In addition, our results highlighted the need for routine monitoring of high-risk individuals for drug-related problems. Therefore, future studies are required to identify the rate of polypharmacy among other healthcare settings and assess the impact of pharmacist-led interventions on the rate of polypharmacy in patients with diabetes.

CONCLUSION

Polypharmacy is very common among adults with diabetes; particularly among individuals with multiple chronic conditions. Older adults patients have a higher rate of polypharmacy, which could be due to the increased number of multiple chronic conditions in this population. Moreover, patients with co-existing cardiovascular, mental and musculoskeletal chronic conditions are at a high risk of polypharmacy. Individuals with diabetes may benefit from simplified treatment regimens; thereby enhancing the health outcomes of this population.

Ethics and Data Confidentiality

Confidentiality of the data was maintained throughout the research process. Data extracted were stored at the Research Unit at the tertiary hospital on secured, password protected, and limited accessed computers. An encrypted identification was assigned to each participant and replaced patients' medical record number.

Authors' contribution

Dr.Monira Alwhaibi, Dr.Bander Balkhi,Dr.Tariq Alhawassi,Dr.Hadeel Alkofide, Nouf Alduhaim, Rawan Alabdulali, Hadeel Drweesh and Prof.Usha Sambamoorthi have all participated in designing the study, drafting the manuscript, analysis, interpretation of the findings, revising the manuscript content and gave final approval of the final version of this manuscript.

Acknowledgement: The project was fully supported financially by the Vice Deanship of Research Chairs, King Saud University Riyadh, Saudi Arabia.

Conflict of Interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1

Characteristics of the Study Population
Number and Row Percentage of Characteristics by Polypharmacy among Adults with Diabetes
Electronic Health Records Database, 2016

	Total		Polypharmacy		No Polypharmacy			
	N	%	N	%	N	%	chisqval	Sig.
Total	8,932	100.0	6,957	77.9	1,975	22.1		
# of Medications Mean(SD)	6.54 (3.50)		8.06 (2.97)		2.85 (1.14)			
Age Mean (SD)	57.7(12.12)		59.7 (11.3)		52.7(12.68)			
Age Group							517.7	***
18-29	198	2.2	74	37.4	124	62.6		
30-39	463	5.2	253	54.6	210	45.4		
40-49	1,226	13.7	830	67.7	396	32.3		
50-59	3,176	35.6	2,521	79.4	655	20.6		
60-69	2,434	27.3	1909	78.4	525	21.6		
70-79	1,126	12.6	951	84.5	175	15.5		
=>80	309	3.5	269	87.1	40	12.9		
Marital Status							76.5	***
single	957	11.6	635	66.4	322	33.6		
Married	7,310	88.4	5,769	78.9	1,541	21.1		
Gender							122.8	***
Male	3,375	37.8	2,418	71.6	957	28.4		
Female	5,557	62.2	4,539	81.7	1,018	18.3		
Nationality							6.6	**
Saudi	7,957	89.4	6,167	77.5	1,790	22.5		
Non-Saudi	946	10.6	768	81.2	178	18.8		
Chronic kidney disease							25.8	***
Yes	146	1.6	139	95.2	7	4.8		
No	8,786	98.4	6,818	77.6	1,968	22.4		
Cardiovascular Conditions							668.1	***
Yes	7,209	80.7	6,015	83.4	1,194	16.6		
No	1,723	19.3	942	54.7	781	45.3		
Musculoskeletal Conditions							124.4	***
Yes	787	8.8	737	93.6	50	6.4		
No	8,145	91.2	6,220	76.4	1,925	23.6		
Respiratory Conditions							76.8	***
Yes	961	10.8	855	89.0	106	11.0		
No	7,971	89.2	6,102	76.6	1,869	23.4		
Mental Health Conditions							27.3	***

Table 1

Characteristics of the Study Population
Number and Row Percentage of Characteristics by Polypharmacy among Adults with Diabetes
Electronic Health Records Database, 2016

	Total		Polypharmacy		No Polypharmacy			
	N	%	N	%	N	%	chisqval	Sig.
Yes	766	8.6	654	85.4	112	14.6		
No	8,166	91.4	6,303	77.2	1,863	22.8		
# Chronic Conditions							1093.807	***
No co-existing conditions	1250	14.0	607	48.6	643	51.4		
Single co-existing condition	2849	31.9	2,018	70.8	831	29.2		
≥2 co-existing conditions	4833	54.1	4,332	89.6	501	10.4		

Note: Study population comprised of 8,932 adults with diabetes (age ≥18year) who visited outpatient's clinics from a tertiary hospital in 2016. Polypharmacy was defined as the use of five or more medications during the one year period.
Asterisks (*) represent significant differences in polypharmacy from chi-square tests ; ***P< .001

Table 2
Most Prevalent Therapeutic Classes among the Study Population (n = 8,932)

Medication Therapy Class	N	%
Oral Antidiabetic Agent	7,270	81.4
Nonsteroidal Anti-inflammatory Drugs	6,467	72.4
Antihyperlipidemic agents	6,144	68.8
Proton Pump Inhibitor	2,540	28.4
Angiotensin Converting Enzyme Inhibitor	2,321	25.9
Injectable Antidiabetic Agent	2,253	25.2
Calcium Channel Blocker	2,162	24.2
Corticosteroid , Local	1,892	21.1
Diuretic	1,934	21.6
Beta-Adrenergic Blocker, Beta-1 Selective	1,806	20.2
Angiotensin II Receptor Blocker	1,796	20.1
Thyroid Analog	1,355	15.1
Histamine H2 Blocker	822	9.2
Anticoagulants	706	7.9
Corticosteroid , Systemic	600	6.7
Antiplatelet	357	4.0

Table 1

Characteristics of the Study Population
Number and Row Percentage of Characteristics by Polypharmacy among Adults with Diabetes
Electronic Health Records Database, 2016

	Total		Polypharmacy		No Polypharmacy			
	N	%	N	%	N	%	chisqval	Sig.

Table 3
Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CI)
Logistic Regression on Polypharmacy
Adults with Diabetes,
Electronic Health Records database, 2016

	AOR	95% CI	Sig.
Age Group			
18-29 vs. ≥80	0.10	[0.06 , 0.18]	***
30-39 vs. ≥80	0.15	[0.10 , 0.24]	***
40-49 vs. ≥80	0.22	[0.15 , 0.33]	***
50-59 vs. ≥80	0.37	[0.25 , 0.54]	***
60-69 vs. ≥80	0.53	[0.36 , 0.79]	**
70-79 vs. ≥80	0.79	[0.52 , 1.20]	
Marital Status			
Single vs. Married	1.16	[0.96 , 1.40]	
Gender			
Female vs. Male	1.60	[1.43 , 1.79]	***
Nationality			
Non-Saudi vs. Saudi	1.81	[1.50 , 2.19]	***
Cardiovascular Conditions			
Yes vs. No	2.89	[2.54 , 3.29]	***
Musculoskeletal Conditions			
Yes vs. No	3.16	[2.31 , 4.30]	***
Respiratory Conditions			
Yes vs. No	2.42	[1.92 , 3.03]	***
Mental Health Conditions			
Yes Vs. No	2.19	[1.74 , 2.76]	***

Note: Based on 8,932 adults with diabetes, who visited outpatient's clinics from a tertiary hospital in 2016. Polypharmacy was defined as the use of five or more medications during the one year period.

Asterisks (*) represent significant differences on polypharmacy compared to the reference group based on logistic regression.
***P< .001
Ref: Reference Group

Appendix I
Diagnoses codes used to identify the types of chronic conditions
Electronic Health Records database, 2016

Type of Chronic Conditions	ICD-9-CM Codes	ICD-10-CM Codes	SNOMED Codes
Diabetes	250, 250.00	E11, E11.9, E14.9	121589010, 502372015
Cardiovascular Conditions			
Hypertension	401.9	I10, 10	64176011, 2164904016
Ischemic heart disease		I25, I25.9	2534671011, 2537479013, 397667016, 2534663012
Vascular heart disease			1705016
Stroke		I64	2644233012 , 2476091017, 345636015, 345682011
Heart failure	428.0, 428.1	I50,I50.9	1234906013, 143156018, 251680018, 94251011, 2645367010, 18472010, 139475013, 2816764017, 493289014, 70653017, 80720010
Dyslipidemia		E78.5	92826017, 1209706018
Musculoskeletal Conditions			
osteoarthritis			1776248011, 359420013, 359421012, 1785522017
Osteoporosis		M81.99	453855011, 107806013
Respiratory Conditions			
Asthma	493, 493.90	J45	301485011, 301480018
COPD		J44.1, J44.9	23290013, 23287019, 475431013, 475427019
Mental Health Conditions			
Dementia		F02	87274019
Depression	311	F31.3	486186018, 486187010, 110183011, 346973011, 346979010, 55208011, 454082014, 486187010, 124707013, 1208903011, 490537016, 346980013, 1228731019, 486184015
Anxiety		F41.8, F41.9	346980013, 369987018, 303689015, 481155011, 81133019
Schizophrenia		F20	114425016, 405368015, 294764011, 138883015, 96745016

ICD-9-CM codes: International Classifications of Diseases – 9th edition, Clinical Modification
ICD-10-CM codes: International Classifications of Diseases – 10th edition
SNOMED: Clinical Modification Systematized Nomenclature of Medicine
COPD: Chronic Obstructive Pulmonary Disease

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Polypharmacy Use among Patients with Diabetes: A Cross-Sectional Retrospective Study in a Tertiary Hospital in Saudi Arabia
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	A cross-sectional retrospective observational study of adults with diabetes, who visited the outpatient clinic of a tertiary teaching hospital in Saudi Arabia, was conducted. Data were extracted from the Electronic Health Record (EHR) database for a period of twelve-month (January to December 2016). Polypharmacy was defined as the cumulative use of five or more medication classes. Polypharmacy among adults with diabetes was measured by calculating the average number of medication classes prescribed per patient. A multivariable logistic regression model was used to examine the factors associated with polypharmacy after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions. A total of 8,932 adults with diabetes were included in this study. Of these, nearly 78 % had polypharmacy, which was more likely among women as compared to men and more likely among the elderly (age $\geq$ 60 years) as compared to the adults. Also, polypharmacy was two times as likely among patients with coexisting cardiovascular disease (AOR=2.89; 95% CI: 2.54-3.29), respiratory disease (AOR=2.42; 95% CI: 1.92-3.03), and mental health conditions (AOR=2.19; 95% CI: 1.74-2.76), and three times as likely among patients with co-existing musculoskeletal disease as compared to those without these co-existing chronic conditions categories.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Diabetes is a highly prevalent chronic condition among adults in Saudi Arabia; between 21-24% of adults are estimated to have diabetes. It is projected that 27% of adults in Saudi Arabia will have diabetes by 2035.

				Diabetes is one of the top ten causes of morbidity and mortality worldwide. Patients with diabetes often have co-existing chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression and renal disease, which require the use of multiple medications to treat those co-existing chronic conditions. All of this put patients with diabetes at high risk of polypharmacy, with an estimated prevalence of 57% to 84% of patients with diabetes using five or more medications. Limited studies have examined the prevalence of polypharmacy among adults with diabetes living in Saudi Arabia on a large scale, and looking at specific factors that put patients at risk of polypharmacy. Identifying the prevalence and the subgroup of patients at high risk of polypharmacy will facilitate pharmacovigilance efforts in clinical practice settings.
Objectives	3	State specific objectives, including any prespecified hypotheses	5	The primary objective of this study is to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia and to identify the factors that are associated with polypharmacy, specifically the association between co-existing chronic conditions and polypharmacy.
Methods				
Study design	4	Present key elements of study design early in the paper	5	A cross-sectional retrospective observational study was conducted in a tertiary teaching hospital in Saudi Arabia
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6	Outpatient's setting in the tertiary teaching hospital during a one-year period. From 1st January 2016, until 30th December 2016. The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932). This study used data retrieved from the Electronic Health Record (EHR). The data from EHR were derived from demographics file, clinical diagnosis file, and prescription drug file.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases	6	The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary teaching hospital during a one-year period.

		and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		No exclusion criteria were applied to the study population.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	The dependent variable was "polypharmacy use". There are different approaches in the literature to measure polypharmacy such as simultaneous, cumulative and continuous. Also, there is no consensus on the thresholds regarding the number of medications above which we consider the existence of polypharmacy. In the current study, we defined polypharmacy as the cumulative use of five or more medications during a one year period, this threshold has been used more than others. Using this definition, the prevalence of polypharmacy among adults was measured by the sum of unique therapeutic medication classes administered over a twelve-month period. There is no consensus on the medications that should be included in the measurements of the polypharmacy. Also, all the prescription and the non-prescription/Over the Counter (OTC) medications categories were included in our definition of polypharmacy. Independent variables included were age groups in years (18-29, 30-39, 40-49, 50-59, ≥60), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into four categories (cardiovascular, musculoskeletal, respiratory, or mental health conditions).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7	The prevalence of polypharmacy among adults was measured by the sum of different medication classes administered over a twelve-month period. Chronic conditions were identified using the the clinical diagnosis file which

				provided information about the clinical diagnosis from inpatient and outpatient visits. Physicians reported clinical diagnosis using the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes, *International Classifications of Diseases – 10th edition, Clinical Modification* (ICD-10-CM) codes, or the *Systematized Nomenclature of Medicine* (SNOMED) diagnosis codes.
Bias	9	Describe any efforts to address potential sources of bias	11	By using the EHR data; we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR.
Study size	10	Explain how the study size was arrived at	6	The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary teaching hospital during a one-year period. We have included all diabetic adults who visited a tertiary teaching hospital during one year period.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Age groups in years (18-29, 30-39, 40-49, 50-59, ≥60), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into four categories (cardiovascular, musculoskeletal, respiratory, or mental health conditions).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Frequency and percentage were used to describe the categorical variables (age, sex, marital status, nationality, co-existing chronic conditions, and polypharmacy). Mean and Standard deviation were used to describe continuous variables. Chi-square tests were used to examine the factors associated with polypharmacy use. A multivariable logistic regression was used to examine the factors associated with polypharmacy (i.e., use of ≥ 5 medication classes) after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions.
		(*b*) Describe any methods used to examine subgroups and interactions	11	Not Applicable
		(*c*) Explain how missing data were addressed	11	For all the variables, the sum add up to the total study population and we did not have missing data.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		Our study design was cross-sectional data in nature, we have include all adults who visited a tertiary teaching hospital with diabetes diagnosis without sampling strategy.
		(*e*) Describe any sensitivity analyses		Not Applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6	n = 8,932
		(b) Give reasons for non-participation at each stage		Not Applicable
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	The majority were female (62.2%), and 43.3% of the study population were elderly (age ≥60 years). About half of the subjects (54.1%) had two or more diagnosed co-existing chronic health conditions.

		(b) Indicate number of participants with missing data for each variable of interest	11	We did not have missing data in our analysis.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	77.9 % of adults with diabetes were using five or more medication classes.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9	Confounder-adjusted estimates were age, gender and co-existing chronic conditions.
		(*b*) Report category boundaries when continuous variables were categorized		For the age group, we used 10 years category boundry
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not Applicable

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11	Not Applicable
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	Our study estimated the prevalence of polypharmacy among adults with diabetes in Saudi Arabia. In our study population, the rate of polypharmacy was high; nearly eighty percent of adults with diabetes used five or more medication classes. While this rate is within the documented rate in the literature among adults with diabetes 57% to 84%, we could not find a study that reported the rate of polypharmacy among all age groups of adults with diabetes. We observed a higher rate of polypharmacy among the elderly as compared to all age groups.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	This study has some limitations; we used a 12-month period to measure multiple medications use, which is not concurrent use and may have resulted in a very high rate of multiple medications uses. We did not control for the severity of diabetes using the Diabetes Complications Severity Index (DCSI) which may affect the rate of polypharmacy. We have also only observed filled prescriptions and not actual use of the medications. By using the EHR data; so we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR. Due to the cross-sectional nature of the data; it is difficult to assess the causal relationship. People with the end of life care were included and this may have overestimated the rate of polypharmacy. Moreover, we have included all medication classes, including the topical agents, and vitamins in our definition, which may have overestimated the rate of polypharmacy. It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9	The very high rate of polypharmacy observed in our study population suggests that health care providers need to routinely monitor these individuals for potentially inappropriate medications, adverse drug events, and drug-drug interactions. Diabetes patients with polypharmacy may benefit from

			multidisciplinary collaborative care model that involves pharmacist follow up for the patients to assess the medication use.
Generalisability	21	Discuss the generalisability (external validity) of the study results	This study was conducted in a tertiary hospital in Riyadh; therefore the findings from this study cannot be generalized to primary care settings or to other regions in Saudi Arabia.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not Applicable

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Polypharmacy among Patients with Diabetes: A Cross-Sectional Retrospective Study in a Tertiary Hospital in Saudi Arabia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020852.R2
Article Type:	Research
Date Submitted by the Author:	06-Apr-2018
Complete List of Authors:	Alwhaibi, Monira; King Saud University College of Pharmacy, Clinical Pharmacy; King Saud University, Medication Safety Research Chair Balkhi, Bander; King Saud University College of Pharmacy, Clinical Pharmacy; King Saud University, Medication Safety Research Chair Alhawassi, Tariq ; King Saud University College of Pharmacy, Clinical Pharmacy; King Saud University, Medication Safety Research Chair Alkofide, Hadeel; King Saud University College of Pharmacy, Clinical Pharmacy Alduhaim, Nouf; King Saud University College of Pharmacy, Clinical Pharmacy Alabdulaali, Rawan; King Saud University College of Pharmacy, Clinical Pharmacy drweesh, hadeel ; King Saud University College of Pharmacy, Clinical Pharmacy Sambamoorthi, Usha; West Virginia University Health Sciences Center, Pharmaceutical Systems & Policy
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Health services research, Pharmacology and therapeutics
Keywords:	DIABETES & ENDOCRINOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY, Drug Use Evaluation

Polypharmacy among Patients with Diabetes: A Cross-Sectional Retrospective Study in a Tertiary Hospital in Saudi Arabia

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ABSTRACT

Objectives. Patients with diabetes are at high risk for polypharmacy (i.e. use of multiple medications) for treatment of diabetes, associated comorbidities, and other co-existing conditions. This study aims to estimate the prevalence of polypharmacy and factors associated with polypharmacy among adult patients with diabetes.

Methods. A cross-sectional retrospective observational study of adults with diabetes, who visited the outpatient clinic of a tertiary teaching hospital in Saudi Arabia, was conducted. Data were extracted from the Electronic Health Record (EHR) database for a period of twelve-month (January to December 2016). Polypharmacy was defined as the cumulative use of five or more medications. Polypharmacy among adults with diabetes was measured by calculating the average number of medications prescribed per patient. A multivariable logistic regression model was used to examine the factors associated with polypharmacy.

Results. A total of 8,932 adults with diabetes were included in this study. Of these, nearly 78 % had polypharmacy, which was more likely among women as compared to men and more likely among older adults (age $\geq$ 60 years) as compared to the adults. Also, polypharmacy was two times as likely among patients with coexisting cardiovascular conditions (AOR=2.89; 95% CI: 2.54-3.29), respiratory disease (AOR=2.42; 95% CI: 1.92-3.03), and mental health conditions (AOR=2.19; 95% CI: 1.74-2.76), and three times as likely among patients with co-existing musculoskeletal disease (AOR=3.16; 95% CI: 2.31-4.30) as compared to those without these co-existing chronic conditions categories.

Conclusions. Polypharmacy is common among patients with diabetes, with an even higher rate in older adults patients. Health care providers can help in detecting polypharmacy and in providing recommendations for simplifying medication regimens and minimizing medications to enhance the outcome of diabetes care.

Keywords. Diabetes; Polypharmacy; Chronic conditions; Electronic health records; Drug use evaluation.

Strengths and limitations of this study

- This study has provided a real insight into the current prevalence and predictors of polypharmacy among patients with diabetes in Saudi Arabia including a large study population of patients with diabetes.
- Around nine-thousand patients were included in this study, which allowed us to identify the prevalence of polypharmacy among a subgroup of patients.
- This study has not controlled for the severity of diabetes using the Diabetes Complications Severity Index (DCSI) which may affect the rate of polypharmacy.
- This study used a twelve-month period to measure multiple medications use, which is not concurrent use and may have resulted in a very high rate of multiple medications uses.
- It has to be noticed that not all polypharmacy is harmful; however, future studies to assess inappropriate medications associated with polypharmacy is warranted

INTRODUCTION

Diabetes is a highly prevalent chronic condition among adults in Saudi Arabia; between 21-24% of adults are estimated to have diabetes.[1,2] It is projected that 27% of adults in Saudi Arabia will have diabetes by 2035.[3] Diabetes is one of the top ten causes of morbidity and mortality worldwide.[4] Patients with diabetes often have co-existing chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression and chronic kidney disease, which requires the use of multiple medications to treat those co-existing chronic conditions.[5] All of this put patients with diabetes at high risk of polypharmacy,[6,7] with an estimated prevalence of 57% to 84% of patients with diabetes using five or more medications.[8] A study among adults with diabetes in the US documented that the 54% of adults with diabetes have polypharmacy.[9] A multicenter cross-sectional survey conducted in Italy reported that 57% of patients with diabetes use five or more medications.[10] In addition, polypharmacy was reported among 84% older adults patients with diabetes.[8] In Saudi Arabia, a cross-sectional study among 766 adults who visited outpatient's clinic at a tertiary care center, reported that the prevalence of polypharmacy among patients with diabetes was 71%.[11]

An examination of polypharmacy among patients with diabetes is important because polypharmacy increases the probability of the adverse drug events[12,13], drug-drug interactions[14], duplication of therapy,[15] decreases compliance to antidiabetic medications,[16] and leads to suboptimal glycemic control.[17] The presence of polypharmacy is also associated with prescribing cascade, in which adverse drug events are misinterpreted as new medical conditions which can result in the prescription of new medications to treat those conditions.[18] Polypharmacy has other negative health consequences such as increased risk of

hospitalization and medication error,[19,20] higher risk of fall,[21] poor functional status,[22] poor quality of life, and high healthcare cost.[23,24] Polypharmacy among diabetes patients is often associated with many factors. These include age,[11] sex,[10] co-existing conditions,[10] rurality, [25,11] diabetes complications[10], and aggressive diabetes treatment.[26,27]

To date, limited studies have examined the prevalence of polypharmacy among adults with diabetes living in Saudi Arabia on a large scale, and assessed the specific factors that put patients at risk of polypharmacy. Identifying the prevalence and the subgroup of patients at high risk of polypharmacy will facilitate pharmacovigilance efforts in clinical practice settings. Therefore, the primary objective of this observational study is to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia and to identify the factors that are associated with polypharmacy, specifically the association between co-existing chronic conditions and polypharmacy.

METHODS

Study Design

A cross-sectional retrospective observational study was conducted in a tertiary teaching hospital in Saudi Arabia. This hospital is one of the largest tertiary teaching hospitals in Riyadh, Saudi Arabia, with a 1200-bed facility and all general and subspecialty medical services. The hospital provides primary, secondary, and tertiary care services. The patient population is composed predominantly of local citizens as well as residents, from northern region in Riyadh; the hospital also serves the entire country as a referral center.

Data Source and Data Extraction

This study used data retrieved from the Electronic Health Record (EHR) database for the period from 1st January 2016, until 30th December 2016. Institutional review board (IRB) at King Saud University Medical City approval was obtained to conduct the study (IRB number: E-17-2601). Strict confidentiality of the data was maintained throughout the research process. The data from EHR were derived from demographics file, clinical diagnosis file, and prescription drug file. The demographics file contained information about the patients' date of birth, gender, marital status, nationality, and encounter type. The clinical diagnosis file provided information about the clinical diagnosis from inpatient and outpatient visits. Physicians reported clinical diagnosis using the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes, *International Classifications of Diseases – 10th edition, Clinical Modification* (ICD-10-CM) codes, or the *Systematized Nomenclature of Medicine* (SNOMED) diagnosis codes. The prescription drug file contained information about the medications used. The demographics, clinical diagnosis, and prescription drug files were merged into one file using the encrypted patient medical record number. The completeness and the validity of the data from EHR in this tertiary teaching hospital in Saudi Arabia has not been studied before; however the researchers of this study examined the completeness of this data and found that 91.0% of the patients had a complete data (i.e., have information on the age, gender, marital status, nationality, encounter type, and clinical diagnosis) and 85.0% of the patients had complete medication-related information.

Study Population

The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary

teaching hospital during a one-year period. No exclusion criteria were applied to the study population.

Patient and Public Involvement

Patients and public were not involved in the design or conduct of this study.

Measures

Dependent Variable

In our study, the dependent variable was "polypharmacy". There are different approaches in the literature to measure polypharmacy such as simultaneous, cumulative and continuous. Also, there is no consensus on the thresholds regarding the number of medications above which we consider the existence of polypharmacy.[28] In the current study, we defined polypharmacy as the cumulative use of five or more medications during a one year period, this threshold has been used more than others.[25,28,29] Using this definition, the prevalence of polypharmacy among adults was measured by the sum of unique therapeutic medication classes administered over a twelve-month period. There is no consensus on the medications that should be included in the measurements of the polypharmacy. Also, all the prescription and the non-prescription/Over the Counter (OTC) medications categories were included in our definition of polypharmacy.

Independent Variables

Independent variables included were age groups in years (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into five categories (cardiovascular, chronic kidney disease, musculoskeletal, respiratory, or mental health conditions) (Appendix I).

Cardiovascular conditions composed of hypertension, ischemic heart disease, vascular heart disease, stroke, heart failure, and dyslipidemia. Musculoskeletal conditions composed of osteoarthritis, and osteoporosis; respiratory conditions include asthma, and chronic obstructive pulmonary disease (COPD). Mental health conditions include dementia, depression, anxiety, and schizophrenia. These conditions have been selected because they are highly prevalent among patients with diabetes and some of them were associated with polypharmacy.[5,30]

Statistical Analysis

Frequency and percentage were used to describe the categorical variables (age, sex, marital status, nationality, co-existing chronic conditions, and polypharmacy). Mean and Standard deviation were used to describe continuous variables. Chi-square tests were used to examine the factors associated with polypharmacy. A multivariable logistic regression was used to examine the factors associated with polypharmacy (i.e., use of $\geq$ 5 medications) after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions. All statistical analyses were carried out using the Statistical analysis software, version 9.2 (SAS® 9.2).

RESULTS

A total of 8,932 adult patients were identified during the twelve-month period. The majority were Saudi (89.4%), female (62.2%), and 43.3% of the study population were older adults (age ≥60 years), the mean age of the study population was 57 years old. About half of the subjects (54.1%) had two or more diagnosed co-existing chronic health conditions. Hypertension, dyslipidemia, asthma, osteoarthritis, and anxiety were among the most common chronic conditions in our study population. Characteristics of the study population are presented in Table 1.

Polypharmacy among Patients with Diabetes

Overall 77.9 % of adults with diabetes have used (cumulative) five or more medications. Also, when we identified the rate of hyperpolypharmacy (i.e, taking 10 or more medications) we found that 17.2% of adults have a hyperpolypharmacy. The most commonly used medications in our study population were antidiabetic medications (81.4%), followed by nonsteroidal anti-inflammatory drugs (72.4%) and antihyperlipidemic agents (68.8%) (Table 2).

The study population characteristics by polypharmacy status are summarized in Table 1. This study found a significantly higher percentage of polypharmacy among older adults as compared to patients with age between 18-29 (84.8% vs 37.4%, P-value <0.001). Women with diabetes had a significantly higher percentage of polypharmacy as compared to men (81.7% vs. 71.6%, P-value <0.001). Moreover, polypharmacy was significantly higher among diabetes patients with two or more co-existing comorbid conditions versus those with no co-existing chronic conditions (89.6% vs. 48.6%, P-value <0.001). Looking at comorbid conditions closely, polypharmacy was significantly higher among patients with cardiovascular (83.4%, P-value <0.001), chronic kidney disease (95.2%, P-value <0.001), musculoskeletal (93.6%, P-value <0.001), respiratory (89.0%, P-value <0.001), and mental health conditions (85.4%, P-value <0.001) as compared to those without those co-existing chronic conditions.

Logistic Regression: Factors Associated with Polypharmacy

The adjusted odds ratios (AOR) and 95% confidence intervals (CI) from multivariable logistic regression on polypharmacy are displayed in Table 3. Several factors were identified: age, gender, and co-existing chronic conditions. Polypharmacy was more likely among older adults as compared to younger adults. Women were more likely to have polypharmacy compared to men (AOR=1.60; 95% CI: 1.43-1.79). Cardiovascular diseases, mental conditions, respiratory

and musculoskeletal diseases were all significantly associated with polypharmacy. For example, adults with diabetes and musculoskeletal disease were three times more likely to have polypharmacy (AOR=3.16; 95% CI: 2.31-4.30) as compared to adults with diabetes and without musculoskeletal conditions.

DISCUSSION

Our study was set out to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia. In this large sample of subjects with diabetes, the rate of polypharmacy was high, as nearly four out of five adults with diabetes were prescribed five or more medications. Similar rates were reported in the literature among patients with diabetes 54-84%,[8-10] however, to our knowledge, no study has attempted to measure the rate of polypharmacy among all age groups of adults with diabetes, which is a major contribution of our study. A higher rate of polypharmacy among older individuals (age 60 and above) as compared to all age groups was also observed in this study. Studies among adults in the general population have reported that older adults (defined as age ≥60 or age ≥65 years) have a higher risk of polypharmacy use as compared to adults.[31,32] One possible reason for the high rate of polypharmacy among this population is the coexistence of other chronic conditions.

Furthermore, a noteworthy finding of the current study is the high prevalence of chronic conditions and the higher rate of polypharmacy among diabetic individuals with co-existing chronic conditions. Previous studies have shown that 90% of patients with diabetes had at least one co-existing chronic condition,[5] our study found that 86% of patients with diabetes had at least one co-existing chronic condition. It is plausible that the high rate of polypharmacy in this study is potentially associated with the number of comorbidities among the study population.

The finding of this study support that diabetic patients with multiple chronic conditions were at higher risk of polypharmacy.[5,33] Although there is a well-documented literature on the relationship between the higher number of coexisting conditions and polypharmacy,[5,10,34] our study extended the literature by analyzing the association between the type of chronic conditions and polypharmacy. We observed that the polypharmacy rates differed by the type of co-existing chronic conditions; with the highest use among those with musculoskeletal conditions. This is not surprising because individuals with musculoskeletal conditions such as osteoarthritis use analgesic and non-steroidal anti-inflammatory drugs (NSAIDs) to relieve the chronic pain. We also observed that patients with cluster of diseases (diabetes and cardiovascular diseases) have a higher rate of polypharmacy as compared to adults without the cluster of diseases which is consistent with the published literature.[31,35] Patients with diabetes and mental health conditions have also a high rate of polypharmacy as compared to those without mental health conditions. Further studies are required to explore the contributing factors, as there is no supporting evidence in the literature. Polypharmacy was also highly prevalent among diabetic patients with respiratory diseases, which is consistent with data from previous studies, which showed higher rates of medication use in patients with COPD. [36]

Accordingly, health care providers need to routinely monitor these individuals for potentially inappropriate medications, adverse drug events, and drug-drug interactions. For instance, in older individuals, comprehensive geriatric assessment has shown effective impact in decreasing the number of medications prescribed.[37] Further, patients with diabetes and polypharmacy may benefit from multidisciplinary collaborative care model that involves pharmacist follow up for the patients to assess the medication use and minimize polypharmacy. In an open-label, parallel-arm, randomized, controlled study, collaborative care has been

associated with improvement in the management of diabetes and reduction the healthcare cost.[38] Pharmacists can help other healthcare providers in detecting polypharmacy, drug interactions, and in providing recommendations for simplified medication regimens and minimizing medications to positively impact health outcomes of diabetes care. [39,40]

We also looked at other related factors for polypharmacy. We observed that women were more likely to have a polypharmacy compared to men, this is consistent with the findings from data among patients with diabetes.[10] In addition, studies have reported that women in the general population have a higher use of prescribed and non-prescribed medications, and higher healthcare utilization as compared to men.[41-44] This could be because women tend to be more concerned about their health and seek health services more often than men.[45] It has to be noted that the majority of patients with diabetes in our study were women, this is not surprising since the rate of diabetes is higher in women as compared to men in Saudi Arabia.[2]

Strengths and limitations

"This study has some limitations; we defined polypharmacy as the cumulative use of five or more medications during a one year period rather than the concurrent use of medications, using this definition may have overestimated the rate of polypharmacy". We did not control for the severity of diabetes using the Diabetes Complications Severity Index (DCSI), which may affect the rate of polypharmacy. We have also only observed filled prescriptions and not actual use of the medications. By using the EHR data, we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR. Due to the cross-sectional nature of the data, it is difficult to assess any causal relationships. People with the end of life care were included in the study, which may have also overestimated the rate of polypharmacy.[46] Moreover, we have included all therapeutic medication classes, including over the counter medications and

vitamins in our definition, which may have overestimated the rate of polypharmacy. It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not. This study was conducted in a tertiary hospital in Riyadh; therefore, the findings from this study cannot be generalized to primary care settings or to other regions in Saudi Arabia. In addition, we cannot exclude selection-bias; patients included in this study may be sicker, have sever diabetes, and higher rates of comorbidities as compared to individuals seen in primary care settings.

Despite these limitations, this study has many advantages such as the use of large sample size, which allowed us to identify the prevalence of polypharmacy among a subgroup of patients. Furthermore, findings from this study added to the existing literature on the prevalence of polypharmacy among all age groups and identified the individuals who have a high risk of polypharmacy based on their comorbidities. In addition, our results highlighted the need for routine monitoring of high-risk individuals for drug-related problems. Therefore, future studies are required to identify the rate of polypharmacy among other healthcare settings and assess the impact of pharmacist-led interventions on the rate of polypharmacy in patients with diabetes.

CONCLUSION

Polypharmacy is very common among adults with diabetes; particularly among individuals with multiple chronic conditions. Older adults patients have a higher rate of polypharmacy, which could be due to the increased number of multiple chronic conditions in this population. Moreover, patients with co-existing cardiovascular, mental and musculoskeletal chronic conditions are at a high risk of polypharmacy. Individuals with diabetes may benefit from simplified treatment regimens; thereby enhancing the health outcomes of this population.

Ethics and Data Confidentiality

Confidentiality of the data was maintained throughout the research process. Retrieved data was stored and saved as coded excel files. A customized formula was used to generate study-encrypted identification assigned to each participant and replaced patients' medical record number. Data extracted were stored at the Research Unit at the tertiary hospital on secured, password protected, and limited accessed computers.

Authors' contribution

Dr.Monira Alwhaibi, Dr.Bander Balkhi, Dr.Tariq Alhawassi, Dr.Hadeel Alkofide, Nouf Alduhaim, Rawan Alabdulali, Hadeel Drweesh and Prof.Usha Sambamoorthi have all participated in designing the study, drafting the manuscript, analysis, interpretation of the findings, revising the manuscript content and gave final approval of the final version of this manuscript.

Acknowledgement

The project was fully supported financially by the Vice Deanship of Research Chairs, King Saud University Riyadh, Saudi Arabia.

Data sharing statement

No additional data are available.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1
Characteristics of the Study Population
Number and Row Percentage of Characteristics by Polypharmacy among Adults with Diabetes Electronic Health Records Database, 2016

	Total		Polypharmacy		No Polypharmacy			
	N	%	N	%	N	%	chisqval	Sig.
Total	8,932	100.0	6,957	77.9	1,975	22.1		
# of Medications Mean(SD)	6.54 (3.50)		8.06 (2.97)		2.85 (1.14)			
Age Mean (SD)	57.7(12.12)		59.7 (11.3)		52.7(12.68)			
Age Group							517.7	***
18-29	198	2.2	74	37.4	124	62.6		
30-39	463	5.2	253	54.6	210	45.4		
40-49	1,226	13.7	830	67.7	396	32.3		
50-59	3,176	35.6	2,521	79.4	655	20.6		
60-69	2,434	27.3	1909	78.4	525	21.6		
70-79	1,126	12.6	951	84.5	175	15.5		
=>80	309	3.5	269	87.1	40	12.9		
Marital Status							76.5	***
single	957	11.6	635	66.4	322	33.6		
Married	7,310	88.4	5,769	78.9	1,541	21.1		
Gender							122.8	***
Male	3,375	37.8	2,418	71.6	957	28.4		
Female	5,557	62.2	4,539	81.7	1,018	18.3		
Nationality							6.6	**
Saudi	7,957	89.4	6,167	77.5	1,790	22.5		
Non-Saudi	946	10.6	768	81.2	178	18.8		
Chronic kidney disease							25.8	***
Yes	146	1.6	139	95.2	7	4.8		
No	8,786	98.4	6,818	77.6	1,968	22.4		
Cardiovascular Conditions							668.1	***
Yes	7,209	80.7	6,015	83.4	1,194	16.6		
No	1,723	19.3	942	54.7	781	45.3		
Musculoskeletal Conditions							124.4	***
Yes	787	8.8	737	93.6	50	6.4		
No	8,145	91.2	6,220	76.4	1,925	23.6		
Respiratory Conditions							76.8	***
Yes	961	10.8	855	89.0	106	11.0		
No	7,971	89.2	6,102	76.6	1,869	23.4		
Mental Health Conditions							27.3	***
Yes	766	8.6	654	85.4	112	14.6		
No	8,166	91.4	6,303	77.2	1,863	22.8		
# Chronic Conditions							1093.8	***
No co-existing conditions	1250	14.0	607	48.6	643	51.4		
Single co-existing condition	2849	31.9	2,018	70.8	831	29.2		
≥2 co-existing conditions	4833	54.1	4,332	89.6	501	10.4		

Note: Study population comprised of 8,932 adults with diabetes (age >18year) who visited outpatient's clinics from a tertiary hospital in 2016. Polypharmacy was defined as the cumulative use of five or more medications during the one year period. Chisqval: Chi square value; Sig: significance; #: Number. Asterisks (*) represent significant differences in polypharmacy from chi-square tests ; ***P< 0.001, **

$0.001 \leq P < 0.01$

Table 2
Most Prevalent Therapeutic Classes among the Study Population (n = 8,932)

Medication Therapy Class	N	%
Oral Antidiabetic Agent	7,270	81.4
Nonsteroidal Anti-inflammatory Drugs	6,467	72.4
Antihyperlipidemic agents	6,144	68.8
Proton Pump Inhibitor	2,540	28.4
Angiotensin Converting Enzyme Inhibitor	2,321	25.9
Injectable Antidiabetic Agent	2,253	25.2
Calcium Channel Blocker	2,162	24.2
Corticosteroid , Local	1,892	21.1
Diuretic	1,934	21.6
Beta-Adrenergic Blocker, Beta-1 Selective	1,806	20.2
Angiotensin II Receptor Blocker	1,796	20.1
Thyroid Analog	1,355	15.1
Histamine H2 Blocker	822	9.2
Anticoagulants	706	7.9
Corticosteroid , Systemic	600	6.7
Antiplatelet	357	4.0

Table 3
Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CI)
Logistic Regression on Polypharmacy
Adults with Diabetes,
Electronic Health Records database, 2016

	AOR	95% CI	Sig.
Age Group			
30-39 vs. 18-29	1.48	[1.00 , 2.18]	**
40-49 vs. 18-29	2.13	[1.47 , 3.08]	***
50-59 vs. 18-29	3.54	[2.46 , 5.11]	***
60-69 vs. 18-29	5.11	[3.51 , 7.44]	***
70-79 vs. 18-29	7.59	[5.07 , 11.35]	***
≥80 vs. 18-29	9.65	[5.69 , 16.38]	***
Marital Status			
Single vs. Married	1.16	[0.96 , 1.40]	
Gender			
Female vs. Male	1.60	[1.43 , 1.79]	***
Nationality			
Non-Saudi vs. Saudi	1.81	[1.50 , 2.19]	***
Cardiovascular Conditions			
Yes vs. No	2.89	[2.54 , 3.29]	***
Musculoskeletal Conditions			
Yes vs. No	3.16	[2.31 , 4.30]	***
Respiratory Conditions			
Yes vs. No	2.42	[1.92 , 3.03]	***
Mental Health Conditions			
Yes Vs. No	2.19	[1.74 , 2.76]	***

Note: Based on 8,932 adults with diabetes, who visited outpatient's clinics from a tertiary hospital in 2016.
Polypharmacy was defined as the cumulative use of five or more medications during the one year period.
Asterisks (*) represent significant differences on polypharmacy compared to the reference group based on logistic regression.
***P< 0.001, ** 0.001≤ P< 0.01
Ref: Reference Group

Appendix I
Diagnoses codes used to identify the types of chronic conditions
Electronic Health Records database, 2016

Type of Chronic Conditions	ICD-9-CM Codes	ICD-10-CM Codes	SNOMED Codes
Diabetes	250, 250.00	E11, E11.9, E14.9	121589010, 502372015
Cardiovascular Conditions			
Hypertension	401.9	I10, 10	64176011, 2164904016
Ischemic heart disease		I25, I25.9	2534671011, 2537479013, 397667016, 2534663012
Vascular heart disease			1705016
Stroke		I64	2644233012 , 2476091017, 345636015, 345682011
Heart failure	428.0, 428.1	I50,I50.9	1234906013, 143156018, 251680018, 94251011, 2645367010, 18472010, 139475013, 2816764017, 493289014, 70653017, 80720010
Dyslipidemia		E78.5	92826017, 1209706018
Musculoskeletal Conditions			
osteoarthritis			1776248011, 359420013, 359421012, 1785522017
Osteoporosis		M81.99	453855011, 107806013
Respiratory Conditions			
Asthma	493, 493.90	J45	301485011, 301480018
COPD		J44.1, J44.9	23290013, 23287019, 475431013, 475427019
Mental Health Conditions			
Dementia		F02	87274019
Depression	311	F31.3	486186018, 486187010, 110183011, 346973011, 346979010, 55208011, 454082014, 486187010, 124707013, 1208903011, 490537016, 346980013, 1228731019, 486184015
Anxiety		F41.8, F41.9	346980013, 369987018, 303689015, 481155011, 81133019
Schizophrenia		F20	114425016, 405368015, 294764011, 138883015, 96745016

ICD-9-CM codes: International Classifications of Diseases – 9th edition, Clinical Modification
ICD-10-CM codes: International Classifications of Diseases – 10th edition
SNOMED: Clinical Modification Systematized Nomenclature of Medicine
COPD: Chronic Obstructive Pulmonary Disease

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Polypharmacy Use among Patients with Diabetes: A Cross-Sectional Retrospective Study in a Tertiary Hospital in Saudi Arabia
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	A cross-sectional retrospective observational study of adults with diabetes, who visited the outpatient clinic of a tertiary teaching hospital in Saudi Arabia, was conducted. Data were extracted from the Electronic Health Record (EHR) database for a period of twelve-month (January to December 2016). Polypharmacy was defined as the cumulative use of five or more medication classes. Polypharmacy among adults with diabetes was measured by calculating the average number of medication classes prescribed per patient. A multivariable logistic regression model was used to examine the factors associated with polypharmacy after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions. A total of 8,932 adults with diabetes were included in this study. Of these, nearly 78 % had polypharmacy, which was more likely among women as compared to men and more likely among the elderly (age $\geq$ 60 years) as compared to the adults. Also, polypharmacy was two times as likely among patients with coexisting cardiovascular disease (AOR=2.89; 95% CI: 2.54-3.29), respiratory disease (AOR=2.42; 95% CI: 1.92-3.03), and mental health conditions (AOR=2.19; 95% CI: 1.74-2.76), and three times as likely among patients with co-existing musculoskeletal disease as compared to those without these co-existing chronic conditions categories.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Diabetes is a highly prevalent chronic condition among adults in Saudi Arabia; between 21-24% of adults are estimated to have diabetes. It is projected that 27% of adults in Saudi Arabia will have diabetes by 2035.

				Diabetes is one of the top ten causes of morbidity and mortality worldwide. Patients with diabetes often have co-existing chronic health conditions such as hypertension, dyslipidemia, coronary artery disease, depression and renal disease, which require the use of multiple medications to treat those co-existing chronic conditions. All of this put patients with diabetes at high risk of polypharmacy, with an estimated prevalence of 57% to 84% of patients with diabetes using five or more medications. Limited studies have examined the prevalence of polypharmacy among adults with diabetes living in Saudi Arabia on a large scale, and looking at specific factors that put patients at risk of polypharmacy. Identifying the prevalence and the subgroup of patients at high risk of polypharmacy will facilitate pharmacovigilance efforts in clinical practice settings.
Objectives	3	State specific objectives, including any prespecified hypotheses	5	The primary objective of this study is to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia and to identify the factors that are associated with polypharmacy, specifically the association between co-existing chronic conditions and polypharmacy.
Methods				
Study design	4	Present key elements of study design early in the paper	5	A cross-sectional retrospective observational study was conducted in a tertiary teaching hospital in Saudi Arabia
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6	Outpatient's setting in the tertiary teaching hospital during a one-year period. From 1st January 2016, until 30th December 2016. The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932). This study used data retrieved from the Electronic Health Record (EHR). The data from EHR were derived from demographics file, clinical diagnosis file, and prescription drug file.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases	6	The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary teaching hospital during a one-year period.

		and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		No exclusion criteria were applied to the study population.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	The dependent variable was "polypharmacy use". There are different approaches in the literature to measure polypharmacy such as simultaneous, cumulative and continuous. Also, there is no consensus on the thresholds regarding the number of medications above which we consider the existence of polypharmacy. In the current study, we defined polypharmacy as the cumulative use of five or more medications during a one year period, this threshold has been used more than others. Using this definition, the prevalence of polypharmacy among adults was measured by the sum of unique therapeutic medication classes administered over a twelve-month period. There is no consensus on the medications that should be included in the measurements of the polypharmacy. Also, all the prescription and the non-prescription/Over the Counter (OTC) medications categories were included in our definition of polypharmacy. Independent variables included were age groups in years (18-29, 30-39, 40-49, 50-59, ≥60), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into four categories (cardiovascular, musculoskeletal, respiratory, or mental health conditions).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7	The prevalence of polypharmacy among adults was measured by the sum of different medication classes administered over a twelve-month period. Chronic conditions were identified using the the clinical diagnosis file which

				provided information about the clinical diagnosis from inpatient and outpatient visits. Physicians reported clinical diagnosis using the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes, *International Classifications of Diseases – 10th edition, Clinical Modification* (ICD-10-CM) codes, or the *Systematized Nomenclature of Medicine* (SNOMED) diagnosis codes.
Bias	9	Describe any efforts to address potential sources of bias	11	By using the EHR data; we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR.
Study size	10	Explain how the study size was arrived at	6	The study population comprised of all adult patients with diabetes (Type I and Type II) (age ≥18-year) (n = 8,932) who received their treatment at the outpatient's setting in the tertiary teaching hospital during a one-year period. We have included all diabetic adults who visited a tertiary teaching hospital during one year period.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Age groups in years (18-29, 30-39, 40-49, 50-59, ≥60), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried), and documented chronic conditions which were classified into four categories (cardiovascular, musculoskeletal, respiratory, or mental health conditions).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Frequency and percentage were used to describe the categorical variables (age, sex, marital status, nationality, co-existing chronic conditions, and polypharmacy). Mean and Standard deviation were used to describe continuous variables. Chi-square tests were used to examine the factors associated with polypharmacy use. A multivariable logistic regression was used to examine the factors associated with polypharmacy (i.e., use of ≥ 5 medication classes) after adjusting for age, sex, marital status, nationality, and co-existing chronic conditions.
		(*b*) Describe any methods used to examine subgroups and interactions	11	Not Applicable
		(*c*) Explain how missing data were addressed	11	For all the variables, the sum add up to the total study population and we did not have missing data.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		Our study design was cross-sectional data in nature, we have include all adults who visited a tertiary teaching hospital with diabetes diagnosis without sampling strategy.
		(*e*) Describe any sensitivity analyses		Not Applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6	n = 8,932
		(b) Give reasons for non-participation at each stage		Not Applicable
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	The majority were female (62.2%), and 43.3% of the study population were elderly (age ≥60 years). About half of the subjects (54.1%) had two or more diagnosed co-existing chronic health conditions.

		(b) Indicate number of participants with missing data for each variable of interest	11	We did not have missing data in our analysis.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	77.9 % of adults with diabetes were using five or more medication classes.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9	Confounder-adjusted estimates were age, gender and co-existing chronic conditions.
		(*b*) Report category boundaries when continuous variables were categorized		For the age group, we used 10 years category boundry
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not Applicable

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11	Not Applicable
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	Our study estimated the prevalence of polypharmacy among adults with diabetes in Saudi Arabia. In our study population, the rate of polypharmacy was high; nearly eighty percent of adults with diabetes used five or more medication classes. While this rate is within the documented rate in the literature among adults with diabetes 57% to 84%, we could not find a study that reported the rate of polypharmacy among all age groups of adults with diabetes. We observed a higher rate of polypharmacy among the elderly as compared to all age groups.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	This study has some limitations; we used a 12-month period to measure multiple medications use, which is not concurrent use and may have resulted in a very high rate of multiple medications uses. We did not control for the severity of diabetes using the Diabetes Complications Severity Index (DCSI) which may affect the rate of polypharmacy. We have also only observed filled prescriptions and not actual use of the medications. By using the EHR data; so we cannot eliminate some risk of bias; inaccurate information, or missing data related to the use of EHR. Due to the cross-sectional nature of the data; it is difficult to assess the causal relationship. People with the end of life care were included and this may have overestimated the rate of polypharmacy. Moreover, we have included all medication classes, including the topical agents, and vitamins in our definition, which may have overestimated the rate of polypharmacy. It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9	The very high rate of polypharmacy observed in our study population suggests that health care providers need to routinely monitor these individuals for potentially inappropriate medications, adverse drug events, and drug-drug interactions. Diabetes patients with polypharmacy may benefit from

			multidisciplinary collaborative care model that involves pharmacist follow up for the patients to assess the medication use.
Generalisability	21	Discuss the generalisability (external validity) of the study results	This study was conducted in a tertiary hospital in Riyadh; therefore the findings from this study cannot be generalized to primary care settings or to other regions in Saudi Arabia.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not Applicable

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.