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ORIGINAL ARTICLE

Polypharmacy and Glycemic Status in Individuals with Diabetes and Pre-diabetes: Iranian Multi-Center Osteoporosis Study 2021

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ABSTRACT

Objectives: This study examined the association between polypharmacy and glycemic status among adults aged ≥ 50 years.

Materials and Methods: This cross-sectional analysis included 1,117 participants from the 2021 Iranian Multi-center Osteoporosis Study (XXX). Data on sociodemographic characteristics, lifestyle factors, clinical and biochemical measures, and medication use were collected using standardized questionnaires, physical examinations, laboratory assessments, and direct observation of medication packages. Polypharmacy was assessed using thresholds of ≥ 3 and ≥ 5 concurrent medications. Weighted prevalence estimates with 95% confidence intervals (CIs) were calculated, and multivariable logistic regression models were used to examine the association between polypharmacy and glycemic status, with adjustment for relevant demographic and health-related factors.

Results: Polypharmacy was more common in individuals with diabetes than in those with pre-diabetes (≥ 3 medications: 49.89% vs. 28.25%; ≥ 5 medications: 26.28% vs. 9.82%).The mean number of medications was also higher among individuals with diabetes than among those with pre-diabetes (2.94 vs. 1.58). Among individuals receiving antidiabetic medications, polypharmacy defined as ≥ 5 medications was associated with higher odds of uncontrolled diabetes [adjusted odds ratio (AOR) = 2.21; 95% CI: 1.49, 3.29]. Each additional medication was also associated with higher odds of uncontrolled diabetes (AOR = 1.20; 95% CI: 1.12, 1.28).

Conclusion: Polypharmacy was associated with poorer glycemic control among adults aged ≥ 50 years. The association between polypharmacy and uncontrolled diabetes was particularly evident among those using ≥ 5 medications. These findings highlight the importance of considering overall medication burden when managing diabetes in this population.

Keywords: Polypharmacy, diabetes, pre-diabetes, Iran

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INTRODUCTION

Diabetes is a major public health concern among older adults and is frequently accompanied by multiple chronic conditions that require the use of several medications.[1] The coexistence of diabetes and other chronic conditions often results in complex treatment regimens and increases the likelihood of polypharmacy. In addition to the challenges associated with managing multiple medications, polypharmacy may increase the risk of drug–drug interactions, adverse drug reactions, treatment burden, and poor health outcomes.[2] Therefore, understanding the relationship between polypharmacy and glycemic status is clinically important, particularly among older adults with diabetes who are more likely to have multiple comorbidities and complex medication regimens.

Among the various definitions of polypharmacy, the use of five or more medications simultaneously is the most common.[3] However, according to a recent report from the World Health Organization (WHO), there is no generally accepted definition of polypharmacy.[4] Polypharmacy is prevalent among individuals with diabetes, with approximately two–thirds of older people with diabetes taking multiple medications at the same time.[5]

The reported prevalence of polypharmacy across different studies ranged from 47% to 97.5% in older adults with diabetes, and the pooled prevalence in the study by Remelli et al.[5] was 64%. A survey conducted in Finland showed that patients with type 2 diabetes used considerably more medications and had a significantly greater medication burden than non–diabetic patients.[6] The need to add multiple medications to an individual's treatment regimen is strongly influenced by diabetes-related comorbidities and advanced age.[7]

Polypharmacy is clinically important because of its potential implications for overall health, quality of life, and life expectancy.[7] Although the use of multiple medications may reflect a greater burden of disease, it may also independently increase the risk of drug interactions and adverse events.[7,8] Individuals with diabetes and multiple chronic conditions are more vulnerable to the adverse effects of polypharmacy because of neuropathy, dysautonomia, and vascular disease.[7] Although it's reported that a statistically significant relationship exists between polypharmacy and mortality and myocardial infarction, a non-statistically significant relationship was found between polypharmacy and stroke and hospitalization in a systematic review and meta-analysis study.[9]

Previous studies have provided important evidence regarding polypharmacy among individuals with diabetes. For instance, the survey by Remelli et al.[5] reported a high prevalence of polypharmacy among older adults with diabetes and highlighted its association with several health-related outcomes, including glycemic control, syncope, hospitalization, and mortality. However, most studies in Iran on polypharmacy among individuals with diabetes have been hospital–based and have primarily focused on the prevalence of polypharmacy rather than the relationship between polypharmacy and glycemic status. Therefore, this study aimed to explore the association between polypharmacy and both glycemic status among adults aged ≥ 50 years with diabetes or pre-diabetes, using data from the 2021 Iranian Multi-center Osteoporosis Study (IMOS).

MATERIALS AND METHODS

Study population

IMOS is a national and population-based, cross-sectional survey which has been administered in Iran to estimate the prevalence of osteoporosis and its risk factors.[6] A multi-stage stratified random sampling approach was applied, in which the 31 provinces of Iran were stratified into five homogeneous strata based on potential osteoporosis risk factors, and one or two provinces were randomly selected from each stratum. Ultimately, eight provinces (Tehran, Isfahan, Mazandaran, West Azerbaijan, North Khorasan, Fars, Kermanshah, and Khuzestan) were included. Details of the IMOS study were published previously.[6]

The inclusion criteria for IMOS comprised sufficient physical and mental health abilities, including both females and males aged ≥ 50 years who reside in rural and urban areas. The exclusion criteria of the study were cystic fibrosis, inability to measure bone mineral density, pregnancy, weighing more than 150 kg, and having undergone X-ray imaging with contrast in the last 14 days. In the IMOS study, 1450 individuals aged 50 years and older participated. Of these, 260 participants with normal blood glucose levels (fasting blood sugar < 100 mg/dL), no previous diagnosis of diabetes, and no current use of glucose-lowering medications were excluded from the study population. After removing 73 cases with missing data, we retained a sample of 1117 individuals for analysis. Figure 1 summarizes the selection process and variable-specific missing data.

Study instruments and validation

Data were collected using version 3.2 of the WHO questionnaires, which were translated and standardized for use in Iran.[10] The instruments were evaluated for internal consistency, face validity, and content validity and pilot–tested prior to their implementation.

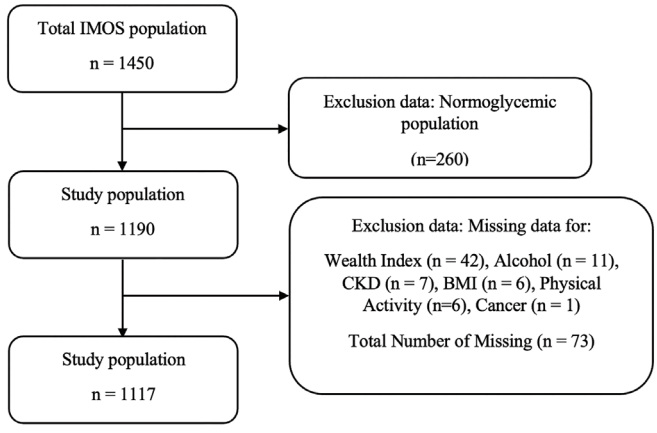


Figure 1. Missing and inclusion flowchart of the study
CKD, chronic kidney disease; BMI, body mass index.

Sociodemographic and lifestyle variables measurements

Demographic data included age, sex, residential area, wealth index (WI), employment status, marital status, and years of schooling. WI was measured using a questionnaire consisting of 36 questions that evaluated household assets and covered different dimensions of participants' assets. Principal component analysis (PCA), a statistical method, was employed to simplify and condense this information.[11] PCA utilizes all the collected data to derive new summary variables, termed principal components. The initial principal component, which explained the largest variation in wealth, was WI.[11] WI was categorized as 0 (lowest), 1 (moderate), and 2 (highest). The question used to determine participants' employment status was: "What has been your employment status during the past 12 months?" Years of schooling were divided into three groups: 6 years or less, 7 to 11 years, and 12 years or more of successfully completed schooling.

Anthropometric factors included body mass index (BMI) and waist circumference (WC). BMI, defined as the weight (kg) to the square of height (M) ratio, was divided into three categories: less than 25 as underweight or normal weight, 25 to 30 as overweight, and more than 30 as obese.[12] WC was divided into two categories of less than 95 cm as non-central obesity and ≥ 95 as central obesity.[12]

Systolic and diastolic blood pressures were measured three times with standard Beurer sphygmomanometers at the brachial artery; the interval between measurements was three minutes, and measurements were taken in a sitting position after 15 minutes of rest. The second and third measurements' average was reported as the final blood pressure

Lifestyle factors included alcohol consumption, smoking, and physical activity. Alcohol consumption was evaluated using the question: "During the past 12 months, how often did you drink alcohol?" The question "do you currently smoke any tobacco products?" was used to evaluate tobacco use during the past 12 months. Based on their responses, participants were classified into two groups: current smokers and non–current smokers. To evaluate physical activity, the Global Physical Activity Questionnaire version two, developed by WHO, was used.[13] This study measured physical activity in minutes per week.[14] Participants were classified as engaging in 150 minutes or more per week or less than 150 minutes per week.

Biochemical assessments

Laboratory measurements—glycosylated hemoglobin A1C (HbA1C), fasting plasma glucose (FPG), and creatinine—were assessed using the auto-analyzer (Roche-Hitachi Cobas C311, High-Technologies Corporation, Tokyo, Japan).[10] Blood samples were obtained after a 12-hour fasting period. The prestige premium 24i analyzer was used to assess urinary albumin. The estimated glomerular filtration rate (eGFR) was calculated using patients' age, sex, and the measured serum creatinine.[10] GFR was estimated from calibrated serum creatinine values using equations such as the Modification of Diet in Renal Disease (MDRD) Study equation and the Cockcroft-Gault formula.[15]

Definitions of clinical conditions

Diabetes was defined as fasting blood sugar levels ≥ 126 mg/dL, HbA1c ≥ 6.5%, or self-reported medical diagnosis or use of glucose-lowering medications, including oral medications or insulin.[16] Pre-diabetes was defined as fasting blood sugar levels between 100 mg/dL and 126 mg/dL, HbA1c between 5.7% and 6.5%, and not being on medication for diabetes.[16]

Individuals with diabetes were classified into two main categories: those who were unaware of their condition and those who were aware. The aware group was further divided into individuals not receiving treatment and those receiving treatment. Among those receiving treatment, glycemic status was categorized as controlled or uncontrolled based on HbA1c levels. HbA1c < 7.0% was considered controlled diabetes, whereas HbA1c ≥ 7.0% was considered uncontrolled diabetes, consistent with the glycemic target recommended by the American Diabetes Association.[17]

The variable "multiple long-term conditions" was defined as the co-occurrence of at least two chronic conditions in the same individual, including cardiovascular diseases (CVDs), cancer, hypertension, chronic kidney disease (CKD), and diabetes. CVD was evaluated by a self-reported response to the question: "Have you ever had a heart attack or chest pain from heart disease (angina) or a stroke (cerebrovascular accident or incident)?" The history of cancer was also assessed by self-report, using the question: "During the past 12 months, did a doctor or other health worker tell you that you had cancer?. Hypertension can be defined by any of the following criteria: systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or a history of antihypertensive medication use. CKD was defined as an eGFR < 60 mL/min/1.73 m^2 or urine albumin excretion > 30 mg/g in individuals with diabetes.[15]

Assessment of polypharmacy

Polypharmacy in this study is defined both as taking three or more medications at one time and as taking five or more medications. In the main analysis, vitamin supplements are included in the list of medications and in the definition of polypharmacy. However, tables presenting polypharmacy data excluding vitamins from the list of medications are provided in the supplementary file. Participants were asked to bring their medication packages with them to the interview, and the interviewer recorded medication information after directly observing the medications.

Statistical analysis

All analyses used weighted data to reflect the national population accurately. The final weight was derived by combining sampling, response, and post-stratification weights. Detailed procedures for weight construction are described in the study protocol.[6] By excluding observations with missing values (6.13%), a complete-case approach was used in the analyses. Descriptive statistics, including weighted prevalence estimates and 95% confidence intervals (CIs), were calculated. The association between polypharmacy and diabetes control among individuals receiving antidiabetic medication was examined using three

models: a crude model, a model adjusted for age and sex, and a fully adjusted model that included all demographic and health–related variables assessed in the study. The variables included in the adjustment were age, sex, WI, years of schooling, physical activity, and multiple long-term conditions. A stepwise backward-elimination method was applied to fully adjusted models, and a *p*-value threshold of less than 0.2 was used for inclusion. All the statistical analyses were conducted via Stata version 14.2 (Stata Corp LLC, College Station, TX, USA)[18] and the figures were produced via Microsoft Excel 2016.[19]

Ethical considerations

Prior to participation, all individuals gave written informed consent. The study protocol was reviewed and approved by Tehran University of Medical Sciences Ethics Committee (approval ID: IR.TUMS.EMRI.REC.1403.144, date: 23.02.2025). The research was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki.

RESULTS

In the total population, the mean age of participants was 61.18 (95% CI: 60.65–61.70), and 53.46% (95% CI: 50.08–56.82) of participants were female. Of the 1,117 participants included in the analysis, 670 had pre-diabetes and 447 had diabetes. Among individuals with pre-diabetes, 69 used ≥ 5 medications and 180 used ≥ 3 medications. In the diabetic group, 111 participants used ≥ 5 medications and 212 used ≥ 3. After excluding vitamins and supplements from the medication list, the number of individuals with polypharmacy was slightly lower, with 63 pre-diabetic and 103 diabetic participants used ≥ 5 medications, and 168 and 205, respectively, used ≥ 3 medications.

Association between polypharmacy and diabetes or pre-diabetes

Polypharmacy was more prevalent among females than males in both glycemic groups. In pre-diabetics, 32.75% (95% CI: 27.23–38.79) of females and 23.50% (95% CI: 18.32–29.61) of males used ≥ 3 medications; corresponding figures in diabetics were 51.46% (95% CI: 44.69–58.17) and 47.82% (95% CI: 39.63–56.12), respectively. Use of ≥ 5 medications was also higher in females (pre-diabetics: 10.22% (95% CI: 7.17–14.37) vs. 9.40% (95% CI: 6.29–13.83); diabetics: 29.13% (95% CI: 23.29–35.75) vs. 22.54% (95% CI: 16.23–30.40). Polypharmacy was also more prevalent among participants aged ≥ 60 years than among those aged < 60 years, particularly among individuals with diabetes (56.20% vs. 40.44% for ≥ 3 medications) (Table 1).

The prevalence estimates in Table 1 describe the distribution of polypharmacy across participant characteristics and should not be interpreted as statistically significant associations in the absence of corresponding inferential tests.

The prevalence of polypharmacy varied across educational categories, but the pattern was not clearly linear. For example, for ≥ 5 medications, prevalence was 31.16% (95% CI: 25.21–37.80) among participants with ≤ 6 years of schooling, 13.36% (95% CI: 6.63–25.10) among those with 7–11 years, and 21.10% (95% CI: 13.75–30.97) among those with ≥ 12 years of schooling. Polypharmacy was also more prevalent among unemployed than among employed participants in both glycemic groups.

The prevalence of polypharmacy varied across WI categories. In the pre-diabetic group, the prevalence of ≥ 3 medication use ranged from 24.95% (95% CI: 19.09–31.90) in the lowest wealth category to 31.26% (95% CI: 24.27–39.22) in the highest category. Among individuals with diabetes, the prevalence ranged from 45.62% (95% CI: 37.02–54.49) in the lowest wealth category to 52.69% (95% CI: 43.59–61.62) in the middle wealth category.

Polypharmacy also varied across BMI and WC categories. Among pre-diabetic individuals, the highest prevalence of ≥ 3 medication use was observed among those with BMI ≥ 30 kg/m^2 (35.71%; 95% CI: 28.17–44.02). Among individuals with diabetes, the prevalence of ≥ 3 medication use was 55.76% (95% CI: 47.83–63.41) among those with BMI >30 kg/m^2. Participants with WC ≥ 95 cm had a prevalence of 30.19% (95% CI: 25.19–35.72) and 51.21% (95% CI: 45.17–57.23) for ≥ 3 medications among pre-diabetic and diabetic groups, respectively, while the corresponding prevalence for ≥ 5 medications was 10.74% (95% CI: 7.77–14.67) and 29.84% (95% CI: 24.49–35.81).

Polypharmacy prevalence was lower among participants reporting ≥ 150 minutes of physical activity per week than among those reporting < 150 minutes per week. For ≥ 3 medications, the corresponding prevalence was 21.70% (95% CI: 16.92–27.39) versus 34.16% (95% CI: 28.46–40.36) in pre-diabetic individuals and 47.50% (95% CI: 38.91–56.23) versus 51.21% (95% CI: 44.63–57.74) in individuals with diabetes.

The strongest descriptive gradient was observed across categories of multiple long-term conditions. Among pre-diabetic individuals, the prevalence of ≥ 3 medications increased from 15.04% (95% CI: 10.60–20.92) among those without multiple long-term conditions to 55.86% (95% CI: 45.43–65.80) among those with two or more conditions. Among individuals with diabetes, the corresponding prevalence increased from 37.09% (95% CI: 26.80–48.72) to 63.75% (95% CI: 55.13–71.57). A similar pattern was observed for the ≥ 5-medication threshold.

In the Supplementary Table S1, the prevalence of polypharmacy was re-evaluated separately in diabetic and pre-diabetic groups, with vitamins and dietary supplements excluded from the medication list.

Figure 2 illustrates the prevalence of polypharmacy in individuals with diabetes and pre-diabetes, stratified by comorbid conditions. The highest prevalence estimates for both polypharmacy thresholds were observed among participants with CVD.

Cumulative prevalence and categories of medication use among diabetic and pre-diabetic population

According to Table 2, the mean number of medications used was 1.58 (95% CI: 1.39–1.77) for individuals with pre-diabetes and 2.94 (95% CI: 2.66–3.21) for individuals with diabetes. The prevalence of medication use was consistently higher among individuals with diabetes across the medication-count categories. For example, 35.52% (95% CI: 30.56–40.80) of

Table 1. Prevalence of polypharmacy among pre-diabetics and diabetics population.

	Pre-diabetes population		Diabetic population	
Polypharmacy	≥ 3	≥ 5	≥ 3	≥ 5
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Total	28.25 (24.36, 32.49)	9.82 (7.54, 12.71)	49.89 (44.64, 55.13)	26.28 (21.86, 31.25)
Age				
< 60	23.79 (18.90, 29.49)	6.75 (4.28, 10.48)	40.44 (32.63, 48.77)	17.78 (12.29, 25.02)
≥ 60	33.06 (27.24, 39.45)	13.15 (9.49, 17.92)	56.20 (49.50, 62.69)	31.97 (25.90, 38.73)
Sex				
Female	32.75 (27.23, 38.79)	10.22 (7.17, 14.37)	51.46 (44.69, 58.17)	29.13 (23.29, 35.75)
Male	23.50 (18.32, 29.61)	9.40 (6.29, 13.83)	47.82 (39.63, 56.12)	22.54 (16.23, 30.40)
BMI [kg/(m)^2]				
< 25	19.01 (13.18, 26.61)	5.52 (3.07, 9.74)	46.95 (35.46, 58.77)	21.11 (12.86, 32.64)
25-30	28.82 (23.05, 35.38)	12.47 (8.57, 17.78)	45.23 (36.77, 53.98)	22.82 (16.18, 31.18)
> 30	35.71 (28.17, 44.02)	9.37 (5.98, 14.38)	55.76 (47.83, 63.41)	32.23 (25.24, 40.12)
Waist (cm)				
< 95	25.36 (19.51, 32.26)	8.46 (5.32, 13.20)	46.30 (35.98, 56.95)	16.68 (10.27, 25.92)
≥ 95	30.19 (25.19, 35.72)	10.74 (7.77, 14.67)	51.21 (45.17, 57.23)	29.84 (24.49, 35.81)
Residential area				
Rural	23.24 (17.05, 30.84)	7.97 (4.77, 13.04)	41.74 (31.89, 52.30)	20.17 (13.20, 29.56)
Urban	30.14 (25.44, 35.29)	10.52 (7.73, 14.16)	52.47 (46.43, 58.44)	28.23 (22.99, 34.13)
Wealth index				
0 (lowest)	24.95 (19.09, 31.90)	10.87 (7.05, 16.40)	45.62 (37.02, 54.49)	22.33 (15.89, 30.44)
1	28.72 (22.15, 36.34)	8.94 (5.27, 14.78)	52.69 (43.59, 61.62)	29.59 (21.78, 38.81)
2 (highest)	31.26 (24.27, 39.22)	9.67 (6.34, 14.49)	51.32 (42.04, 60.51)	26.78 (19.29, 35.88)
Employment status				
Unemployed	30.68 (26.18, 35.57)	12.03 (9.07, 15.78)	53.70 (47.74, 59.55)	28.62 (23.49, 34.37)
Employed	21.68 (14.60, 30.93)	3.87 (1.95, 7.53)	35.28 (25.64, 46.30)	17.34 (10.30, 27.71)
Marital status				
Single	26.02 (17.18, 37.37)	10.49 (5.87, 18.06)	53.49 (41.32, 65.26)	29.20 (19.16, 41.78)
Married	28.62 (24.41, 33.25)	9.71 (7.23, 12.93)	49.04 (43.26, 54.85)	25.60 (20.80, 31.07)
Years of schooling (years)				
≤ 6	27.60 (22.82, 32.95)	10.91 (7.95, 14.81)	52.05 (45.43, 58.59)	31.16 (25.21, 37.80)
7-11	25.39 (16.00, 37.82)	7.89 (3.83, 15.54)	38.76 (26.13, 53.11)	13.36 (6.63, 25.10)
≥ 12	31.21 (23.54, 40.08)	8.68 (4.67, 15.59)	50.62 (39.84, 61.35)	21.10 (13.75, 30.97)
Alcohol consumption during past 12 months				
No	28.77 (24.81, 33.07)	10.05 (7.72, 13.00)	50.26 (44.95, 55.57)	26.40 (21.92, 31.42)
Yes	6.02 (0.80, 33.82)	0	35.63 (12.16, 68.86)	22.08 (4.66, 62.18)
Current smoking				
No	29.23 (25.04, 33.81)	9.53 (7.26, 12.42)	50.30 (44.75, 55.86)	25.96 (21.31, 31.22)

Table 1. Continued.

	Pre-diabetes population		Diabetic population	
Yes	22.07 (13.14, 34.64)	11.65 (5.02, 24.73)	46.48 (31.53, 62.09)	28.95 (16.63, 54.44)
Physical activity				
< 150 min/week	34.16 (28.46, 40.36)	12.73 (9.39, 17.04)	51.21 (44.63, 57.74)	30.15 (24.39, 36.61)
≥ 150 min/week	21.70 (16.92, 27.39)	6.60 (3.91, 10.93)	47.50 (38.91, 56.23)	19.28 (13.23, 27.22)
Multiple long-term Conditions				
No disease	15.04 (10.60, 20.92)	3.89 (2.13, 7.00)	37.09 (26.80, 48.72)	12.66 (6.60, 22.90)
One disease	29.06 (23.32, 35.56)	9.25 (6.05, 13.89)	43.60 (35.60, 51.94)	21.32 (15.33, 28.85)
Two or more diseases	55.86 (45.43, 65.80)	24.26 (16.38, 34.36)	63.75 (55.13, 71.57)	39.18 (31.11, 47.90)

CI, confidence interval; BMI, body mass index.

individuals with diabetes used ≥ 5 medications compared with 16.01% (95% CI: 13.08–19.45) of those with pre-diabetes. Similar results were observed when excluding vitamins from the list of medications (Supplementary Table S2).

Supplementary Table S3 in the supplementary files presents the five therapeutic drug groups most frequently used by individuals with diabetes and pre-diabetes. Cardiovascular medications were the most commonly reported class of drugs in both groups.

Diabetes status according to polypharmacy

Among pre-diabetic individuals, mean HbA1c was 5.93% (95% CI: 5.83–6.03) among those using ≥ 5 medications and 5.91% (95% CI: 5.88–5.93) among those using < 5 medications. A similar, difference was observed when polypharmacy was defined as ≥ 3 medications (5.93% vs. 5.90%). Given the overlap in CIs, these findings are best interpreted as descriptive differences rather than as evidence of meaningful differences in glycemic measures (Table 3).

Among individuals with diabetes, mean HbA1c was 8.30% (95% CI: 7.94–8.66) among those using ≥ 5 medications compared with 8.06% (95% CI: 7.81–8.31) among those using < 5 medications. Mean FPG was also higher among participants using ≥ 5 medications (156.36 mg/dL; 95% CI: 148.08–164.65) than among those using < 5 medications (151.00 mg/dL; 95% CI: 141.69–161.00).

Regarding diabetes status, the proportion of unaware individuals with diabetes was lower among those using ≥ 5 medications (27.03%; 95% CI: 18.72–37.33) than among those using < 5 medications (52.52%; 95% CI: 46.46–58.50). A similar pattern was observed using the ≥ 3-medication threshold (34.32% vs. 57.27%). In individuals receiving treatment, the prevalence of uncontrolled diabetes was higher in those meeting either of the polypharmacy thresholds. For the ≥ 5-medication definition, 56.58% (95% CI: 46.05–66.56) had uncontrolled diabetes compared with 35.15% (95% CI: 29.68–41.05) among those using < 5 medications. For the ≥ 3-medication definition, the corresponding figures were 51.96% (95% CI: 44.35–59.48) and 29.66% (95% CI: 23.51–36.65), respectively (Table 3).

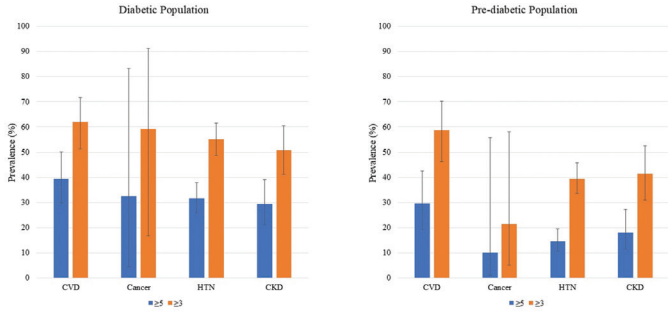


Figure 2. Prevalence of polypharmacy stratified by comorbidity status in diabetic and pre-diabetic individuals; Polypharmacy was defined in this figure as the use of ≥ 5 medications and alternatively as ≥ 3 medications

CKD, chronic kidney disease; CVD, cardiovascular diseases; HTN, hypertension.

Association between polypharmacy and uncontrolled diabetes among individuals using antidiabetic medications

Table 4 presents the association between polypharmacy and uncontrolled diabetes among 243 individuals using antidiabetic medications, of whom 188 had uncontrolled diabetes. In the crude analysis, both polypharmacy definitions were associated with higher odds of uncontrolled diabetes. For ≥ 5 medications, the crude odds ratio (OR) was 3.16 (95% CI: 2.19–4.56; $p < 0.001$), while for ≥ 3 medications it was 2.84 (95% CI: 2.07–3.90; $p < 0.001$).

Model 1 was adjusted for age and sex to account for the two basic demographic factors that may be associated with both medication burden and glycemic control. After this adjustment, the associations remained similar: the adjusted OR (AOR) was 2.99 (95% CI: 2.06–4.36; $p < 0.001$) for ≥ 5 medications and 2.78 (95% CI: 2.01–3.83; $p < 0.001$) for ≥ 3 medications.

Model 2 was additionally adjusted for years of schooling, physical activity, multiple long-term conditions, and WI. Following this more extensive adjustment, the association between ≥ 5 medications and uncontrolled diabetes remained statistically significant (AOR = 2.21; 95% CI: 1.49–3.29; p < 0.001). In contrast, the association for ≥ 3 medications was attenuated and was no longer statistically significant (AOR = 1.58; 95% CI: 0.81–3.09; $p = 0.178$).

Table 2. Cumulative prevalence of medication use among pre-diabetics and diabetics population

	Number of medication use	
	Pre-diabetic population	Diabetic population
	% (95% CI)	% (95% CI)
Mean	1.58 (1.39, 1.77)	2.94 (2.66, 3.21)
0	47.20 (42.85, 51.60)	23.77 (19.77, 28.29)
≥ 1	52.80 (48.40, 57.15)	76.23 (71.71, 80.23)
≥ 2	38.20 (34.01, 42.57)	64.68 (59.61, 69.45)
≥ 3	28.25 (24.37, 32.48)	49.89 (44.66, 55.12)
≥ 4	16.01 (13.08, 19.45)	35.52 (30.56, 40.80)
≥ 5	9.82 (7.54, 12.70)	26.28 (21.86, 31.25)
≥ 6	5.72 (3.92, 8.26)	16.61 (13.08, 20.87)
≥ 7	3.07 (1.88, 4.96)	9.01 (6.50, 12.35)
≥ 8	1.50 (0.67, 3.33)	6.35 (4.29, 9.31)
≥ 9	1.20 (0.46, 3.13)	3.00 (1.67, 5.34)
≥ 10	1.12 (0.40, 3.10)	2.12 (1.03, 4.28)

Data have been weighted to account for overall non-response, non-response at each step, and sample distribution across provinces, adjusted for age, sex, and area of residence.
The reported percentages represent column-wise prevalence.
CI, confidence interval.

Table 3. Diabetes status according to polypharmacy

			Number of medication use			
Variable			**< 5**	**≥ 5**	**< 3**	**≥ 3**
Pre-diabetes population (n = 670)						
Mean HbA1c, % (95% CI)			5.91 (5.88, 5.93)	5.93 (5.83, 6.03)	5.90 (5.87, 5.92)	5.93 (5.88, 5.98)
Mean FPG, mg/dL (95% CI)			97.97 (97.18, 98.76)	99.82 (97.35, 102.28)	98.09 (97.24, 98.94)	98.31 (96.75, 99.87)
Diabetes population (n = 447)						
Mean HbA1c, % (95% CI)			8.06 (7.81, 8.31)	8.30 (7.94, 8.66)	7.95 (7.63, 8.27)	8.30 (8.04, 8.57)
Mean FPG, mg/dL (95% CI)			151.00 (141.69, 161.00)	156.36 (148.08, 164.65)	153.80 (146.78, 160.82)	156.28 (145.09, 167.48)
Diabetes status						
Unaware, % (95% CI)			52.52 (46.46, 58.50)	27.03 (18.72, 37.33)	57.27 (49.98, 64.25)	34.32 (27.28, 42.12)
Aware	**No treatment, % (95% CI)**		2.10 (1.05, 4.17)	3.60 (1.12, 10.95)	1.89 (0.80, 4.40)	3.10 (1.33, 7.06)
	Under treatment	**Uncontrolled, % (95% CI)**	35.15 (29.68, 41.05)	56.58 (46.05, 66.56)	29.66 (23.51, 36.65)	51.96 (44.35, 59.48)
		Controlled, % (95% CI)	10.23 (7.13, 14.46)	12.79 (7.44, 21.09)	11.18 (7.25, 16.85)	10.62 (7.02, 15.75)

Data have been weighted to account for overall non-response, non-response at each step, and sample distribution across provinces, adjusted for age, sex, and area of residence. The reported percentages represent column-wise prevalence.
CI, confidence interval; HbA1c, glycosylated hemoglobin A1C; FPG, fasting plasma glucose.

Table 4. Relationship between polypharmacy and uncontrolled diabetes (n = 188) in anti-diabetic medication consumers (n = 243) using stepwise logistic regression

	Crude		Model 1		Model 2	
	OR (95% CI)	*p*-value	AOR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
Polypharmacy						
< 5	Reference		Reference		Reference	
≥ 5	3.16 (2.19, 4.56)	< 0.001	2.99 (2.06, 4.36)	< 0.001	2.21 (1.49, 3.29)	< 0.001
Polypharmacy						
< 3	Reference		Reference		Reference	
≥ 3	2.84 (2.07, 3.90)	< 0.001	2.78 (2.01, 3.83)	< 0.001	1.58 (0.81, 3.09)	0.178
Medication use (per each medication)	1.27 (1.19, 1.34)	< 0.001	1.26 (1.18, 1.34)	< 0.001	1.20 (1.12, 1.28)	< 0.001

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, years of schooling, physical activity, comorbidity and wealth index; OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio.

When medication count was analyzed as a continuous variable, each additional medication was associated with higher odds of uncontrolled diabetes. This association remained statistically significant after adjustment, with an AOR of 1.20 (95% CI: 1.12–1.28; $p < 0.001$) in Model 2, corresponding to approximately 20% higher odds of uncontrolled diabetes for each additional medication.

DISCUSSION

Polypharmacy was more prevalent in individuals with diabetes than in those with pre-diabetes. The mean number of medications was also higher in individuals with diabetes than in those with pre-diabetes (2.94 vs. 1.58), indicating a greater medication burden in the diabetes group. The prevalence of polypharmacy also varied by age, sex, anthropometric characteristics, residential area, physical activity, and comorbidity. Mean HbA1c and FPG levels were higher among individuals with polypharmacy. Uncontrolled diabetes was more common among individuals with polypharmacy. Among individuals receiving antidiabetic medications, the association between polypharmacy and uncontrolled diabetes remained statistically significant after adjustment when polypharmacy was defined as ≥ 5 medications.

The substantially higher medication burden observed among individuals with diabetes compared with those with pre-diabetes is consistent with the greater complexity of disease management in diabetes. In our study, individuals with diabetes used nearly twice as many medications on average as those with pre-diabetes, and the prevalence of both ≥ 3 and ≥ 5 medication use was considerably higher in the diabetes group. This difference is also consistent with previous evidence indicating a high prevalence of polypharmacy among individuals with diabetes and a greater medication burden compared with individuals without diabetes.[5] The higher medication burden among individuals with diabetes may partly reflect the need for glucose-lowering therapy together with medications for diabetes-related comorbidities and other chronic conditions. Clinically, these findings highlight the importance of considering overall medication burden when managing individuals with diabetes, particularly those with multiple chronic conditions.

Polypharmacy was more common among adults older than 60 years in our study. This may be because older adults often have multiple coexisting medical conditions and take several medications concurrently.[20] Women may also be at greater risk of receiving potentially inappropriate medications. There are several reasons for this matter; for instance, women seek more medical care than men.[21] They have better social aptitude for expressing their symptoms to their healthcare practitioner. Therefore, women are more likely to be diagnosed with multiple medical conditions. On the other hand, for some men, masculine ideologies act as a barrier to seeking healthcare, thereby reducing their likelihood of being diagnosed with chronic conditions.[22-27]

As stated previously, the prevalence of polypharmacy varied across educational categories, without a clear linear pattern. The literature suggests that there are various reasons for this. Firstly, individuals with less education tend to be less involved in preventive health measures, thereby placing them at greater risk of conditions that may require polypharmacy.[28,29] Secondly, people with lower education are less proactive in shared decision making.[30] Therefore, are more likely to take multiple medications without asking for further explanation.[31,32] However, given the non–linear pattern observed in our study, these potential explanations should be interpreted cautiously.

As indicated in the study results, individuals with different levels of socioeconomic status (SES) showed variation in the prevalence of polypharmacy. People with higher SES may still have as much multimorbidity but because of their social status they benefit from better access to healthcare services and preventive care, which may influence medication usage.[33] Some reviews have indicated that low SES is related to medication non-adherence, which may be associated with a greater burden of chronic conditions and polypharmacy.[34-37] Also, people with better social status use more preventive services, diagnostic services, and receive better treatment quality.[38]

Obesity and overweight which is a manifestation of high BMI and large WC, were associated with higher prevalence of polypharmacy in our study. This may partly reflect the coexistence of obesity with several non–communicable diseases and metabolic conditions, which may increase the overall medication burden.[39,40] In this study, alcohol consumption also showed differences in polypharmacy prevalence across categories. However, some studies have found that in women exclusively, alcohol consumption is related to lower risk of polypharmacy.[41,42]

This study also revealed that polypharmacy prevalence was higher among individuals with a greater number of comorbidities. Clinical condition of individuals is one of the major factors of physical function.[43] The coexistence of multiple chronic conditions may require management with several medications and may therefore contribute to a greater medication burden.[39]

As indicated in the results, polypharmacy was associated with uncontrolled diabetes among individuals receiving antidiabetic medications, particularly when polypharmacy was defined as the use of ≥ 5 medications. This association may have several possible explanations. A higher medication burden may reflect greater disease complexity and a higher prevalence of comorbid conditions, which may also be related to poorer glycemic control. In addition, treatment adherence may influence glycemic control, and several factors, including forgetfulness, financial constraints, disappearance of symptoms, and being busy, have been reported as reasons for non–adherence to treatment.[44] However, medication adherence and drug–drug interactions were not assessed in the present study; therefore, their potential roles in the observed association cannot be directly evaluated.

Study limitations

This study is based on IMOS survey as a nationwide study which includes participants aged ≥ 50 years across provinces of Iran, enhancing the generalizability of findings. Simultaneous assessment of diabetes and pre-diabetes allows for comparison and early recognition of risk patterns associated with polypharmacy. The main limitation of this study is its cross-sectional design, which does not allow the establishment of temporal or causal relationships between polypharmacy and associated factors. Medication use and comorbidities were self-reported, which may introduce recall bias. Although antidiabetic medications were included in the polypharmacy definition to capture the overall medication burden among individuals receiving treatment for diabetes, this approach may partly reflect treatment intensity and influence the observed association with glycemic control. This should be considered when interpreting the findings. This study did not include an evaluation of medication appropriateness or adherence.

CONCLUSION

Uncontrolled diabetes was associated with polypharmacy among adults aged ≥ 50 years receiving antidiabetic medications, particularly when polypharmacy was defined as the use of ≥ 5 medications. The observed association does not establish a causal relationship, and the potential roles of medication adherence and drug–drug interactions could not be assessed in this study. These findings highlight the relevance of considering overall medication burden in the clinical management of individuals with diabetes.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by Tehran University of Medical Sciences Ethics Committee (approval ID: IR.TUMS.EMRI.REC.1403.144, date: 23.02.2025)

Informed Consent: Prior to participation, all individuals gave written informed consent.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: O.T.M., A.O., Concept: O.T.M., A.O., Design: O.T.M., Data Collection or Processing: M.K., P.Z., Analysis or Interpretation: S.S., N.C., S.G., Literature Search: A.R., Writing: S.S., A.R.

S.S. and A.R. contributed equally as first authors.

Supplementary Table Link: https://d2v96fxpocvxx.cloudfront.net/25021570-dd5c-48cc-b052-771af43e75cc/content-images/bc3d88fe-a8cb-4c72-9bd5-6e53e1bee2cc.pdf

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