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The prevalence and determinants of Polypharmacy in middle-aged population of two Russian cities.

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ABSTRACT

Introduction: Polypharmacy has been a global threat these days and raised a question about its determinants. Differences in socioeconomic conditions, comorbid conditions, healthcare services use of individuals were expected to be related to Polypharmacy. Populations with cardiovascular diseases are more likely to be on multiple medications. However, no studies investigated the effects of socioeconomic differences and differences in healthcare use and multi-morbidity in the Russian middle-aged population. So, this study aims to determine the prevalence and determinants of Polypharmacy in two Russian cities.

Materials and methods: Data were collected in a cross-sectional Know You Heart study conducted in two big Russian cities from November 2015 to December 2017 (4051 participants). The descriptive statistics for the socioeconomic factors, health care use, and multi-morbidity were presented using percentages, mean and standard deviations. Chi-square test was done to test the difference in proportions. Logistic regression models were used to study the association between study variables and Polypharmacy, and. Odds Ratios (OR) with 95% confidence interval CI) were presented as the measures of association.

Results: Out of 4051 participants, 374 were on Polypharmacy. Participants on Polypharmacy were significantly older, were either overweight or obese (86%), with multimorbidity (80%), and used more health care services. 47% of them were above 65 years, 39% were at 55-64 years, 10% were at 45-54 years and only 4% were at 35-44 years. These findings were confirmed by multivariable analysis. Relative to age group 35-44 years the OR and CI for age groups; 55-64 years and 65 years were 4.05(2.32-7.09) and 8.77(5.009-15.388) respectively; for obese relative to normal weight was 2.99(2.15-4.15); for multimorbid participants relative to one or less disease was 4.83(3.68-6.33) where p-trend was <0.001. Similarly, with OR and CI 6.30(4.49-8.85) and 7.72(1.62-36.67) for 5+ times of GP visits and hospitalization respectively relative to no GP visits or hospitalizations, was found that as increased numbers of times of GP visits and hospitalization increased odds of being on PP also increased.

Conclusion: One out of ten of our sample was on Polypharmacy. Increasing age, body mass index, comorbidities and uses of health care services increases the likelihood of being on Polypharmacy.

Abbreviations

Polypharmacy (PP)

Cardiovascular disease (CVD)

Chronic obstructive pulmonary disease (COPD)

World health organization (WHO)

General practitioner (GP)

Know your heart (KYH)

Myocardial infraction (MI)

Body mass index (BMI)

Systolic blood pressure (SBP)

Diastolic blood pressure (DBP)

Adverse drug’s reaction (ADR)

Odds Ratio (OR)

Confidence interval (CI)

1. Introduction

With the increase in chronic diseases and the aging population globally, there is a rise in prescription of medications, or Polypharmacy (PP). As there is no exact definition, Polypharmacy, also known as multi-medication, can be explained as the use of multiple medications at a time to treat one or multiple conditions. Different studies have defined Polypharmacy as the use of multiple medications ranging from over five to over 11 at a time. Usually, the use of medication over five is considered Polypharmacy, and over 10 were considered hyper Polypharmacy or excessive Polypharmacy. (77) The prevalence of PP among different European countries ranges from 26.3% to 39.9%.(15) From 1995 to 2010, patients with Polypharmacy with medications ≥5 increased from 11.4% to 20.8%, and with medications ≥10 increased from 1.7% to 5.8% (6) and within a decade, the use of multiple drugs and use of more than five drugs increased by 20% and 70% respectively in 2010. (7) The prevalence rates over the world is considerably range from 10 % in Greek general population to 75% in Australian nursing care home. (75,76)

1.1 Adverse health outcomes and Polypharmacy

The use of multiple medications and the presence of multiple chronic conditions increases the therapeutic complexity for both health care professionals and patients. This results in adverse health outcomes, usually associated with a high chance of adverse effects, drug interactions, prolonged hospitalization, increased medication costs, and drug-related mortality.(1,2,3,4) The magnitude of harm could result from drug interactions and drug-disease interactions. In drug-disease interactions, the worsening of another disease happens while taking medication for one condition. Usually, older adults above 50 with chronic diseases and multiple specialist physicians in long-term care facilities are the most risk groups for Polypharmacy with at least five medications daily. (5,23) As a result of an increasing number of older people living with multi-morbidity, the risk of adverse events and poor health outcomes increases. Polypharmacy also brings the worst-quality life, leading to medication-related symptoms, adverse effects, and other symptoms due to medication administration errors. (18) It is seen that Polypharmacy is one of the risk factors for hospital admission and residence in care homes. The length of a hospital stay and adverse drug effects also increase due to multiple medications.

Although the causality between death and Polypharmacy is unclear, increased mortality is related to higher Polypharmacy. The meta-analysis of 47 studies showed a significant dosedependent association between categorically defined medications (one to four, five, and six to nine medications) and mortality. (12) Polypharmacy has also shown that the risk of frailty in older adults, and co-occurrence of Polypharmacy and frailty led to poorer health outcomes. (30) Unplanned and drug-related hospitalization are due to inappropriate prescriptions and adverse effects of drugs. (13) Also, from a study among the people living with HIV in 24 countries, PP is associated with lower health-related quality of life outcomes, and most people prefer lesser medications. (15)

1.2 Factors associated with Polypharmacy

Different factors contribute to the Polypharmacy, such as physical inactivity, number of diseases, quality of life, socioeconomic factors, number of physicians involved, and abnormal body weight. These factors may directly or indirectly contribute to the high prevalence of Polypharmacy. For example, physicians may directly prescribe different medications for patients with multiple diseases if they think they need them. At the same time, factors that help increase the risk of diseases indirectly increase the risk of Polypharmacy.

1.2.1 Age-sex

Studies suggested that Polypharmacy varies according to age groups and gender.(4,13,15,16) An increase in age was seen to be directly related to Polypharmacy. As age increases, the disease burden also increases, leaving the complexity for treatments with different medications resulting in drug-related side effects, drug interactions, and drug adherence. (4,20,26,31,35) The only study estimating Polypharmacy prevalence in Russia found that Polypharmacy and multi-morbidity were associated and tended to increase the older population's Adverse Drug Reactions (ADRs). (26) The degree of exposure to Polyharmacy varies for men and women varies. Women were more likely to be at risk due to Polypharmacy than men and people living in urban areas than in rural areas. (19,20,44,48) The prevalence of comorbid conditions for both genders and differences in health-seeking behaviors were thought to be major factors contributing to Polypharmacy in different degrees.

1.2.2 Socioeconomic conditions (Education and Income)

Adverse socioeconomic conditions of patients may influence the choice of treatment by the physicians and increase the risk of Polypharmacy; the lower the income and education, the higher was the risk of Polypharmacy.(24,25,72,74) The patient's level of education and knowledge about drug use have been significant factors related to Polypharmacy. Older adults with no or minimal educations are more likely to take multiple medications. Insufficient knowledge about medication use, adverse effects, and comorbidities in older patients might contribute to Polypharmacy (70,71). In a study in Sweden, the lower education level of participants increased the probability of Polypharmacy.(21,22,23). Patients with higher education tend to have more interaction with physicians and drugs-related information. This lowers the risk of being on PP. Population with low income are believed to be at greater risk of Polypharmacy. Different disease burdens due to poor socioeconomic conditions might put them at greater risk of PP. Whereas studies in Brazil and Sweden, people with higher income are also at greater risk as they can offer more healthcare services than low-income groups. (68,69,72,74) This trend put both income groups in different degrees of Polypharmacy.

1.2.3 Multi-morbidity

Polypharmacy is believed to be a clinical consequence of multi-morbidity generally in older adults. The multi-morbidity trends in different European countries are increasing, and this prevalence increases with age. (75) Multi-morbidity, the co-occurrence of at least two or more chronic conditions, is related to poor health outcomes and increased healthcare costs. Different diseases such as cardiovascular diseases (CVD), diabetes mellitus, chronic obstructive pulmonary disease (COPD), and dementia are associated with multi medications. Among them, PP is strongly associated with treatment for CVD as it is recommended by different international guidelines with complex regimens and combinations of drugs.(8) Due to this, patients with cardiovascular diseases are exposed to various medication-related burdens. About 90% percent of people taking multiple drugs take medications that are active on the cardiovascular system.(9) Around the globe, CVD is one of the significant causes of death and disability. In 2015, age-standardized CVD mortality in Russia was 368.8 per 100,000 population. Though CVD mortality started decreasing in 2003 in Russia, it is one of the leading causes of death.(11)

1.2.4 Lifestyle factors

Smoking, alcohol consumption, physical inactivity are the individuals' behaviors that contribute to PP. Usually, increased smoking and alcohol consumption and sedentary lifestyles are unhealthy behaviors believed to increase the Polypharmacy. All these factors increase the risk for multi-morbidity, thereby increasing the demand for more medications at a time. Older adults with chronic diseases having unhealthy behaviors are the most vulnerable groups for exposure to Polypharmacy. (3,59,18,62)

1.2.5 Health care service use

Generally, clinical visits and hospitalizations tend to increase the number of medications. As any medical condition arises, healthcare-seeking behaviors increase, and the probability of using different health care services also increases. To combat the medical conditions, clinicians or any medical staff will prescribe or suggest the different medications. This could directly increase the chance of exposure towards Polypharmacy. Different studies had suggested an increase in the risk of Polypharmacy with an increase in the use of health care services. But a reverse impact is also seen as more medication increased the adverse effects and increased the need for hospitalization. (65,66) So, the knowledge about the association between the utilization of health care services and Polypharmacy is of great importance to minimize the risk.

1.3 Motivation and aim of the study

To achieve a good therapeutic outcome, along with the drug-related need of the patient, is challenging. There are increasing drug-related problems associated with inappropriate prescribing and adverse health outcomes. It is necessary to measure or assess the prevalence of PP from a clinical perspective since it can be a marker of multi-morbidity, adverse drug reactions, and inappropriate prescriptions. In 2017, WHO also mentioned Polypharmacy as a risk factor and concern for patient's safety and listed it as one of the three actions to reduce the severe avoidable harm related to multiple medications by 50% in 5 years.(10) From the public health perspective, it is essential to know the prevalence and factors related to Polypharmacy in the middle-aged population. In the case of multi-morbidity, it is essential to take multiple medications, but risks related to the concurrent use of different drugs must be calculated, or Polypharmacy should be avoided. (27,28)

To the best of literature search, very little is known on the prevalence and determinants of PP in Russia's middle-aged population. The only identified study is based on a small number of participants.(26) Therefore, this study aims to report the prevalence of Polypharmacy in two Russian cities based on the Know Your Heart study. The relationship of Polypharmacy with socioeconomic characteristics and health care services use is likely to differ depending on the country's health care system characteristics. Therefore, it is of interest to look at how these variables relate to Polypharmacy in Russia.

This study aims :

a) To determine the prevalence of Polypharmacy among the middle-aged population of two Russian cities and identify the association with socioeconomic factors (income, education), age, and sex.

b) To assess Polypharmacy's relationship with cardiometabolic multi-morbidity, and use of health care services in Know Your Heart study.

Research question: what is the difference in different socio-demographic factors, use of health care services, and comorbidities among participants with and without Polypharmacy?

2. Materials and methods

2.1 Study population and design:

Know your Heart study is a cross-sectional study of cardiovascular health in two big cities in Russia. The study was conducted as a baseline interview and followed by a health check at polyclinics (within 2 weeks). The baseline interview was conducted from November 2015 to December 2017 and included 5089 participants aged 35-69, of whom 4542 attended health checks.

Three types of response percentage were calculated based on the outcome of every visit made to each address and the overall response percentage of the health check component were 67% in Arkhangelsk and 37% in Novosibirsk. This analysis will be based on 4051 participants (men and women) who attended the health check and answered the question about their current medication use.

2.2 Data and Sample collection:

A minimum of 3 attempts was made to get a response from each address. At the *baseline interview*, a trained interviewer administered a questionnaire using a computer-assisted personal interviewing device. The questionnaire includes sections on sociodemographic factors, physical activity, physical health (including health service use), and various self-reported health measures. The questionnaire also included questions about diet quality score, smoking, household structure, socioeconomic circumstances, and alcohol use.

Health check included the questionnaire and physical examination of the cardiovascular system and was administered by either a nurse or a cardiologist. It included questions on past medical history. Participants were asked to bring all their medications with them during the health check, including inhalers, and names and doses used per day were recorded. A maximum of 7 medications was recorded for each person.

Physical examination included blood pressure measurements, anthropometry (height, waist and hip circumference, weight), and blood sample collection.

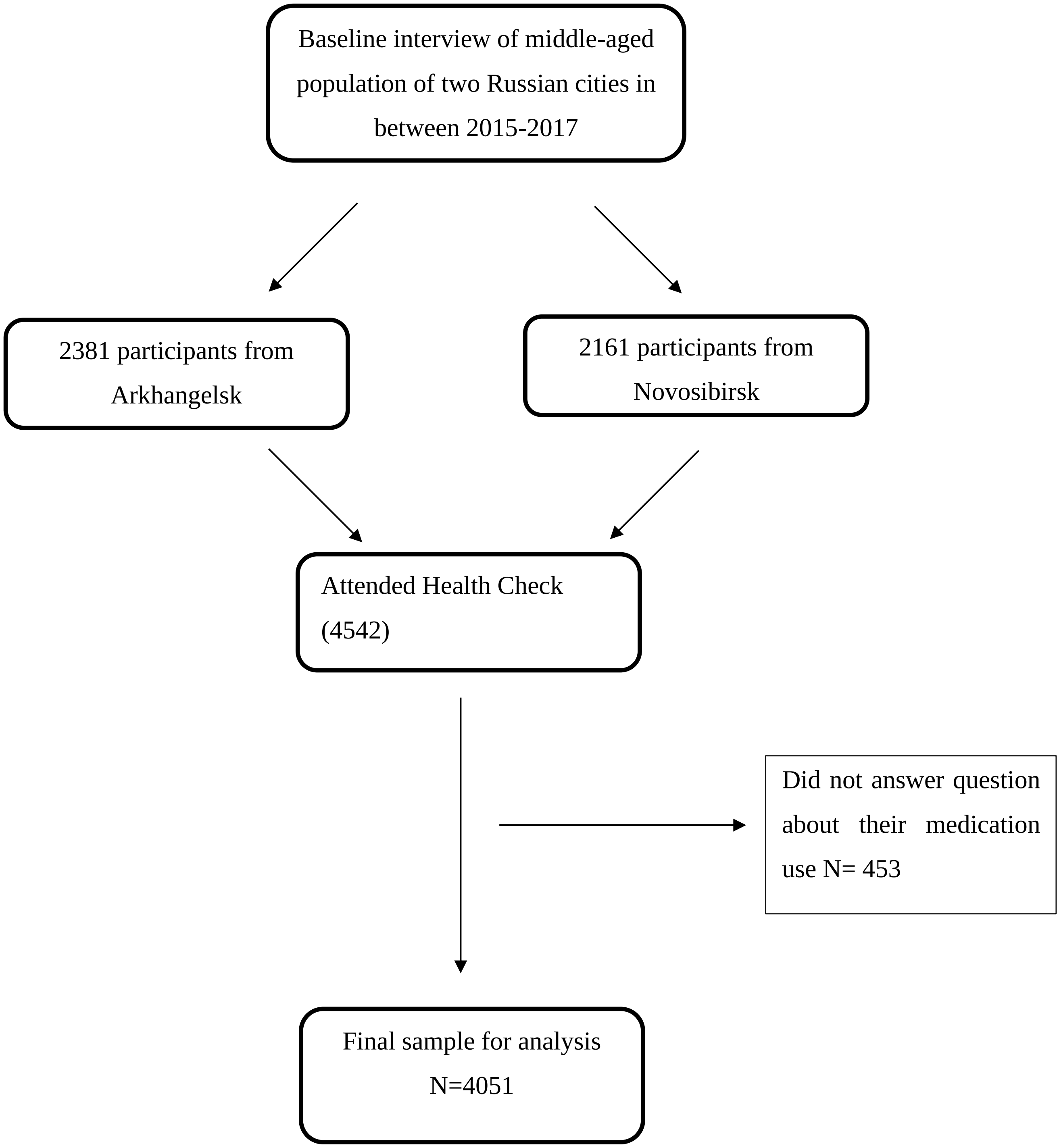

Figure 1: flow diagram for the study population

2.3 Study Variables

2.3.1 Dependent Variable:

Polypharmacy: Polypharmacy was defined as the self-reported use of 5 or more medications. The number of medications will be calculated based on the question, "Do you currently use any medications, including inhalers?" This question was asked only to health check participants.

2.3.2 Independent Variables:

2.3.2.1 Main exposures:

- Age and Gender. Age was analysed as a categorical variable: 35-44 years, 45-54 years, 55-64 years and 65-69 years.

- Education and income: In Know Your Heart study, participants answered a question: 'what is your level of education?' with 7 answer options. The responses result was further categorized into three levels as 1) incomplete secondary (incomplete secondary or lower), 2) secondary level ((complete secondary, professional school (without secondary degree, PTU), professional school and secondary (e.g., PTU and secondary education), Specialized secondary (e.g., medical, pedagogical college, technicum)) and 3) higher education levels (incomplete higher and higher)).

The participants' income level was determined by asking a question, "Which of the phrases below best describes this household's financial situation during the past year?" The responses were grouped into three categories: 1) "There is not enough money for food or clothes and other items", 2) "enough money for food and clothes but it is difficult to buy large domestic appliances, a large new car, a flat or a 3) house" and 3) "we have no financial constraints."

- **Cardiometabolic multi-morbidity:** Multimorbidity was defined as the co-occurrence of two or more of the following conditions: diabetes mellitus, stroke, heart failure, arterial fibrillation, angina, myocardial infarction, hypertension. These conditions were defined based on self-report: during the baseline interview, participants were asked if doctors had ever told them if they had MI, stroke, or diabetes and if they were ever diagnosed with diseases such as myocardial infarction/heart attack, angina/coronary heart disease, stroke, chronic kidney disease.

Hospitalizations/physician visits: The number of hospitalizations in the past 12 months were asked and recorded in days. The number of general practitioner (GP) visits and number ofof hospitalization in the past 12 months were recorded.

2.3.2.2 Confounders

- Alcohol consumption and smoking: CAGE was used to screen for alcohol problems, and participants with a score >2 will be categorized as having alcohol problems (76). The question about current smoking was asked in the baseline questionnaire with response options: current smoker, non-smoker, and ex-smoker.

- Biological markers

BMI- Body Mass Index was calculated during the health check-up and was further divided into 5 categories as <18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and 35+. BMI from 25 to 29.9 was considered overweight and BMI over 30 as obese, whereas BMI from 18.8-24.9 was considered normal BMI and below 18.5 as underweight.

Blood pressure- Systolic and diastolic blood pressure were measured using a device ((OMRON 705 IT (OMRON Healthcare)), and the mean from the second and third recording was recorded in mmHg.

Total cholesterol- From blood samples at the health check, total cholesterol level was measured using AU 680 Chemistry System Beckman Coulter device in the central laboratory and expressed in mmol/L.

2.4 Statistical analysis:

Statistical analysis were carried out using Statistical Package for Social Sciences (SPSS), IBM, version -27.

Standard descriptive statistics were calculated for Polypharmacy as well as other study variables. Means were presented for continuous variables (BMI, Total cholesterol, HDL, LDL, SBP, DBP) and frequencies were be presented for categorical variables (Age, Sex, study site, Education level, financial situation, Smoking, Alcohol use, Use of any medication, Times of GP visits and Times of hospitalizations).

In bivariate analysis cross-tabulations for all study variables by Polypharmacy were conducted to compare frequencies of categorical variables with chi-square test for statistical significance. In addition, the differences in means between groups for continuous variables were tested using Student's T-test.

To examine the association between age, sex, socioeconomic determinants (income and education), use of health care services, multi-morbidity and PP, the univariate logistic regression model was fit with each risk factor separately. Then in the multivariate analysis, logistic regression models were adjusted for age and sex, BMI, high blood pressure, total cholesterol, smoking, and alcohol use, diabetes. Those factors were chosen for adjustment because they are strongly related to both exposure and the outcome, and can potentially explain the observed univariate associations.

The numbers of GP visits and number of hospital visits were additionally adjusted for multi-morbidity.

The analysis was based on complete cases (with no missing values on any covariate in the analysis).

2.5 Ethical approval

Ethical approval for the Know Your Heart study was obtained from the ethics committees of the London School of Hygiene & Tropical Medicine (approval number 8808), Novosibirsk State Medical University (approval number 75; 21 May 2015), the Institute of Preventative Medicine (approval received 26 December 2014), Novosibirsk and the Northern State Medical University, Arkhangelsk (approval number 01/01-15; 27 January 2015)[29]. This Master project was based on anonymized data and did not require approval from REK.

Signed informed consent was obtained both at baseline interview and at the health check for all participants.

2.6 Data Access

Data access was given following an application to the database of "Know your Heart" study. Application instruction and metadata can be obtained through the website https://metadata.knowyourheart.science/

3. RESULTS

3.1 Baseline characteristics of study sample:

A cross-sectional study of 4504 participants at two Russian cities (Novosibirsk and Arkhangelsk) recruited a higher percentage of female (58%) participants compared to male (42%) participants (Table 1). The age range of the was 35 to 69 years old. The proportion of people aged in between 55-65 years (32%) was highest in comparison to other age groups; 35-45 years (21%), 45-55 years (28%), and 65-69 years (18%).

More than half of the sample (55%) had completed the secondary level of education, 41.5% had the higher level, and 3.5% had the incomplete secondary level. The average BMI of the population was 28.19 kg/m^{2,} and cholesterol level was 5.54 mmol/L. Most of the population (76.5%) had enough money for food, clothes, and other items compared to those who did not have enough (19.4%), and the remaining (1.9%) had no financial constraints. More than half of the population (57%) said they used at least one medication the last month. The proportion of never smokers, current smokers, and ex-smoker were 49.5%, 25.2%, and 25.3%, respectively. In addition, 88.6% and 88.9% of the population had CAGE score of less than 2 (no alcohol-related problems), and 40.7% of the population had two or more diseases (multi-morbidity).

Table 1. Descriptive characteristics of the study sample, N = 4504.

Variable Name	Mean (sd) or percent (N)	Missing (N)
Sex		
Male, %	41.9% (1888)	
Female, %	58.9% (2616)	
Age (at health check)		
35-44 years	21.3% (958)	
45-54 years	27.9% (1258)	
55-65 years	32.3% (1457)	

65-69 years	18.5% (831)	
Site		
Novosibirsk	47.6% (2142)	
Arkhangelsk	52.4% (2362)	
Education level		
Incomplete secondary (%)	3.4% (154)	
Secondary (%)	55.2% (2486)	
Higher (%)	41.4% (1864)	
BMI (kg/m2)	28.19 (5.64)	15
Total cholesterol (mean, mmol/L)	5.54 (1.15)	70
HDL-cholesterol (mean, mmol/L)	1.44 (0.36)	70
LDL- cholesterol (mean, mmol/L)	3.73 (0.93)	70
SBP (mean, mmHg) 2/3rd reading	132.72 (20.16)	356
DBP (mean, mmHg) 2/3rd reading	83.09 (11.41)	356
Financial situation		80
Not enough money for food, clothes and other items	19.4% (874)	

Have enough money for food, clothes and other items	76.9% (3465)	
Have no financial constraints	1.9% (85)	
Use of any medication		453*
Yes	57.1% (2313)	
No	42.9% (1738)	
Smoking		13
Never smoker, %	49.5% (2223)	
Ex-smoker, %	25.2% (1133)	
Current smoker, %	25.3% (1135)	
Alcohol (CAGE score)		
<2	88.67% (3994)	
≥2	11.33% (510)	
Times of GP visits		3
0	45.6%(2056)	
1 to 4	43.4(1955)	
5+	10.9%(490)	
Times of Hospitalization		
0	84.5%(3808)	
1 to 4	15.3%(689)	
5+	0.2%(7)	

Multi-morbidity		
Presence of one or less disease	59.3% (2672)	
Presence of two or more diseases	40.7% (1832)	

3.2 Prevalence of Polypharmacy in the study sample:

The overall prevalence of Polypharmacy was 9% i.e., 374 participants out of 4051, of which around 2/3rd were women (64%). As age increases the proportion of having Polypharmacy also increases; for 35-45 years, 45-54 years, 55-65 years and 65-69 years are 4%, 10%, 39% and 47% respectively. Table 2 shows that higher proportion of participants with Polypharmacy were overweight (27.5%) and obese (58%), compared to people without Polypharmacy (overweight – 38%, obese – 30%). Mean BMI was also higher in participants with Polypharmacy compared to those without Polypharmacy.

People having secondary education level (56.15%) has the highest participants with Polypharmacy while with incomplete secondary level (8.83%) has least. Among participants with Polypharmacy, there was a smaller percent with higher education (35.0%) than those without Polypharmacy (41.3%). Also, for participants who have enough money (69.9%) for food, clothes, and other items are among the highest Polypharmacy compared to participants with the least financial constraints (2%). Higher percentage of those with polypharmacy have financial constraints (28.1%) compared to those without polypharmacy (18.4%)

Table 2 also shows that 57.5% of participants with Polypharmacy did not smoke, while 24.34% were ex-smokers, and the rest (17.91%) were current smokers. Only a few (7.22%) participants with Polypharmacy were defined as problem drinkers by CAGE score of >=2, versus 12% in the group without Polypharmacy. 80% of the participants with Polypharmacy had at least two or more diseases compared to 36% among participants without Polypharmacy suggesting that prevalence of Polypharmacy increases with presence of comorbidities.

Table 2 also suggested that as the number of visits to General Practitioner (GP) increases, the proportion of participants with Polypharmacy also increases. For five or more times of GP visits maximum (40%), proportions of participants were with Polypharmacy compared to 8% without Polypharmacy. For numbers of hospitalizations also, as the number of hospitalizations increased, the proportion of participants with Polypharmacy increased compared to those without Polypharmacy.

Table 2. The differences in CVD risk factors between participants with and without Polypharmacy (n=4051) *

	Polypharmacy Yes (374)	Polypharmacy No (3677)	p-value**
Sex			0.019
Male, %	36% (136)	42.64%(1568)	
Female, %	64% (238)	57.36% (2109)	
Age (at health check)			<0.001
35-44 years	4%(15)	23.36%(859)	
45-54 years	10%(37)	29.4%(1081)	
55-65 years	39%(146)	31.82%(1170)	
65-69 years	47%(176)	15.42% (567)	
Site			
Novosibirsk	35.3%(132)	57.6% (2118)	
Arkhangelsk	64.7%(242)	42.4% (1559)	
Education level			0.044
Incomplete secondary(%)	8.83%(33)	7%(255)	
Secondary (%)	56.15%(210)	51.7%(1903)	

Higher (%)	35.02%(131)	41.3%(1519)	
BMI (kg/m2)	31.47(6.37)	27.81(5.43)	<0.001
BMI categorical			<0.001
Underweight(>18.5)	0	1.25% (46)	
Normal(18.5-25)	13.9% (52)	30.86%(1135)	
Overweight(25-30)	27.5% (103)	38%(1398)	
Obese(30+)	58% (217)	29.89%(1085)	
Total cholesterol (mean, mmol/L)	5.08(1.22)	5.56(1.13)	<0.001
HDL-cholesterol (mean, mmol/L)	1.34(0.34)	1.45(0.36)	<0.001
LDL- cholesterol (mean, mmol/L)	3.35(0.95)	3.75(0.91)	<0.001
Triglycerides, (mean, mmol/L)			
SBP (mean, mmHg)	136.70(20.34)	132.33(20.08)	<0.001
DBP (mean, mmHg)	82.27(10.68)	83.21(11.49)	0.131
Smoking			0.001
Never smoker, %	57.5% (215)	48.5% (1783)	
Ex-smoker, %	24.34% (91)	25% (921)	
Current smoker, %	17.91% (67)	26.25% (965)	
Alcohol (CAGE score)			0.007
<2	92.78% (347)	88% (3239)	
≥2	7.22% (27)	12% (438)	

Financial situation			<0.001
Not enough money for food, clothes and other items	28.1% (103)	18.4% (666)	
Have enough money for food, clothes and other items	69.9% (256)	79.5% (2881)	
Have no financial constraints	2% (7)	2.1% (76)	
Numbers of GP visits			<0.001
0	17.9% (67)	48.6% (1786)	
1 to 4	42% (157)	43.3% (1590)	
5+	40.1% (150)	8.1% (299)	
Numbers of Hospitalization			<0.001
0	65.2% (244)	86.4% (3178)	
1 to 4	33.7%(126)	13.5%(496)	
5+	1.1%(4)	0.1%(3)	
Multi-morbidity			<0.001
Presence of one or less disease	20%(75)	64%(2355)	
Presence of two or more diseases	80%(299)	36%(1322)	

*453 who did not answer the question about their medication use were excluded from the analysis.

** P-values were obtained from the Pearson's chi-square test for categorical variables and Student's t-test for continuous variables

3.3 Relationship between sample characteristics and Polypharmacy

Table 3 summarizes the result of univariate and multivariate analysis of different factors associated with Polypharmacy. The prevalence of Polypharmacy was higher by 30% (OR=1.3;95% CI: 1.04-1.62) in women compared to men in the univariate analysis, but attenuated in the multivariate analysis adjusted for CVD risk factors(BMI, high blood pressure, cholesterol level, smoking and alcohol consumption). As age increases, the prevalence of Polypharmacy also increases. In univariate analysis all age groups 45-54 years (OR= 1.96; 95% CI:1.06-3.59), 55-64 years (OR= 7.14;95% CI: 4.17-12.27) and 65-69 years (OR=17.77; CI: 10.30-30.43) were significantly associated with higher polypharmacy compared to the youngest age group (35-39). But in multivariate analysis, only age group 55-60 years (OR= 4.05; CI: 2.32-7.09) and 65-69years (OR= 8.77; CI: 5.009-15.388) were significantly associated with an increase in Polypharmacy.

In univariate analysis the prevalence of having polypharmacy increased by 50 % and 28 % with having incomplete secondary level of education (OR=1.50; 95% CI: 1.002-2.24) and secondary education level (OR= 1.28; 95% CI: 1.01-1.26), respectively compared with having higher education. While in multivariable analysis, the association doesn't seem to be significantly associated. For financial situations, none of those subgroups were associated considerably with Polypharmacy in both univariate and multivariate analysis.

In univariate analysis, multi-morbidity (two or more disease) was significantly associated with Polypharmacy (OR=7.102; 95% CI: 5.46-9.23). After adjusting for BMI, high blood pressure, cholesterol level, smoking and alcohol consumption in multivariable analysis, multi-morbidity was participants with multimorbidity had still 4.83 higher odds of polypharmacy (OR= 4.83; 95% CI: 3.68-6.33) compared to those who with one or less disease.

In univariate analysis, times of GP and times of hospitalization in last 12 months were also significantly associated with an increase in Polypharmacy. The probability of having Polypharmacy increased by 2.63 times (OR=2.63; 95% CI: 1.96-3.53) for the group with 1 to 4 GP visits and by 13.37 times (OR=13.37; 95% CI: 9.77-18.28) for the group with 5+ GP visits compared to no GP visits. After adjusting for BMI, high blood pressure, cholesterol level, smoking, alcohol consumption, and multi-morbidity, the prevalance Polypharmacy increased by 1.16 times (OR=1.16;95% CI: 1.22-2.33) and by 5.81 times (OR= 5.81; 95% CI: 4.06-8.31) respectively for (1 to 4) and (5+) GP visits.

Similarly, the increase in the number of hospitalizations was associated with an increase in Polypharmacy. For (1 to 4) times and 5+ of hospitalization, the odds of having Polypharmacy increased by 3.30 times (OR=3.30; 95% CI: 2.61-4.18) and 17.36 times (OR=17.36; 95% CI: 3.86-78.03) respectively compared to no hospitalization. While adjusting for BMI, high blood pressure, cholesterol level, smoking, alcohol consumption and multi-morbidity in multivariate analysis, the association was still significant, i.e., for 1 to 4 times of hospitalization probability of Polypharmacy increased by 2.36 times (OR=2.36;95% CI: 1.80-3.09) and by 5.40 times (OR= 5.40; 95% CI: 1.00-29.18) respectively for (1 to 4) and (5+) times of hospitalizations.

Table 3: The association of age, sex, education, income, use of health services, multi-morbidity with Polypharmacy in Univariate and Multivariate logistic regression models.

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Sex		0.019		0.896
Male, %	1		1	
Female, %	1.3(1.04-1.62)		1.01(0.77-1.34)	
Age (at health check)		<0.001		<0.001
35-44 years	1		1	
45-54 years	1.96(1.06-3.59)	0.03	1.51(0.811-2.84)	0.191
55-65 years	7.14(4.17-12.27)	<0.001	4.05(2.32-7.09)	<0.001
65+ years	17.77(10.30-30.43)	<0.001	8.77(5.009-15.388)	<0.001
Education level		0.045		0.948*
Incomplete secondary (%)	1.5(1.002-2.24)	0.049	0.96(0.75-1.23)	0.76
Secondary (%)	1.28(1.01-1.60)	0.034	0.84(0.55-1.29)	0.44

Higher (%)	1		1	
Financial situation				0.051*
Not enough money for food and clothes	1.67(1.16-2.60)	0.205	1.43(0.62-3.28)	0.398
Have enough money for food and clothes	0.96(0.44-2.11)	0.92	1.04(0.46-2.35)	0.917
Have no financial constraints	1		1	
Multi-morbidity				<0.001*
Presence of one or less disease	1	<0.001	1	
Presence of two or more diseases	7.102(5.46-9.22)		4.83(3.68-6.33)	
Times of GP visits				<0.001**
0	1			
1 to 4	2.63(1.96-3.53)	<0.001	1.69(1.22-2.33)	0.001
5+	13.37(9.77-18.28)	<0.001	5.81(4.06-8.31)	<0.001
Times of Hospitalization				<0.001**
0	1			
1 to 4	3.30(2.61-4.18)	<0.001	2.36(1.80-3.09)	<0.001
5+	17.36(3.8-78.03)	<0.001	5.40(1.00-29.18)	0.050

*****- adjusted for age, sex, BMI, high blood pressure, cholesterol level, smoking and alcohol consumption.

****-** adjusted for age, sex, BMI, high blood pressure, cholesterol level, smoking, alcohol consumption and multi morbidity.

4. DISCUSSION

This study sought to find the prevalence and determinants of Polypharmacy in the population of two Russian cities, Arkhangelsk and Novosibirsk. The prevalence of Polypharmacy in the study sample (35-69 years old) was 9.2%. Compared to the results of prevalence rates worldwide ranging from 10 % in the Greek general population to 75% in Australian nursing care home(75,76), this rate falls on the lower side. In other countries in Europe, the prevalence ranges from 26.3% to 39.9%(15) and an increasing trend was observed.(7) I found that in the sample of oldest (65-69 years old) participants, the prevalence of Polypharmacy was high (47%) while in the youngest age group (35-44 years), it was just 4%.

In this analysis, I focused on differences in socio-demographic factors, use of health care services, and comorbidities among participants with Polypharmacy and without Polypharmacy. It was observed that the prevalence of Polypharmacy was significantly related to age, sex, education, number of GP visits, number of hospitalizations, and multi-morbidity, but not with income.

4.1 Age, sex and Polypharmacy

In this study, as age increased, the prevalence of Polypharmacy also increased. Almost half (47%) of the participants with Polypharmacy were in the age group 65-69 old years. In univariate and multivariate analysis, the probability of having Polypharmacy also increased with age. In univariate analysis, with the increase in age above 65 years the likelihood of having Polypharmacy increased by almost 18 times compared to 35-39 years old participants. But after adjusting for CVD risk factors (BMI, high blood pressure, cholesterol level, smoking and alcohol consumption), the likelihood dropped by almost half (8.77 times). Therefore, some higher risks of Polypharmacy in older age are due to the higher prevalence of CVD risk factors. Comparing the result with a similar setting in Russia was difficult as not many studies of PP were done in Russia. These results can be compared with a similar study in Switzerland and The United States (4,31). A study in Switzerland having almost the same setting as this study had the prevalence following the same trend of increasing from the age of 40 years and the likelihood of having Polypharmacy above the 65 years almost 10 times compared to the middle-aged group of population. (4) Despite of large population, in the polish cross-sectional study, similar associations between age and PP were observed. (38) These patterns over the different parts of world suggests the higher prevalence in elderly specially above 65 years similar as in our study.

Age is a risk factor for CVD; it was seen that many CVDs were present among most older adults compared to the general population (38,39), so the chance of cardiovascular-specific Polypharmacy would be high. In an Ethiopian study of cardiovascular outpatients, the prevalence of cardiovascular Polypharmacy for the elderly was almost double compared to another study for all outpatient's prescriptions in the same setting (16,37). Different cardiac conditions and the presence of other comorbidities with an increase in age can explain the increase in Polypharmacy in older adults. With the increase in cardiac comorbidities, prescriptions to alleviate these conditions resulted in increased Polypharmacy. (45,47) In different studies, it was also seen that elderly age was associated with Polypharmacy related side effects, adverse reactions, drug interactions, and poor drug adherence. (20,26,34,35,36) These results also support that the elderly group of the population is at high risk of Polypharmacy, with the associated risk of adverse effects and drug interactions.

Sex was associated with Polypharmacy in the univariate analysis, but no significant association was seen in our multivariable analysis after adjustment for CVD risk factors. There were no consistent results in previous studies for gender and Polypharmacy. In many studies, females were more prevalent to Polypharmacy than male participants, though some results suggest male participants were more prominent to Polypharmacy than females (19,20,42,43,44,48,52,53). One study in Finland shows females using more prescription drugs than males, but another study in Saudi Arabia shows male participants are more likely to be exposed to Polypharmacy than females (42,43). In another review, males and females were exposed to many medications to a different degrees with the difference in their medical conditions (44). These could be explained by different comorbid conditions for both genders responsible for Polypharmacy. Prescription attitudes of physicians towards males and females and different socioeconomic gradients and their health-seeking behaviors could also be for such differences in the results (41). This also indicates that gender could affect Polypharmacy differently in different condition and the relationship could be subjective. In context of Russia, the association between polypharmacy and sex is interesting because of the huge gender gap in mortality – men have a much lower life expectancy than women(78). Attenuation of association between polypharmacy and sex after adjustment for CVD risk factors may indicate that study sample was biased due to the recruitment of healthier men.

4.2 Comorbidities and Polypharmacy

In this study, the probability for Polypharmacy increased by 7 times for participants with 2 or more disease conditions. While adjusting BMI, high blood pressure, high cholesterol level, smoking and alcohol as confounders for comorbidities in multivariable analysis, results still shows significant association. In multivariable analysis, the probability of being on Polypharmacy was almost 5 times (OR=4.83) for those with at least 2 or more diseases conditions. This was consistent with what was found in previous studies. (26,44,45,55,56,57) In a cross-sectional study in Canada, the prevalence of Polypharmacy increased for community-dwelling adults with an increase in numbers of chronic disease conditions (56,57). In another study in the primary health care setting, the prevalence of Polypharmacy increased from 13% with one chronic illness condition to 33% with two chronic illnesses and up to 62% with three or more chronic conditions. (55) Also, another Russian study showed that elderly patients with comorbidities have a higher prevalence of Polypharmacy. (26) In all these studies, as age increased, the number of chronic conditions also increased, leading to more drug use.

As cardiac conditions require multiple medications simultaneously to alleviate the condition and, with an increase in CVD risk factors (age and obesity), multi-morbidity such as diabetics, hypertension, hyperlipidemia also increases, requiring multiple treatments at the same time. (4,37,58) These could have potentially elevated the risk to be on Polypharmacy for patients with cardiovascular diseases with aging. Also, other conditions unrelated to cardiovascular conditions had contributed equally towards the Polypharmacy potentially risking the person on drugs related problems such as ADRs, drug reactions and drug adherences. (26,59,60)

4.3 Hospitalization, Clinician visits and Polypharmacy

As the number of times of GP visits and times of hospitalization increased, the tendency to be on Polypharmacy also increased in this study. The probability would be around 2.6 times and 13.3 times more to be on Polypharmacy with 1 to 4 times , and five or more times of GP visits compared to no GP visits. In multivariable analysis, after adjusting comorbidities, smoking, alcohol consumption, BMI, high blood pressure and total cholesterol level, patients would be around 1.6 times and 5.8 times more potential risk on Polypharmacy with 1-4 times and, five or more times of GP visits. Similarly, for 1 to 4 and, five and more times of hospitalization, the risk to be on polypharmacy increased by 3.3 times and 17.3 times respectively. After adjusting for comorbidities, smoking, alcohol consumption, BMI, high blood pressure and total cholesterol level, the risk drops to 2.3 times and 5.4 times, respectively.

Recent studies have shown similar results, an increase in the utilization of health services was associated with the increase in Polypharmacy. (46,61,62) A cohort study in Italy showed Polypharmacy and excessive Polypharmacy are risk factors for emergency return and hospitalization.(65) Also, another observational study in Australia among community-dwelling older men showed an association between all types of hospital admission with the number of used medication.(64) As number of chronic diseases increased in a patient, the need of treatment (clinician visits and hospitalization) also could increase, resulting in a higher chance of Polypharmacy. This trend could also result from drug-related adverse reactions, drug interactions, and drug adherences while taking multiple medications. Drug-related hospitalization could result from the use of inappropriate prescriptions among older adults with the presence of risk factors such as change in pharmacokinetics and pharmacodynamics. (66) Multiple medications were also associated with a higher risk of unplanned hospitalizations. (67) Another study in Japan's primary care also showed the same results. Also, this study showed that patients consulting multiple numbers of the medical institution were on higher Polypharmacy compared to consulting with different practitioners of the same institutions. (63) This could be due to lack of time to physicians to review the prescriptions by another physicians and lack of communications between these institutions. An integrated electronic prescription method with easy access for physicians would solve these problems.

4.4 Education and Income

Generally, poor socioeconomic indicators were believed to increase medication use. But this study found no significant association between some socioeconomic gradients such as education and income with Polypharmacy in the analysis adjusted for CVD risk factors. Results of several other studies had shown associations in both directions. Studies in Brazil showed the positive association of Polypharmacy with higher income and health insurances. (68,69,70) This could be due to financially more affluent individuals having more access to healthcare facilities compared with low-income groups. Whereas some other studies had shown a negative association of income with Polypharmacy. (72,74) This could be explained due to the presence of many diseases with low socioeconomic position. Also, different studies showed the association of low education level with an increase in the probability of Polypharmacy (70,71,73). Patients' education level could also increase the awareness towards the

Polypharmacy and help to interact with physicians. Generally, for educated older adults, it was easy to know about the drugs information and more active on patient-physician interactions. These could lower the risk of Polypharmacy. (72)

In our study, incomplete secondary education level and secondary level of education were significantly associated with an increase in Polypharmacy in univariate analysis. After adjusting for CVD risk factors in the multivariate analysis, the association was attenuated. This can be explained by the fact that participants with higher education had a better risk factor profile (lower blood pressure, never smoking, lower cholesterol, lower BMI) than participants in other education categories. Association of lower education with unhealthy behaviors, like unhealthy eating habits, physical inactivity, or smoking, alcohol use has been shown in many countries. In Russia, most population has access to health care services. Therefore we can suggest that observed inequality in Polypharmacy is mostly driven by behavioral risk factors prevalent in lower education groups. Interventions aimed at unhealthy behaviours among lower education groups would be beneficial by decreasing cardiometabolic multimorbidity, and therefore polypharmacy at last decades of life. Further studies of socioeconomic determinants on medication use, use of health care services are warranted in Russia.

5. STRENGTH AND LIMITATIONS

This study is one of a few studies examining the prevalence and determinants of Polypharmacy in Russia. It provides much-needed evidence of the high prevalence of Polypharmacy among middle-aged adults in Russia and factors related to it. Another strength is a larger sample size allowing providing sufficient statistical power. All medications were recorded as they were told to bring with them, which increases the study's reliability. Though no medication-specific study was conducted, medications used in Polypharmacy were classified according to ATC classification, so makes the results more valid. This standardized classification makes the comparison more reliable.

Only up to 7 medications were recorded during the health check examination for each person. This could limit the study only to Polypharmacy with five or more medications. Getting information about more numbers would have helped to assess the prevalence of hyper Polypharmacy. Only income and education might not cover the entire socioeconomic status of the study population; besides, measurement error is very likely for both variables. As smoking and drinking behaviors being self-reported, there can be some bias or under-reporting. All diseases were also self-reported by participants, so might exclude or miss other potential diseases with maximum Polypharmacy. The health check component's overall response percentage was 67% in Arkhangelsk and 37% in Novosibirsk. This also can leave out participants with potential Polypharmacy and lead to selection bias. An important limitation of this study is its cross-sectional design, therefore we could not establish whether the association between hospitalization and Polypharmacy was causal, and what explains this association – adverse drug reactions or need for more hospitalizations and medications for the treatment of some of the conditions.

6. CONCLUSION

This study shows just 9% of middle-aged adults from two Russian cities were exposed to Polypharmacy. A significant association between Polypharmacy with age, comorbidities and health care service utilizations were also seen. With the increase in age, the association also become stronger, suggesting older age with high chance of Polypharmacy. Education was associated with Polypharmacy in the univariate models, but not the income. A greater risk of being on Polypharmacy was also seen in groups with cardiometabolic multi-morbidity. In participants who visited general practitioners more often or were hospitalized more, the odds of being on Polypharmacy also increased.

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