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Polypharmacy and Grip Strength: A longitudinal Study for the Survey of Health, Ageing and Retirement in Europe (SHARE)

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Dissertação especialmente elaborada para obtenção do grau de
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ABSTRACT

Introduction: Polypharmacy is emerging as a significant public health concern associated with adverse health consequences, including reduced quality of life, higher hospitalization rates, and increased mortality. Several studies have explored the implications of multiple medications on psychological and physical well-being. Despite the evidence highlighting polypharmacy's adverse effects across various health domains, its specific impact on muscle strength remains unclear. **Objective**: To investigate the associations between polypharmacy and muscle strength, controlling for sex, age, education, body mass index, and country of residence among middle-aged and older adults. **Methods**: This was a longitudinal and transversal study of 23,980 individuals using data from the SHARE database. Participants were from 25 European Countries and Israel, aged 50 years and older at baseline. Polypharmacy was categorized as the use of five or more drugs. The handgrip strength assessed muscular strength - a well-established indicator of muscular strength measured with a dynamometer. ANCOVA and a logistic regression analysis were performed. Data analyses were conducted between August and September 2023. **Results and discussion:** Around 27.4% of participants had polypharmacy, and these individuals tended to be older, have higher BMIs, have more chronic diseases, and exhibit lower handgrip strength than those without polypharmacy. ANCOVA-adjusted analyses revealed that people with polypharmacy showed significantly lower handgrip strength. The difference in reduction in muscle strength ranged from 1.4 kg to 1.8 kg in women and from 1.4 kg to 1.6 kg in men compared to the group without polypharmacy. Logistic regression models confirmed that polypharmacy was associated with a higher odds ratio (OR) for low handgrip strength, even after adjusting for covariables. These results emphasize the association between polypharmacy and reduced handgrip strength, especially in an aging population. These findings highlight the importance of recognizing and managing polypharmacy when indicated and possible, as it may contribute to physical frailty and decreased muscle strength, potentially impacting older individual's overall well-being and functional abilities. **Conclusion**: This study supports the assertion that polypharmacy is associated with lower muscle strength. Additional studies to explore this phenomenon further could enhance the comprehension of this relationship. Moreover, it is reasonable to conclude that public health and clinical interventions to mitigate inappropriate medication use may positively influence muscle strength, contributing to overall health and well-being.

Keywords: polypharmacy; muscular strength; handgrip strength; older adults.

RESUMO

Introdução: A polifarmácia está emergindo como um problema significativo de saúde pública. Está associada a consequências adversas para a saúde, incluindo redução da qualidade de vida, taxas de hospitalização mais elevadas e aumento da mortalidade. Vários estudos investigaram as implicações do uso de vários medicamentos no bem-estar psicológico e físico. Apesar das evidências substanciais que destacam os efeitos adversos da polifarmácia em vários domínios da saúde, a sua relação específica e o impacto na força muscular permanecem pouco claros. **Objetivo**: Investigar a associação entre a polifarmácia e a força muscular, controlando sexo, idade, escolaridade, índice de massa corporal e país de residência entre adultos de meia-idade e idosos. **Métodos**: Este foi um estudo longitudinal e transversal com 23.980 indivíduos através do banco de dados SHARE. Os participantes eram de 25 países europeus e de Israel, com idade igual ou superior a 50 anos no início do estudo. A polifarmácia foi categorizada como uso de cinco ou mais medicamentos. A força de preensão manual avaliou a força muscular - um indicador bem estabelecido de força muscular - medida com um dinamômetro. ANCOVA e uma análise de regressão logística foi executada. As análises dos dados foram realizadas entre agosto e setembro de 2023. **Resultados e discussão**: Cerca de 27,4% dos participantes apresentavam polifarmácia. Esses participantes eram mais idosos, tinham maior IMC e apresentavam mais doenças crônicas. Além disso, demonstravam menor força de preensão manual do que aqueles sem polifarmácia. Análises ajustadas por ANCOVA revelaram que pessoas com polifarmácia exibiram uma força de preensão manual significativamente menor. A diferença na redução da força muscular variou de 1,4 kg a 1,8 kg em mulheres e de 1,4 kg a 1,6 kg em homens, quando comparadas ao grupo sem polifarmácia. Modelos de regressão logística confirmaram que a polifarmácia estava associada a maior razão de chances para baixa força de preensão manual, mesmo após ajuste para covariáveis. Estes resultados enfatizam a associação entre polifarmácia e redução da força de preensão manual, especialmente numa população idosa. Isso destaca a importância de reconhecer e gerir a polifarmácia quando indicada e possível, pois esta pode contribuir para a fragilidade física e diminuição da força muscular, potencialmente impactando o bem-estar geral e as capacidades funcionais do indivíduo mais velho. **Conclusão**: Este estudo corrobora a afirmação de que a polifarmácia está associada à menor força muscular. Estudos adicionais para explorar ainda mais esse fenômeno poderiam melhorar a compreensão dessa relação. Além disso, é razoável concluir que as intervenções clínicas e de saúde pública para mitigar o uso inadequado de medicamentos podem influenciar positivamente a força muscular, contribuindo para a saúde e o bem-estar geral.

Palavras-chave: polifarmácia, força muscular, força de preensão palmar; idosos

LIST OF TABLES

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
OR	Odds Ratio
PIP	Potentially Inappropriate Prescribing
SHARE	Survey of Health, Ageing and Retirement in Europe

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INTRODUCTION

The usage of multiple medications is generally referred to as polypharmacy. There is no standard definition for the number of drugs that categorize polypharmacy; however, studies commonly define it as the concomitant daily use of at least five drugs, including over-the-counter medications or supplements(1,2).

Polypharmacy is a significant growing challenge in public health and clinical settings(3,4). The prevalence of polypharmacy is increasing in all ages; nevertheless, it is more evident in the older population(5,6). With the increase in life expectancy, there was also an increase in the number of people living with chronic conditions, leading to a higher prevalence of multimorbidity and polypharmacy. For example, a retrospective cohort study in Italy's outpatient setting found that 35% of older patients received five or more medications(7). Similarly, a prospective cohort study in Sweden using a national coverage of data registers observed a 44% prevalence of polypharmacy in individuals 65 years or older(8).

Polypharmacy is a particular problem in the older population not only for its prevalence but also due to an increased vulnerability to drug-associated harm connected to age-related processes that influence pharmacokinetics and pharmacodynamics(4). In addition, this population's increased risk of multimorbidity contributes to adverse drug reactions due to possible drug-disease interaction(9).

In the literature on polypharmacy, several studies highlight the importance of the difference between appropriate polypharmacy (many drugs) as opposed to inappropriate polypharmacy (too many drugs)(1,10,11). In the cases of inappropriate prescriptions, the harm related to polypharmacy is even more significant because the potential harms outweigh the potential benefits(12).

While polypharmacy does not directly imply inappropriate prescribing (PIP), it presents an elevated risk for PIP(13), including overprescribing (unnecessary treatment), misprescribing (incorrect prescription), and underprescribing (failure to prescribe necessary treatment)(14). Underprescribing is a significant concern in clinical practice, as patients with polypharmacy are more likely to miss out on potentially beneficial and recommended medications than patients taking fewer medications(15).

The ascending prevalence of polypharmacy has also raised concerns regarding the financial burden healthcare systems face. Mismanaged polypharmacy is estimated to have contributed to 4% of the avoidable costs worldwide(2). According to the World Health Organization, appropriately managing polypharmacy can potentially avoid US$ 18 billion, equivalent to 0.3% of global healthcare expenses. The rise in healthcare costs can be attributed to various factors associated with polypharmacy(16). These include higher costs due to increased prescribed and consumed medications by patients. Furthermore, hospitalizations, emergency room visits, and the need for tests or treatments are more likely to cause medication complications and adverse events(17). Frequent consultations for medication or dosage adjustments also contribute to the overall increase in healthcare expenses.

Many negative health consequences are associated with polypharmacy, such as lower quality of life and an increased risk of hospitalization and mortality(18). Additionally, some studies evaluate the impact of multiple drug use on psychological and physical health(19–22). In the physical domain, some studies address the worsening of physical fitness, which is particularly important because its deterioration is associated with several health impacts(23–26).

Even though there are potential risks of polypharmacy, it is crucial to acknowledge and stand out the importance and benefits to patients when the medications are known to contribute to the prevention and treatment of conditions, symptom reduction, and improvement in the quality of life. Balancing the potential harms and benefits of various drug therapies for older adults is an essential task for healthcare providers(4). Therefore, actions aimed to reduce polypharmacy (markedly the inappropriate) are beneficial as they could mitigate harmful health outcomes, such as strength.

Muscle strength is a significant determinant of healthy ageing, as demonstrated in a seminal study prospective cohort with a follow-up of over 18 years assessing the relation of muscle strength on health outcomes in the older population(27). This study observed an independent and inverse association between muscular strength and all causes of death. Furthermore, a direct association with the risk of death from cancer was also found. Both findings were valid even after adjusting for various potential confounders, such as cardiopulmonary fitness.

A widely common use to measure overall muscle strength and physical functioning is the evaluation of handgrip strength. The handgrip strength test evaluates the performance of the upper limb muscles by measuring the maximal grip force generated in a single contraction(28). The handgrip strength has been extensively used in observational and clinical studies to evaluate physical fitness and as an indicator of overall muscle strength(29). Low grip force is associated with poor health outcomes such as chronic diseases and all-cause mortality(23). A cut-off point for low grip force in older adults could be understood as a handgrip strength of less than 27kg for men and less than 16kg for women(30).

When considering Hill's criteria for causality, indications support a causal relationship between polypharmacy and handgrip strength. The plausible biological mechanisms that may explain the implications of polypharmacy on physical fitness are the drug's interactions with muscular strength or the occurrence of adverse effects. Examples of possible mechanisms are the disruption of muscle protein synthesis, the impairment of muscle contractility and damage, or the interference with neural pathways responsible for motor control and coordination(31). Imbalances in electrolytes can also occur and contribute to these effects. As mentioned, it is essential to note that the older population is particularly vulnerable to these consequences due to reduced drug metabolism, such as lower hepatic enzyme activity and diminished renal function, which can increase adverse effects(32). Another of Hill's criteria is the dose-response gradient. Studies have shown that there is a stronger relationship between polypharmacy and worse functional abilities (including muscle weakness) with patients using ten or more medications when compared to patients using five to nine drugs, although in both worse than when compared to patients without polypharmacy(33,34). Until this moment, the consistency criteria are still to be met. In the literature, limited studies were found on the cumulative impact of polypharmacy on handgrip strength, nor did they consider a diverse population.

On the other hand, it is relevant to consider another perspective on the association between polypharmacy and handgrip strength, as a causal relationship in the other direction could also be true. It is biologically plausible that the likelihood of older adults requiring polypharmacy increases as their physical function or activity level declines.

This could be explained since worse physical function is a risk factor for chronic diseases, leading to the use of more medications(35). As a result, it is relevant to explore whether causality criteria are met in both directions and if a potential confounder exists between these factors, all of which require a comprehensive analysis of the available evidence.

Considering the impacts of polypharmacy on physical fitness and the potential harmful consequences, this study aims to evaluate the association between polypharmacy and handgrip strength, an important indicator of overall muscle function and health.

OBJECTIVE

To analyze the association between polypharmacy and handgrip strength, controlling for sex, age, education, body mass index (BMI), and country of residence among middle-aged and older adults from 25 European countries and Israel.

METHODS

The present study uses data from the Survey of Health, Aging and Retirement in Europe (SHARE). The SHARE project is a cross-national panel database that, since 2004, collects biennial survey waves from individuals 50 years or older in several European countries and Israel. The data collection process occurs through a 90-minute-long face-to-face interview where the participant responds to a questionnaire (translated and validated into the local language) regarding health, socio-economic status, and social and family networks. The microdata survey is of potential scientific relevance since it is a cross-national survey comparable over time (interviews the same people for as long as possible) and multidisciplinary(36–38).

Currently, there are eight waves available at the SHARE Research Data Center. This study accessed the two most recent waves: wave 7 (2017) and wave 8 (2019)(39). For this research, the individuals considered in the analysis were those present in both waves and provided answers to the questions regarding the polypharmacy, handgrip strength, and the covariables included. As a result, the sample of participants selected for this study was 23,980.

Through identification codes, it is possible to identify the population sample that is present in both data sources: wave 7 and wave 8. Strict measures were adopted to ensure the consistency of the identification codes and the coherence of the sample between years to provide the validity and reliability of the longitudinal comparative analysis.

Ethics statement

The SHARE databases could be attained by registering and accepting the SHARE Research Data Center at https://share-eric.eu/data/data-access as long as the data is used for scientific purposes. SHARE is released in "scientific-use files" with anonymous data (German Federal Statistics Act and the German Federal Data Protection Law) with no information that could identify the participants.

The SHARE project is constantly ongoing an ethics review. The Ethics Council of the Max-Planck Society for the Advancement of Science approved wave 7 and wave 8 of the

SHARE study, with the proper verification of the procedures to warrant confidentiality and data privacy(37).

In addition, the project of this master thesis research was approved by the Ethical Committee at the Centro Académico de Medicina de Lisboa (annex I).

Variables

The variables included were the following: sociodemographic variables (sex, age, education, and country of residence), the number of chronic diseases, BMI, Grip Strength (measured by using a handheld dynamometer on each hand), and the polypharmacy variable. These variables are described below:

Sociodemographic Variables

The SHARE database provided information on participant's age, gender, educational attainment (by the ISCED-97 coding of education), and country of residence. Age was recoded into two groups: 50 to 64 years and 65 years and older. Education attainment was categorized into three tiers: low (indicating no formal education or ISCED-97 codes 1 and 2), middle (representing ISCED-97 codes 3 and 4), and high education level (corresponding to ISCED-97 codes 5 and 6), as done previously(40).

Number of Chronic Diseases

Participants were asked to report if they were ever diagnosed or currently with a list of the following diseases: heart attack, high blood pressure, stroke, diabetes, chronic lung disease, cancer, stomach or duodenal ulcer/peptic ulcer, Parkinson's disease, cataract, Alzheimer's disease or other affective disorders, arthritis or rheumatism, chronic kidney disease, and other conditions. The total number of diseases was summed to obtain a single score as previously done(41). A systematic review shows that the standard definition for multimorbidity is the presence of two or more diseases(42). To evaluate for multimorbidity, the variable was recoded into a categorical variable: "less than two diseases" and "two or more diseases."

Body Mass Index

The participants' self-reported weight and height were used to calculate the BMI by dividing the weight in kilograms by the square of the height in meters. From the calculation, the BMI values were also categorized into four groups following World

Health Organization guidelines: underweight < (18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25–29.9 kg/m2) and obese (30 kg/m2)(43).

Polypharmacy

The SHARE database assesses polypharmacy by asking, "*Do you take at least five different drugs on a typical day? Please include drugs prescribed by your doctor, drugs you buy without a prescription, and dietary supplements such as vitamins and minerals.*"

Handgrip strength

Handgrip strength was measured by a handheld dynamometer (Smedley, S Dynamometer, TTM, Tokyo, Japan, 100 kg) with a response option between 0 and 100 kg. The measurements were taken twice on each hand, alternating between the hands(44).

Before the handgrip strength evaluation, the participants were asked if they were willing (agreed/able) to have their handgrip measured. If they agreed and were able to take the measurement, the test was described and demonstrated, and participants could practice. During the evaluation, participants could choose to either sit or stand, as long as they stayed with their elbow at a 90º angle, kept the upper arm close to the trunk and the wrist in a neutral position and adjusted the inner lever of the dynamometer to the hand while squeezing it as hard as they could for 5 seconds(45).

The SHARE database contains the first and second measurements for each hand for participants. For a participant to have their measurement registered, it had to have two valid measures for both hands. When two measurements for one hand had a difference of over 20 kg or when the measurement was equal to zero kilograms or ≥ one hundred kilograms, it was considered invalid and therefore excluded.

To analyze handgrip strength, the results were categorized into acceptable and low cut-off points according to the revised European consensus on the definition of sarcopenia: less than 27kg for men and less than 16kg for women(30).

Statistical Analyses

The statistical analyses were carried out between August and September 2023, with the support of the IBM SPSS Statistics (v. 28)(46). Given the difference in the established cut-off points to define low handgrip strength for both men and women, the results

were separated by gender. Descriptive statistics were performed at baseline (wave 7) to provide a comprehensive overview of the initial population characteristics, with measures reported as counts and percentages or means and standard deviations.

A bivariate analysis was conducted to examine population characteristics at baseline (wave 7) according to polypharmacy status. Statistical significance for numerical variables was determined by calculating p-values, using independent samples t-tests or appropriate non-parametric tests. Meanwhile, categorical variables were evaluated by the chi-square test. For symmetric measures in categorical variables, Phi was considered for variables with two groups and Cramer's V for three groups; for numerical variables, Spearman correlation was considered.

Multivariate inferential statistical analysis was conducted using ANCOVA, with homogeneity of variances tested via Levene's test. These analyses were adjusted for age, education, country, the number of chronic diseases, and BMI in cross-sectional and longitudinal contexts.

Logistic regression assessed the association between polypharmacy and low handgrip strength thresholds. Based on gender-specific cut-off points, the handgrip strength numerical variable was transformed into a categorical variable (0: acceptable handgrip strength; 1: low handgrip strength). A crude (unadjusted) and adjusted model, with adjustments made for age, gender, educational level, BMI, and the number of chronic diseases, was computed. Odds Ratios (ORs) and their corresponding 95% Confidence Intervals (CIs) were calculated for the models.

Additionally, a new variable was created to categorize the population based on the possible polypharmacy transitions, as described in Table 1. Four possible scenarios were considered: having polypharmacy at both wave 7 and wave 8 (PF-PF), not having polypharmacy at either wave (NPF-NPF), having polypharmacy at wave 7 but not at wave 8 (PF-NPF), and not having polypharmacy at wave 7 but having it at wave 8 (NPF-PF). This categorization allowed the comparison of the handgrip strength across the different scenarios. The analysis was assessed using Kruskal-Wallis and ANCOVA adjusted for covariables.

***Table 1**. Categorization based on the possible polypharmacy transitions from wave 7 to wave 8*

Scenarios	Polypharmacy status at wave 7	Polypharmacy status at wave 8
Scenario 1	No polypharmacy	No polypharmacy
Scenario 2	Polypharmacy	Polypharmacy
Scenario 3	No polypharmacy	Polypharmacy
Scenario 4	Polypharmacy	No Polypharmacy

The statistical significance was set at $p< 0.01$.

RESULTS

The participants included in this study were those in wave 7 and wave 8 of the SHARE database, which answered the questions related to age, gender, polypharmacy, handgrip strength, and the covariables, making a total of 23,980 participants. The participant's characteristics were assessed at baseline (wave 7) and are described in Table 2. A total of 13,709 (57.1%) of the sample were women, while 10,271 (42.8 %) were men. In general, there were no significant differences between the characteristics of both genders. For this reason, the following results for Table 2 and Table 3, unless otherwise stated, are in reference to the overall (men and women) group. The participants' mean (standard deviation) age was 69.4 years (± 8.7). Most individuals, constituting a total of 16,531 (68.9%), had between 65 years old or more, with ages ranging from a minimum of 50 years to a maximum of 101 years. The middle education status (representing ISCED-97 codes 3 and 4) constitutes the group with the most people, with 10,272 (42.8%). Germany and the Czech Republic had the most individuals, respectively, corresponding to 1,780 (7.4%) and 1,718 (7.2%). The total mean BMI index was 27.9 (± 4.8), and the number of chronic diseases was 2.3 (± 1.5), where most people were categorized as having multimorbidity (64.2%). The number of people with polypharmacy was 6,573 (27.4%). Most individuals were considered to have an acceptable handgrip strength (above the cut-off points), and the mean for men was 41.4 (± 9.6) and for women 25.6 (± 6.5).

Table 2. *Participants' characteristics at baseline (wave 7)*

	Men (n = 10271)	Women (n = 13709)	Overall (n = 23980)
Age	69.8 ± 8.5	69.1 ± 8.9	69.4 ± 8.7
Age-group			
50-64	2904 (28.3)	4545 (33.2)	7449 (31.1)
≥65	7367 (71.7)	9164 (66.8)	16531 (68.9)
Education			
Low	3164 (30.8)	5178 (37.8)	8342 (34.8)
Middle	4568 (44.5)	5704 (41.6)	10272 (42.8)
High	2539 (24.7)	2827 (20.6)	5366 (22.4)
Country			
Austria	369 (3.6)	567 (4.1)	936 (3.9)
Germany	869 (8.5)	911 (6.6)	1780 (7.4)
Sweden	650 (6.3)	728 (5.3)	1378 (5.7)
Spain	397 (3.9)	462 (3.4)	859 (3.6)
Italy	537 (5.2)	603 (4.4)	1140 (4.8)
France	576 (5.6)	788 (5.7)	1364 (5.7)
Denmark	549 (5.3)	598 (4.4)	1147 (4.8)
Greece	560 (5.5)	710 (5.2)	1270 (5.3)
Switzerland	491 (4.8)	503 (3.7)	994 (4.1)
Belgium	597 (5.8)	714 (5.2)	1311 (5.5)
Israel	168 (1.6)	171 (1.2)	339 (1.4)
Czech Republic	687 (6.7)	1031 (7.5)	1718 (7.2)
Poland	529 (5.2)	714 (5.2)	1243 (5.2)
Luxembourg	176 (1.7)	176 (1.3)	352 (1.5)
Hungary	163 (1.6)	239 (1.7)	402 (1.7)
Slovenia	559 (5.4)	825 (6.0)	1384 (5.8)
Estonia	470 (4.6)	917 (6.7)	1387 (5.8)
Croatia	296 (2.9)	444 (3.2)	740 (3.1)
Lithuania	266 (2.6)	596 (4.3)	862 (3.6)
Bulgaria	189 (1.8)	339 (2.5)	528 (2.2)
Cyprus	116 (1.1)	174 (1.3)	290 (1.2)
Finland	351 (3.4)	388 (2.8)	739 (3.1)
Latvia	137 (1.3)	281 (2.0)	418 (1.7)
Malta	182 (1.8)	223 (1.6)	405 (1.7)
Romania	247 (2.4)	409 (3.0)	656 (2.7)
Slovakia	140 (1.4)	198 (1.4)	338 (1.4)
BMI	28.0 ± 4.3	27.8 ± 5.1	27.9 ± 4.8
Number of chronic diseases	2.2 ± 1.5	2.3 ± 1.5	2.3 ± 1.5
Multimorbidity			
No	3796 (37.0)	4793 (35.0)	8589 (35.8)
Yes	6475 (63.0)	8916 (65.0)	15391 (64.2)
Handgrip strength	41.4 ± 9.6	25.6 ± 6.5	32.4 ± 11.2
Low	618 (6.0)	868 (6.3)	1486 (6.2)
Acceptable	9653 (94.0)	12841 (93.7)	22494 (93.8)
Polypharmacy			
No	7470 (72.7)	9937 (72.5)	17407 (72.6)
Yes	2801 (27.3)	3772 (27.5)	6573 (27.4)

Abbreviations: CI, confidence interval; BMI, body mass index.
Measures are reported as mean ± standard deviation or count and percentage.

In order to evaluate the distribution of characteristics among individuals with polypharmacy in contrast to those without polypharmacy, a prevalence study was conducted, and its results are presented in Table 3. From these results, it was observed that the population with polypharmacy had a higher mean age (71.5 ± 8.7 vs. 68.6 ± 8.6), higher BMI index (28.9 ± 5.3 vs. 27.5 ± 4.5), a higher number of total chronic diseases (3.4 ± 1.7 vs. 1.9 ± 1.2) and a lower handgrip strength (30.1 ± 10.9 vs. 33.2 ± 11.1). The geographical prevalence of polypharmacy was also observed for the countries in the study, ranging from 16.8% to 37.2%. Greece and Slovenia had the lowest polypharmacy prevalence, while Israel and the Czech Republic had the highest prevalence. All results were found significant, and to assess the extent of the difference between the groups, a correlation analysis was conducted to examine the strength of the association between the study variables. The symmetric measurements found were low, with the highest correlation between polypharmacy and the number of chronic diseases (0.4).

Table 3. *Polypharmacy prevalence according to participant's characteristics at baseline (wave 7)*

	Men (n = 10271)	Women (n = 13709)	Overall (n = 23980)	p*
Age	71.8 ± 8.4 (69.1 ± 8.4)	71.2 ± 8.8 (68.3 ± 8.8)	71.5 ± 8.7 (68.6 ± 8.6)	<0.01
Age-group				
50-64	565 (19.5)	906 (19.9)	1471 (19.7)	<0.01
≥65	2236 (30.4)	2866 (31.3)	5102 (30.9)	<0.01
Education				
Low	1006 (31.8)	1692 (32.7)	2698 (32.3)	<0.01
Middle	1171 (25.6)	1460 (25.6)	2631 (25.6)	<0.01
High	624 (24.6)	620 (21.9)	1244 (23.2)	<0.01
Country				
Austria	108 (29.3)	154 (27.2)	262 (28.0)	<0.01
Germany	239 (27.5)	196 (21.5)	435 (24.4)	<0.01
Sweden	193 (29.7)	197 (27.1)	390 (28.3)	<0.01
Spain	102 (25.7)	137 (29.7)	239 (27.8)	<0.01
Italy	133 (24.8)	113 (18.7)	246 (21.6)	<0.01
France	160 (27.8)	174 (22.1)	334 (24.5)	<0.01
Denmark	153 (27.9)	203 (33.9)	356 (31.0)	<0.01
Greece	82 (14.6)	131 (18.5)	213 (16.8)	<0.01
Switzerland	103 (21.0)	95 (18.9)	198 (19.9)	<0.01
Belgium	158 (26.5)	232 (32.5)	390 (29.7)	<0.01
Israel	69 (41.1)	57 (33.3)	126 (37.2)	<0.01
Czech Republic	249 (36.2)	356 (34.5)	605 (35.2)	<0.01
Poland	217 (41.0)	295 (41.3)	512 (41.2)	<0.01
Luxembourg	40 (22.7)	37 (21.0)	77 (21.9)	<0.01
Hungary	67 (41.1)	97 (40.6)	164 (40.8)	<0.01
Slovenia	108 (19.3)	136 (16.5)	244 (17.6)	<0.01
Estonia	114 (24.3)	227 (24.8)	341 (24.6)	<0.01
Croatia	67 (22.6)	118 (26.6)	185 (25.0)	<0.01
Lithuania	51 (19.2)	162 (27.2)	213 (24.7)	<0.01
Bulgaria	61 (32.3)	120 (35.4)	181 (34.3)	<0.01
Cyprus	39 (33.6)	55 (31.6)	94 (32.4)	<0.01
Finland	106 (30.2)	126 (32.5)	232 (31.4)	<0.01
Latvia	18 (13.1)	76 (27.0)	94 (22.5)	<0.01
Malta	37 (20.3)	44 (19.7)	81 (20.0)	<0.01
Romania	86 (34.8)	167 (40.8)	253 (38.6)	<0.01
Slovakia	41 (29.3)	67 (33.8)	108 (32.0)	<0.01
BMI	28.8 ± 4.8 (27.7 ± 4.0)	29.0 ± 5.6 (27.3 ± 4.8)	28.9 ± 5.3 (27.5 ± 4.5)	<0.01
Number of chronic diseases	3.2 ± 1.7 (1.8 ± 1.2)	3.5 ± 1.7 (1.9 ± 1.2)	3.4 ± 1.7 (1.9 ± 1.2)	<0.01
Multimorbidity				
No	407 (10.7)	406 (8.5)	813 (9.5)	<0.01
Yes	2394 (37.0)	3366 (37.8)	5760 (37.4)	<0.01
Handgrip strength	38.8 ± 9.5 (42.4 ± 9.4)	23.7 ± 6.5 (26.4 ± 6.4)	30.1 ± 10.9 (33.2 ± 11.1)	<0.01
Low	281 (45.5)	391 (45.0)	672 (45.2)	<0.01
Acceptable	2520 (26.1)	3381 (26.3)	5901 (26.2)	<0.01

Abbreviations: CI, confidence interval; BMI, body mass index

Categorical variables are reported as count and percentage of population with polypharmacy. Numerical variables are reported as mean ± standard deviation of polypharmacy following in between parentheses the mean ± standard deviation of no polypharmacy.

*P-values were computed in relation to the entire dataset (overall group). The Independent-Samples Mann-Whitney U Test was applied to assess numerical variables, while the chi-square test was employed for categorical variables.

An ANCOVA analysis was done to explore the relationship between polypharmacy (categorical variable) and handgrip strength (continuous variable), as shown in Table 4. Considering the differences in the definition of cut-off points for low handgrip strength, the outcomes were split by gender. This analysis was conducted cross-sectionally (at wave 7) and longitudinally (across waves 7 and 8).

The results revealed that individuals with polypharmacy exhibited lower handgrip strength in both cross-sectional and longitudinal analyses, even after adjusting for covariates. These differences in mean handgrip strength were statistically significant. In the cross-sectional analysis, the magnitude of this strength reduction in the polypharmacy group ranged from 1.4 kg (women) to 1.8 kg (men), while in the longitudinal analysis, it ranged from 1.4 kg (women) to 1.6 kg (men) when compared to the group without polypharmacy.

Table 4. *Relationship between polypharmacy and handgrip strength: cross-sectional and longitudinal analysis*

		Muscle strength			
Polypharmacy		Cross-sectional (wave 7)	p	Longitudinal (wave 7 and 8)	p
Men	No	41.9 (41.7,42.1)	<0.01	40.0 (39.8, 40.1)	<0.01
	Yes	40.1 (39.7, 40.4)		38.4 (38.1, 38.7)	
Women	No	26.0 (25.9, 26.1)	<0.01	25.1 (24.9, 25.2)	<0.01
	Yes	24.6 (24.4, 24.8)		23.7 (23.5, 23.9)	

Tested by ANCOVA; Homogeneity of variances tested by Levene's test >0.01
Analysis adjusted for age, education, country, number of chronic diseases and body mass index

Following the ANCOVA, logistic regression was done to calculate the odds ratio (OR) and model the probability of having lower handgrip strength in relation to polypharmacy, as presented in Table 5. The analysis indicated that polypharmacy was associated with an unadjusted OR of 2.3 (95% CI: 2.1, 2.6) and an adjusted OR of 1.9 (95% CI: 1.7, 2.1) for low handgrip strength in the cross-sectional analysis. In the longitudinal study, the unadjusted OR was 2.1 (95% CI: 1.9, 2.3), and after adjustment, it was 1.7 (95% CI: 1.6, 1.9).

Several statistical analyses were conducted to assess the models' performances comprehensively. First, the Hosmer-Lemeshow test yielded a p-value greater than 0.01, suggesting that the model exhibits a good fit for the data. ROC curve analysis revealed that the model consistently achieved an area under the curve (AUC) greater than 0.7

across all scenarios. This indicates robust predictive power and superior performance compared to random guessing in categorizing the data. Furthermore, an omnibus test demonstrated that the predictors significantly influenced handgrip strength (p-value < 0.01). Despite these positive indications, it is essential to note that the model's Nagelkerke R^2 value was 0.1, indicating that the included predictors explain only approximately 10% of the variability observed in handgrip strength. This indicates that while the models showed promise in predictive and explanatory capabilities, other unaccounted factors may contribute to the remaining variability in the data.

In the cross-sectional analysis, the adjusted model revealed that the categories with an OR and IC above 1 were multimorbidity and 65 years or older, meaning that the factor of having two or more long-term health conditions (vs not having) and having an older age (vs being younger) were both associated with lower handgrip strength. The categories of the BMI variable all had an OR and IC under 1. The result from all three categories (normal, overweight, and obesity) suggests a lower likelihood of having lower handgrip strength compared to underweight BMI. This indicates that an underweight BMI is associated with a lower handgrip strength. An OR and IC englobing 1 was observed in the sex variable of being a woman, suggesting no statistically significant difference between men and women in terms of having lower or acceptable handgrip strength, considering the gender-specific cut-off points. The longitudinal analysis had relatively similar results for all OR results.

Table 5. *Logistic regression analyses for the outcome "low handgrip strength": Cross-sectional and longitudinal analysis*

Cross-sectional	Unadjusted OR (95% CI) wave 7	p	Adjusted OR (95% CI) wave 7	p
Polypharmacy				
No	1.0 (reference)		1.0 (reference)	
Yes	2.3 (2.1, 2.6)	<0.01	1.9 (1.7, 2.1)	<0.01
Longitudinal	Unadjusted OR (95% CI) wave 8	p	Adjusted OR (95% CI) wave 8	p
Polypharmacy				
No	1.0 (reference)		1.0 (reference)	
Yes	2.1 (1.9,2.3)	<0.01	1.7 (1.6, 1.9)	<0.01

Abbreviations: OR, odds ratio.
Adjusted for age, gender, educational level, body mass index and number of chronic diseases. Omnibus test: $p < 0.01$; Hosmer and Lemeshow tests: $p > 0.01$. Nagelkerke R Square: 0.1. Model parameters evaluated by ROC curve: area under the curve > 0.7.

Table 6 provides the mean handgrip strength values according to the categorization based on changes in the quantity of drug usage. Individuals with polypharmacy in both waves (PF-PF) exhibited the lowest average handgrip strength for both men and women. In contrast, those without polypharmacy in either wave (NPF-NPF) had the highest average handgrip strength. This pattern persisted even after considering other factors, as shown in Table 7.

In men, the mean strength for PF-PF was 36.8 kg (95% CI: 36.4, 37.2), while for NPF-NPF, it was 41.1 kg (95% CI: 40.8, 41.3). Among women, the mean strength for PF-PF was 22.3 kg (95% CI: 22.0, 22.5), compared to NPF-NPF, with a mean of 25.9 kg (95% CI: 25.7, 26.0). The results also indicated that the PF-NPF group had slightly higher muscle strength than the NPF-PF group.

Table 6. *Handgrip strength across polypharmacy transitions from wave 7 to wave 8*

Polypharmacy timeline		Muscle strength Mean	p
Men	0 NPF-NPF	41.1 (40.8, 41.3)	<0.01
	1 PF-PF	36.8 (36.4, 37.2)	
	2 PF-NPF	37.9 (37.2, 38.6)	
	3 NPF-PF	37.6 (37.0, 38.1)	
Women	0 NPF-NPF	25.9 (25.7, 26.0)	<0.01
	1 PF-PF	22.3 (22.0, 22.5)	
	2 PF-NPF	23.6 (23.2, 24.0)	
	3 NPF-PF	23.3 (22.9, 23.6)	

Tested by Kruskal-Wallis.
Abbreviations: NPF, non polypharmacy; PF, polypharmacy

Table 7. *Handgrip strength across polypharmacy transitions from wave 7 to wave 8, adjusted for covariables*

Polypharmacy timeline		Muscle strength Mean	p
Men	0 NPF-NPF	40.7 (40.4, 40.9)	<0.01
	1 PF-PF	37.5 (37.1, 37.9)	
	2 PF-NPF	38.2 (37.6, 38.9)	
	3 NPF-PF	38.1 (37.7, 38.6)	
Women	0 NPF-NPF	25.6 (25.4, 25.7)	<0.01
	1 PF-PF	22.8 (22.6, 23.1)	
	2 PF-NPF	24.0 (23.6, 24.3)	
	3 NPF-PF	23.6 (23.3, 23.9)	

Abbreviations: NPF, non polypharmacy; PF, polypharmacy
Tested by ANCOVA. Homogeneity of variances tested by Levene's test >0.01
Analysis adjusted for age, education, country, multimorbidity and body mass index

DISCUSSION

This study explored the association of polypharmacy and handgrip strength, a well-known proxy for muscular strength, among middle-aged and older adults from 25 European countries and Israel. A consistent association between polypharmacy and diminished handgrip strength was identified in cross-sectional and longitudinal investigations, even when accounting for other factors through adjustment. The cross-sectional analyses revealed a more substantial decline in muscle strength when contrasted with the findings from the longitudinal studies. Several factors may contribute to this difference, significantly the capability of longitudinal analysis to track individual changes and potentially mitigate the influence of confounding variables more effectively than in a cross-sectional study.

In addition to the statistical analyses revealing a significant association between polypharmacy and a decrease in handgrip strength, the magnitude of this association can increase in specific contexts and populations. It can be amplified in acute illnesses or during recovery, especially if hospitalization occurs(47). Furthermore, it is essential to consider the possible cumulative effect over a more extended time. Despite the association found, it is relevant to note that according to the criteria outlined in the revised European consensus, the observed reduction compared to the non-polypharmacy group (ranging from 1.4 kg to 1.8 kg) was generally insufficient to cause sarcopenia by itself(30).

In the findings, the logistic regression model highlights polypharmacy as a notable risk factor for diminished handgrip strength, resulting in an odds ratio of 1.9 in the cross-sectional analysis and 1.7 in the longitudinal study. While the model presented might not thoroughly explain the variation in the outcome, it reasonably suggests that polypharmacy plays a role in a multifaceted phenomenon contributing to a more pronounced decline in muscle strength. Thus, it is plausible that unidentified variables or non-linear connections are also involved. Further investigations are needed to understand these factors. A more comprehensive model and additional variables might be necessary for this understanding. Enhancing the SHARE questionnaire by integrating a broader selection of variables would significantly contribute to a better comprehension of the relationship under study. This could be carried out by the

extension of medication-related variables such as detailed inquiries into the specific medications, dosage, and duration of use, which can all substantially enrich the understanding of the analysis between polypharmacy and muscle strength.

The changes in the binary status of polypharmacy (present/not present) were also assessed in this study. Participants with sustained polypharmacy at waves 7 and 8 consistently showed lower mean handgrip strength compared to those without polypharmacy at either wave. This suggests that a prolonged period of polypharmacy is associated with a gradual decline in handgrip strength over time, aligning with the existing literature(48). The observed trends in handgrip strength were consistent for both men and women, reinforcing the notion that the impact of sustained polypharmacy on physical strength is relevant for both men and women. Individuals who had polypharmacy but did not sustain it (PF-NPF group) had a slightly better handgrip strength than those who presently have polypharmacy (NPF-PF group). This suggests that the impact of polypharmacy might be both cumulative and potentially reversible.

All these findings indicate that polypharmacy has a statistically significant association and is a risk factor for reduced handgrip strength in older adults, independent of other variables. While the observed reductions in handgrip strength may not, in isolation, warrant immediate clinical intervention, they serve as an essential signal to healthcare providers and researchers about the potential consequences of this identified risk factor.

The results of this study highlight the importance of recognizing and managing polypharmacy, as it may contribute to physical frailty and decreased muscle strength, potentially impacting older individuals' overall well-being and functional abilities. Furthermore, research findings have identified an independent and inverse association between muscle strength and mortality across all causes, emphasizing the importance of muscular strength in promoting the process of healthy aging(49–51). This correlation was true even when considering muscle mass, sedentary habits, and leisure-time physical activity, which underline the crucial role of muscle strength as a predictive indicator for health outcomes related to aging in the older adult population(52). Therefore, additional research in this domain is potentially beneficial to understand this multifaceted phenomenon better.

In addition, it seems crucial to explore interventions aimed at mitigating the adverse effects of polypharmacy. One such strategy involves mitigating PIP, and thoroughly optimizing medication use. This can be achieved by implementing comprehensive medication reviews that assess the appropriateness and necessity of each prescribed drug(53). Deprescribing unnecessary medications should also be considered, acknowledging that reducing the overall medication burden can contribute to better health outcomes.

Moreover, the integration of advanced medication management tools holds promise in enhancing the precision and efficiency of drug administration. These tools could assist healthcare providers in improving monitoring medication regimens, identifying potential drug interactions, and ensuring adherence to prescribed protocols. By exploring these targeted interventions, healthcare professionals can work towards minimizing the adverse effects of polypharmacy and promoting the overall well-being of individuals. These interventions have the potential to benefit patients and help mitigate the economic impact on healthcare systems since polypharmacy has significant cost implications for healthcare systems(13). A Cochrane review on "Interventions to improve the appropriate use of polypharmacy in older people" aimed to identify effective interventions for the appropriate use of polypharmacy(54). Validated instruments, such as implicit tools (which rely on professional judgment) and explicit tools (which are criterion-based and consist of lists of drugs to be avoided in older individuals), were considered in this literature review. However, this review showed that further research with more rigorous study designs is still needed to understand if the tools can improve appropriate polypharmacy and if the reduction impacts clinical outcomes, such as hospital admissions, medication-related issues, and the overall quality of life for patients(54).

The findings of this study were extended to identify the prevalence of polypharmacy in the study population. The polypharmacy country prevalence ranged from 16.8% to 37.2%. Greece and Slovenia had the lowest prevalence, and Israel and the Czech Republic had the highest. These findings emphasize substantial differences in the prevalence of polypharmacy among the countries observed. This prevalence variation across countries could suggest potential differences such as prescribing patterns and

healthcare practices, regulatory oversight, healthcare infrastructure, cultural attitudes, and population demographics. Some differences can be found when comparing the prevalence of polypharmacy in this study to others in the literature. This can be due to the sample population. Given the broad nature of the terms older population and polypharmacy, some inconsistency exists regarding the age at which someone is classified as an older adult and the number of medications required to define polypharmacy. For example, a study done in a previous wave (wave 6) of the SHARE database found a polypharmacy prevalence of 32.1% but it was taken into account the population of 65 years and older(55). In comparison, the finding from this study found a lower prevalence (27.4%), but it included people 50 years and older. When considering only people above 65 years, the polypharmacy prevalence in this study would rise to a similar value (30.9%). On the other hand, the characteristics of the polypharmacy population found in this study were aligned with the existing literature. Individuals with polypharmacy tended to be older, have higher BMIs, and have more chronic conditions(56,57). Also, being female had a slightly higher prevalence, which is also according to the present literature(57,58).

Strengths and limitations

The strength of the current study lies in its utilization of a diverse and transnational database, including individuals with distinct geographical and cultural backgrounds. This approach ensures a comprehensive representation of sociodemographic characteristics, enabling a thorough exploration of patterns and trends that may vary across populations. Moreover, this diversity improves the applicability of the findings by increasing the generalizability and external validity. Another noteworthy strength of this study is its focus on an emerging and significant public health concern, which has received limited attention in the existing literature. To our knowledge, this research is the first to address the issue on an international database.

In terms of limitations, this study could not explore variations in medication quantity, such as minor, major, or extreme polypharmacy, and the specific drug classes employed by individuals experiencing polypharmacy. Different medications or combinations may exhibit distinct correlations with handgrip strength. This limitation could not be overcome due to the unavailability of data on these aspects in the database.

There were also limitations in how the handgrip strength and BMI variables were collected. Handgrip strength is limited due to the absence of data regarding hand size, which has the potential to impact grip strength. As only participants who were willing were measured at the collection site, a selection bias is possible. Concerning the BMI, it is relevant to mention that the calculations were based on self-reported measurements. Even though some studies suggest that people tend to underreport weight and overstate height (which can lead to inaccuracy), other evidence indicates that these discrepancies are not substantial enough to significantly impact the overall validity of the BMI measurements(59,60).

Another limitation is the fact that physical activity was not considered in the analyses. As there is a possible influence of exercise on grip strength, this could represent a confounding bias.

Furthermore, this study faces a limitation by predominantly exploring the connection between polypharmacy and handgrip strength in one direction. A unidirectional approach could have overlooked the potential bidirectional nature of the association.

To fully understand the causal relationship, it might be necessary to investigate dynamics in both directions. Therefore, future research should adopt a bidirectional approach.

CONCLUSION

This study contributes to the knowledge of a significant health topic by exploring the relationship between polypharmacy and low muscle strength, a connection not extensively addressed in the current literature. Given the plausible association between polypharmacy and lower muscle strength along with the supporting evidence from the findings in this study, it seems reasonable to recommend the formulation of comprehensive strategies and actions from both public health and clinical standpoints to address the adverse outcome of polypharmacy on muscle strength effectively. This could be done by implementing mitigation approaches on evidently inappropriate polypharmacy, as this may positively influence muscle strength and contribute to the overall health and well-being of older adults.

This study showed that polypharmacy contributes to a multicausal phenomenon that contributes to diminished muscle strength more than would be expected with ageing. These findings could be used as groundwork for future investigations. Considering that only a unidirectional direction was explored, it is reasonable to suggest that future research explores the bidirectional relationship as it can contribute to a better understanding of how medication use may impact muscle strength, providing further insights for holistic healthcare strategies on this issue.

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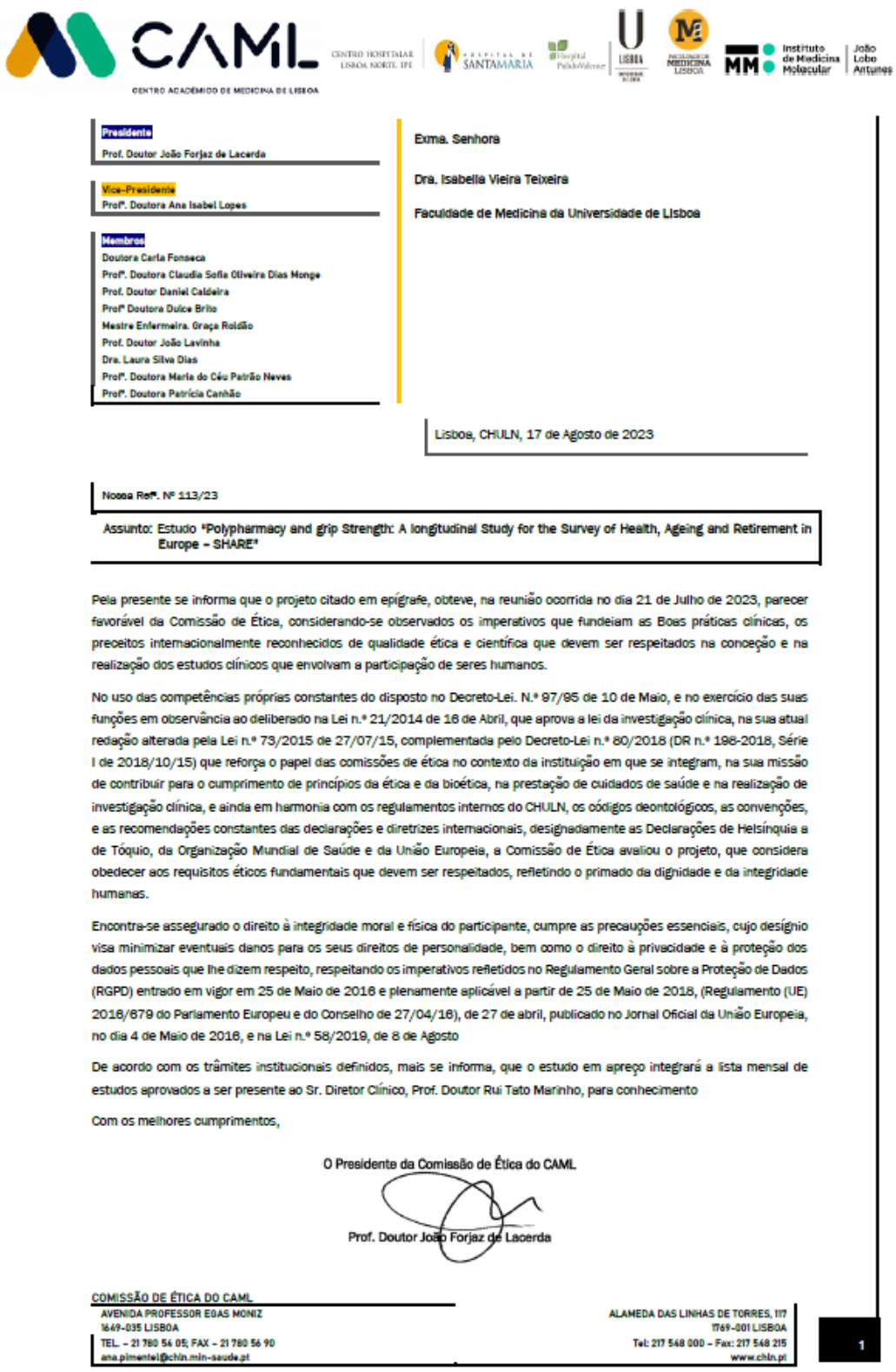
ANNEXES

Annexe I - Approval granted by the Ethical Committee at the Centro Académico de Medicina de Lisboa within the framework of the Epidemiology Master's thesis project



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Profª. Doutora Patrícia Canhão

Exma. Senhora

Dra. Isabella Vieira Teixeira

Faculdade de Medicina da Universidade de Lisboa

Lisboa, CHULN, 17 de Agosto de 2023

Nossa Refª. Nº 113/23

Assunto: Estudo "Polypharmacy and grip Strength: A longitudinal Study for the Survey of Health, Ageing and Retirement in Europe – SHARE"

Pela presente se informa que o projeto citado em epígrafe, obteve, na reunião ocorrida no dia 21 de Julho de 2023, parecer favorável da Comissão de Ética, considerando-se observados os imperativos que fundeiam as Boas práticas clínicas, os preceitos internacionalmente reconhecidos de qualidade ética e científica que devem ser respeitados na conceção e na realização dos estudos clínicos que envolvam a participação de seres humanos.

No uso das competências próprias constantes do disposto no Decreto-Lei. N.º 97/95 de 10 de Maio, e no exercício das suas funções em observância ao deliberado na Lei n.º 21/2014 de 16 de Abril, que aprova a lei da investigação clínica, na sua atual redação alterada pela Lei n.º 73/2015 de 27/07/15, complementada pelo Decreto-Lei n.º 80/2018 (DR n.º 198-2018, Série I de 2018/10/15) que reforça o papel das comissões de ética no contexto da instituição em que se integram, na sua missão de contribuir para o cumprimento de princípios da ética e da bioética, na prestação de cuidados de saúde e na realização de investigação clínica, e ainda em harmonia com os regulamentos internos do CHULN, os códigos deontológicos, as convenções, e as recomendações constantes das declarações e diretrizes internacionais, designadamente as Declarações de Helsínquia e de Tóquio, da Organização Mundial de Saúde e da União Europeia, a Comissão de Ética avaliou o projeto, que considera obedecer aos requisitos éticos fundamentais que devem ser respeitados, refletindo o primado da dignidade e da integridade humanas.

Encontra-se assegurado o direito à integridade moral e física do participante, cumpre as precauções essenciais, cujo desígnio visa minimizar eventuais danos para os seus direitos de personalidade, bem como o direito à privacidade e à proteção dos dados pessoais que lhe dizem respeito, respeitando os imperativos refletidos no Regulamento Geral sobre a Proteção de Dados (RGPD) entrado em vigor em 25 de Maio de 2016 e plenamente aplicável a partir de 25 de Maio de 2018, (Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27/04/16), de 27 de abril, publicado no Jornal Oficial da União Europeia, no dia 4 de Maio de 2016, e na Lei n.º 58/2019, de 8 de Agosto

De acordo com os trâmites institucionais definidos, mais se informa, que o estudo em apreço integrará a lista mensal de estudos aprovados a ser presente ao Sr. Diretor Clínico, Prof. Doutor Rui Tato Marinho, para conhecimento

Com os melhores cumprimentos,

O Presidente da Comissão de Ética do CAML

Prof. Doutor João Forjaz de Lacerda

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