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## UVODNIK

*Jelka ZALETEL, Jerneja FARKAŠ LAINŠČAK*

PROJEKT SKUPNEGA UKREPANJA JACARDI SPREMINJA OBZORJA NA  
PODROČJU BOLEZNI SRCA IN OŽILJA TER SLADKORNE BOLEZNI V EVROPI (109-112)

## IZVIRNI ZNANSTVENI ČLANKI

*Herion MUJA, Suela VASIL, Dorina TOČI, Timo CLEMENS, Helmut BRAND, Genc BURAZERI*

SPOSOBNOST OHRANJANJA IN IZBOLJŠANJA ZDRAVJA TER  
SOCIODEMOGRAFSKI KORELATI PRI OTROCIH V ALBANIJI (113-122)

*Lana VRANIČ, Zrinka BILOGLAV, Petar MEDAKOVIĆ, Jasminka TALAPKO, Ivana ŠKRLEC*

UČINEK PROGRAMA PLJUČNE REHABILITACIJE NA FUNKCIONALNO  
SPOSOBNOST IN MOČ DIHALNIH MIŠIČ PRI BOLNIKI Z DOLGIM COVIDOM (123-131)

*Elvir ZVRKO, Nataša POPOVIĆ, Miodrag RADUNOVIĆ, Goran NIKOLIĆ*

MOTIVACIJSKI DEJAVNIKI, KI VPLIVAJO NA IZBIRO ŠTUDIJA MEDICINE IN  
POKLICNE NAČRTE ZA PRIHODNOST MED ČRNOGORSKIMI ŠTUDENTI (132-141)

*Jurij Bojan ŽMAVC, Miha VERDENIK, Zala SKOMINA, Nataša IHAN HREN*

OZOBLJENOST STAROSTNIKOV V SLOVENIJI TER NJIHOVE  
SOČASNE BOLEZNI IN STANJA: PRESEČNA RAZISKAVA SOČASNEGA  
VPLIVA USTNEGA IN SISTEMSKEGA ZDRAVJA NA IZGUBO ZOB (142-151)

## PREGLEDNI ZNANSTVENI ČLANEK

*Tanja CARLI, Igor LOCATELLI, Mitja KOŠNIK, Andreja KUKEC*

OCENA GLOBALNE PREVALENCE SAMOPOROČANE SISTEMSKA  
ALERGIJSKE REAKCIJE ZA STRUP KOŽEKRIKILCEV PRI ČEBELARJIH:  
SISTEMATIČNI PREGLED LITERATURE IN META-ANALIZA (152-159)

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# CREATION OF A DIFFERENT LANDSCAPE FOR CARDIOVASCULAR DISEASES AND DIABETES IN EUROPE THROUGH JACARDI JOINT ACTION

## PROJEKT SKUPNEGA UKREPANJA JACARDI SPREMINJA OBZORJA NA PODROČJU BOLEZNI SRCA IN OŽILJA TER SLADKORNE BOLEZNI V EVROPI

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### ABSTRACT

#### Keywords:

Diabetes mellitus  
Cardiovascular disease  
Europe  
Interventions  
Collaboration  
Sustainability

The Joint Action on CARdiovascular diseases and DIabetes (JACARDI) aims to reduce the burden of cardiovascular disease and diabetes in European countries, both at the individual and societal levels. The initiative covers the entire patient journey, from improving health literacy and awareness of cardiovascular diseases and diabetes, travelling through primary prevention among high-risk populations and screenings, reaching people living with cardiovascular diseases and diabetes, improving service pathways, self-management, and labour participation. The project involves 21 European countries, 76 partners and plans to implement 142 pilot interventions, ensuring diversity in terms of cultural backgrounds, public health priorities, and healthcare systems.

In Slovenia, interventions will be developed and tested to improve screening for diabetes through community involvement, the involvement of people with diabetes in education programmes in health centres, and the involvement of people with diabetes in a screening programme for diabetic retinopathy. A set of unified, comprehensive and integrated health education materials and approaches will be developed for both healthcare providers and patients referred to the outpatient cardiovascular rehabilitation programme. The effectiveness of the upgraded health education intervention will be tested in a randomized trial. Furthermore, Slovenian experts are involved in developing a harmonized implementation methodology across all 142 pilot interventions, including contextual analysis at the country and pilot levels, multidimensional assessment and evaluation.

JACARDI will enhance cross-national collaboration, maximizing the exploitation of lessons learned through a clear strategy, promoting the integration and sustainability of approaches to achieve high-level impact, including the implementation of effective interaction, cooperation and co-creation between science and policy.

### IZVLEČEK

#### Ključne besede:

sladkorna bolezen  
bolezni srca in ožilja  
Evropa  
intervencije  
sodelovanje  
trajnost

Projekt skupnega ukrepanja JACARDI je namenjen zmanjšanju bremena bolezni srca in ožilja ter sladkorne bolezni v evropskih državah, tako na individualni kot družbeni ravni. Pobuda zajema celotno pot pacienta, od izboljšanja zdravstvene pismenosti in ozaveščenosti o boleznih srca in ožilja ter sladkorni bolezni, preko ukrepov primarne preventive za osebe z visokim tveganjem in presejanj, doseganja pacientov z boleznimi srca in ožilja in/ali sladkorno boleznijo, izboljšanja zdravstvenih storitev, samooskrbe bolezni ter spodbujanja vračanja na delo. Projekt vključuje 21 evropskih držav, 76 partnerjev in načrtuje izvedbo 142 pilotnih intervencij, ki zagotavljajo raznolikost v smislu kulturnih okolij, prioritet javnega zdravja in sistemov zdravstvenega varstva.

V Sloveniji se bodo razvijale in testirale intervencije za izboljšanje presejanja za sladkorno bolezen z vključevanjem skupnosti, vključevanjem pacientov s sladkorno boleznijo v zdravstvenovzgojne programe v zdravstvenih domovih in vključevanjem pacientov s sladkorno boleznijo v presejalni program za diabetično retinopatijo. Razviti bodo poenoteni, celoviti in integrirani zdravstvenovzgojni materiali in pristopi tako za izvajalce zdravstvenih storitev kot za paciente, napotene v program ambulantne srčno-žilne rehabilitacije. Učinkovitost nadgrajene zdravstvenovzgojne intervencije bo preverjena v randomizirani raziskavi. Poleg tega so slovenski strokovnjaki vključeni v razvoj metodologije izvajanja v vseh 142 pilotnih intervencijah, vključno s kontekstualno analizo na ravni države in pilotne intervencije, večdimenzionalno oceno in evalvacijo.

V projektu JACARDI se bo okrepilo mednarodno sodelovanje, kar najbolj izkoristilo pridobljene izkušnje preko spodbujanja integracije in trajnosti pristopov za doseganje učinkov na visoki ravni, vključno z izvajanjem učinkovite interakcije, sodelovanja in soustvarjanja med znanostjo in politikami.

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## 1 INTRODUCTION

Non-communicable diseases significantly undermine the health and well-being of the European population, the sustainability of healthcare systems, and social prosperity. Through a usually long natural history, these diseases additionally interfere with economic development, causing productivity losses due to disability in daily work and life for patients, and informal care offered by family, friends and others (1). The main non-communicable diseases are cardiovascular diseases, diabetes, cancer, chronic respiratory diseases and mental disorders (2); they carry about 80% of the disease burden in European Union (EU) countries, which translates into the leading cause of avoidable premature deaths (3). Cardiovascular diseases, mainly myocardial infarctions and strokes, remain Europe's leading cause of death, impacting the lives of more than 60 million Europeans every day, and costing the EU economy 210 billion euros annually (4, 5). Moreover, the number of adults with diabetes has almost doubled over the last decade, reaching over 32 million in 2019 (6).

Hence, it is obvious that managing the growing non-communicable disease burden requires coordinated and integrated action across Europe. The EU Health Programme (EU4H) has therefore set as a key priority the combination of policy actions, research, and concrete interventions to strengthen activities along the entire non-communicable disease patient journey. These include health promotion and primary prevention at the population level, improvements in secondary prevention through timely detection, equal access to high-quality patient-centred healthcare, and an increased uptake of rehabilitation and self-care behaviours (7). As the resources and implementations of comprehensive strategies for the prevention and management of cardiovascular diseases and diabetes vary among countries, and may be further strengthened through collaborative action, the EU4H Programme launched a Joint Action grant under the thematic area of cardiovascular diseases and diabetes (EU4H-2022-JA-03) (7, 8).

## 2 JACARDI SCOPE AND GENERAL OBJECTIVES

The Joint Action on CARdiovascular diseases and DIabetes (JACARDI) aims to support EU countries in their efforts to reduce the burden of cardiovascular diseases and diabetes along with related risk factors, both at individual and societal levels, while assuring healthcare systems sustainability and equity (8). In particular, JACARDI aims to enhance and promote the implementation of (cross-sectional) best practices, and pilot testing of innovative practices throughout the whole patient journey: addressing healthy people and people at risk of developing cardiovascular diseases/diabetes, along with those already diagnosed with

cardiovascular diseases/diabetes at risk of disease progress and multimorbidity, both at the individual and population levels, and within different settings. JACARDI will begin this journey by improving health literacy and increasing the awareness of cardiovascular diseases and diabetes to reach general and target populations, moving through primary prevention and screening of cardiovascular diseases and diabetes among high-risk populations, then addressing people living with cardiovascular diseases and diabetes and their care providers, developing improved service pathways and (self-)management, also through digital tools, and finally completing the journey by supporting labour participation of people living with these diseases. The journey will also cover transversal and intersectional issues, such as equity in health, health determinants, social, cultural, and ethnic diversity, and the improvement of transnational data availability, quality and accessibility. The activities are divided into 11 work packages, with five transversal work packages, one innovative work package on the development of a common methodological framework and integrative approach, and six technical work packages (8, 9).

JACARDI is coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità - ISS), which has ample experience of participating in and leading projects of similar size and complexity (like Joint Actions CHRODIS, CHRODIS PLUS, ADVANTAGE, JAHEE, PERCH, CARE4DIABETES) (10). The European Commission will support the action for the next four years with 53 million euros of cofunding. JACARDI involves 21 European countries and 76 partners, ensuring diversity in terms of cultural backgrounds, public health priorities, and healthcare systems. The project plans to implement 142 pilot interventions that aim to target millions of people in Europe (7, 8). The wide geographical coverage and extensive pilot implementations are expected to provide a wealth of data for mutual learning and the identification of successful practices. A key feature of JACARDI is the adoption of a common methodology for pilot implementation. This approach aims to harmonize procedures and tools across various fields, from health literacy to patient care pathways. It will benefit the scalability of interventions targeting cardiovascular diseases and diabetes, standardizing the methodological approach of EU healthcare systems. Another core element of the JACARDI project is sustainability. The goal is to ensure that the benefits of JACARDI extend beyond the project's duration, ultimately resulting in the permanent introduction of proven effective solutions into European healthcare systems (8, 9).

### 3 KEY FOCUS AREAS FOR IMPROVING CARDIOVASCULAR AND DIABETES CARE THROUGH SLOVENIAN JACARDI PILOT IMPLEMENTATIONS

Slovenia is significantly involved in JACARDI action through the work of more than 50 experts in the fields of diabetes, cardiovascular diseases and social sciences, who come from the National Institute of Public Health and University of Ljubljana Faculty of Social Sciences, Faculty of Health Sciences and Faculty of Medicine. Additionally, experts from several different clinical settings will make a key contribution to the pilot implementations (11).

Interventions will be developed and tested to improve screening for diabetes through community involvement, the involvement of people with diabetes in education programmes in health centres, and the involvement of people with diabetes in a systematic screening programme for diabetic retinopathy. A set of unified, comprehensive and integrated health education materials and approaches (12, 13) will be developed for both healthcare providers and patients referred to the outpatient cardiovascular rehabilitation programme. The effectiveness of the upgraded health education intervention will be tested in a randomized trial. Based on modern approaches, an adapted approach for systematic screening for the detection of cardiovascular diseases and diabetes will also be developed. With its international environment, JACARDI offers Slovenian partners inexhaustible opportunities for cooperation in the search and testing of solutions that will be adapted to the Slovenian healthcare system, and also directly applicable during and after the project (9, 11).

The National Institute of Public Health also holds leadership positions together with the Italian National Institute of Health and Finnish Institute for Health and Welfare, linking 11 international teams in developing and facilitating a harmonized implementation methodology across all 142 pilot interventions, including contextual analysis at the country and pilot levels, multidimensional assessment and evaluation, capacity building, learning from other good or validated practices, and consistently applying an equity and diversity lens. Special focus is given to further exploitation of the results of JACARDI when the project ends, by supporting from “day one” the linkage of JACARDI pilot interventions to existing policies and initiatives, identifying and empowering the holders of sustainability and by emphasizing a culture of collaboration and consensus-seeking, thus increasing the potential of JACARDI having a sustainable impact (8, 9, 11).

### 4 CONCLUSIONS

JACARDI represents an important step forward in the fight against cardiovascular diseases and diabetes in Europe. Its approach prioritizes inclusive solutions to complex public health challenges and the commercial determinants of health, cultural diversity and equality. It has strong policy relevance, as it will support EU countries, including Slovenia, in implementing new evidence-based policies and actions on the prevention of cardiovascular diseases and diabetes, empowerment of patients, and cost-effective disease management. The resulting roadmap of the pilot implementations will operate as proof-of-concept case studies that will be analysed in order to potentially extend and scale up the experience at the regional or national levels, and/or transfer the pilot interventions to other EU countries. Finally, JACARDI will enhance cross-national collaboration to maximize the implementation of lessons learned through a clear strategy, engaging groups of interest, promoting the integration and sustainability of approaches to achieve high-level impacts, including the implementation of effective interaction and co-creation between science and policy (9). Based on all the listed contributions, JACARDI researchers believe that the creation of a different landscape for cardiovascular and diabetes health in Europe can be achieved.

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### CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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## ETHICAL APPROVAL

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

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# ABILITY TO MAINTAIN AND IMPROVE HEALTH AND SOCIO-DEMOGRAPHIC CORRELATES AMONG CHILDREN IN ALBANIA

## SPOSOBNOST OHRANJANJA IN IZBOLJŠANJA ZDRAVJA TER SOCIODEMOGRAFSKI KORELATI PRI OTROCIH V ALBANIJI

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### ABSTRACT

**Objective:** Our aim was to assess the level and socio-demographic correlates of the ability to maintain health among children in Albania, a post-communist country in the Western Balkans.

### Keywords:

Ability to maintain health  
Albania  
Children  
Health promotion  
Health protection  
Schoolchildren  
Sociodemographic factors

**Methods:** A cross-sectional study was conducted in Albania in September 2022. The study population consisted of a nationwide representative sample of 7,831 schoolchildren (=54% girls) aged 12-15 years. A structured self-administered and anonymous questionnaire inquired about the children's attitudes toward health promotion (ability to maintain and improve health) and a range of key dimensions on knowledge and practices regarding healthcare services. Socio-demographic data were also collected. Binary logistic regression was used to assess the socio-demographic correlates of children's ability to maintain health.

**Results:** Overall, about 71% of schoolchildren exhibited the best attitudes toward health promotion (ability to maintain and improve health). In the multivariable adjusted logistic regression models, poorer attitudes toward health promotion (ability to maintain and improve health) were significantly related to older age (OR=1.2, 95%CI=1.0-1.3), middle/low maternal education (OR=1.2, 95%CI=1.1-1.3), poor/very poor economic situation (OR=1.5, 95%CI=1.2-1.8), lack of appropriate knowledge about rights to healthcare (OR=1.3, 95%CI=1.1-1.5), lack of knowledge about obtaining healthcare services (OR=1.7, 95%CI=1.4-2.2), and lack of consultations/visits with health professionals excluding vaccinations (OR=1.2, 95%CI=1.1-1.4).

**Conclusions:** Almost 1/3<sup>rd</sup> of Albanian schoolchildren included in this study did not exhibit the best attitudes toward health promotion (ability to maintain and improve health). The best attitudes were related to a higher socioeconomic level and adequate knowledge and practices regarding healthcare services. There is thus a need to increase health literacy levels among children in order to ultimately induce sustainable healthy behavioural/lifestyle practices.

### IZVLEČEK

**Cilj:** Naš cilj je bil oceniti raven in sociodemografske korelate sposobnosti ohranjanja zdravja pri otrocih v Albaniji - postkomunistični državi na Zahodnem Balkanu.

### Ključne besede:

sposobnost ohranjanja zdravja  
Albanija  
otroci  
spodbujanje zdravja  
varovanje zdravja  
šolarji  
sociodemografski dejavniki

**Metode:** Presečno študijo smo opravili septembra 2022 v Albaniji. Populacijo študije je sestavljal reprezentativni vzorec 7831 šolarjev (=54% deklic), starih 12-15, ki prihajajo iz celotne države. V strukturiranem samoocenjevalnem in anonimnem vprašalniku so otroci odgovarjali na vprašanja o odnosu do spodbujanja zdravja (sposobnosti ohranjanja in izboljšanja zdravja) in vrsti ključnih razsežnosti glede znanja in praks v zvezi z zdravstvenimi storitvami. Zbrali smo tudi sociodemografske podatke. Za ocenjevanje sociodemografskih korelatov sposobnosti otrok za ohranjanje zdravja smo uporabili binarno logistično regresijo.

**Rezultati:** Skupno je približno 71 % otrok izkazalo najboljši odnos do spodbujanja zdravja (sposobnosti ohranjanja in izboljšanja zdravja). V modelih multivariatne prilagojene logistične regresije je bil slabši odnos do spodbujanja zdravja (sposobnosti ohranjanja in izboljšanja zdravja) pomembno povezan z višjo starostjo (RO = 1,2, 95-% IZ = 1,0-1,3), nizko/srednjo izobrazbo matere (RO = 1,2, 95-% IZ = 1,1-1,3), slabimi/zelo slabimi gospodarskimi razmerami (RO = 1,5, 95-% IZ = 1,2-1,8), pomanjkanjem ustreznega znanja o pravicah do zdravstvenega varstva (RO = 1,3, 95-% IZ = 1,1-1,5), pomanjkanjem znanja o pridobitvi zdravstvenih storitev (RO = 1,7, 95-% IZ = 1,4-2,2) in pomanjkanjem posvetovanja z zdravstvenimi delavci ali njihovih obiskov, razen za cepljenja (RO = 1,2, 95-% IZ = 1,1-1,4).

**Zaključki:** Skoraj 1/3 albanskih šolarjev, ki so bili vključeni v študijo, ni izkazala najboljšega odnosa do spodbujanja zdravja (sposobnosti ohranjanja in izboljšanja zdravja). Najboljši odnos je povezan z višjo družbeno-gospodarsko ravno ter ustreznim znanjem in praksami glede zdravstvenih storitev. Treba je izboljšati raven zdravstvene pismenosti pri otrocih za spodbujanje trajnostnih zdravih vedenjskih praks in življenjskega sloga.

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## 1 INTRODUCTION

Wellness encompasses individual characteristics, physical and living environment conditions, as well as social and socioeconomic factors (1). Wellness is a self-conscious, self-directed, evolving process of achieving one's full potential or the ability to function optimally within a given current environment (2), contributing to both health and wellbeing. In this context, health promotion (ability to maintain and improve health) also becomes a personal responsibility, depending on an individual's behaviour and lifestyle choices, besides relying on external factors (3). According to UNESCO, education is the foundation of health and wellbeing through enabling knowledgeable actions to prevent disease and promote health (4), with optimal health being both the start and endpoint. Such skills, values and attitudes that enable citizens to lead healthy and fulfilled lives, make informed decisions and respond to changing circumstances, are largely taught during childhood and adolescence. This teaching occurs through formal and informal education and continuous interactions with others at various levels and settings. Skills and attitudes are also maintained and reinforced repeatedly during a person's entire lifecycle (5, 6). Formal education is critical to protect and maintain health and wellbeing throughout one's life, because lifestyle patterns begin in early childhood and persist during later life (7). At least 80% of all cases of major chronic disease could be prevented through adequate health education and promotion activities in school settings (8), preferably started as early as possible (7, 8).

Children are also responsible for their health choices, but this depends on their level of health literacy. The more health literate children are, the more they are inclined to make sound health decisions (9, 10), whereas children with low health literacy are more likely to be involved in unhealthy behaviours (11). Even very young children (under the age of eight) are able to understand the relationship between health and nutrition, and the importance of oral health, and they are able to be actively involved in decision-making related to their own health (12).

While childhood health literacy is still a complex and under-researched concept (6, 9), the current findings link childhood health literacy (or the ability to maintain and improve health) with various factors. Besides education, parental health literacy in particular affects children's behaviour, health literacy levels and ultimately their health and wellbeing. Among German children, a higher parental health literacy was associated with a healthier lifestyle, including more physical activity, healthier nutrition and regular toothbrushing (13). Moreover, own consumption of sweets and spicy/salty foods as well as TV viewing time were inversely associated with maternal education level among very young children, whereas the consumption of fruits and vegetables and outdoor time were positively

associated with it (7). A similar association between the health literacy of parents/guardians and children's time spent watching TV and playing outside was reported by a Japanese study (14). Other research has indicated that parental educational level is an important predictor of child literacy (15) and achievement (16), even though this relationship is complex.

Other factors are associated with children's health promotion (ability to maintain and improve health), too. In a review study, a high level of physical activity was associated with younger age, male gender, higher parental education, higher family income, and higher adolescent education level, whereas a highly sedentary lifestyle was associated with lower parental education and a low family income (17). Furthermore, low physical activity, high sedentary behaviour, high screen time and high consumption of fat/high sugar snacks were all associated with being overweight or obese (17). In a study among teenagers, low health literacy levels were associated with more risky behaviour such as smoking and drinking (18), implying lower health protection behaviour and worse health maintenance. Peer pressure is another important risk factor for young children's involvement in behaviours that put their health at risk (19).

In contrast with the increasing amount of information linking child health protection behaviour with various external factors, the scientific evidence about the level and predictors of health promotion (ability to maintain and improve health) among Albanian children is rather scarce. In this context, we aimed for assessing the attitudes and selected correlates of the ability to maintain and improve health among schoolchildren in Albania, a post-communist country in south-eastern Europe that has been undergoing profound socioeconomic changes in the past few decades. We hypothesized a lower ability to maintain and improve health among schoolchildren belonging to low socioeconomic groupings and/or those with inadequate knowledge and practices regarding healthcare services.

## 2 METHODS

A cross-sectional study was conducted in September 2022, including a nationwide sample of children aged 12-15 years in Albania.

### 2.1 Study population

The study population consisted of a nationwide sample of Albanian schoolchildren attending grades 6-9 (age-group: 12-15 years). The sampling frame (registered schoolchildren pertinent to grades 6-9) is available from the General Directorate of Pre-University Education. WIN-PEPI (<http://www.brixtonhealth.com/pepi4windows.html>) was used to calculate the sample size based on different hypotheses



tapping selected aspects of children's knowledge and practices regarding healthcare services. Based on conservative assumptions, the minimum required sample size was estimated at around 1,400 participants. However, we decided to invite all registered schoolchildren belonging to grades 6-9 in Albania (N=123,998), as this was an online survey. However, as the survey was available online for the whole duration of September 2022, the number of participants substantially exceeded the minimum required sample size.

At the end of September 2022, when the online survey was closed, there were 7,928 participants (6.4% of all registered schoolchildren in grades 6-9) who had completed the questionnaire. Of these, 97 questionnaires were either partially completed (n=59), or invalid (n=38). The final sample included in the analysis thus consisted of 7,831 schoolchildren (about 54% girls) aged 12-15 years (grades 6-9). Participating children (n=7,928) had similar socio-demographic characteristics (gender, age, place of residence) as the overall number of registered schoolchildren belonging to grades 6-9 (N=123,998).

## 2.2 Data collection

Data collection consisted of the use of Google Forms (a survey administration platform), and self-administration by the children of an online structured and anonymous questionnaire that was hosted there. The schoolchildren used the computer labs available at their respective schools and/or their personal/family devices (PCs, tablets, or smartphones) to complete the survey.

Health promotion (ability to maintain and improve health) was assessed based on the following four items/statements (all measured using a Likert-scale ranging from 0 [strongly disagree] to 3 [strongly agree]):

- i) "Healthy nutrition is important for children's health and wellbeing";
- ii) "Physical activity is important for children's health and wellbeing";
- iii) "Mental health is important for children's physical health and wellbeing";
- iv) "Good hygiene is important for children's health and wellbeing".

A summary score was calculated based on each of the four statements about schoolchildren's attitudes to health promotion (ability to maintain and improve health). The summary score for each participant ranged from 0 (strongly disagreeing with all four statements on health protection) to 12 (strongly agreeing with all four statements about health protection). In the analysis, the summary score was dichotomized into: "best attitudes" including children who strongly agreed with all four statements (score: 12) vs. "poor attitudes" consisting of children with a range of scores from 0 to 11.

In addition, the questionnaire asked about the children's knowledge of their rights to healthcare services, barriers to accessing healthcare services, knowledge on obtaining healthcare services, knowledge about the location of healthcare facilities in the children's respective home areas, and visits/consultations with health professionals, excluding the mandatory vaccination calendar. Potential responses to each of these items were: "yes" vs. "no".

Socio-demographic information was also collected, including gender ("boys" vs. "girls"), age (in the analysis dichotomized into: "12-13 years" vs. "14-15 years"), place of residence ("urban" vs. "rural" areas), ethnicity (ethnic "Albanians" vs. "Roma/Egyptian" communities), maternal education (in the analysis dichotomized into: "high" vs. "middle/low"), and family economic situation (in the analysis dichotomized into: "not poor" vs. "poor/very poor").

## 2.3 Statistical analysis

Fisher's exact test was employed to compare the distribution of socio-demographic factors between schoolchildren with "best attitudes" vs. those with "poor attitudes" toward health promotion (ability to maintain and improve health) [Table 1]. Likewise, Fisher's exact test was used to compare the distribution of selected key dimensions on knowledge and practices regarding healthcare services between children with "best attitudes" vs. those with "poor attitudes" toward health protection (Table 2).

Conversely, binary logistic regression was employed to assess the association of attitudes toward health promotion (ability to maintain and improve health) [dependent variable] with socio-demographic characteristics (gender, age, place of residence, ethnicity, maternal education, and family economic situation) [Table 3]. Initially (left panel), crude (unadjusted) odds ratios [OR: "poor attitudes" vs. "best attitudes" toward health promotion (ability to maintain and improve health)], their respective 95% confidence intervals (95% CIs) and p-values were calculated. Next (right panel), all sociodemographic factors were entered simultaneously into the binary logistic regression models and multivariable-adjusted ORs, and their respective 95% CIs and p-values were calculated.

Subsequently (Table 4), all sociodemographic characteristics and the other important dimensions of knowledge and practices regarding healthcare services (knowledge about rights to healthcare; knowledge about obtaining healthcare; knowledge about the location of health facilities in their respective home areas; perceived barriers to healthcare services; and consultations/visits with a health professional, excluding vaccinations) were entered into the logistic regression models in a backward stepwise elimination procedure with a P-value to exit set at  $P > 0.10$ . Multivariable-adjusted ORs, their respective 95% CIs and p-values

were calculated from the final models. The Hosmer-Lemeshow test was used to assess the overall goodness-of-fit of the multivariable-adjusted regression models, and the final model fit the criterion (footnote to Table 4).

For all the statistical analyses, a p-value <0.05 was considered as statistically significant. The Statistical Package for Social Sciences (SPSS, version 19.0) was employed for all the statistical analyses.

#### 2.4 Ethical considerations

The study was approved by the Albanian Ministry of Education and Sport in June 2022. All schoolchildren were informed by their respective teachers about the aim and procedures of the study, and all the aspects of the survey were explained in sufficient detail, including the aim and objectives, the content of all sections of the questionnaire and particularly the aspects related to the anonymity of the survey and the successive aggregated data analysis. Passive consent was sought from the parents through teachers from each of the schools involved.

### 3 RESULTS

Overall, 38% of study participants were from rural areas; 33% reported a higher maternal education; 40% reported a very good economic situation; and 2.3% of the children were part of the Roma and/or Egyptian communities (data not shown in the tables).

Of the 7,831 schoolchildren included in the survey, the best attitudes toward health promotion (ability to maintain and improve health) were evident in 5,534 (71%) of them (Table 1).

The best attitudes toward health promotion (ability to maintain and improve health) were slightly more prevalent in younger children (12-13 years) compared to their older counterparts (72% vs. 69% respectively,  $p=0.02$ ) [Table 1]. Furthermore, the best attitudes toward health promotion (ability to maintain and improve health) were more prevalent among children who reported a higher maternal education than those with middle/low maternal education (74% vs. 70% respectively,  $P<0.01$ ). In addition, the prevalence of the best attitudes toward health promotion (ability to maintain and improve health) were substantially lower among children who reported a poor economic situation compared with their better-off peers (61% vs. 72% respectively,  $P<0.01$ ). On the other hand, there were no significant differences regarding the gender, place of residence, or ethnicity of the children (Table 1).

**Table 1.** Attitudes toward health promotion (ability to maintain and improve health) by socio-demographic factors in a nationwide sample of schoolchildren in Albania, 2022.

Socio-demographic factor	Best attitudes (N=5534)	Poor attitudes (N=2297)	P <sup>b</sup>
<b>Gender:</b>			
Girls	2,987 (71.1) <sup>a</sup>	1,217 (28.9)	0.426
Boys	2,547 (70.2)	1,080 (29.8)	
<b>Age:</b>			
12-13 years	2,755 (72.0)	1,074 (28.0)	0.015
14-15 years	2,779 (69.4)	1,223 (30.6)	
<b>Place of residence:</b>			
Urban areas	3,427 (70.8)	1,411 (29.2)	0.701
Rural areas	2,086 (70.4)	876 (29.6)	
<b>Ethnicity:</b>			
Roma/Egyptian community	116 (66.7)	58 (33.3)	0.206
Ethnic Albanian	5,188 (71.1)	2,111 (28.9)	
<b>Mother's education:</b>			
High	2,213 (73.8)	785 (26.2)	<0.001
Middle/Low	3,299 (69.8)	1,424 (30.2)	
<b>Economic situation:</b>			
Not poor	5,234 (72.0)	2,033 (28.0)	<0.001
Poor/very poor	289 (61.1)	184 (38.9)	

<sup>a</sup> Absolute numbers and their respective row percentages (in parentheses). Discrepancies in the totals are due to the missing covariate values.

<sup>b</sup> P-values from Fisher's exact test.

Better attitudes to health promotion (ability to maintain and improve health) were positively associated with other important dimensions of knowledge and practice regarding healthcare services (Table 2), including knowledge of the rights to healthcare services (79% among children with the best attitudes vs. 73% among those with poor attitudes), knowledge about obtaining healthcare services (96% vs. 92%, respectively), knowledge about the location of health facilities in the home area (89% vs. 85%, respectively), perceived barriers to accessing health services (41% vs. 44%, respectively), and consultations/visits with health professionals other than mandatory vaccinations (75% vs. 70%, respectively) [all  $P \leq 0.03$ , Table 2].

In the crude (unadjusted) binary logistic regression analysis (Table 3, left panel) poorer attitudes toward health promotion (ability to maintain and improve health) were positively related to the older age of the schoolchildren (OR=1.1, 95%CI=1.0-1.2), middle/low maternal education (OR=1.2, 95%CI=1.1-1.3), and especially a poor/very poor economic situation (OR=1.6, 95%CI=1.3-2.0). Conversely, no significant relationships were evident for the other socio-demographic factors. Upon simultaneous multivariable adjustment for all socio-demographic characteristics (Table 3, right panel), the associations with age, maternal education and economic situation persisted.

**Table 2.** Attitudes toward health promotion (ability to maintain and improve health) by other dimensions of knowledge and practices regarding healthcare services.

Knowledge about and use of healthcare services	Best attitudes (N=5534)	Poor attitudes (N=2297)	P <sup>b</sup>
<b>Do you know your rights to healthcare services?</b>			
Yes	4,357 (79.4) <sup>a</sup>	1,579 (72.7)	<0.001
No	1,129 (20.6)	592 (27.3)	
<b>Do you know where to receive healthcare services?</b>			
Yes	5,278 (96.0)	1,989 (91.7)	<0.001
No	220 (4.0)	179 (8.3)	
<b>Do you know the location of health facilities in your area?</b>			
Yes	4,883 (89.0)	1,841 (85.3)	<0.001
No	603 (11.0)	318 (14.7)	
<b>Do you perceive any barriers to accessing healthcare services?</b>			
No	3,216 (58.9)	1,208 (56.0)	0.022
Yes	2,241 (41.1)	948 (44.0)	
<b>Excluding the vaccination calendar, have you ever consulted/visited a health professional?</b>			
Yes	4,121 (75.3)	1,498 (69.8)	<0.001
No	1,352 (24.7)	648 (30.2)	

<sup>a</sup> Absolute numbers and their respective column percentages (in parentheses).

Discrepancies in the totals are due to the missing covariate values.

<sup>b</sup> P-values from Fisher's exact test.

A backward stepwise elimination procedure was used with the P-value to exit set at  $P > 0.10$  in the multivariable-adjusted logistic regression models controlling for socio-demographic variables and the other dimensions related to knowledge and practices on healthcare services (variables presented in Table 2), and the results showed that poorer attitudes toward health promotion (ability to maintain and improve health) were positively related to (Table 4): older age (OR=1.2, 95%CI=1.0-1.3), middle/low maternal education (OR=1.2, 95%CI=1.1-1.3), poor/very poor economic situation (OR=1.5, 95%CI=1.2-1.8), lack of appropriate knowledge about rights to healthcare (OR=1.3, 95%CI=1.1-1.5), lack of knowledge about obtaining healthcare services (OR=1.7, 95%CI=1.4-2.2), and lack of consultations/visits with health professionals excluding vaccinations (OR=1.2, 95%CI=1.1-1.4).

**Table 3.** Association of attitudes toward health promotion (ability to maintain and improve health) with the socio-demographic factors of the schoolchildren, with the results from the binary logistic regression.

Variable	Left panel: unadjusted models		Right panel: multivariable-adjusted models	
	OR (95%CI)	P	OR (95%CI)	P
<b>Gender:</b>				
Girls	1.00 (reference)	0.422	1.00 (reference)	0.951
Boys	1.04 (0.94-1.15)		1.01 (0.91-1.11)	
<b>Age-group:</b>				
12-13 years	1.00 (reference)	0.015	1.00 (reference)	0.006
14-15 years	1.13 (1.02-1.24)		1.15 (1.04-1.28)	
<b>Place of residence:</b>				
Urban areas	1.00 (reference)	0.700	1.00 (reference)	0.507
Rural areas	1.02 (0.92-1.13)		0.96 (0.87-1.07)	
<b>Ethnicity:</b>				
Ethnic Albanian	1.00 (reference)	0.206	1.00 (reference)	0.273
Roma/Egyptian	1.23 (0.89-1.69)		1.20 (0.87-1.67)	
<b>Mother's education:</b>				
High	1.00 (reference)	<0.001	1.00 (reference)	0.001
Middle/Low	1.22 (1.10-1.35)		1.19 (1.07-1.33)	
<b>Economic situation:</b>				
Not poor	1.00 (reference)	<0.001	1.00 (reference)	<0.001
Poor/very poor	1.64 (1.35-1.99)		1.54 (1.26-1.88)	

**Table 4.** Multivariable-adjusted association of attitudes toward health promotion (ability to maintain and improve health) with socio-demographic factors and knowledge and practices regarding healthcare services, with the results from the binary logistic regression.

Variable	OR <sup>a</sup>	95%CI <sup>a</sup>	P <sup>a</sup>
<b>Age-group:</b>			
12-13 years	1.00	reference	0.008
14-15 years	1.16	1.04-1.28	
<b>Mother's education:</b>			
High	1.00	reference	0.001
Middle/Low	1.21	1.09-1.35	
<b>Economic situation:</b>			
Not poor	1.00	reference	<0.001
Poor/very poor	1.49	1.21-1.84	
<b>Do you know your rights to healthcare services?</b>			
Yes	1.00	reference	<0.001
No	1.31	1.15-1.49	
<b>Do you know where to receive healthcare services?</b>			
Yes	1.00	reference	<0.001
No	1.75	1.39-2.19	
<b>Excluding the vaccination calendar, have you ever consulted/visited a health professional?</b>			
Yes	1.00	reference	<0.001
No	1.24	1.09-1.40	

<sup>a</sup>The table presents only the variables which were retained into the final model (Hosmer Lemeshow test for the overall goodness-of-fit of the final model: chi-square statistic=3.8, d.f.=7, P=0.803).

## 4 DISCUSSION

### 4.1 Main findings

The main finding of this study, which included a nationwide sample of Albanian schoolchildren aged 12-15 years old, consists of the fact that almost 1/3rd of participants did not exhibit the best attitudes toward health promotion (ability to maintain and improve health). It also found that the best attitudes toward health promotion (ability to maintain and improve health) were positively and significantly related to younger age, a higher maternal education, a more favourable economic situation, and a range of dimensions related to adequate knowledge and practices regarding healthcare services.

### 4.2 Comparisons with previous studies

The ability to protect and/or maintain health is important for children, since the behavioural patterns instilled during childhood will most likely be carried out in later life, and thus be associated with long-term health outcomes (20-22). Children's health attitudes and behaviour are formed gradually alongside the growing process and under the influence of formal education, experience and interaction with close family members and other individuals and the environment on multiple levels (23), not forgetting the role of the genetic uniqueness of every child, which largely determines their temperament and learning style (24, 25). These complex and dynamic factors will ultimately determine the attitudes, literacy, health literacy, health protection and health maintenance profiles of children, a profile that is unique for every child.

In this context, our findings might also be largely a reflection of such processes occurring in Albanian settings. We found that children of less educated mothers were significantly more likely to have suboptimal attitudes towards health promotion (ability to maintain and improve health) compared to children of highly educated mothers, which is in line with previous research (15).

Children's attitudes towards health are largely shaped by their parents' attitudes toward health (26, 27). More specifically, behaviour is determined generally by attitude and social/normative factors, interplaying with the motivation to comply, and changing/adapting to specific situations (28). Since parents' attitudes are rather stable over time and children have continuous direct experience with them, the attitudes and behaviour of the children are more likely to be influenced by their parents independently of other factors (29). In addition, parenting style also has psychological consequences for children's behaviour (25, 30), further highlighting the multiple influences of parents' attitudes/behaviours on children's attitudes/behaviours.

As for the association of low maternal education level with the suboptimal health attitudes of their children, this might be explained by the association of maternal education with

health behaviour and attitudes: lower education among mothers is associated with lower use of health services (31), higher risk of smoking (32), harmful alcohol use (33), lower physical activity (34), poor nutrition (35), poorer mental health (36), and so on, and such practices (and other associated behaviours) will be conveyed to their children. This thus generates a relationship between a mother's education level and her children's attitudes to health promotion (ability to maintain and improve health). However, this relationship was weak in the present study (Table 4).

In our study, older children were significantly more likely to have suboptimal attitudes toward health promotion (ability to maintain and improve health) compared to younger children. This finding might also be explained by the parents' effect on their children's attitudes, beliefs and behaviours, which tends to diminish as children grow older and other factors take precedence in shaping their attitudes. Indeed, while a child's behaviour is influenced by their parents' attitudes and attributes (accounting for 20%-50% of child behaviour variation), children also have the freedom and power to select which aspects of parental input they will attend and conform to (25). Hence, while growing, children learn and are willing to rely more often on other influences rather than their parents' system of attitudes, beliefs and behaviour, and so they come to rely more and more on their friends (37), or social networks and social support for their wellbeing as they grow older (38, 39).

The inverse significant association of children's suboptimal attitude toward health promotion (ability to maintain and improve health) with economic situation might also be explained through the influence of parental education, economic status and social class on children's behaviour, fitting the pathways discussed earlier. The socioeconomic-parenting association is likely to be mediated and moderated by parental knowledge and expectations, parental mental health, access to resources and cultural norms and values (40). Hence, poorer children are more likely to adopt suboptimal attitudes toward health promotion (ability to maintain and improve health).

As expected, significant associations were identified between suboptimal attitudes toward health promotion (ability to maintain and improve health) and children's knowledge of health rights, knowledge about where to receive healthcare and previous contacts with a health professional. These findings are compatible with the theory of parental influence over their children (26, 27). In addition, children are also able to understand, process and apply information and health information received through various sources (12). Young children (aged 8-11 years) have considerable knowledge about health, diseases and risks, they are health conscious and have positive attitudes toward health and health promotion (41). Hence, children who pay more attention, or are more interested in knowing about health issues have, logically, the best

attitudes toward health promotion (ability to maintain and improve health), in addition to the parental effects.

#### 4.3 Limitations and shortcomings

Our study may have some limitations related to sample representativeness, possibility of information bias, and the study design. Our study included a nationwide sample of schoolchildren aged 12-15 years. Of note, all registered schoolchildren of this age-group were invited to participate over a one-month period (September 2022). During this time period, 6.4% of schoolchildren (N=7,831) completed the online survey, which constitutes a much larger sample than the minimum required sample size (of ≈1,400 participants). Moreover, teachers had no role in the selection process. However, the respondents may still have been self-selected, an issue which may compromise the sample representativeness. Still, there were no significant differences regarding the distribution of socio-demographic factors between survey participants and the overall number of registered schoolchildren attending grades 6-9, which is reassuring. Furthermore, the instrument of data collection consisted of a previously validated, simple and anonymous questionnaire, although the possibility of information bias cannot be excluded completely. In particular, self-assessment of maternal education and especially economic status may have been subject to differential reporting. In addition, the findings from cross-sectional studies are not assumed to be causal.

## 5 CONCLUSIONS

Our findings offer useful evidence about the prevalence of the best attitudes toward health promotion (ability to maintain and improve health) and selected important correlates of this, including not only socio-demographic factors, but also a range of other key dimensions related to knowledge and practices about healthcare services. These findings should be replicated in future studies in Albania and other countries worldwide, employing similar instruments for measurement of health literacy levels and its related socio-demographic factors and other key determinants.

Curriculum development reforms in pre-university education in Albania should consider an increase in material related to health promotion in order to strengthen health literacy levels in children, as this is a prerequisite for the fostering of sustainable, healthy behaviours. Alongside this, there is need for further studies on the curriculum reforms and their relations to health literacy in children aged 12-15 years old in Albania and elsewhere.

Promoting health literacy among children is crucial for their overall wellbeing and development. Strengthening the health literacy of children should consist of the integration of health education into a age-specific school

curriculum focusing on a wide range of topics, such as healthy nutrition, the promotion of physical exercise, and prevention of accidents. Furthermore, strengthening of peer education programmes should be considered, as peers are key agents of change in this age group. In addition, there is need for establishment of health literacy libraries and other resource centres in schools with age-specific content. Importantly, there is need for the use of mobile applications to make the children's learning entertaining and engaging. Moreover, joint interventions targeting mothers and their children should be considered, in light of the relationship that children's health literacy has with their mothers' own health literacy.

In conclusion, our findings from Albania point to the need for increasing health literacy among children to ultimately encourage the adoption of sustainable, healthy behavioural practices.

#### CONFLICT OF INTERESTS

None declared.

#### FUNDING

This study was conducted in the framework of the "Schools for Health", which is a project of the Swiss Development and Cooperation (SDC) Agency implemented in Albania (<http://shkollatpershendetin.al/en/>).

#### ETHICAL APPROVAL

The study was approved by the Albanian Ministry of Education and Sport in June 2022.

#### AVAILABILITY OF DATA AND MATERIALS

All data and materials used in this study are available upon reasonable request.

#### AUTHORS' CONTRIBUTIONS

Herion Muja and Genc Burazeri contributed to the study conceptualization and design, analysis and interpretation of the data and writing of the article. Suela Vasil, Dorina Toçi, Timo Clemens and Helmut Brand commented comprehensively on the manuscript. All authors have read and approved the submitted manuscript.

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# THE EFFECTS OF A PULMONARY REHABILITATION PROGRAMME ON FUNCTIONAL CAPACITY AND STRENGTH OF RESPIRATORY MUSCLES IN PATIENTS WITH POST-COVID SYNDROME

## UČINEK PROGRAMA PLJUČNE REHABILITACIJE NA FUNKCIONALNO SPOSOBNOST IN MOČ DIHALNIH MIŠIČ PRI BOLNIKIHZ DOLGIM COVIDOM

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### ABSTRACT

**Aim:** The aim of this study was to estimate the effects of a pulmonary rehabilitation programme (PR) on the functional capacity and respiratory muscle strength of patients with post-COVID syndrome.

### Keywords:

Dyspnea  
Post-COVID syndrome  
Pulmonary function tests  
Pulmonary rehabilitation  
Respiratory muscle strength

**Methods:** A cross-sectional study was conducted using hospital data on patients who participated in a pulmonary rehabilitation programme at the Clinic for Lung Diseases, University Hospital Centre Zagreb, Croatia, between January 2021 and December 2022. Data on the spirometry, respiratory muscle strength, and functional exercise capacity of patients were collected at baseline and three weeks after the start of rehabilitation. The study included 80 patients (43 females, 37 males) with a mean age of 51±10 years.

**Results:** A significant increase in respiratory muscle strength ( $P < 0.001$ ) was observed after pulmonary rehabilitation, with effect sizes ranging from small to large (Cohen's  $d$  from 0.39 to 1.07), whereas the effect for  $Pl_{max}$  expressed as a percentage was large (Cohen's  $d = 0.99$ ). In addition, the pulmonary rehabilitation programme significantly improved the parameters of the six-minute walk test in patients, and the parameters of lung function, FVC, FEV1, and DLCO also improved significantly after PR ( $P < 0.05$ ).

**Conclusion:** The results showed that the pulmonary rehabilitation programme has clinically significant effects on functional capacity and respiratory muscle strength in patients with post-COVID syndrome.

### IZVLEČEK

**Cilj:** Cilj te študije je bil oceniti učinek programa pljučne rehabilitacije na funkcionalno sposobnost in moč dihalnih mišič pri bolnikih z dolgim covidom.

### Ključne besede:

dispneja  
dolgi covid  
testi pljučne funkcije  
pljučna rehabilitacija  
moč dihalnih mišič

**Metode:** Opravili smo presečno študijo na podlagi bolnišničnih podatkov o bolnikih, ki so med januarjem 2021 in decembrom 2022 sodelovali v programu pljučne rehabilitacije v Kliniki za pljučne bolezni v Univerzitetnem bolnišničnem centru v Zagrebu. Podatke o spirometriji, moči dihalnih mišič in funkcionalni zmogljivosti za telesno aktivnost bolnikov smo zbrali ob izhodišču in tri tedne po začetku rehabilitacije. Študija je vključevala 80 bolnikov (43 žensk, 37 moških) povprečne starosti 51±10 let.

**Rezultati:** Ugotovili smo bistveno povečanje moči dihalnih mišič ( $P < 0,001$ ) po pljučni rehabilitaciji, pri čemer so bile velikosti učinka od majhnih do velikih (Cohen  $d$  od 0,39 do 1,07), učinek za  $Pl_{max}$ , izražen v odstotku, pa je bil velik (Cohen  $d = 0,99$ ). Poleg tega je program pljučne rehabilitacije precej izboljšal parametre 6-minutnega sprehoda pri bolnikih, parametri pljučne funkcije FVC, FEV1 in DLCO pa so se po pljučni rehabilitaciji prav tako znatno izboljšali ( $P < 0,05$ ).

**Zaključek:** Rezultati so pokazali, da ima program pljučne rehabilitacije pri bolnikih z dolgim covidom klinično pomemben učinek na funkcionalno sposobnost in moč dihalnih mišič.

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## 1 INTRODUCTION

In late 2019, the WHO declared a COVID-19 pandemic (1), with the severity ranging from asymptomatic to mild forms of the disease, to multiple organ failure and death (2).

In addition to the acute phase, a distinction is also made with regard to post-COVID syndrome or long COVID. This refers to a duration of disease symptoms - such as shortness of breath, fatigue, chest pain, and cough - for more than two months after onset (3, 4). SARS-CoV-2 virus reduces respiratory muscle strength independently or in combination with other factors, resulting in shortness of breath in patients in acute and post-COVID phases (5). Pathophysiological mechanisms include direct myopathic effects on respiratory muscles (4) or damage to neurological control of breathing (6).

The pulmonary rehabilitation (PR) programme, based on 2013 recommendations of the American Thoracic Society (ATS) and European Respiratory Society (ERS), aims to improve the health status of patients with chronic respiratory diseases (7). Patients with chronic obstructive pulmonary disease commonly use PR, but it is effective with many other pulmonary diseases, such as COVID-19 and post-COVID syndrome. In the long term, it improves the physical and psychological health of patients with chronic lung diseases (7). It improves the quality of life by improving cardiorespiratory and bone-muscular function, reducing dyspnea and fatigue intensity (8). During rehabilitation, the patient's condition is regularly assessed. Exercises are adjusted with a gradual increase in load, and the same tests are performed at the beginning and end of PR programme (9).

Exercises to strengthen respiratory muscles are an important part of PR programme for post-COVID patients (10). Various respiratory muscle strengthening devices are used in rehabilitation, such as an inspiratory muscle training (IMT) device, positive expiratory pressure device (PEP), and Respifit S (an inspiratory muscle training device). The IMT device increases the strength of the patient's respiratory muscles and is more effective than breathing exercises (11), while IMT exercises improve respiratory muscle strength and lung function in COPD patients (12). The efficacy of these exercises has already been demonstrated in patients with some other diagnoses. Morgan et al. examined respiratory muscle-strengthening exercises in post-COVID-19 patients, and their review found that pulmonary function improved in all but one of included studies, and dyspnea and quality of life improved significantly (13). This led to a hypothesis that PR programmes positively affect functional capacity and respiratory muscle strength in patients with post-COVID syndrome. This study aimed to investigate a PR programme's effects on lung functional capacity and respiratory muscles strength in patients with post-COVID syndrome.

## 2 MATERIALS AND METHODS

### 2.1 Patients

This cross-sectional study was approved by the Ethics Committee of University Hospital Centre Zagreb (No.02/013AG). It was conducted in accordance with guidelines for the safety of subjects participating in such studies, including the Declaration of Helsinki. It included analyses of data collected during routine PR.

Patients who had recovered from COVID-19 and, after clinical evaluation by a specialist, had participated in and fully completed the PR programme at the Clinic for Lung Diseases Jordanovac University Hospital Centre Zagreb from January 2021 to December 2022, were eligible for this study. They had been infected with SARS-CoV-2 over two months before starting rehabilitation. All the patients were required to present a test upon arrival to exclude current SARS-CoV-2 infection. All the data for the study were obtained from the hospital information system.

The study included 80 patients aged 25 to 68 (Table 1). The proportion of women was higher, at 53.8% vs. 46.3%.

**Table 1.** Characteristics of patients (N=80, 43 females, 37 males).

Variable	All patients	Females (n=43)	Males (n=37)
Mean age (years)	50.96±10.22	50.46±10.53	51.54±9.97
Age (interval)	25-68	25-68	28-68
Age (mode)	49	49	52
Age (median)	51.5	51	52
BMI>30kg/m <sup>2</sup> *	37 (46.3%)	17 (39.5%)	20 (54.1%)
Comorbidity	56 (70%)	32 (74.4%)	24 (64.9%)

\*BMI-body mass index

### 2.2 Rehabilitation programme

During the three-week PR programme, the patients attended rehabilitation sessions five times a week. They participated in a three-hour rehabilitation activity each session, including tests, education, exercises, and check-ups. Since the PR programme occurred during the pandemic, all the patients were required to present a negative test upon arrival to rule out SARS-CoV-2 infection. Staff and patients wore protective clothing during the exercises and pulmonary function tests.

The patient was first examined by a specialist who determined whether there were any clinical contraindications to performing PR tests. If there were no contraindications, then the tests followed. Pulmonary function tests (spirometry, diffusion, P<sub>lmax</sub>, P<sub>Emax</sub>) were performed first. The pulmonary function tests were performed sitting with the feet flat on the floor. The

patient wore comfortable clothing that did not constrict them anywhere, and thus made breathing difficult. After 10 minutes, when the patient had rested sufficiently, the six-minute walk test (6MWT) began.

The PR programme took place in a room specially equipped for exercise with all the necessary devices. The PR programme was held at two times, at 8 am and noon, and each session lasted three hours. During this time, the patients learned diaphragmatic breathing exercises, exercises to strengthen the muscles of the extremities with the help of supports, and exercises to strengthen the respiratory muscles with the help of various devices (IMT, PEP, Respifit S), they also performed endurance exercises (cycling, walking on treadmill) and learned Nordic walking techniques. Nurses and physiotherapists supervised the patients during all the exercises. In addition to correct execution, during each activity the patients' blood oxygen saturation and pulse rate were monitored, so that they would not be subjected to an effort that was too intense for them at that moment. PR aims to ensure that patients learn the correct breathing techniques and use them daily to improve their quality of life.

Patients who trained on an IMT or PEP device were later given this device to continue training after the PR programme. In contrast, the Respifit S was used exclusively during rehabilitation and under the supervision of medical staff.

### 2.3 Pulmonary function tests and respiratory muscle strength

Pulmonary function tests were performed with a Schiller LFX8 spirometer according to the ATS and ERS standards using the standardized quality control protocol ERS93&GLI2017 (14, 15). The following parameters were compared: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and ratio of FEV1/FVC, i.e., the Tiffeneau index and diffusion capacity of lungs for carbon monoxide (DLCO) to evaluate the effects of PR on lung function (16). Patients had to have at least three technically correct measurements for the results to be acceptable. The results were then compared with the expected values for patient age, sex, height, and weight. Values greater than 80% for FEV1, FVC, and DLCO and >70% for the Tiffeneau index were considered normal (17).

Respiratory muscle strength was determined, with P<sub>lmax</sub> indicating the maximal inspiratory pressure and P<sub>Emax</sub> the maximal expiratory pressure. Measurements for both values were taken at least twice. Any result >80% of patient's reference value, as determined by age, sex, height, and weight, was considered the lowest normal value for P<sub>lmax</sub> and P<sub>Emax</sub>.

### 2.4 Six-minute walk test and grade of dyspnea

The 6MWT determines the functional exercise capacity of patients with moderate to severe lung disease (18), based on the maximum distance a patient can walk in a given period (19). The patient's vital signs at rest (arterial pressure, peripheral blood oxygen saturation (SpO<sub>2</sub>), and pulse) were measured at the test's beginning and end. The degree of dyspnea at rest was determined using the modified Borg scale from 0 to 10, where 0 indicated complete absence of dyspnea and 10 the most severe dyspnea (20). At the end of the 6MWT test, measurements were repeated to determine whether vital signs had changed or SpO<sub>2</sub> had decreased during fast walking.

### 2.5 Statistical methods

Data are presented as the arithmetic mean and standard deviation (SD), arithmetic mean difference, and 95% confidence interval (95%CI). The differences in pulmonary function tests before and after completion of the PR programme were calculated using Student's t-test for paired samples. The comparison of proportions was assessed with a chi-square test. Differences between PR initiation time after COVID-19 were tested by one-way ANOVA. Effect sizes were calculated for all differences in measured outcomes after the PR programme using Cohen's d index. The SPSS statistical programme (26.0, SPSS, USA) was used for statistical analysis, and P<0.05 was considered significant.

## 3 RESULTS

Most patients (71.3%) started the rehabilitation programme more than four months after having COVID-19 (Figure 1).

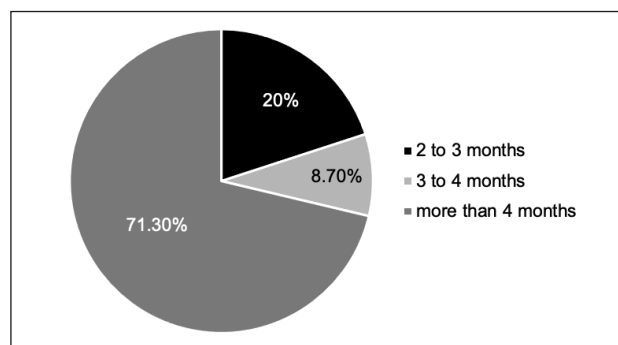


Figure 1. The distribution of patients depends on the time of initiation of PR after COVID-19 (N=80, 43 females, 37 males).

Over half of the patients had decreased respiratory muscle strength (<80%) and functional capacity before the PR programme. After rehabilitation, 51.3% and 16.3% of patients had  $PI_{max}$  and  $PE_{max}$  values <80% of the predicted threshold, respectively, whereas only 21.3% had a 6MWT distance <80% of the predicted reference value (Table 2).

The effects of PR on patients' respiratory muscle strength (Table 3) showed significant differences ( $P<0.001$ ), with small to large effect sizes. The effect and difference are very large for  $PI_{max}$ . The mean value of  $PI_{max}$  increased by 18.16 cmH<sub>2</sub>O and  $PE_{max}$  by 8.50 cmH<sub>2</sub>O. The results for all other pulmonary function parameters in patients with COVID-19 syndrome showed significant improvement after PR ( $P<0.05$ ), except for the Tiffeneau index. However, the effect sizes of PR ranged from very small to small, with a Cohen's d index from 0.18 to 0.48. PR significantly improved functional capacity as measured by 6MWT, with a large effect size. Peripheral oxygen saturation improved significantly, but the effect size was small. A significant reduction in dyspnea, as measured on the modified Borg scale, was observed after PR, with a small effect.

**Table 2.** Pathological values of pulmonary parameters and respiratory muscle strength before and after the PR programme (N=80, 43 females, 37 males)

Variable	Baseline n(%)	After PR n(%)	P*	Cohen's d
$PI_{max}<80\%$	57 (71.3)	41 (51.3)	<b>&lt;0.001</b>	0.89
$PE_{max}<80\%$	28 (35)	13 (16.3)	<b>&lt;0.001</b>	0.15
FVC<80%	14 (17.5)	8 (10)	0.251	0.06
FEV1<80%	19 (23.8)	14 (17.5)	0.338	0.59
FEV1/FVC<70%	16 (20)	18 (22.5)	0.699	0.41
DLCO<80%	15 (18.8)	13 (16.3)	0.677	0.26
6MWT<80 %	44 (55)	17 (21.3)	<b>0.007</b>	0.65

\*Chi-square test.

**Table 3.** The effects of the PR programme on muscle strength (N=80, 43 females, 37 males).

Variable	Baseline M±SD	After PR M±SD	Mean difference (95%CI)	P*	Cohen's d
$PI_{max}$	69.90±26.49	88.06±26.23	18.16 (-21.94-(-14.38))	<b>&lt;0.001</b>	1.07
$PI_{max}$ (%)	64.74±25.01	80.84±24.57	16.10 (-19.72-(-12.48))	<b>&lt;0.001</b>	0.99
$PE_{max}$	92.16±30.03	100.66±30.49	8.50 (-12.78-(-4.22))	<b>&lt;0.001</b>	0.44
$PE_{max}$ (%)	90.80±27.26	99.78±25.82	8.98 (-14.13-(-3.82))	<b>0.001</b>	0.39
FVC	4.14±1.28	4.33±1.29	-0.14 (-0.21-(-0.07))	<b>&lt;0.001</b>	0.48
FVC(%)	98.16±18.28	100.49±16.97	-2.92 (-4.64-(-1.19))	<b>0.001</b>	0.39
FEV1	3.04±0.93	3.15±0.96	-0.08 (-0.13-(-0.04))	<b>0.001</b>	0.42
FEV1(%)	90.61±18.97	92.16±18.58	-2.36 (-3.76-(-0.97))	<b>0.001</b>	0.39
FEV1/FVC	74.28±11.62	73.47±11.93	0.68 (-0.18-1.54)	0.122	0.18
DLCO	24.34±7.58	24.96±7.81	-1.17 (-2.02-(-0.33))	<b>0.007</b>	0.35
DLCO(%)	95.23±21.57	95.88±21.72	-4.03 (-7.11-(-0.95))	<b>0.011</b>	0.33
6MWT(m)	442.76±96.22	503.11±105.15	-66.92 (-84.01- (-49.82))	<b>&lt;0.001</b>	0.91
6MWT(%)	77.72±16.06	87.68±13.86	-9.66 (-11.78-(-7.55))	<b>&lt;0.001</b>	1.08
SpO <sub>2</sub> (before 6MWT)	96.59±2.10	97.14±1.64	-0.64 (-1.09-(-0.19))	<b>0.006</b>	0.33
SpO <sub>2</sub> (after 6MWT)	94.15±4.89	94.60±4.29	-0.56 (-1.09-(-0.04))	<b>0.036</b>	0.25
Dyspnea (Borg)	3.53±2.32	2.63±1.94	0.95 (0.44-1.45)	<b>&lt;0.001</b>	0.44
Heart rate	81.43±12.67	113.65±18.27	-32.22 (-36.39)-(-31.99))	<b>&lt;0.001</b>	1.75

\*Student's t-test for paired samples.

In Table 4, we compared the outcomes after PR between patient groups according to the time elapsed between onset of COVID-19 and start of rehabilitation. Significant differences ( $P < 0.05$ ) were observed for higher  $PI_{max}$  in patients who started rehabilitation after two to three months than in those who started rehabilitation more than four months after the onset of COVID-19. The lowest values of  $PI_{max}$  were measured in patients who started rehabilitation more than four months after disease onset. Post-hoc analysis showed that  $PI_{max}$  in terms of cmH<sub>2</sub>O was significantly higher in patients who started PR two to three months after disease onset than in patients who started rehabilitation more than four months after it (Tukey  $P = 0.024$ ). The same was true for  $PI_{max}$  in percentage terms (Tukey  $P = 0.012$ ). For  $PE_{max}$ , no significant difference was found between patients who started PR two to three months after COVID-19 and patients who started rehabilitation three to four months after COVID-19 (Tukey  $P = 0.369$ ). For  $PE_{max}$ , there was no significant difference with regard to the time when rehabilitation started after COVID-19. The time elapsed from disease onset to initiation of PR had no significant effect on other spirometric pulmonary function test results or DLCO, 6MWT, and dyspnea. A post-hoc analysis showed that patients who started PR two to three months after disease onset had a significantly higher heart rate than patients who started rehabilitation more than four months after it (Tukey  $P = 0.038$ ).

#### 4 DISCUSSION

COVID-19 and post-COVID syndrome, relatively new clinical entities for acute and chronic patients' health problems, have become subject of numerous studies. The results of this study support the clinical use of a PR programme with post-COVID-19 patients, since it significantly improved most indicators of pulmonary function.

At the end of rehabilitation, the values of FEV<sub>1</sub>, FVC, DLCO, 6MWT, and respiratory muscle strength improved significantly, with effect sizes ranging from small to large (Cohen's  $d$  from 0.35 to 1.08). In contrast, the Tiffeneau index remained unchanged, as both the numerator (FEV<sub>1</sub>) and denominator (FVC) improved significantly. Lung function increased in litres from  $4.14 \pm 1.28$  to  $4.33 \pm 1.29$  for FVC and from  $3.04 \pm 0.93$  to  $3.15 \pm 0.96$  for FEV<sub>1</sub>. Functional capacity increased in metres from  $442.76 \pm 96.22$  to  $503.11 \pm 105.15$ , with an increase in the predicted value from 77.7% to 87.7%. In addition to the significant effects of PR on lung function, a previous study of older adults who had recovered from COVID-19 confirmed a positive impact on other areas of health, such as quality of life and anxiety. In that study, a six-week PR programme included 10-minute exercises twice weekly to strengthen respiratory muscles and the diaphragm, as well as stretching exercises (21). After hospitalization, post-COVID patients usually have muscle weakness and difficulty breathing after exercise.

**Table 4.** Differences in outcomes of the PR programme according to the time elapsed between disease onset and the beginning of rehabilitation (N=80, 43 females, 37 males).

Variable	2 to 3 months (n=16) M±SD	3 to 4 months (n=7) M±SD	More than 4 months (n=57) M±SD	P*	Cohen's d
$PI_{max}$	21.44±24.07	17.86±14.38	17.28±15.05	<b>0.032</b>	3.36
$PI_{max}$ (%)	19.88±22.78	16.43±13.29	15.00±14.51	<b>0.021</b>	3.29
$PE_{max}$	7.56±21.62	2.86±25.24	9.46±18.01	0.180	3.30
$PE_{max}$ (%)	8.38±20.33	0.57±23.32	10.18±24.00	0.785	3.86
FVC	0.31±0.34	0.02±0.27	0.11±0.28	0.363	3.33
FVC(%)	5.47±6.69	1.29±8.75	2.40±7.45	0.269	5.92
FEV <sub>1</sub>	0.15±0.21	0.02±0.18	0.08±0.19	0.124	3.29
FEV <sub>1</sub> (%)	3.87±4.82	1.00±6.71	2.38±6.14	0.812	4.96
FEV <sub>1</sub> /FVC	1.48±4.89	2.35±5.04	0.23±3.10	0.327	6.16
DLCO	2.99±3.59	3.61±5.04	0.29±2.91	0.275	3.20
DLCO(%)	8.33±10.36	14.86±15.12	1.14±11.12	0.709	4.41
6MWT(m)	525.87±105.47	468.43±146.46	501.21±99.61	0.483	4.78
6MWT(%)	88.07±11.06	91.17±17.52	87.16±12.68	0.798	6.33
SpO <sub>2</sub> (before 6MWT)	97.60±0.99	97.43±1.40	96.96±1.81	0.374	59.08
SpO <sub>2</sub> (after 6MWT)	94.40±3.38	93.71±3.15	94.78±4.68	0.813	22.07
Dyspnea	1.97±1.64	2.93±1.43	2.78±2.07	0.332	1.35
Heart rate	84.19±16.14	81.71±10.45	80.57±11.87	<b>0.047</b>	6.43

\*ANOVA test.

For them, rehabilitation is crucial to improving fitness and muscle strength because the muscles of whole body are weakened in addition to respiratory muscles (22).

PR significantly improved P<sub>lmax</sub>, P<sub>E</sub><sub>max</sub>, and respiratory muscle strength. A total of 71.3% of patients had a pathological value <80% of the predicted value for P<sub>lmax</sub> at the first measurement, and 51.3% of them at the last measurement. For P<sub>E</sub><sub>max</sub>, pathological values were found in 35% of patients at the first measurement and in 6.3% of them at the last measurement. Vieira da Costa et al. confirmed the improvement of respiratory muscle strength after PR in a study of nine post-COVID patients with different clinical presentations, dry cough, shortness of breath, and chest pain (23). In addition to improving lung function and respiratory strength, the endurance of the respiratory muscles and diaphragm, main respiratory muscle, and quadriceps all improved (23). Villelaiteia-Jaureguizar et al. studied SARS-CoV-2 patients who were treated with invasive mechanical ventilation in an intensive care unit, and then performed low-intensity respiratory muscle exercises after discharge (24). The results suggest that low-intensity respiratory muscle training improves respiratory strength and quality of life associated with health status and shortness of breath.

In this study the COVID-19 patients who took part in the PR programme recovered better and faster than those who did not participate in it. Their muscle strength, balance, and psychosocial status also improved significantly compared to patients who suffered only respiratory failure. Long-term ICU treatment significantly damages muscle function in the short term, limits physical performance, and reduces quality of life. Al Chikhanian et al. suggest that PR programmes may reduce posttraumatic stress (25). The increased P<sub>lmax</sub> and P<sub>E</sub><sub>max</sub> values after PR indicate that improved inspiratory and expiratory muscle strength is associated with greater mobility of the chest wall and diaphragmatic movements (10, 26). Respiratory muscle training improves muscle strength, airway resistance, and diaphragm thickness. It also reduces dyspnea, as weakness of the respiratory muscles is associated with shortness of breath (10).

The development of fibrosis is partly genetically determined. The angiotensin-converting enzyme-2 gene is expressed in the myofiber membrane of the diaphragm, allowing infiltration of the SARS-CoV-2 virus and increasing gene expression involved in fibrosis (4,27). COVID-19 also changes the function of the diaphragm and decreases its thickness (27). A decrease in diaphragm muscle significantly increases the risk of pneumonia, and low thickness and density at CT are predictors for a severe form of COVID-19 (28). Diaphragm thickness at the end of expiration decreased in COVID-19 patients, and the thickening proportion increased (29). Various pathophysiological mechanisms are involved in the damage to the respiratory muscles that occurs with COVID-19, such

as the decreased contractility of the respiratory muscles, myopathy of the respiratory muscles caused by the virus, unilateral paralysis of diaphragm due to unilateral injury of the phrenic nerve, severe atrophy and weakness due to dysfunction of the diaphragm, and baseline respiratory muscle weakness (4). COVID-19 may also affect neural control of breathing and cause unilateral diaphragm paralysis, unrelated to mechanical ventilation and normal lung parenchyma (6, 30).

Fibrous abnormalities and lung fibrosis affect about one-third of COVID-19 patients (31). Risk factors include older age, chronic comorbidities, use of mechanical ventilation during the acute phase of COVID-19, and female gender. The development and progression of pulmonary fibrosis is influenced by each individual's genetic background, i.e., the genes involved in innate antiviral defence, inflammatory lung injury, and the ABO system of blood groups (31, 32). Aging increases lung parenchyma stiffness and facilitates pulmonary fibrosis progression (33). For all these reasons, it is obvious why exercise in PR alleviates the severe symptoms of post-COVID-19 pulmonary fibrosis (34).

The results are consistent with a systematic review, which showed that PR significantly improved exercise tolerance as determined by 6MWT (35). PR improves the pulmonary function parameters and reduces anxiety, depression, and symptoms of dyspnea and fatigue. Moreover, the lung function parameters and respiratory muscle strength were significantly better in patients who took part in a PR programme than in patients who did not (35).

The time between onset of COVID-19 and start of PR had no significant effects on most of the parameters of lung function, except P<sub>lmax</sub>, suggesting that the time of starting PR is not as important clinically as simply starting rehabilitation in terms of achieving faster recovery and improvement in quality of life in post-COVID syndrome patients.

The PR programme is effective in patients recovering from severe acute respiratory syndrome (SARS). In these patients, pulmonary abnormalities are present in up to 75.4% of patients six months after onset of the disease (36), and abnormalities in pulmonary function are present in one-third one year after SARS (37). Some studies reported reductions in DLCO scores ranging from 11% to 45% among patients after one year, while the 6MWT results improved (38). Wu et al. showed radiological abnormalities resembling pulmonary fibrosis seven years after SARS (39). The results of studies on SARS patients, in whom the consequences of damage to pulmonary function are visible seven years after onset of the disease, point to the importance of a timely PR programme in post-COVID-19 patients. Although the short-term consequences of COVID-19, such as weakened lung function, decreased muscle strength, and reduced mobility, are described in detail, further studies are needed to determine whether

COVID-19 permanently impairs lung function. In this way, rehabilitation programmes in the acute and later phases of the disease can be maximally individualized and thus enable the best possible quality of life for each person (40).

In the context of all the previously mentioned studies on patients who have recovered from COVID-19, the use of the PR programme has been shown to have numerous positive effects, with sufficient supporting evidence. This complex programme includes physical activity and breathing exercises that increase respiratory muscle strength and lung function. The results are clinically significant since, at the end of rehabilitation, the patients had the ability to walk a greater distance with a lower grade of dyspnea. The use of the correct breathing patterns and exercises helped the patients to make tremendous efforts and achieve a higher workload with less breathlessness. This underscores the importance of referring patients in the post-COVID phase for PR. Learning the correct breathing patterns, strengthening specific limb muscles, increasing fitness, strengthening the respiratory muscles, improving the pulmonary function parameters, and increasing the functional capacity all help to improve the quality of life. Corral et al. have shown that an inspiratory and expiratory muscle training programme effectively improves the quality of life of people with long-term COVID-19 symptoms (41). In addition, a systematic review with a meta-analysis found that rehabilitation interventions are associated with significant improvements in quality of life, functional exercise capacity, and dyspnea in post-COVID patients (42).

It should be noted that the programme investigated in this study is neither financially nor technically demanding for medical personnel. A clinical psychologist was included in the PR programme and had an important role in treating people with post-COVID syndrome, since anxiety and depression are not uncommon in this population (43). However, psychological monitoring of patients during PR has shown that this medical intervention can improve mental health.

#### 4.1 Study limitations

One of the limitations of this work is that it is a single-centre study. All patients who met the inclusion criteria and had a clinical indication for participation in a PR programme were included in the study. Given such a sampling frame, which implies consecutive sampling, it was impossible to estimate the required sample size before study was conducted. Moreover, data are lacking on the patients' premorbid respiratory status, which might have influenced the measured parameters of lung function and respiratory muscle strength even before the disease, and whether SARS-CoV-2 infection was responsible for their worsening or was a clinical course of another, underlying condition.

Nevertheless, these limitations could not significantly affect the study's results because most patients (91.3%) who participated in PR had not previously received pulmonary treatment. The collected data did not include information on the clinical presentation of COVID-19 and hospitalizations. In the Croatian health system, secondary and tertiary medical institutions are not linked by a single hospital information system, and it is impossible to conduct multicentre studies. Although the severity of clinical presentation could be associated with other comorbidities affecting respiratory muscle strength and functional capacity, it could not be subsequently categorized based on secondary use of the collected data. Undoubtedly, further research is needed to determine whether clinical improvement in post-COVID syndrome is attributable to the natural course of the disease, or if PR is crucial in improving the patient's quality of life. However, identifying and quantifying the consequences of COVID-19 and its dynamics over time requires a longitudinal study, extensive clinical follow-up, and many participants. Still, the methodological approach adopted in the current work makes it possible to compare the results with those of previous studies, although the statistical associations that it obtained have some limitations, usually due to the cross-sectional research design.

## 5 CONCLUSION

PR significantly strengthens the respiratory muscles in patients with post-COVID syndrome, particularly in terms of P<sub>lmax</sub>, by 18.16 litres, it improves lung functional capacity-FVC by 0.14 and FEV<sub>1</sub> by 0.08, and reduces dyspnea by 0.95. Besides statistical significance, these positive effects on respiratory muscle strength have clinical relevance. The pulmonary function parameters of FVC, FEV<sub>1</sub>, and DLCO significantly improved in the patients, as did endurance based on the results of the 6MWT test. The time elapsed between disease onset and starting the PR programme was not found to be significant in improving lung function, but it did affect respiratory muscle strength.

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## CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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## ETHICAL APPROVAL

Ethical approval to conduct the study was obtained from the Ethics Committee of the University Hospital Centre Zagreb (No. 02/013 AG).

Informed consent: The manuscript does not contain any individual person's data in any form.

## AVAILABILITY OF DATA AND MATERIALS

All data and materials used in this study were collected from the hospital's information system and are available upon reasonable request.

## CONTRIBUTIONS

All the authors contributed equally to the manuscript, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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# MOTIVATIONAL FACTORS INFLUENCING THE CHOICE OF MEDICAL STUDIES AND FUTURE CAREER PLANS AMONG MONTENEGRIN STUDENTS

## MOTIVACIJSKI DEJAVNIKI, KI VPLIVAJO NA IZBIRO ŠTUDIJA MEDICINE IN POKLICNE NAČRTE ZA PRIHODNOST MED ČRNOGORSKIMI ŠTUDENTI

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### ABSTRACT

#### Keywords:

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**Introduction:** There is a concerning trend of emigration among highly educated individuals in Montenegro. This includes medical professionals who seek better job opportunities abroad. The aim of the present study was to identify the primary motivational factors driving Montenegrin medical students to pursue a career in medicine, and whether these factors undergo changes over the course of their studies.

**Methods:** A cross-sectional study included 210 medical students in Montenegro, 27.62% were males, and 72.38% were females. The mean age of the students was 21.90 years (SD=3.05) (range 19-39). Their academic motivation was analysed using the Academic Motivation Scale, previously validated in various cultural contexts.

**Results:** The results showed that autonomous motivation levels were higher than controlled motivation levels ( $p < 0.001$ ) among students in Montenegro, which has been previously associated with better learning outcomes. Students with medical doctors among their family members had higher extrinsic motivation related to rewards and punishments (extrinsic motivation with external regulation  $p = 0.018$ ). Amotivation showed a trend of increasing as the students got closer to graduation ( $p = 0.057$ ). Only 8.1% of students planned a career in primary healthcare, and 1% wished to specialize in family medicine.

**Conclusions:** This study's findings, which indicate high levels of autonomous motivation among medical students, are of significant importance. They contribute to a comprehensive understanding of the motivation factors among medical students and young healthcare professionals in Montenegro. Moreover, they provide a basis for the implementation of strategic interventions to retain highly skilled medical professionals within the country's workforce, thereby addressing the concerning trend of emigration among this group.

### IZVLEČEK

#### Ključne besede:

študenti medicine  
medicinsko  
izobraževanje  
akademska motivacija  
poklicni načrti

**Uvod:** Med visokošolsko izobraženimi posamezniki v Črni gori obstaja skrb vzbujajoč trend izseljevanja, kar vključuje zdravstvene delavce, ki iščejo boljše zaposlitvene možnosti v tujini. Cilj te študije je bil opredeliti primarne motivacijske dejavnike, zaradi katerih črnogorski študenti medicine izberejo poklicno pot v medicini, in ugotoviti, ali se ti dejavniki med njihovim študijem spremenijo.

**Metode:** V presečno študijo smo vključili 210 študentov medicine v Črni gori, med katerimi je bilo 27,62 % moških in 72,38 % žensk. Povprečna starost študentov je bila 21,90 leta (SD = 3,05) (razpon 19-39). Njihovo akademsko motivacijo smo analizirali z lestvico akademske motivacije, ki je bila predhodno validirana v različnih kulturnih okoljih.

**Rezultati:** Rezultati so pokazali, da so ravni avtonomne motivacije večje od kontrolirane ( $p < 0,001$ ), kar je bilo prej povezano z boljšimi učnimi rezultati. Študenti, ki imajo zdravnike med družinskimi člani, so imeli višjo zunanjo motivacijo, povezano z nagrajevanjem in kaznovanjem (zunanja motivacija z zunanjo regulacijo  $p = 0,018$ ). Trend pomanjkanja motivacije se povečuje, ko se študenti približujejo zaključku študija ( $p = 0,057$ ). Samo 8,1 % študentov je načrtovalo poklicno pot v primarnem zdravstvenem varstvu, 1 % pa jih je želelo opravljati specializacijo družinske medicine.

**Zaključki:** Ugotovitve študije, ki kažejo visoke ravni avtonomne motivacije med študenti medicine, so zelo pomembne, saj prispevajo k celovitemu razumevanju motivacijskih dejavnikov med študenti medicine in mladimi zdravstvenimi delavci. Poleg tega zagotavljajo podlago za izvedbo strateških ukrepov, s katerimi bi zadržali visoko usposobljene zdravstvene delavce na delovnih mestih v državi in tako obvladali skrb vzbujajoč trend izseljevanja v tej skupini.

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## 1 INTRODUCTION

Medical practice requires dedication, knowledge, strenuous work, good interpersonal skills, empathy, and professional and ethical behaviour toward patients. Because of the high demands associated with the medical profession, medical students should possess and maintain a high level of motivation throughout their education. Motivation can be defined as a process that initiates, guides, and stimulates individuals to act in a certain fashion to achieve a specific goal. Of the several theories that explain motivation, a widely used approach in medicine is the self-determination theory proposed by Deci and Ryan (1, 2). According to this theory there are two main types of motivation - intrinsic and extrinsic (3). Intrinsic motivation (IM) leads people to perform activities simply for the internal emotions associated with the action (pleasure, enjoyment, curiosity) (3, 4). IM can be further classified into three subscales (4, 5). IM to know refers to the pleasure related to learning or exploring something new. IM to accomplish things refers to the feeling of satisfaction associated with trying to achieve or create something. IM to experience stimulation refers to the feeling of stimulating sensations during the activity. On the other hand, extrinsic motivation (EM) makes people act to attain some specific result. There are three subscales of EM (4-6). Identified EM occurs when an individual identifies that a certain behaviour is ranked highly in their personal system of values (e.g., studying medicine to reach a personal goal). Introjected EM occurs when social expectations influence behaviour. External regulation occurs when the reason for doing something is connected with rewards or punishments (4-6). IM and identified EM are considered "autonomous motivation", while introjected EM and external regulation are considered "controlled motivation" (4). The self-determination theory also includes amotivation, which is the absence of any motivation (3, 4).

In Montenegro there is a concerning trend of emigration among highly educated individuals, including medical professionals, who seek better job opportunities abroad. This "brain drain" not only diminishes the quality of healthcare domestically, but also represents significant economic loss for society (7). Higher education in Montenegro is currently subsidized by the government, which makes higher education at public universities tuition-free. As such, the departure of young medical professionals from the country is not just a healthcare challenge, but also an economic setback. The Faculty of Medicine at the University of Montenegro was founded in 1997, which makes it one of the youngest public medical programmes in the region. The significance of these unique features of medical education in Montenegro becomes clear in the light of the findings of a systematic review by Goel et al. (8), which showed that the motivational factors

among medical students are significantly influenced by the level of socioeconomic development of the country they are studying in. In most high-income countries, scientific interests, such as a passion for medical subjects, primarily drive students towards pursuing medicine. Conversely, in low-income countries, financial security, parental aspirations, and societal expectations are among the primary motivators (8).

The aim of the present study is to identify the primary motivational factors driving Montenegrin medical students to pursue careers in medicine, and whether these factors undergo changes over the course of their studies. By comprehensively understanding students' motivations, educators and policymakers can implement strategic interventions to retain highly skilled medical professionals within the country's workforce. To the best of our knowledge, no similar studies have been conducted in Montenegro.

## 2 MATERIALS AND METHODS

This was a questionnaire-based cross-sectional study.

### 2.1 Ethics

The study was approved by the Ethics Committee of the Medical Faculty at the University of Montenegro (Approval number: 769/2, Date: June 1, 2023.) and conducted according to the ethical principles of the Declaration of Helsinki for research with human beings.

The participants were informed about the study and assured about their confidentiality and data security. The students were given instructions for completing the questionnaire, along with assurances that they were free to refuse to participate or to withdraw consent for participation at any point, and that their answers would not affect their grades. The questionnaires were anonymous and self-administered, and informed consent confirmed the voluntary participation of each participant at the beginning of the survey. A check box was provided on the answer sheet of the survey to indicate non-consent.

### 2.2 Study setting

This study was carried out at the Faculty of Medicine of the University of Montenegro in Podgorica, which is the only medical faculty in the country. The medicine study programme follows a six-year undergraduate curriculum. In the academic year of 2022/2023, this study programme enrolled a total of 386 students, which included all students from year 1 to year 6.

### 2.3 Study participants

All the students enrolled in the medicine study programme were invited to participate in the study. The consent information and a link to the questionnaire were distributed to the students via email or Viber. The study was conducted in June and July of 2023 using an online survey management tool, <https://app.freeonlinesurveys.com/>.

Valid responses were defined as those that had no missing data. The students who did not consent to participation, and those whose responses had missing data, were thus not included in the study.

### 2.4 Instruments

We used the Academic Motivation Scale (AMS) developed by Vallerand et al. (9). This is a validated instrument designed to measure motivation in an academic setting, with satisfactory levels of internal and external consistency demonstrated across various cultural contexts and countries.

The AMS questions were translated by the forward- and back-translation procedure from English to Montenegrin for this study. The AMS contains 28 items rated on a Likert-type scale ranging from 1 (no agreement) to 7 (total agreement), with a mean of 4 (moderate correspondence). The students were asked to indicate their agreement with a statement, allowing the calculation of each type of motivation. The AMS is divided into seven subscales assessing three types of IM: 1) IM to know, 2) to accomplish things, and 3) to experience stimulation; three types of EM: 1) identified EM, 2) introjected EM, and 3) external regulation; and one type of amotivation. Four questions are assigned to each subscale in a random order.

The questionnaire used in the present study included three additional sections: participants' informed consent, background information (including gender, age, years studying, family members who are physicians, influences of individuals), and expectations about future careers (two questions).

### 2.5 Statistical analysis

The sample size was calculated by the following formula:  $n = z^2 * p(1-p) / e^2$ . At a prevalence rate of 0.50, an error rate of 0.05, and a z-value of 1.96, the required sample size was 193.

Descriptive statistics were used to analyse demographic data. The frequencies and percentages of the qualitative variables were obtained, as well as the means and medians of the quantitative variables. Chi-square and Fisher's exact tests were used to compare the nominal variables. For differences in academic motivation, we used the independent samples t-test and one-way analysis

of variance (ANOVA). A test for normality was performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Cronbach's alpha was calculated to assess the internal consistency of the study questionnaire, and the result of 0.88 indicated the high reliability of the AMS. A p-value of less than 0.05 was considered statistically significant. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM, New York, USA).

## 3 RESULTS

Out of 386 students, 239 filled out the questionnaire, achieving a response rate of 61.92%. However, 21 responses were invalid and excluded according to the exclusion criteria, and eight participants indicated their non-consent. A total of 210 responses were thus used for data analysis, representing 54.40% of all students enrolled in the medicine study programme at the University of Montenegro.

The sociodemographic characteristics of the student population and their professional plans are shown in Table 1. Of the respondents, 27.62% were males and 72.38% were females. The mean age of the students was 21.90 years (SD=3.05) (range 19-39).

A total of 85.71% of the students said they made their own decision with regard to studying medicine, while for 9.05% their parents played the most significant role in this choice. More than 40% of the students (43.33%) had a medical doctor among their family members, but less than 15% had parents in the medical profession.

Almost two-thirds (57.14%) of the students planned to work in the public sector, while only 11.90% preferred the private sector. The share of students stating they would like to work abroad was 16.19%. Most of the respondents (48.10%) wanted to work at the Clinical Centre of Montenegro, which is a tertiary care hospital. The proportion of students who would specialize in non-surgical disciplines was the highest (29.53%), and the most popular specialties were internal medicine (13.81%), followed by surgery (10.95%), and paediatrics (8.58%). Most importantly, only a small proportion of the students planned to work in primary health care (8.10%) and specialize in family medicine (0.95%).

**Table 1.** Comparison of sociodemographic characteristics and professional plans by gender.

	Male n (%)	Female n (%)	Total n (%)	*p-value
<b>Year of study</b>	58 (27.62)	152 (72.38)	210 (100.00)	<b>0.284</b>
1st	18	50	68 (32.38)	
2nd	6	27	33 (15.71)	
3rd	7	16	23 (10.95)	
4th	6	21	27 (12.86)	
5th	11	27	38 (18.10)	
6th	10	11	21 (10.00)	
<b>Age (years)</b>				<b>0.683</b>
19-20	21	65	86 (40.95)	
21-23	23	53	76 (36.19)	
24 and more	14	34	48 (22.86)	
<b>Most influential person in the choice to study medicine</b>				<b>0.349</b>
Self	47	133	180 (85.71)	
Parent(s)	6	13	19 (9.05)	
Other	5	6	11 (5.24)	
<b>Family members as medical doctors</b>				<b>1.000</b>
No	33	86	119 (56.67)	
Yes	25	66	91 (43.33)	
Father and/or mother	12	17	29 (13.81)	
Grandfather and/or grandmother	5	10	15 (7.14)	
Brother and/or sister	7	8	15 (7.14)	
Other	10	43	53 (25.24)	
<b>Preferred sector of work</b>				<b>0.397</b>
Public in Montenegro	29	91	120 (57.14)	
Private in Montenegro	7	18	25 (11.90)	
Other country	9	25	34 (16.19)	
Other plans	2	2	4 (1.90)	
Do not know	11	16	27 (12.87)	
<b>Preferred setting of work</b>				<b>0.396</b>
Clinical Centre of Montenegro	32	69	101 (48.10)	
Hospital	4	16	20 (9.52)	
Outpatient clinic	1	16	17 (8.10)	
Private practice	9	23	32 (15.24)	
Medical faculty	2	6	8 (3.81)	
Other	5	14	19 (9.05)	
Do not know	5	8	13 (6.18)	
<b>Preferred professional plan</b>				<b>0.657</b>
Surgical specialty	16	28	44 (20.95)	
Non-surgical specialty	14	48	62 (29.53)	
Family medicine	1	3	4 (1.90)	
Research work	4	11	15 (7.14)	
Preclinical specialty	1	6	7 (3.33)	
Other	14	42	56 (26.67)	
Do not know	8	14	22 (10.48)	
<b>Preferred specialization</b>				<b>0.079</b>
Dermatovenerology	2	5	7 (3.33)	
Public health	1	2	3 (1.43)	

	Male n (%)	Female n (%)	Total n (%)	*p-value
Gynaecology/Obstetrics	2	10	12 (5.71)	
Surgery	8	15	23 (10.95)	
Internal medicine	10	19	29 (13.81)	
Neurosurgery	3	3	6 (2.86)	
Neurology	3	8	11 (5.24)	
Ophthalmology	0	13	13 (6.19)	
Orthopaedics	3	0	3 (1.43)	
Otorhinolaryngology	2	2	4 (1.90)	
Paediatrics	2	16	18 (8.58)	
Family medicine	0	2	2 (0.95)	
Psychiatry	2	2	4 (1.90)	
Radiology	4	5	9 (4.29)	
Forensic medicine	2	6	8 (3.81)	
Other	14	44	58 (27.62)	

\*p-value for the chi-square test and Fisher's exact test.

Table 2 and Table 3 summarize the results of the AMS. The highest mean motivation scores were observed for item 3 ( $6.40 \pm 1.05$ ) and item 10 ( $6.15 \pm 1.33$ ). The lowest score was observed for item 19 ( $1.56 \pm 1.29$ ).

**Table 2.** The mean value, standard deviation and ranking of all 28 items of the Academic Motivation Scale.

Scale	Statements	mean $\pm$ SD	Ranking according to the mean value
Intrinsic motivation to know	2. Because I experience pleasure and satisfaction while learning new things.	5.76 $\pm$ 1.41	9
	9. For the pleasure I experience when I discover new things never seen before.	5.84 $\pm$ 1.42	7
	16. For the pleasure that I experience in broadening my knowledge about subjects which appeal to me.	5.89 $\pm$ 1.29	5
	23. Because my studies allow me to continue to learn about many things that interest me.	5.88 $\pm$ 1.32	6
Intrinsic motivation towards accomplishment	6. For the pleasure I experience while surpassing myself in my studies.	4.90 $\pm$ 1.79	18
	13. For the pleasure that I experience while I am surpassing myself in one of my personal accomplishments.	5.55 $\pm$ 1.61	10
	20. For the satisfaction I feel when I am in the process of accomplishing difficult academic activities.	4.42 $\pm$ 1.94	22
	27. Because college allows me to experience a personal satisfaction in my quest for excellence in my studies.	5.37 $\pm$ 1.63	14
Intrinsic motivation to experience stimulation	4. For the intense feelings I experience when I am communicating my own ideas to others.	5.28 $\pm$ 1.57	16
	11. For the pleasure that I experience when I read interesting authors.	5.39 $\pm$ 1.73	12
	18. For the pleasure that I experience when I feel completely absorbed by what certain authors have written.	4.59 $\pm$ 1.88	20
	25. For the "high" feeling that I experience while reading about various interesting subjects.	5.37 $\pm$ 1.59	13

Scale	Statements	mean±SD	Ranking according to the mean value
Extrinsic motivation: external regulation	1. Because with only a high-school degree I would not find a high-paying job later on.	4.37±2.22	23
	8. In order to obtain a more prestigious job later on.	5.54±1.66	11
	15. Because I want to have “the good life” later on.	5.78±1.57	8
	22. In order to have a better salary later on.	5.36±1.70	15
Extrinsic motivation: introjected regulation	7. To prove to myself that I am capable of completing my college degree.	4.55±2.12	21
	14. Because of the fact that when I succeed in college, I feel important.	4.73±1.98	19
	21. To show myself that I am an intelligent person.	4.12±1.94	24
	28. Because I want to show myself that I can succeed in my studies.	5.23±1.79	17
External motivation: identified regulation	3. Because I think that a college education will help me better prepare for the career I have chosen.	6.40±1.05	1
	10. Because eventually it will enable me to enter the job market in a field that I like.	6.15±1.33	2
	17. Because this will help me make a better choice regarding my career orientation.	6.11±1.16	3
	24. Because I believe that a few additional years of education will improve my competence as a worker.	6.04±1.32	4
Amotivation	5. Honestly, I don't know; I really feel that I am wasting my time in school.	1.76±1.38	26
	12. I once had good reasons for going to college; however, now I wonder whether I should continue.	2.49±1.95	25
	19. I can't see why I go to college and frankly, I couldn't care less.	1.56±1.29	28
	26. I don't know; I can't understand what I am doing in school.	1.61±1.50	27

**Table 3.** Difference in academic motivation scores between students by gender, and between students who have a medical doctor among their family members vs. those who do not.

Scale	Total (n=210) mean±SD	Gender			Family members as medical doctors		
		Male (n=58) mean±SD	Female (n=152) mean±SD	p-value	Yes (n=91) mean±SD	No (n=119) mean±SD	p-value
Intrinsic motivation (IM)	5.35±1.19	5.40±1.20	5.33±1.19	0.702	5.34±1.18	5.36±1.20	0.865
IM to know	5.84±1.13	5.86±1.06	5.83±1.16	0.786	5.83±1.12	5.85±1.15	0.928
IM towards accomplishment	5.06±1.40	5.12±1.46	5.03±1.39	0.687	5.04±1.31	5.07±1.48	0.906
IM to experience stimulation	5.16±1.35	5.21±1.34	5.13±1.35	0.714	5.13±1.43	5.18±1.29	0.801
Extrinsic motivation (EM)	5.37±1.06	5.17±1.10	5.44±1.04	0.105	5.54±0.91	5.23±1.15	<b>0.031</b>
EM external regulation	5.26±1.45	5.14±1.63	5.31±1.38	0.457	5.52±1.23	5.06±1.57	<b>0.018</b>
EM introjected regulation	4.66±1.61	4.37±1.60	4.77±1.60	0.103	4.85±1.45	4.52±1.71	0.134
EM identified regulation	6.18±0.94	6.01±0.99	6.24±0.91	0.122	6.25±0.79	6.12±1.04	0.295
Amotivation	1.86±1.29	1.89±1.44	1.84±1.24	0.825	1.89±1.26	1.83±1.32	0.738
*Autonomous motivation	5.56±1.04	5.55±1.09	5.56±1.02	0.985	5.56±1.00	5.55±1.07	0.935
**Controlled motivation	4.96±1.32	4.75±1.38	5.04±1.29	0.162	5.19±1.16	4.79±1.42	<b>0.027</b>

P-value for independent samples t-test. \*Autonomous motivation = intrinsic motivation and extrinsic identified regulation: \*\*Controlled motivation = extrinsic introjected regulation and external regulation. Bold text denotes values that are statistically significant.

**Table 4.** One way analysis of variance (ANOVA) of the academic motivation scores between students by study year and age.

Scale	Study Year		Age	
	F	Overall p-value	F	Overall p-value
Intrinsic motivation (IM)	0.721	0.608	1.113	0.331
IM to know	0.508	0.770	0.274	0.761
IM towards accomplishment	1.562	0.172	2.345	0.098
IM to experience stimulation	0.256	0.936	1.047	0.353
Extrinsic motivation (EM)	1.499	0.192	0.608	0.545
EM external regulation	3.463	<b>0.005</b>	2.918	0.056
EM introjected regulation	1.425	0.217	0.710	0.493
EM identified regulation	1.459	0.205	0.246	0.782
Amotivation	2.298	0.053	2.947	0.057
*Autonomous motivation	0.760	0.580	1.010	0.366
**Controlled motivation	1.269	0.279	0.889	0.413

\*Autonomous motivation = intrinsic motivation and extrinsic identified regulation: \*\*Controlled motivation = extrinsic introjected regulation and external regulation. Bold text denotes values that are statistically significant.

Students showed somewhat higher levels of EM (5.37±1.06) than IM (5.35±1.19). More specifically, especially high scores were found for identified and external regulation (6.18±0.94, and 5.26±1.45, respectively). Among IMs, the mean score of internal motivation to know (5.84±1.13) was the highest. The mean score of AM was 1.86±1.29. The IM mean score was higher among male students, while the EM mean score was higher among female students. However, there was no statistically significant difference in the seven subscales when grouped according to gender. The mean autonomous motivation (mean±SD=5.56±1.04) score was significantly higher than the controlled motivation (mean±SD=4.96±1.32) score ( $p<0.001$ , data not shown in the table). Interestingly, students who had a medical doctor among their family members had significantly higher controlled motivation scores ( $p=0.027$ ), EM scores ( $p=0.031$ ), and specifically EM external regulation scores ( $p=0.018$ ), compared to the group of students who had no medical doctors among their family members.

Table 4 shows the results of the AMS across study years and ages. The EM external regulation value was significantly lower among 3rd year students ( $p=0.005$ ). The AM value was highest in the oldest group of students, with near statistical significance ( $p=0.057$ ).

#### 4 DISCUSSION

This study found high levels of autonomous motivation among medical students, with the highest-rated motivational item being to gain knowledge for one's future career. The leading motivation sub-scales were "identified extrinsic motivation" and "intrinsic motivation to know". The IM score was higher among male students, while the EM score was higher among female students. Students with a medical doctor in the family had lower IM and higher amotivation compared to those who had no medical doctors among their family members.

Motivational factors influence medical students' enrolment in medical studies and affect their academic performance. These factors are influenced by other characteristics of the individual, such as socioeconomic status and cultural background (8). According to the self-determination theory, IM and EM identified motivation, which are together considered "autonomous motivation", are desirable for studying medicine since they have been associated with better student performance, improved study strategies, and more efficient learning (10, 11). The autonomous factors were also the primary factors that motivated the Montenegrin students to study medicine. A study conducted in Lebanon of 206 students also showed a higher level of autonomous rather than controlled motivation (12). Our results suggest that "identified EM" and "IM to know" were the leading motivation sub-scales for students to undertake medical study. The highest-rated motivational items were to gain knowledge for one's future career in the medical field. Our findings agree with the results of studies performed in Singapore (13) and in Pakistan (14). Diwan et al. found that the



motivations for entering medical education in India included personal ambition, altruistic reasons, parental desire, the opportunity for a respected profession, and financial incentives (15). Kavousipour et al. conducted a study in Iran and also identified parental wishes, the ability to learn, get a good job in the future, and higher social and professional status as primary motivation factors in this context (16). Another study in Latin America found that significant motivations in choosing to study medicine included: social/altruist, economic/prestige, and academic performance motivation (17). Polish medical students reported that the main reasons for choosing medicine were altruistic and scientific motives (18). Similarly, social/altruist motivation was the primary factor in selecting medical careers among students in Hungary and Ireland, followed by EM: obtaining a degree, getting good job, and accessing career opportunities (19, 20).

In the last decade women have started to represent the majority of those who receive advanced academic degrees in Montenegro, including medical degrees (21). As such it is not surprising that the majority of surveyed students were female (72.38%), similar to in studies from Croatia (22), Serbia (23), and Lebanon (24). Several studies have also shown that females are more intrinsically motivated than males (24). However, the difference in motivational factors between genders was not statistically significant in our study, similarly to in Sarkis et al. (12).

Students' motivation tends to change during their medical education. We found the highest score for autonomous motivation was for students in the first year, with the lowest score for the sixth-year students. The second- and fifth-year students had the highest scores for controlled motivation. A higher AM score was found in the final-year students. Our findings are supported by studies conducted in Brazil (25) and Lebanon (12), which showed a higher level of autonomous motivation in the initial semesters of medical school, and higher levels of amotivation in the final semesters.

Finally, significantly higher controlled, EM and external regulation scores were found in students with a medical doctor among their family members, which indicates that they are motivated by rewards and constraints. These results suggest that the most prevalent academic motivations for a career in this group of students were getting better career opportunities, outcomes, and salaries. Moreover, students whose family members were medical professionals had lower IM and higher AM compared to those who did not have a medical doctor in the family. These observations align with observations from a study conducted in Japan (26). Parental higher education and having medical doctors in the family were also motivators for choosing medical studies in Poland (18) and Brazil (27).

Most Montenegrin medical students wish to be employed in the public sector, while 16.2% would like to work abroad. Internal medicine and surgery were the most popular specialties among our students, while only a small proportion of planned to specialize in family medicine and practice medicine in a primary healthcare setting. These findings are comparable to the preferred career plans of students in Serbia (23). In contrast, family medicine was one of the preferred choices among German medical students (28). Our findings highlight that additional efforts from educational institutions, healthcare organizations and policymakers are urgently needed in order to make a career in family medicine more desirable, as a more efficient healthcare system would put more emphasis on primary healthcare.

The strengths of the present study are the use of the cross-culturally validated AMS. This allows comparison of the results presented here with others from the future, or to the results of studies conducted in other countries that used the same questionnaire. More importantly for the contribution of this research is the fact that there has been no similar study examining the academic motivational factors of medical students in Montenegro. The main limitation of the present study is the relatively low number of participants, although it did include more than 50% of all the medical students in the country. Another limitation could be a recall bias, since some students might over- or underestimate their answers to specific questions.

## 5 CONCLUSION

The findings of the present study provide important insights that can enable educators, policymakers, future employers and healthcare institutions to better understand the motivations and perceptions of medical students. This is the first step that will enable them to make meaningful changes in education, designing the curriculum and educational activities that will enhance and maintain autonomous motivation, and improve study outcomes. Teaching methods can improve or weaken medical students' motivation levels. The curriculum must be regularly assessed and evaluated to identify areas for improvement and ensure it meets the desired outcomes. It should be more clinical competency-based and focused on practical education that reinforces the application of the students' knowledge. Amidst the current challenges in policymaking and the organization of work within healthcare institutions, it is imperative to enhance the quality of healthcare and retain our highly skilled young medical professionals. Given the prevailing lack of interest in family medicine, we propose the provision of early and meaningful clinical experience in family medicine settings for medical students. This initiative is a crucial step towards fostering interest and understanding of the

specialty, and addressing the pressing need for more family medicine practitioners in our healthcare system.

## CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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## ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of Montenegro (Approval number: 769/2, Date: 1st of June 2023), and conducted according to the ethical principles of the Declaration of Helsinki.

## AVAILABILITY OF DATA AND MATERIALS

All data and materials used in this study are available upon reasonable request.

## LLM STATEMENT

During the preparation of this work the authors used ChatGPT 3.5 in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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# TOOTH LOSS AND SYSTEMIC DISEASES IN THE SLOVENIAN ELDERLY POPULATION: A CROSS-SECTIONAL STUDY OF THE ASSOCIATION BETWEEN ORAL AND SYSTEMIC HEALTH

## OZOBLENOST STAROSTNIKOV V SLOVENIJI TER NJIHOVE SOČASNE BOLEZNI IN STANJA: PRESEČNA RAZISKAVA SOČASNEGA VPLIVA USTNEGA IN SISTEMSKEGA ZDRAVJA NA IZGUBO ZOB

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### ABSTRACT

**Introduction:** This study aimed to assess the prevalence of edentulism and tooth loss in the Slovenian elderly population, along with the associated risk factors, and investigate the association between systemic and oral health.

### Keywords:

Edentulism  
Elderly population  
Systemic diseases

**Methods:** The study included 445 individuals aged 65 or older (average age: 79.7±8.9 years). Data on preserved teeth, dental history, chronic diseases, and medications were collected through clinical examinations. Height and weight were recorded in order to calculate body mass index (BMI), and the education level was also collected. Chronic systemic diseases and medications were categorized. Statistical analysis was conducted using linear regression and nonparametric tests.

**Results:** Participants had an average of 4.7±7.7 teeth, with no significant gender differences. Higher age ( $\beta = -0.185$ ,  $p < 0.001$ ) and lower education level ( $p < 0.001$ ) were associated with fewer teeth, while higher BMI showed no correlation ( $\beta = -0.085$ ,  $p = 0.325$ ). Diabetes mellitus ( $p = 0.031$ ), cardiovascular diseases ( $p = 0.025$ ), and thyroid diseases ( $p = 0.043$ ) were inversely related to retained teeth. This inverse relationship also applied to individuals who recovered from malignancies, not including head and neck malignancies ( $p = 0.019$ ). No significant relationship was found between osteoporosis and the number of teeth ( $p = 0.573$ ). Notably, antidiabetic drug use was inversely related to the number of teeth ( $p = 0.004$ ), while analgesics showed a positive relationship ( $p = 0.022$ ).

**Conclusions:** This study highlights the association between specific sociodemographic factors, chronic diseases, and retained teeth among elderly individuals in Slovenia. High edentulism rates among the elderly emphasize the need for enhanced preventive measures and risk factor management, particularly for high-risk groups like the elderly.

### IZVLEČEK

**Izhodišče:** Namen študije je bil ugotoviti prevalenco popolne brez zobosti in izgube zob pri starostnikih v Sloveniji, s tem povezane dejavnike tveganja ter raziskati povezavo med sistemskim in oralnim zdravjem.

**Ključne besede:**  
brez zobost  
starostniki  
sistemske bolezni

**Metode:** V raziskavo smo vključili 445 starostnikov, starih povprečno 79,7 ± 8,9 let. Vključitveni kriterij je bil starost 65 let ali več. S pomočjo kliničnega pregleda ustne votline in protokola raziskave smo pridobili podatke o številu ohranjenih zob, zobozdravniški anamnezi, kroničnih boleznih in zdravilih, ki jih jemljejo. Hkrati smo pridobili podatke o njihovi teži in višini za izračun indeksa telesne mase (ITM) ter podatke o stopnji izobrazbe. Kronične sistemske bolezni in zdravila smo razvrstili v smiselne skupine. Statistična analiza je bila opravljena z uporabo linearne regresije in neparametričnih testov (Kruskal-Wallisova enosmerna analiza variance, Mann-Whitneyjev U-test za neodvisne vzorce) za oceno povezav različnih dejavnikov s številom ohranjenih zob v ustni votlini.

**Rezultati:** Povprečno število ohranjenih zob je bilo 4,7 ± 7,7 in se ni bistveno razlikovalo med spoloma. Starost ( $\beta = -0,185$ ,  $p < 0,001$ ) in izobrazba ( $p < 0,001$ ) sta statistično značilno povezana z manjšim številom zob, medtem ko povišan ITM nima vpliva na manjše število zob ( $\beta = -0,085$ ,  $p = 0,325$ ). Z manjšim številom zob je značilno povezana tudi sladkorna bolezen ( $p = 0,031$ ). Tudi kardiovaskularne bolezni ( $p = 0,025$ ) in bolezni ščitnice ( $p = 0,043$ ) so bile značilno povezane z manjšim številom ohranjenih zob, prav tako stanje po preboleli neoplazmi brez področja glave in vratu ( $p = 0,019$ ). Značilne povezave med osteoporozo in manjšim številom zob nismo uspeli dokazati ( $p = 0,573$ ). Ugotovili smo tudi značilno povezavo med antidiabetiki in manjšim številom zob ( $p = 0,004$ ) in zanimivo povezavo med analgetiki ( $p = 0,022$ ) in večjim številom zob.

**Zaključki:** Oralno in splošno zdravje sta medsebojno povezana, saj so določeni sociodemografski dejavniki in nekatere kronične sistemske bolezni povezane z manjšim številom ohranjenih zob. Razvidno je, da je popolna brez zobost med starostniki v Sloveniji še vedno visoka. To nakazuje, da bi bilo potrebno izboljšanje programov preventivnega zobozdravstva za starostnike kot tudi vzajemnega sodelovanja zobozdravnikov in splošnih zdravnikov pri kontroli dejavnikov tveganja.

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## 1 BACKGROUND

The World Health Organization (WHO) recognizes edentulous individuals as physically weakened or disabled because the absence of teeth restricts essential functions such as chewing, eating, and speaking. Edentulism significantly affects self-confidence, self-image, and overall quality of life, and serves as an indicator of oral health (1). This condition predominantly affects individuals aged 65 and older. Data from the Statistical Office reveal that as of January 1, 2021, there were 435,715 elderly individuals living in Slovenia, which constituted approximately one-fifth of the overall population. Women accounted for 57% of that elderly population (2).

The prevalence and incidence of severe tooth loss have consistently declined, particularly in developed countries like Sweden, due to enhanced preventive measures, heightened awareness of oral health, and more efficient dental care practices (3, 4). Despite this decline in prevalence, the number of edentulous individuals continues to rise. In 2002 Douglas projected that, despite a diminishing proportion of the edentulous population, the number of edentulous individuals in the United States would increase by 10% in 30 years (5), which relates to increased life expectancy among the elderly (6).

Various biological and nonbiological factors influence tooth loss. The most common biological causes are caries (tooth decay) and periodontal disease (7, 8). Apart from oral diseases, many sociodemographic and socioeconomic factors, including age, sex, socioeconomic status, education, social class, residency, smoking, lifestyle, dental health behaviour, and access to dental care, contribute significantly to increased tooth loss and subsequent edentulism (3, 9-11). Therefore, oral health promotion and education are vital in mitigating tooth loss (12).

Furthermore, the existing literature has highlighted evidence of a relationship between systemic chronic diseases and tooth loss. Studies have shown that systemic health conditions, such as diabetes mellitus (DM) (13, 14), rheumatoid arthritis (15), osteoporosis (16), neurodegenerative diseases (17, 18), liver diseases (19), hypertension (20), and stroke (21) can impact oral health, potentially leading to issues such as periodontal disease and tooth loss and vice versa. The number of retained teeth is also a predictor of mortality (22, 23). Additionally, medications used for chronic systemic diseases, along with their adverse effects, play an important role in the interplay of these conditions.

This study aimed to assess the prevalence of edentulism and tooth loss in the Slovenian elderly population, as well as the associated risk factors, and investigate the association between systemic and oral health.

## 2 METHODS

The non-randomized cross-sectional study consisted of 445 elderly people over 65. The sample mean age was  $79.7 \pm 8.9$ , ranging from 65 to 102 years. The elderly were divided into three age subgroups: 65-69, 70-74, and over 75. Almost two-thirds (63%) of the study sample were 75 years of age or more, 20% were 70-74, and 17% were 65 to 69. Among the participants, 153 (34%) were male, while 292 (66%) were female. A total of 89 participants were selected from nursing homes (DSO). Specifically, 32 participants were from DSO Tabor, 20 from DSO Bežigrad, 16 from DSO Poljane, 14 from DSO Bokalce, six from DSO Strunjan, and one from DSO Moste. The remaining participants (356) were from the Clinical Department of Maxillofacial and Oral Surgery and Stomatology clinic at the University Clinical Centre of Ljubljana. The required inclusion criterion was age 65 years or older. We did not include immobile patients, patients with memory loss, and individuals incapable of making decisions or expressing their will. Subjects were inhabitants of different rural and urban areas of Slovenia. A letter explaining the purpose of the study and requesting informed consent to participate was handed to every participant. The study protocol was approved by the Medical Ethics Committee of the Republic of Slovenia (0120-173/2021/8). Data was collected from 2016 to 2022.

Data for this study were gathered through a brief oral examination and a questionnaire. Information on the number of retained teeth, basic demographics (name, age, sex), chronic diseases, medications, allergies, tooth loss causes, weight and height for BMI calculation, and education level were collected. Participants' general practitioners provided a list of medications and systemic diseases. Only 250 (56.2%) participants reported the cause of tooth loss. The primary reported reason was periodontal disease (31.7%), followed by caries and caries-related consequences (20.9%). A total of 43.8% of participants either did not mention or did not know the exact cause of tooth loss. Education levels were numerically categorized: 1 = completed primary school, 2 = completed secondary school, 3 = bachelor's degree, master's degree, or PhD. Among 301 participants who reported their level of education, the majority had completed high school (46.5%), whereas only 17.6% of participants had a bachelor's degree, master's degree, or PhD. Based on the clinical examination, the dental status and number of retained teeth were recorded separately for each jaw and the total, as well as the presence and type of dental prosthetic restorations and dental implants. Dental implants, residual roots (radices relicta), and dental prosthetic restorations such as removable prostheses, pontics, and implant-retained prostheses

were not considered as teeth and, therefore, were not included in the tooth count. Data about the type of dental prosthetic restorations and implants was collected solely to determine natural teeth. Teeth with fixed prosthodontic crowns were counted as normal teeth and included in the study. The dentate group included all subjects with at least one tooth in the upper or lower jaw. The criterion of fully preserved dentition was the presence of all 28 teeth in the upper and lower jaws, excluding wisdom teeth. All participants (edentulous and dentate) were included in calculating the average number of teeth.

Chronic systemic diseases were arranged into ten logical groups: DM, cardiovascular diseases (CVDs), respiratory diseases, rheumatic diseases, recovered after oncologic treatment (excluding the head and neck area), neurologic diseases, psychiatric conditions, thyroid diseases, prostate diseases, and osteoporosis. Medications were arranged into groups following the ATC classification (Anatomical Therapeutic Chemical classification).

IBM SPSS Statistics, version 18 (IBM Corporation, Armonk, USA) was used for statistical data analysis. First, we performed a descriptive analysis of the sample. The distribution of the observed variables, especially the number of teeth, was not normal, so we used nonparametric tests in the further analyses. Using the Mann-Whitney U test for independent samples, we

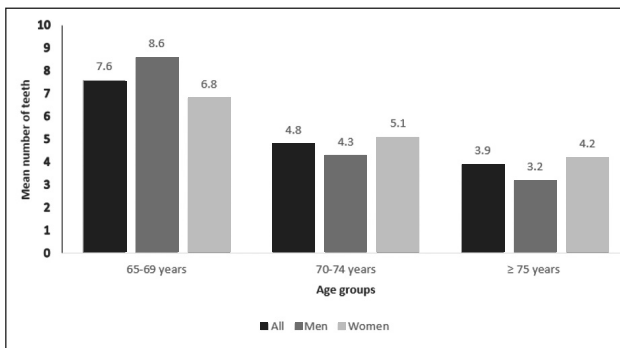


Figure 1. The mean number of teeth by age group and sex.

checked the differences in the number of teeth between people who have a particular disease or take a specific medication, and people who do not have the condition or do not take this medication. Using the Kruskal-Wallis one-way analysis of variance, we checked the influence of the categorical variables of sex and education on the number of teeth. We used linear regression to check the influence of the independent numerical variables (BMI, age, number of medications) on the dependent variable (number of teeth). The statistical significance level was set at  $p \leq 0.05$ .

### 3 RESULTS

#### 3.1 Number of teeth, sex, education level, and BMI

The mean number of retained teeth in our population was  $4.7 \pm 7.7$ . Specifically, men had an average of  $4.6 \pm 7.3$  teeth, while women had an average of  $4.7 \pm 7.9$  teeth. The number of teeth decreased over the years, from 7.6 among those aged 65 to 69 to an average of only 3.9 teeth in persons 75 or older (Figure 1).

The regression analysis revealed that age significantly influenced the number of teeth ( $\beta = -0.185$ ,  $p < 0.001$ ). The negative coefficient  $\beta$  indicates that older age is associated with a lower number of teeth.

As illustrated in Table 1, the upper jaw had, on average, 2.1 teeth, while the lower jaw had, on average, 2.6 teeth.

Among only dentate elderly people, the mean number of teeth was  $5.5 \pm 4.6$  in the upper jaw and  $6.6 \pm 4.4$  in the lower jaw.

Gender-based differences in tooth distribution were not statistically significant. Tooth loss increased over the years in both sexes (Figure 1), with men exhibiting a slightly higher average tooth loss (5.4 teeth) compared to women (2.6 teeth). However, this difference was statistically nonsignificant ( $p\text{-value} = 0.783$ ).

Among the participants, 273 (61%) were completely edentulous, with none meeting the criterion of fully preserved dentition (all 28 teeth in the upper and lower jaws, excluding wisdom teeth). In the age group of 65-69, 33 participants (46%) were completely edentulous. Among

Table 1. Mean number of teeth in both arches across age groups.

Scale	UPPER ARCH				LOWER ARCH			
	65-69 years	70-74 years	>75 years	All	65-69 years	70-74 years	>75 years	All
Men	3.2 (4.2)	2.0 (4.1)	1.4 (2.8)	1.9 (3.5)	5.4 (5.6)	2.3 (4.0)	1.9 (3.6)	2.7 (4.3)
Women	3.0 (4.7)	2.5 (4.0)	2.0 (4.0)	2.3 (4.1)	3.8 (4.7)	2.6 (4.3)	2.2 (4.0)	2.5 (4.2)
All	3.1 (4.5)	2.3 (4.0)	1.8 (3.7)	2.1 (3.9)	4.4 (5.1)	2.5 (4.2)	2.1 (3.9)	2.6 (4.2)

Legend: Numbers in parentheses represent the standard deviations for each corresponding value.

those aged 70-74, 56 participants (61%) were completely edentulous. For those aged 75 years or older, the number of completely edentulous participants was 184 (66%).

A total of 141 (31.7%) participants reported periodontal disease as the primary cause of tooth loss. Caries and caries-related consequences, reported by 93 (20.9%) participants, were the second most common cause, followed by head and neck cancer treatment, reported by 11 (2.5%) participants, and traumatic injuries, reported by five (1.1%) participants. One hundred and ninety-five (43.8%) participants either did not state the primary cause of tooth loss or were unaware of it.

Table 2 shows the distribution of elderly individuals and the mean number of teeth based on education level. A statistically significant association was observed, indicating that individuals with lower educational levels had fewer retained teeth ( $p$ -value<0.001). Specifically, those who completed elementary school had, on average, 2.9 times fewer retained teeth compared to those with a bachelor's degree, master's degree, or PhD.

**Table 2.** Number of subjects and mean number of teeth by education level (n=301).

Education level	1	2	3
n	108	140	53
Mean number of teeth	2.9	5.2	8.5

Legend: 1 = primary school education, 2 = secondary school education, 3 = bachelor's degree, master's degree, PhD; n represents sample size.

The mean BMI was 26.9, ranging from 16.6 to 40.0 (Table 3). However, as an independent variable, BMI did not significantly influence the number of retained teeth ( $\beta$ = -0.085,  $p$ =0.325). The influence was also independent of sex, with  $p$ -values of 0.717 ( $\beta$ = -0.055) for men and 0.307 ( $\beta$ = -0.109) for women.

**Table 3.** Mean age, BMI, and number of medications in the studied population with linear regression results.

	All (n=445)		All (n=445)		Men (n=153)	
	Mean (SD)	Beta coef. (sig.)*	Mean (SD)	Beta coef. (sig.)*	Mean (SD)	Beta coef. (sig.)*
Age [years]	79.7 (8.9)	-0.185 ( $p$ <0.001)	77.7 (8.1)	-0.312 ( $p$ <0.001)	80.7 (9.1)	-0.134 ( $p$ =0.11)
BMI [kg/m <sup>2</sup> ]	26.9 (4.2)	-0.085 ( $p$ =0.325)	27.2 (3.9)	-0.055 ( $p$ =0.717)	26.8 (4.3)	-0.109 ( $p$ =0.307)
Number of medications	3.9 (3.8)	0.163 ( $p$ =0.116)	3.2 (2.9)	0.205 ( $p$ =0.332)	4.4 (4.0)	0.140 ( $p$ =0.250)

Legend: SD stands for standard deviation; n represents sample size; \* results of the linear regression model (beta coefficient and significance) with teeth number as a dependent variable

### 3.2 The correlation between chronic diseases and the number of teeth

A total of 376 participants (84.5%) reported having at least one chronic disease and regularly taking medication. The prevalent chronic diseases were CVDs (73.3% of the elderly), followed by DM (18.4%). A significant relationship was found between a smaller number of retained teeth and DM ( $p$ =0.031), CVDs ( $p$ =0.025), thyroid diseases ( $p$ =0.043), and people after oncologic treatment, excluding head and neck malignancies ( $p$ =0.019). Tables 4 and 5 show data and  $p$ -values for specific disease groups.

**Table 4.** Distribution of the elderly with specific diseases and mean number of teeth, stratified by sex.

	Total (n=445)			Men (n=153)			Women (n=292)		
	n/%	Number of edentulous	Mean number of teeth	n/%	Number of edentulous	Mean number of teeth	n/%	Number of edentulous	Mean number of teeth
DM	82/18	60	3.6 (7.2)	29/19	22	2.6 (6.0)	53/18	38	4.1 (7.8)
CVD	327/73	210	4.2 (7.4)	114/75	69	4.1 (6.6)	213/73	141	4.3 (7.8)
Respiratory diseases	42/9	22	4.7 (7.2)	14/9	9	2.7 (5.0)	28/10	13	5.7 (8.0)
Rheumatic diseases	32/7	16	4.0 (6.0)	6/4	1	9.5 (7.4)	26/9	15	2.8 (4.9)
Post oncologic treatment	40/9	32	2.7 (6.3)	12/8	8	3.7 (6.8)	28/10	24	2.3 (6.2)
Neurologic diseases	42/9	24	4.4 (7.8)	9/6	6	2.4 (4.2)	33/11	18	4.9 (8.5)
Psychiatric diseases	57/13	35	5.0 (8.0)	8/5	4	5.5 (7.2)	49/17	31	4.9 (8.2)
Thyroid diseases	60/13	44	3.0(6.1)	5/3	3	5.2 (7.4)	55/19	41	2.9 (6.0)
Prostate diseases	42/9	27	3.6 (6.1)	42/27	27	3.6 (6.0)	/	/	/
Osteoporosis	67/15	43	4.2 (7.2)	1/<1	0	14	66/23	43	4.0 (7.2)

Numbers in parentheses represent the standard deviations for each corresponding value; n represents sample size.

We checked the statistical significance of osteoporosis and thyroid diseases separately for females, and for prostate diseases we assessed only males. Women with osteoporosis did not show a statistically significant inverse relationship with the number of teeth ( $p$ -value=0.494), and the same was true for men with prostate diseases ( $p$ -value=0.209). On the other hand, women with thyroid diseases had a significantly lower number of teeth ( $p$ -value=0.033).

### 3.3 The correlation between the number of medications and the number of teeth

There were 69 (16%) elderly patients without any medications. The overall mean medication count was 3.9, significantly increasing with age ( $p$ -value<0.001). However, the total number of medications did not significantly influence the number of teeth ( $\beta$ =0.163,  $p$ =0.116). Only two medication groups showed a significant association

**Table 5.** Number of subjects and mean number of teeth by education level (n=301).

Education level		N (%)	Mean age	Mean number of teeth	Number of edentulous	p-value
DM	0	363 (82)	79.9	4.9		<b>0.031</b>
	1	82 (18)	78.7	3.6	60	
CVD	0	118 (27)	77.6	6.0		<b>0.025</b>
	1	327 (73)	80.4	4.2	210	
Respiratory diseases	0	403 (28)	79.4	4.7		0.407
	1	42 (9)	81.9	4.7	22	
Rheumatic diseases	0	413 (93)	79.4	4.7		0.515
	1	32 (7)	83.3	4.0	16	
Post oncologic treatment	0	405 (91)	79.7	4.9		<b>0.019</b>
	1	40 (9)	79.1	2.7	32	
Neurologic diseases	0	403 (91)	79.2	4.7		0.800
	1	42 (9)	84.7	4.4	24	
Psychiatric diseases	0	388 (87)	79.2	4.6		0.886
	1	57 (13)	83.2	5.0	35	
Thyroid diseases	0	385 (87)	79.6	4.9		<b>0.043</b>
	1	60 (13)	80.0	3.1	44	
Prostate diseases	0	403 (91)	79.5	4.8		0.513
	1	42 (9)	81.0	3.6	27	
Osteoporosis	0	378 (85)	78.7	4.8		0.573
	1	67 (15)	85.0	4.2	43	

Legend: The presence of a medical condition is indicated by a value of 1, while the absence of a medical condition is indicated by a value of 0; bold text indicates statistically significant p-values; n represents sample size.



with the number of teeth (Table 6). The first group, antidiabetic medications (p-value=0.004), was associated with a lower number of retained teeth. Conversely, the second group, analgesic medications (p-value=0.022), showed a positive association, suggesting that individuals regularly taking analgesics had more teeth than those without such therapy.

#### 4 DISCUSSION

The mean number of teeth among the elderly in our study was low at  $4.7 \pm 7.7$ , with a high prevalence of edentulism at 61.2%. The primary reported cause of tooth loss was periodontal disease and caries-related consequences, though self-reported data may lack accuracy. In 1990, Vrbič reported a 29.3% edentulism rate in Slovenia for individuals aged 65-74 years and 51.6% for those aged 75 years or more (24). It was estimated in 2016 that the prevalence of edentulism would decrease to 19.2% by 2020 in Slovenia (25), though Artnik reported an even lower prevalence in 2019, which stood at 12% for the age

**Table 6.** Comparison of mean age and mean number of teeth between two groups with p-values.

Education level		n/(%)	Mean age	Mean number of teeth	p-value
Insulins	0	427	79.7	4.5	0.056
	1	18	80.1	8.6	
Antidiabetics	0	389	79.8	5.0	<b>0.004</b>
	1	56	78.5	2.7	
Antihypertensives	0	206	78.1	5.0	0.322
	1	239	81.0	4.4	
Diuretics	0	377	78.9	4.6	0.600
	1	68	83.7	5.2	
Statins	0	309	79.6	4.2	0.067
	1	136	79.9	5.8	
Cardiac therapy drugs	0	299	78.4	4.9	0.294
	1	146	82.4	4.3	
Antiresorptives	0	407	79.4	4.7	0.861
	1	38	83.1	4.0	
Chemotherapeutics	0	435	79.8	4.8	0.174
	1	10	76.1	1.3	
Immunosuppressives	0	435	79.6	4.6	0.777
	1	10	82.3	5.9	
Adrenergics	0	418	79.6	4.7	0.920
	1	27	80.2	4.4	
Antithrombotics	0	383	79.1	4.7	0.955
	1	62	83.5	4.8	
Psychoanaleptics	0	401	79.3	4.6	0.717
	1	44	83.4	5.1	
Analgesics	0	375	78.6	4.4	<b>0.022</b>
	1	70	85.3	6.3	
Anticonvulsants	0	426	79.5	4.6	0.327
	1	19	82.6	5.4	
Psycholeptics	0	387	78.6	4.7	0.504
	1	58	86.6	4.3	
Other nervous system drugs	0	436	79.6	4.6	0.594
	1	9	83.2	6.6	
Drugs used in benign prostatic hypertrophy	0	412	79.5	4.8	0.303
	1	33	82.1	3.5	
Thyroid therapy drugs	0	402	79.6	4.8	0.123
	1	43	80.5	3.3	

Legend: 0 represents those not taking medication, and 1 represents those receiving medication; bold text indicates statistically significant p-values.

group 65-74 years (26). For better epidemiologic reliability and representativeness, we calculated the prevalence of edentulism without 100 subjects who came to the Centre for Removable Prosthodontics solely for rehabilitation with total dentures. Even after excluding these subjects, the prevalence of edentulism was high at 50%, aligning with Vrbic's earlier findings. The calculation was done to emphasize that the prevalence remains high and has not improved much over the last 30 years. Notably, the exclusion of participants over 74 years old in the 2019 study, constituting almost two-thirds of our subjects, could contribute to a significant difference in edentulism prevalence. Nursing home residents, known to have poorer oral health, also represented a substantial proportion of the participants (20%). Therefore, in order to achieve a more representative prevalence, elderly participants should be selected blindly from across Slovenia.

In comparison, Sweden and Finland have much lower rates of complete edentulism among elderly individuals (aged 65 or more): 20.6% and 34.9%, respectively (4). In 2014, Germany reported a 12.4% prevalence of complete edentulism among individuals aged 65-74, 28.9% for those aged 75-84, and 44.8% for those over 85 (27). This highlights Slovenia's higher prevalence of edentulism compared to European countries like Sweden and Germany.

As expected, the number of teeth in the oral cavity significantly declines with age. This reflects the broader physiological changes occurring in the body over time, which are also reflected in the periodontal tissues and the number of preserved teeth. Schiffner et al. (28) found more inflammation of the periodontal tissues and more dental plaque in dentate elderly people than in adults; therefore, periodontal disease and caries, as the leading causes of tooth loss, are expressed to a greater extent in elderly individuals.

We did not find a relationship between sex and the number of teeth, which is supported by the results of previous studies (4, 29, 30). In contrast to our findings, the results of some studies indicated greater tooth loss and a higher prevalence of edentulism in women (1, 9, 10), mainly due to biological characteristics of sex (e.g., hormonal changes, pregnancy, greater susceptibility to caries) (31). Regardless, historical differences seem to be disappearing, possibly due to women's more equal socioeconomic status.

Consistent with other studies, a higher level of education was associated with a greater number of teeth in the oral cavity (32), likely influenced by better oral health knowledge and hygiene habits and more frequent dental practice visits (33).

Unexpectedly, increased BMI was not associated with a lower number of teeth. While obesity or high BMI may impact the number of teeth in younger people, in older

people factors such as the ageing process, socioeconomic status, and lifestyle habits appear to play a more dominant role than actual BMI (34). Notably, a substantial portion of our study population had a BMI exceeding 24.9 kg/m<sup>2</sup>, indicating elevated body weight, with almost half falling into the overweight category (BMI: 24.9-29.9 kg/m<sup>2</sup>). This distribution may influence our findings, especially considering previous studies suggesting a reciprocal relationship between fewer teeth and obesity (21, 35). It has also been reported that BMI can be a valuable tool for predicting poor oral hygiene habits in diabetic patients, and thereby possible oral health issues in this population (36).

DM was significantly associated with a lower number of teeth. DM acts through the progression of periodontal disease. The bidirectional relationship between diabetes mellitus and periodontal disease has already been studied in detail. Our findings are supported by those of Patel et al. (37), who claimed that patients with diabetes are more susceptible to complete edentulism. While we did not differentiate between diabetes types, further research is needed to clarify how each type affects the number of teeth.

Moreover, CVDs were significantly associated with a lower number of teeth, but the existing literature lacks evidence supporting the influence of CVDs on increased tooth loss. Our analysis did not differentiate between cause and effect, and therefore we can assume that, in this case, a smaller number of teeth influences the greater expression of CVDs. The literature mentions associations between tooth loss and increased risk of hypertension (20), coronary heart disease (38), peripheral arterial disease (39), and myocardial infarction (40). Although our results suggest that CVDs negatively influence the number of teeth, further studies are needed to answer this question.

Furthermore, our study observed significant associations between the prevalence of thyroid diseases, and post-oncologic treatment, excluding head and neck malignancies. Given that thyroid hormones have a proven influence on bone metabolism (41), disturbances in hormone secretion could influence the quantity and quality of alveolar bone and, consequently, tooth loss (42). The interpretation of the inverse association between past neoplasm treatment and the number of teeth is difficult due to the diverse nature of the assessed group, which included elderly individuals who had recovered from neoplasms of various origins and treatment methods, but excluded elderly people with head and neck tumours. Therefore, it is difficult to determine the mechanism behind this relationship from these criteria alone. No statistically significant associations existed between the number of teeth and the remaining systemic disease groups.

Since elderly individuals are exposed to more medications, we assessed their potential impact on tooth number. Antidiabetic drug use was inversely associated with tooth number, likely reflecting the influence of diabetes mellitus. Conversely, regular analgesic therapy was positively linked to a higher number of teeth, suggesting a potential protective effect on tooth loss. The anti-inflammatory properties of certain analgesics, like paracetamol and NSAIDs (43), may contribute to this protective effect on teeth and periodontal tissues.

Oral health significantly impacts overall well-being and quality of life, and has a broader impact beyond clinical signs and symptoms (44). Poor oral health not only contributes to systemic conditions, but is also influenced by diseases and medications, potentially resulting in tooth loss. Unfortunately, oral health is often neglected in elderly care, leading to undiagnosed conditions. To address this, increased awareness, education, and integration of oral health into elderly care plans are essential, as well as promoting better communication between dentists and general practitioners for holistic healthcare.

The key strengths of our study include a large sample size, which provides strong evidence. A comprehensive assessment of medication use and systemic diseases provides valuable insights into potential associations with tooth loss, contributing to a deeper understanding of the association between oral and systemic health.

This study has certain limitations related to the representativeness of the sample, potentially affecting the generalizability of the findings to the broader elderly population in Slovenia. Factors like a higher proportion of female participants and fully edentulous individuals could impact the generalizability of the results. The nonrandomized recruitment process may have introduced a selection bias and thus also limited the generalizability of the findings. The involvement of the Statistical Office of Slovenia and a blinded selection process for recruiting representative individuals are recommended to enhance the reliability of any future research. Additionally, the cross-sectional design of the current study limited our ability to establish causal relationships between the variables of interest, and longitudinal studies would provide more robust evidence in this regard.

Self-reporting introduces a potential recall bias, impacting data accuracy on dental history and the cause of tooth loss, which could affect the validity of the observed associations. The study also lacks consideration of factors like oral hygiene, smoking, socioeconomic status, and dental care access, which could influence the relationships observed between the variables. Addressing these limitations in future research is thus essential for a stronger evidence base on the relationship between the number of teeth and systemic diseases.

## 5 CONCLUSIONS

The findings of this study highlight that certain socioeconomic factors and chronic systemic diseases are strongly associated with the number of retained teeth among the elderly in Slovenia, and that edentulism remains high among this population. This suggests more attention needs to be paid to at-risk groups, like the elderly, to improve preventive measures and minimize the impact of risk factors on oral health. Improved awareness among general practitioners regarding the interconnection between general and oral health is also vital to encourage better cooperation with dentists and the promotion of overall well-being.

## CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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The study received no funding.

## ETHICAL APPROVAL

Ethical approval to conduct the study was obtained from the National Medical Ethics Committee of the Republic of Slovenia (NMEC), No. 0120-173/2021/8.

## CONSENT TO PARTICIPATE

Written informed consent to participate in the research was obtained from all respondents prior to data collection.

## AVAILABILITY OF DATA AND MATERIALS

All data and materials used in this study were collected from publicly available sources and are available upon reasonable request.

## AUTHORS' CONTRIBUTIONS

JBŽ: conceptualization, collected and analysed data, drafted the manuscript; NIH: conceptualization, supervised the study, assisted with data collection, reviewed, and edited the manuscript; MV: conceptualization, performed statistical analysis, reviewed, and edited the manuscript; ZS: conceptualization, supervised the study, assisted with data collection and analysis. All authors read and approved the final manuscript.

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# THE PREVALENCE OF SELF-REPORTED SYSTEMIC ALLERGIC REACTION TO HYMENOPTERA VENOM IN BEEKEEPERS WORLDWIDE: A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

## OCENA GLOBALNE PREVALENCE SAMOPOROČANE SISTEMSKA ALERGIJSKE REAKCIJE ZA STRUP KOŽEKRIKCEV PRI ČEBELARJIH: SISTEMATIČNI PREGLED LITERATURE IN META-ANALIZA

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### ABSTRACT

#### Keywords:

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Beekeeping

**Background:** Beekeepers represent a high-allergic risk population group due to their unavoidable seasonal or persistent exposure to the elicitors of *Hymenoptera* venom allergy, bees in particular. A systematic literature review and meta-analysis aimed to estimate the prevalence of self-reported systemic allergic reaction to *Hymenoptera* venom among beekeepers worldwide.

**Methods:** We rigorously reviewed and conducted meta-analysis on observational studies retrieved from seven electronic databases (MEDLINE via PubMed, Web of Science Core Collection, Scopus, Academic Search Complete, ScienceDirect, Cumulative Index to Nursing and Allied Health Literature, Zoological Record), spanning data from inception to August 1, 2023. The Joanna Briggs Institute Prevalence Critical Appraisal Tool was employed to assess the risk of bias. A meta-analysis was conducted to synthesize evidence.

**Results:** Out of 468 studies, eight original articles met the inclusion criteria. The estimated overall lifetime and one-year prevalence of self-reported systemic allergic reaction to bee venom were 23.7% (95% CI: 7.7-53.4) and 7.3% (95% CI: 5.8-9.2), respectively. The estimated lifetime prevalence of self-reported systemic allergic reaction to bee venom for grades III-IV (severe systemic allergic reaction) was 6.0% (95% CI: 3.0-11.7). In general, substantial heterogeneity and a high risk of bias were observed across the majority of studies. The impact of geographical location and climate differences on the estimated lifetime prevalence is suggestive for severe systemic allergic reaction.

**Conclusions:** Future observational cross-sectional studies should employ rigorous study designs, using validated questionnaires, and thoroughly report the observed health outcomes, verified by physicians.

### IZVLEČEK

#### Ključne besede:

javno zdravje  
preobčutljivost  
prevalenca  
čebelarjenje

**Uvod:** Izpostavljenost ponavljajočim se pikom kožekrilcev (čebele, ose, čmrlji) je glavni okoljski dejavnik tveganja za razvoj alergijske reakcije. Čebelarji sodijo med ogrožene populacijske skupine, saj je sezonska ali celoletna izpostavljenost pikom kožekrilcev (zlasti čebelam) pomembno večja v primerjavi s splošno odraslo populacijo. Namen sistematičnega pregleda literature in meta-analize je oceniti globalno prevalenco samoporočane sistemske alergijske reakcije za strup kožekrilcev med čebelarji.

**Metode:** Časovno okno pregleda je segalo od prvih objav na področju opazovanja do 1. avgusta 2023. Iskanje virov je potekalo v sedmih elektronskih podatkovnih zbirkah (MEDLINE z iskalnim sistemom PubMed, Web of Science Core Collection, Scopus, Academic Search Complete, ScienceDirect, Cumulative Index to Nursing and Allied Health Literature, Zoological Record). V analizo so bile vključene epidemiološke opazovalne raziskave v vseh tujih jezikih. Za oceno tveganja pristranosti je bilo uporabljeno orodje za kritično vrednotenje raziskav o prevalenci Inštituta Joanne Briggs. Meta-analiza je bila izvedena v programskem okolju R (paket »meta«), pri čemer je bil uporabljen model naključnih učinkov.

**Rezultati:** Od 468 zadetkov je bilo v končno analizo vključenih 8 izvirnih znanstvenih člankov, ki so ustrezali vključitvenim kriterijem. Ocenjena globalna vseživljenjska in enoletna prevalenca samoporočanih sistemskih alergijskih reakcij po piku čebele je bila 23,7 % (95-% IZ: 7,7-53,4) in 7,3 % (95-% IZ: 5,8-9,2). Ocenjena globalna vseživljenjska prevalenca samoporočanih sistemskih alergijskih reakcij po piku čebele za razrede III-IV (težka sistemska alergijska reakcija) je bila 6,0 % (95-% IZ: 3,0-11,7). Vključene raziskave so bile heterogene z visokim tveganjem za pristranost. Vpliv geografske lege in podnebni razlik na ocenjeno globalno vseživljenjsko prevalenco je bil nakazan za težko sistemska alergijsko reakcijo.

**Zaključki:** Pri načrtovanju epidemioloških presečnih raziskav s področja opazovanja bi bilo potrebno uporabiti veljavna orodja in izboljšati kakovost navajanja podatkov, relevantnih za opazovani zdravstveni izid. Objektivizacija sistemske alergijske reakcije po piku čebele s strani specialista alergologa bi pomenila nadgradnjo in s tem klinično uporabno vrednost zbranih podatkov.

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## 1 INTRODUCTION

*Hymenoptera*, including bees, wasps, ants and sawflies, comprises over 150,000 described species (1). Widely distributed across terrestrial ecosystems (2), this insect order is among the most species-rich and abundant, (3), playing crucial roles as pollinators, herbivores, and natural enemies within ecosystems (2). Despite their ecological significance, direct interactions with humans - often prompted by perceived threats from human activities or competition for food (4) - pose a risk of stinging and venom injection. The likelihood of encountering a specific stinging insect can vary depending on geographical, environmental, and ecological factors in the living environment, as well as the types of activities individuals engage in (5, 6).

In most healthy individuals without *Hymenoptera* venom allergy (HVA), a sting typically results in a well-tolerated, albeit temporarily painful local reaction, characterized by swelling, redness, and itching (7), usually resolving on its own within 24 to 48 hours (8). Conversely, for those sensitized to *Hymenoptera* venom, symptomatic allergic reaction (AR) may occur, with large local reaction (LLR) and systemic allergic reaction (SAR) as the most frequent clinical patterns. Medically important species capable of stinging and causing HVA belong to the *Apidae*, *Vespidae*, and *Formicidae* families (9).

*Hymenopteras* are also a leading cause of occupational anaphylaxis due to the heightened risk associated with exposure to repeated stings, a key factor in the development of AR (6). In terms of exposure intensity, certain population groups, particularly those in outdoor professions and specific occupational settings (6), face increased vulnerability to HVA. Beekeepers, in particular, face a specific risk (10), and epidemiological review findings have consistently reported higher estimated (self-reported) prevalence rates of SAR to bee venom in beekeepers (14%-30% (10); 4%-26% (11)) compared to the general population, affecting up to 3.3% of adults in the USA (12) and 8.9% in Europe (13).

However, none of the existing reviews (10, 11) systematically assessed observational studies among beekeepers worldwide, addressing the epidemiology of SAR to *Hymenoptera* venom. This study aims to fill this gap by conducting the first comprehensive systematic literature review and meta-analysis with the following objectives: 1) to assess the estimated prevalence of self-reported SAR to *Hymenoptera* venom in beekeepers worldwide, and 2) to explore whether geographical location and climate differences affect the estimated self-reported prevalence. Aligning with the observed population, we focused on the most common culprits of HVA among beekeepers (bee, wasp, hornet). In addition, our research specifically focuses on one species of bee,

the honeybee (*Apis mellifera*), rather than bees in general, hereinafter referred to as the "bee".

## 2 METHODS

A comprehensive systematic literature review and meta-analysis were performed following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (14). The study protocol was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42021260922 and is described elsewhere (15).

### 2.1 Eligibility criteria

We included questionnaire-based observational (cohort, cross-sectional) studies, assessing the estimated prevalence of self-reported SAR to *Hymenoptera* (bee, wasp, hornet) or *Hymenoptera* venom among beekeepers of any age, engaged in beekeeping activities. There were no language restrictions, and translations were performed when necessary for literature in languages other than English.

Exclusion criteria comprised studies assessing reactions other than self-reported SAR to *Hymenoptera* venom (e.g., LLR, systemic toxic reaction) or those investigating other causes of SAR. We excluded meta-analysis, (systematic) literature reviews, clinical and qualitative studies, case reports/case series, experimental ex vivo/in vivo studies, articles reporting editorials/comments/opinions and other types of papers that did not report original research data, conference abstracts, articles not related to the systematic literature review and studies not available in a full form.

### 2.2 Information sources and search strategy

A systematic electronic literature search was carried out by two reviewers (TC, AK) across seven databases: MEDLINE via PubMed, Web of Science Core Collection, Scopus, Academic Search Complete (EBSCO host), ScienceDirect, Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO host), and Zoological Record (Web of Science). The search spanned from their inception up to August 3, 2021, and was subsequently repeated between July 11, 2022, and finalized on August 1, 2023. The search strategy, employing two search terms ("hypersensitivity" AND "beekeeping"), was reviewed by an experienced librarian and initially formulated in MEDLINE via PubMed, with subsequent adaptation for use in other electronic databases (data available on request). Manual search of the reference lists was conducted to identify any relevant publications that might have been missed in the electronic search.

### 2.3 Selection process

The search results underwent initial screening for duplicate removal and record management using the Zotero reference manager, either automatically or through manual upload. The selection process, encompassing title and/or abstract screening, as well as a full-text review based on the eligibility criteria, was independently conducted by two reviewers (TC, AK). When necessary, a third reviewer (IL) was consulted.

### 2.4 Data collection process and data items

Prior to final data tabulation, a pre-designed data extraction form in Excel was prepared. Two independent reviewers (TC, AK) manually extracted the following data of interest: study characteristics (first author; year of publication; location, study design, aim); observed population characteristics (sample size, age, gender); observed health outcome, method of data collection and statistical analysis. The observed health outcome was defined as the estimated lifetime ( $\geq 10$  years) and/or one-year prevalence of self-reported SAR to *Hymenoptera* venom, with grading of the severity of clinical symptoms according to the classification, whenever possible. Prevalence of self-reported SAR was defined as the number of beekeepers who reported at least one SAR within a certain time period (lifetime or one-year). In cases where the information was unclear or missing, several efforts were made to contact the authors of the original articles, and the data were updated accordingly.

### 2.5 Study risk of bias assessment

The quality assessment of the included studies was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (16) (data available on request).

### 2.6 Data synthesis

The meta-analysis of the prevalence data and forest plot construction were performed under the R statistical environment (version 4.3.1), utilizing the function `metaprop` within the “meta” package. Due to expected high heterogeneity, the random effect model was applied and the restricted maximum-likelihood estimator (REML) was used for calculating between-study variance ( $\tau^2$ ). Overall prevalence was calculated using the logit transformation. Confidence intervals of prevalence for individual studies were calculated based on exact binominal intervals.

## 3 RESULTS

### 3.1 Study selection

The initial database search yielded a total of 468 publications. After removing duplicates ( $n=235$ ) and conducting screening based on titles and/or abstracts ( $n=233$ ), we identified eight articles that met the criteria for full-text assessment. All of these (17-24) were eligible for inclusion and no additional studies from the reference lists were added. The PRISMA 2020 flow diagram (Figure 1) outlines the selection process.

### 3.2 Study characteristics

The majority of the included studies ( $n=5$ ) were conducted outside Europe, with four in Turkey (18, 22-24) and one in Mexico (21) (Table 1). There was one study each from Northern (Finland) (17), Central (Germany) (19) and Western Europe (Great Britain) (20). The studies were published between 1996 and 2020, and the majority were published after the year 2000 (18-24).

The primary objectives of the studies were to assess the prevalence and types of HVA, specifically stinging *Hymenoptera*-induced SAR (17, 18, 22-24). In two studies (18, 19), the authors initially reported estimating the incidence of bee venom allergies. However, after a detailed text analysis and consensus with reviewers (TC, AK, IL), it became evident that these two studies were also assessing the prevalence of HVA. Therefore, we categorize them as prevalence studies. All studies included beekeepers (17-24) and one study used food-service staff from a restaurant as an occupational control group (24). The sample size of the studies varied substantially, ranging from 69 (24) to 1,541 (21), with a mean (standard deviation) age from  $48.2 \pm 11.5$  (18) to  $61.8 \pm 13.9$  years (19), and with 4,025 men out a total of 5,473 participants.

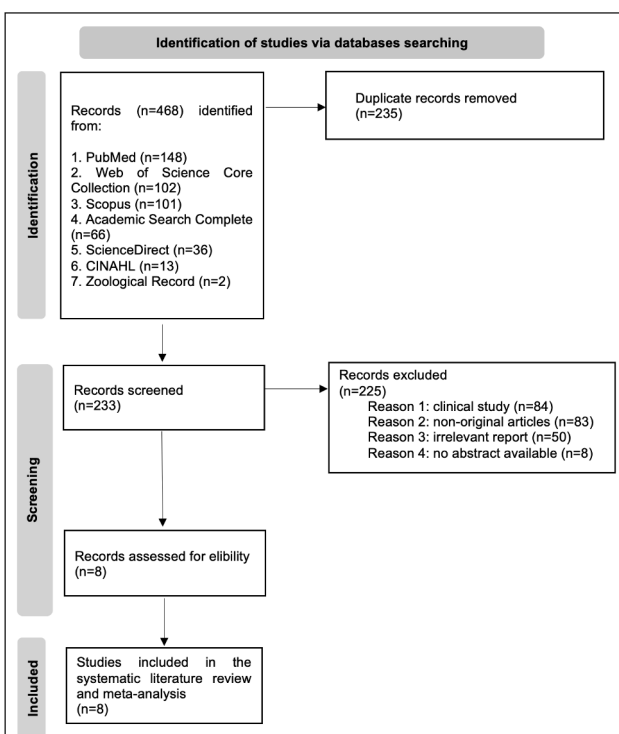


Figure 1. PRISMA 2020 flow diagram of the study selection process.



Table 1. Key items of the self-reported observed health outcome.

	Country	Sample size (N)	Male	Age, years (mean, SD)	1-year	≥10 years	Classification of systemic allergic reaction	Culprit <i>Hymenoptera</i>
Annala et al., 1996 (17)	Finland	191	164	51.8±12.3	✓	✓	Müller	bee wasp ( <i>Vespula</i> spp.)
Celikel et al., 2006 (18)	Turkey	1245	489	48.2±11.5			NA	bee
Münstedt et al., 2008 (19)	Germany	1053	973	61.8±13.9	✓	✓	Müller	bee
Richter et al., 2011 (20)	Great Britain	852	545	range 51-60		✓	modified Müller	bee
Becerril-Ángeles et al., 2013* (21)	Mexico	1541	1289	average 37		✓	Müller	bee
Çeliksoy et al., 2014* (22)	Turkey	301	295	48.2±11.5			Müller	bee
Ediger et al., 2018 (23)	Turkey	221	213	49.9±11.8	✓	✓	Ring-Messmer	bee
Demirkale et al., 2020 (24)	Turkey	69	57	48.4±12.0		✓	NA	bee

Legend: N=number of participants; NA=not available; SD=standard deviation

a:\*additional data gathered upon request

b: ✓ indicates the observed measure(s) of occurrence

Epidemiological data were collected using questionnaires, distributed through various methods, (sending by mail (17, 21), being included in selected journals and sent to subscribers, or made available in electronic form on the internet (19), or only in electronic form (20)). In one study, printed questionnaires were completed during a beekeeping congress meeting under the supervision of the researchers (24). In a few studies how the questionnaires were distributed was not clearly specified (18, 22, 23). Survey response rates varied widely, ranging from as low as 3.0% (19) to 79.6% (17).

Except for three studies (17, 18, 22), the prevalence period for the estimated lifetime self-reported SAR to *Hymenoptera* venom remained unclear, and an assumption was made according to the sociodemographic data (mean age, duration of beekeeping). In most cases, SAR was graded according to the Müller classification (17, 19, 20-22), and bees were the most frequently reported culprit (17-24). A comprehensive summary of the main study characteristics is available on request.

### 3.3 Methodological quality

A summary of the RoB assessments for each study is available on request. None of the studies met all 10 evaluation points for quality assessment, with more than half (n=5) exhibiting a high RoB. Measurements of the outcome (Q7.1 and Q7.2) and the statistical analysis (Q8) applied to a high RoB in most cases.

### 3.4 Meta-analysis results

The estimated overall lifetime prevalence of self-reported SAR to bee venom, graded for severity according to different classification systems, was 23.7% (95% CI: 7.7-53.4). A substantial level of heterogeneity was observed among the studies ( $I^2=99%$ ,  $p<0.01$ , Figure 2A). The estimated lifetime prevalence of self-reported SAR to bee venom for grades III-IV, graded for severity according to different classification systems (classification data not provided in one study (24)), was 6.0% (95% CI: 3.0-11.7). A significant degree of variability in reported event rates was observed ( $I^2=93%$ ,  $p<0.01$ , Figure 2B).

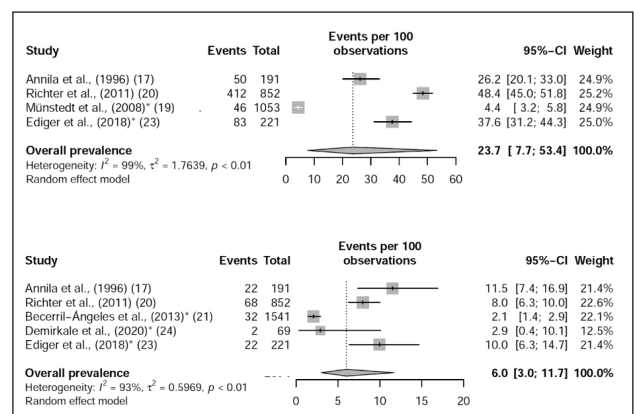
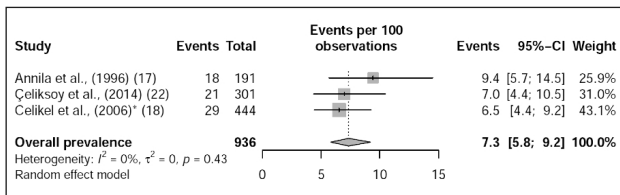


Figure 2. Forest plot of the estimated overall lifetime ( $\geq 10$  years) prevalence of self-reported systemic allergic reaction to bee venom among beekeepers (A) and self-reported systemic allergic reaction to bee venom for grades III-IV (B). \*Studies with high risk of bias.

The estimated overall one-year prevalence of self-reported SAR to bee venom, graded for severity according to different classification systems (classification data not provided for one study (18)), was 7.3% (95% CI: 5.8-9.2). There was no heterogeneity observed among the studies ( $I^2=0\%$ ,  $p=0.43$ , Figure 3).



**Figure 3.** Forest plot of the estimated overall one-year prevalence of self-reported systemic allergic reaction to bee venom among beekeepers.\* Studies with high risk of bias.

#### 4 DISCUSSION

To the best of our knowledge, this systematic literature review and meta-analysis represents the first comprehensive attempt to estimate the global prevalence of self-reported SAR to *Hymenoptera* venom among beekeepers. Compared to the previous reviews, our findings (23.7%) align within the estimated clinical data on SAR, as objectively assessed by physicians (14%-21%) or assessed through interviews (30%), and self-reported data (4%-26%) (10, 11). The estimated lifetime prevalence of self-reported SAR (grades III-IV) to bee venom and overall one-year prevalence of self-reported SAR to bee venom were, as expected, lower, at 6.0% (95% CI: 3.0-11.7) and 7.3% (95% CI: 5.8-9.2), respectively. The observed heterogeneity across the studies was substantial, with  $I^2$  values of 99% for estimated overall lifetime prevalence, and 93% for grades III-IV. The majority of studies were characterized by a high RoB.

Two major reasons could contribute to the observed heterogeneity in the study. Firstly, they may reflect methodological differences, including data collection technique, definition of AR and utilization of diverse classification systems for grading the severity of SAR across different regions (12, 25, 26).

With regard to the definition of AR, variability in how studies categorized and reported AR was observed. With the exception of one study (23), the questionnaires did not distinguish between allergic and non-allergic reactions (i.e., systemic toxic reactions, psychogenic reactions), raising the potential for a false history of self-reported SAR to *Hymenoptera* venom. This is because psychogenic reactions, which can imitate the symptoms of SAR, are relatively common following insect stings (27), and the

high estimated overall lifetime prevalence of self-reported SAR to bee venom among the British beekeepers (48.4%) (20) could be attributed to misinterpretations of anxiety or pain following bee stings. This difference is particularly noteworthy, since the British study included a substantial number of women compared to other studies (see Table 1). Gender differences in self-reported emotional experiences have been well-documented, with previous research indicating that women often report experiencing negative emotions (fear) more frequently and intensely than men (28). Moreover, in this study the absence of a reported response rate, coupled with insufficient information for recalculation, may have caused a selection-bias, as individuals who had experienced SAR might have been more inclined to complete the questionnaire, driven by their heightened awareness of the potential severity of SAR. This selective participation could have led to an overestimation of the overall lifetime prevalence of self-reported SAR to bee venom, particularly for mild grades (grade I: 233 out of 852 (27.3%); grade II: 111 out of 852 (13.0%)) (20). The phenomenon of overestimation in both parental and self-reported data is a well-documented issue in assessing the prevalence of food allergies (29), and has also been reported in the context of HVA. Studies conducted in Poland revealed an overestimation in the prevalence of LLR and mild SAR when comparing self-reported estimates to those objectively assessed by a physician (30).

Importantly, putting aside the fact that a classification other than Müller was used, a high estimated overall lifetime prevalence of self-reported SAR to bee venom (37.6%) was also reported by Ediger et al. (23). However, these results may actually reflect the incidence of new cases rather than the overall prevalence, as the authors observed the course of symptoms over the years following bee stings. Meanwhile, Münstedt et al. (19), aimed to report the incidence of bee venom allergy, but a detailed textual analysis revealed that they reported the prevalence instead. Compared to the other studies, the authors also reported the lowest overall lifetime prevalence of self-reported SAR to bee venom, partly attributed to variations in the age of participants, with the mean age being approximately a decade higher compared to the data from other studies (17, 18, 22-24). Nevertheless, an important shortcoming of the German study is its very low response rate (3.0%), which may affect the accuracy of the prevalence estimates.

Secondly, the observed heterogeneity might be attributed to genuine disparities in sting exposure across different regions, influenced by geographic locations, climate, and beekeeping practices (11, 12, 25, 26).

In relation to bee sting exposure, Bousquet et al. (31) noted a strong correlation between the degree of sensitization to bee venom and the annual number of bee stings. This

correlation is most prominent when the annual number of stings falls below 25 and reaches an optimum when it exceeds 200 (31). Aligning with this data, the potential protective effect of higher sting frequencies, as observed in Turkish studies (18, 22), and less so in the Finnish beekeepers (17), may explain the lower estimated overall one-year prevalence of self-reported SAR to bee venom in Turkey (6.5% (18), 7.0% (22)) compared to Finland (9.4%) (17). However, in Bousquet et al.'s study (31) the specific selection criteria employed (exclusion of numerous allergic beekeepers and individuals with variations in the number of annual bee stings over the previous five years) may have influenced the study's outcomes.

Nonetheless, an intriguing pattern emerges within the estimated lifetime prevalence of self-reported SAR to bee venom in grades III-IV (severe SAR). Studies consistently indicate a higher estimated prevalence of severe self-reported SAR to bee venom in colder European regions (Finland, Great Britain) (17, 20), and a lower one in warmer non-European ones (Mexico, Turkey) (21, 24). In the latter case, it is plausible that favourable climatic conditions permit beekeepers to be exposed to bees throughout most of the year (18, 22, 32), leading to a lasting form of immunological protection (33), presumably on an immunological basis. Notably, heavily exposed beekeepers exhibit higher levels of bee-venom specific IgG4 (sIgG4), reflecting their degree of exposure to stings and believed to induce immune tolerance while mitigating the inflammatory response (34). However, the results of one Turkish study led by Ediger et al. (23) deviate from this expected pattern. It is suggestive that these findings may not be solely attributable to geographic location and climatic conditions, as observed in other studies. Instead, it is conceivable that methodological concerns, as mentioned previously, could significantly impact the observed outcome. However, the risk of developing SAR to bee venom cannot be entirely ruled out, even among beekeepers with a history of numerous bee stings and no prior AR (35, 36).

In contrast to beekeeping in regions with milder climates, apiculture in Europe is inherently seasonal, characterized by the distinct absence of bee sting exposure during the winter months, with this seasonal break lasting from the end of October throughout the entire winter (33). Moreover, the length of the beekeeping season varies across the regions, i.e., in Finland it extends from May to August (17), while in France it spans from early spring to late fall (31). It is conceivable that the natural history of sting reactions may exhibit disparities between the northern and southern regions (17). Moreover, it is plausible that differences between countries may also be due to beekeeping with different subspecies of honeybees (e.g., *Apis mellifera carnica*, *Apis mellifera ligustica*, etc.), because they are not all equally aggressive. Although

Richter (20) noted that beekeeping with a particular subspecies did not increase susceptibility to SAR (data not shown in the original article), future studies should incorporate species-specific behavioural trait data to gain further insights into this research area.

However, regardless of the location, the temporal gap between two working seasons may potentially attenuate the protective effect conferred by prior bee stings, consequently increasing the susceptibility to the development of AR (37). This aligns with the conclusions drawn from a literature review (10), as initial stings in spring were identified as a definitive risk factor for the onset of allergic bee sting reactions among beekeepers. Furthermore, Münstedt et al. (19), reported the occurrence of more severe non-allergic reactions to bee venom during the spring months when compared to later periods. It is also important to consider the impact of climate change, as the available data support the presence of positive correlations between climate change and HVA (38).

Knowing that factors such as geographical location, climate differences, temperature fluctuations, and insect behaviour patterns can heighten the risk of insect stings within this population group, targeted public health interventions are essential. This includes implementing comprehensive risk assessment and management strategies, as well as launching public health campaigns and educational initiatives aimed at raising awareness about SAR and promoting preventive measures.

For allergic beekeepers, the most critical measure to mitigate risk is to reduce exposure by considering cessation of beekeeping activities. However, our meta-analysis reveals that many allergic beekeepers continue beekeeping, thereby exposing themselves to recurrent and potentially life-threatening SAR. Therefore, allergologists, public health professionals, and occupational, traffic and sports medicine specialists should intensify efforts in counselling, emphasizing 1) the importance of wearing full protective equipment during all beekeeping activities, 2) self-medication in emergencies, including regular training in proper use of adrenaline autoinjectors, and 3) considering Venom Immunotherapy (VIT) as a causal treatment option when indicated. In particular, life-long VIT should be considered for individuals with inherited or acquired risk factors.

Finally, when considering the extent of exposure, the differences in beekeepers' status (professional or hobbyist) may also affect the outcome. As only one study included professional beekeepers (17), it would be intriguing to investigate potential differences between these two groups in future research. Moreover, an important knowledge gap is the lack of information regarding the location of hives (i.e., in a rural or urban environment). Urban beekeeping considerations are essential for public

safety, as the estimated prevalence of self-reported SAR to *Hymenoptera* venom among individuals living in close proximity to beehives remains unreported (11).

For future cross-sectional studies, detailed reporting of study design, settings, study participants, and the use of validated questionnaires should be employed to ensure high-quality assessment of the observed health outcomes. In order to reduce the overestimation of the self-reported data, the observed health outcomes should be confirmed by an allergologist. In terms of data collection, comprehensive reporting of health outcomes should include essential elements such as the classification system used (e.g., Müller grading system), grade of SAR, identified culprit *Hymenoptera* species, type and number of bees causing AR, and the prevalence period. Standardizing these parameters will enhance data uniformity, completeness, and comparability across studies. Statistical analyses should employ multivariate regression models to control for potential confounders effectively. Furthermore, distinguishing between family members and first-degree relatives (parents, children, siblings) will provide valuable insights into the heritable risks associated with SAR.

#### 4.1 Limitations and strengths

The quality of our work is subject to several limitations, primarily stemming from the high heterogeneity in self-reported data among the included studies and a high RoB. Additionally, the predominant reliance on Turkish data in more than half of the eligible publications, along with the absence of data about the beekeepers' status, raises concerns about the generalizability of these findings. Therefore, caution is needed when interpreting the results, especially considering the exclusion of clinical studies from our analysis. Specifically, the lack of conformity between self-reported SAR to bee venom observed by beekeepers and verification by physicians suggests potential overestimation, particularly for mild/moderate SAR (grades I-II).

Moreover, the meta-analysis was conducted on cross-sectional studies, thereby limiting the ability to infer causality or temporal relationships. Additionally, our study was constrained by the small number of available studies, which is reflected in the very wide confidence intervals of the reported estimates. However, our research was able to clearly distinguish between the one-year and lifetime prevalence of self-reported SAR to bee venom, thereby explaining much of the variability in the results. Consequently, individual forest plots included only three, four or five studies. We acknowledge that some of the studies are of poor quality, with inadequate reporting. However, the estimates provide valuable indicative trends that can guide further research and highlight areas where larger, better designed, and more

comprehensive studies are needed. For public health professionals and policymakers, even these unstable estimates can raise awareness about the significance of SAR among beekeepers, prompting preliminary guidelines and interventions aimed at mitigating risks until more robust data become available.

Nonetheless, our study's main strength lies in its rigorous methodology. It included comprehensive searches across seven electronic databases without language or publication date restrictions, adhering to PRISMA 2020 guidelines. We made extensive efforts to obtain additional information from the authors, not available in the original articles, and used a JBI algorithm with predetermined criteria, facilitating objective quality assessments. Moreover, we identified methodological aspects warranting improvement in future research, which will help mitigate potential sources of bias and enhance the robustness of estimates. By identifying research gaps and exploring the major sources of heterogeneity across the included studies, our findings could contribute to a more comprehensive understanding of the existing research limitations in this field of science.

#### CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

#### FUNDING

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#### ETHICAL APPROVAL

The method used in this systematic review involves no ethical issues, hence no ethical approval was needed.

#### AVAILABILITY OF DATA AND MATERIALS

The data presented in this study can be obtained upon request from the corresponding author.

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# SLOVENIAN JOURNAL OF PUBLIC HEALTH INSTRUCTIONS FOR AUTHORS

October 2023

These instructions are in accordance with the ICMJE recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. Complete instructions can be found in the following PDF: <http://www.icmje.org/icmje-recommendations.pdf>.

## SHORT DESCRIPTION OF THE SLOVENIAN JOURNAL OF PUBLIC HEALTH

The Slovenian Journal of Public Health has been published since 1962 by the National Institute of Public Health in Slovenia. Since 2003, the journal has been a peer-reviewed scientific journal with English abstracts, and since 2014, an international scientific public health journal in English only. The journal's mission is to promote new achievements in the broad field of public health in Slovenia and Central and South-East Europe. The Slovenian Journal of Public Health publishes internationally oriented articles and encourages an interdisciplinary approach to public health. The journal is a source for exchanging new public health concepts and solutions among researchers. The journal mainly publishes original scientific articles, and on occasion also systematic reviews, methodological articles, and invited editorials. It is published four times a year, with up to 35 articles each year, and has an average annual rejection rate of around 80%. The journal is indexed in major international databases, such as PubMed, Web of Science, and Scopus, and has had an impact factor since 2011, ranging from 0.16 to 1.6. As an open-access journal it is available online on De Gruyter, Sciendo <https://sciendo.com/journal/SJPH>. The manuscripts are peer-reviewed by three international reviewers, and the process is double-blinded, fair and constructive.

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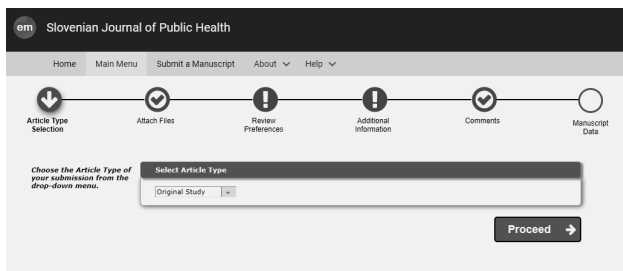
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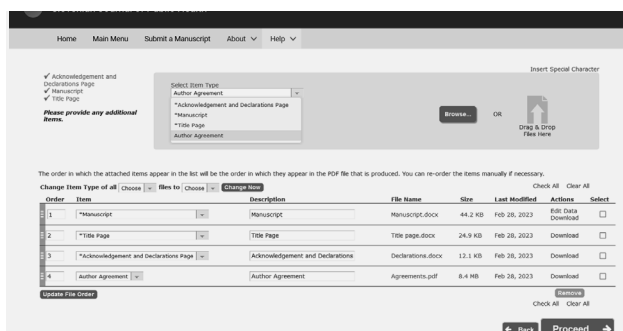


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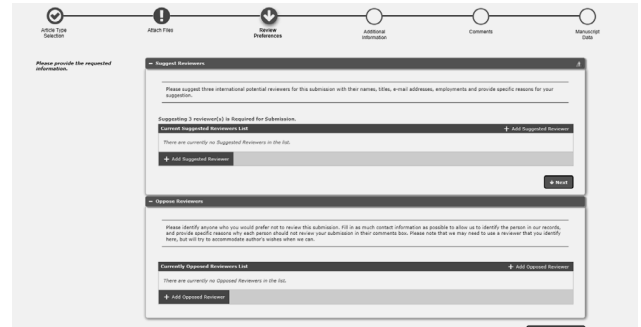


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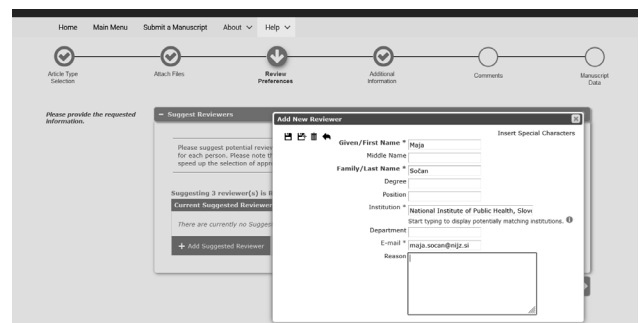


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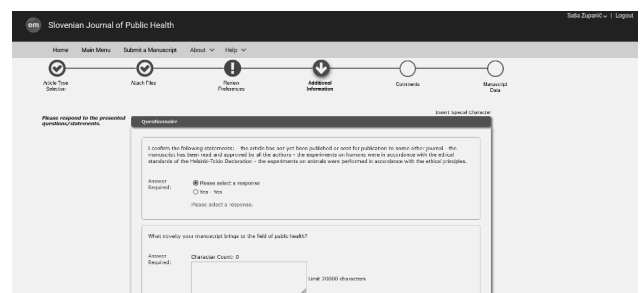
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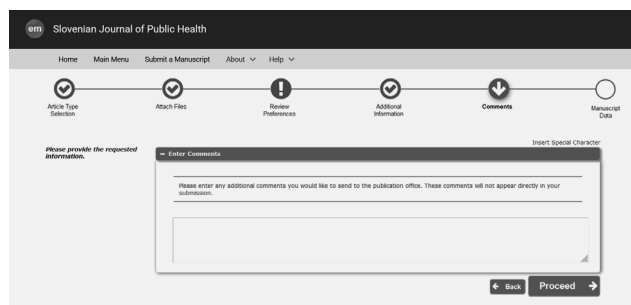
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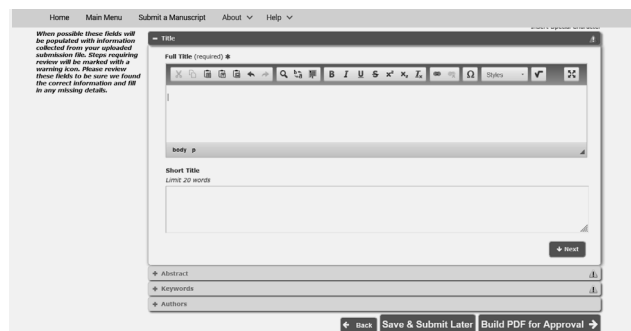
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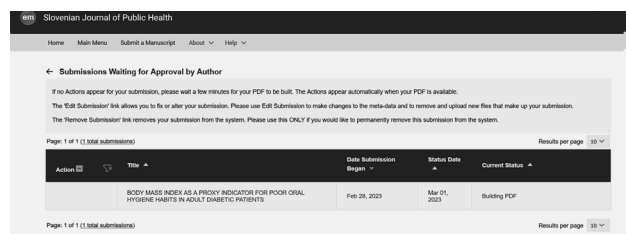
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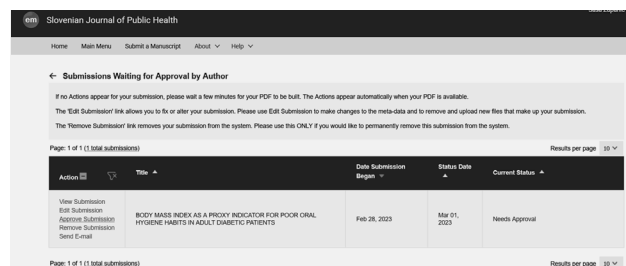


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# NAVODILA AVTORJEM REVIJE ZDRAVSTVENO VARSTVO

Oktober 2023

Navodila so v skladu s priporočili ICMJE recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. Popolna navodila so objavljena na spletni strani <http://www.icmje.org/icmje-recommendations.pdf>.

## KRATEK OPIS REVIJE ZDRAVSTVENO VARSTVO

Revija Zdravstveno varstvo (SJPH) izhaja od leta 1962 in danes predstavlja temeljno znanstveno revijo s področja javnega zdravja na območju centralne in JV Evrope.

Revija objavlja članke s širšo mednarodno tematiko s področja javnega zdravja in spodbuja objavo rezultatov interdisciplinarnih raziskav na tem področju. Objavlja izvirne znanstvene članke, v manjši meri tudi sistematične pregledne znanstvene članke in metodološke članke ter vabljeni uvodniki. Letno objavi štiri številke, skupno do 35 člankov. Povprečni letni osip je okoli 80 %. Revija je vključena v številne mednarodne podatkovne zbirke, tudi v PubMed in v oba citatna indeksa WoS in Scopus ter ima faktor vpliva neprekinjeno že od leta 2011; giblje se med 0,16 in 1,6. Revija Zdravstveno varstvo se v e-obliki nahaja na straneh založbe De Gruyter, Sciendo <https://sciendo.com/journal/SJPH>.

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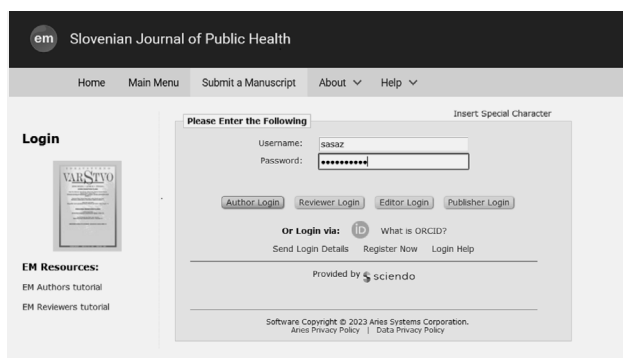
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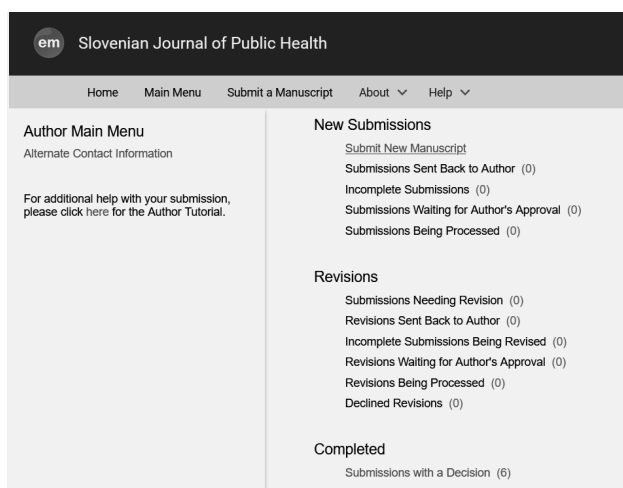
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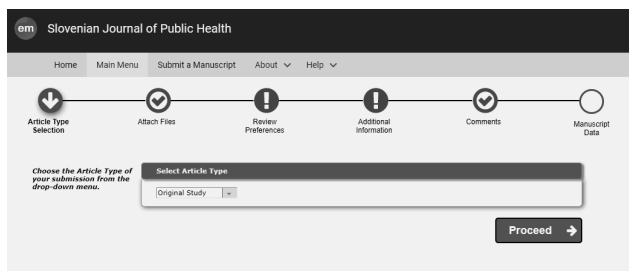
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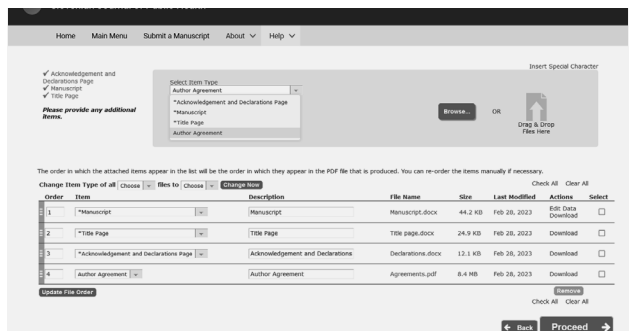
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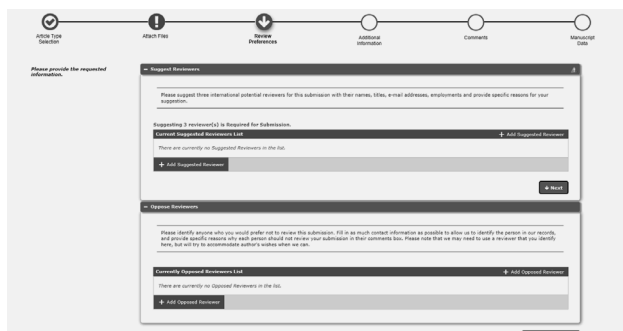
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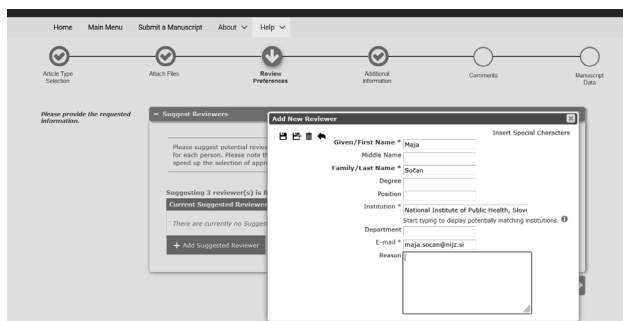
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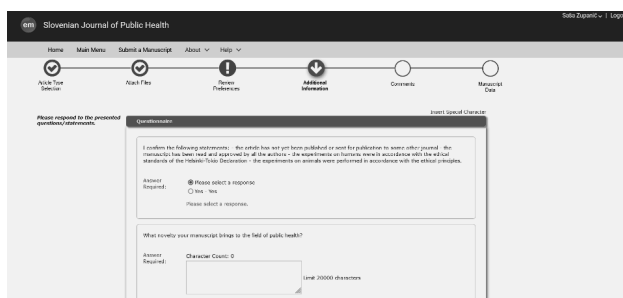
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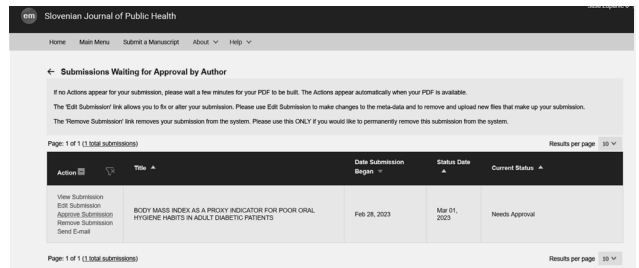
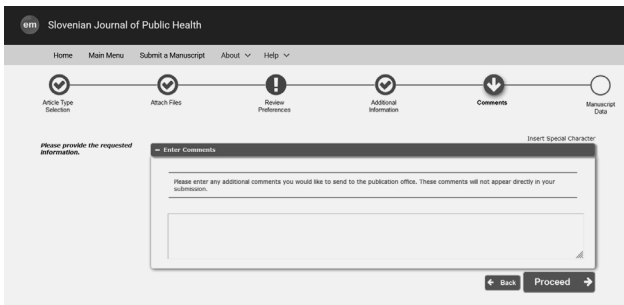
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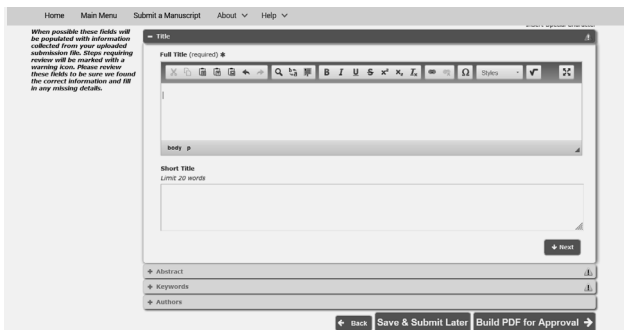
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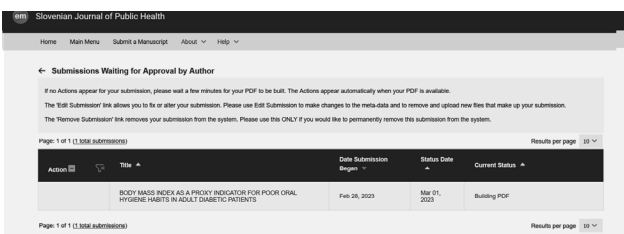
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Adam et al. state that the data is 'unreliable' (1, p. 122).  
This argument is increasingly relevant to the topic (2, 3) ...  
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#### Članek v reviji

Vodička S, Zelko E. Remote consultations in general practice: A systematic review. *Zdr Varst.* 2022 Sep 28;61(4):224-230. doi: 10.2478/sjph-2022-0030.

de Villiers TJ. The role of menopausal hormone therapy in the management of osteoporosis. *Climacteric.* 2015;18 Suppl 2:19-21. doi: 10.3109/13697137.2015.1099806.

#### Knjiga

Wilkinson IB, Raine T, Wiles K, Goodhart A, Hall C, O'Neill H, et al. *Oxford handbook of clinical medicine.* 10th ed. Oxford: Oxford University Press; 2017. 123 p.

Kaplan SJ. *Post-hospital home health care: the elderly's access and utilization [dissertation].* St. Louis (MO): Washington University; 1995.

#### Poglavje v knjigi

Goldberg BW. Population-based health care. In: Taylor RB, Robin S, editors. *Family medicine.* 5th ed. Cambridge: Cambridge University Press; 1999. p. 32-36.

#### Spletna stran

Cancer Research UK. Current research into breast cancer [Internet]. 2020 [cited 2022 Dec 14]. Available from: <https://www.cancerresearchuk.org/our-research/our-research-by-cancer-type/our-research-into-breast-cancer/current-breast-cancer-research>

McNeil DG. Vaccines against HIV, malaria and tuberculosis unlikely, study says. *New York Times.* 2018 Sep 7. [cited 2018 Nov 14]. Available from: <https://www.nytimes.com/2018/09/07/health/vaccines-hiv-malaria-tuberculosis.html>

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Naslovna stran naj zajema sledeče podatke: title / naslov, avtorji, zaposlitve, [ORCID](#) številke avtorjev, e-poštni naslov korespondenčnega avtorja, abstract / izvleček, keywords / ključne besede.

Naslov v angleškem in slovenskem jeziku naj bo informativen in natančen, opisen in ne trdilen (povedi v naslovih niso dopustne). V naslovu naj ne bo kratic.

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## CONFLICTS OF INTEREST

(The authors declare that no conflicts of interest exist.)

## FUNDING

(The study was financed by ...)

## ETHICAL APPROVAL

(Received from the... ali opis etičnega vidika raziskave)

## AVAILABILITY OF DATA AND MATERIALS

(All data and materials used in this study were collected from publicly available sources and are available upon reasonable request.

ali

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.)

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(V LLM izjavi morajo avtorji obvezno navesti morebitno uporabo generativnih jezikovnih modelov (kot je ChatGPT) za izboljšanje jezika in berljivosti rokopisa. Primer: During the preparation of this work the author(s) used [NAME TOOL /SERVICE] in order to [REASON]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.)

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Prav tako morajo avtorji, ki poročajo o ljudeh ali posredujejo javnosti njihovo slikovno gradivo, pridobiti dovoljenja vseh sodelujočih, da se z vključitvijo v raziskavo strinjajo (v primeru otrok so to starši ali skrbniki). Izjavo o pridobitvi teh dovoljenj morajo avtorji podati v poglavju o metodah dela. Uredništvo si pridržuje pravico vpogleda v to dokumentacijo.

Raziskave na živalih morajo biti izpeljane v skladu z navodili "Animal Research: Reporting in Vivo Experiments"- (ARRIVE) in potrjene s strani nacionalne etične komisije. V poglavju o metodah dela in med izjavami morajo avtorji podati izjavo o etiki raziskav na živalih z veljavno številko dovoljenja.

V izjavah morajo biti zapisani morebitni finančni ali drugi interesi farmacevtske industrije ali proizvajalcev opreme ter inštitucij, povezanih z rokopisom.

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## EDITORIAL

*Jelka ZALETEL, Jerneja FARKAŠ LAINŠČAK*

CREATION OF A DIFFERENT LANDSCAPE FOR CARDIOVASCULAR DISEASES  
AND DIABETES IN EUROPE THROUGH JACARDI JOINT ACTION (109-112)

## IZVIRNI ZNANSTVENI ČLANKI

*Herion MUJA, Suela VASIL, Dorina TOČI, Timo CLEMENS, Helmut BRAND, Genc BURAZERI*

ABILITY TO MAINTAIN AND IMPROVE HEALTH AND SOCIO-DEMOGRAPHIC  
CORRELATES AMONG CHILDREN IN ALBANIA (113-122)

*Lana VRANIČ, Zrinka BILOGLAV, Petar MEDAKOVIĆ, Jasminka TALAPKO, Ivana ŠKRLEC*

THE EFFECTS OF A PULMONARY REHABILITATION PROGRAMME  
ON FUNCTIONAL CAPACITY AND STRENGTH OF RESPIRATORY MUSCLES  
IN PATIENTS WITH POST-COVID SYNDROME (123-131)

*Elvir ZVRKO, Nataša POPOVIĆ, Miodrag RADUNOVIĆ, Goran NIKOLIĆ*

MOTIVATIONAL FACTORS INFLUENCING THE CHOICE OF MEDICAL STUDIES  
AND FUTURE CAREER PLANS AMONG MONTENEGRIN STUDENTS (132-141)

*Jurij Bojan ŽMAVC, Miha VERDENIK, Zala SKOMINA, Nataša IHAN HREN*

TOOTH LOSS AND SYSTEMIC DISEASES IN THE SLOVENIAN ELDERLY  
POPULATION: A CROSS-SECTIONAL STUDY OF THE ASSOCIATION  
BETWEEN ORAL AND SYSTEMIC HEALTH (142-151)

## REVIEW ARTICLE

*Tanja CARLI, Igor LOCATELLI, Mitja KOŠNIK, Andreja KUKEC*

THE PREVALENCE OF SELF-REPORTED SYSTEMIC ALLERGIC REACTION  
TO HYMENOPTERA VENOM IN BEEKEEPERS WORLDWIDE: A SYSTEMATIC  
LITERATURE REVIEW AND META-ANALYSIS (152-159)