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# THE PERINATAL LOSS CARE EDUCATIONAL PROGRAMME AND ITS EVALUATION

## IZOBRAŽEVALNI PROGRAM ZDRAVSTVENE NEGE OB PERINATALNI IZGUBI IN NJEGOVA EVALVACIJA

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**ABSTRACT**

**Introduction:** Working with bereaved parents is an immense challenge for professionals in the field of perinatal care and requires a high level of knowledge and skill. This article aims to evaluate the effectiveness of the Perinatal Loss Care blended educational programme.

**Methods:** An evaluative assessment was carried out using a scored questionnaire to gather pre- and post-programme data. Participants were medical and healthcare professionals (n=200) who participated in the programme voluntarily (the Medical Professional/Motivated group and the Others group) or were selected by their employer and for whom attendance was mandatory (the Medical Professional/Non/Motivated group).

**Results:** Participants' perception of their own knowledge and understanding of perinatal bereavement care was significantly higher on completion of the educational programme, proving its effectivity. There was a statistically significant effect on overall score in individual groups of respondents, as well as the whole set ($p<0.001$), with post-intervention scores higher than pre-intervention scores. No statistically significant differences in overall score were detected before participation in the educational programme in individual groups ($p=0.204$). Participants from the Medical Professional/Non/Motivated group achieved lower post-intervention scores to a significantly greater extent ($p<0.05$) and more often perceived the educational programme as being "very difficult" ($x2=20.66$, $df=6$, $P<0.01$) compared to other groups.

***Conclusions:*** The educational programme was assessed as effective. Care of bereaved parents has its specifics and healthcare professionals should possess a basic knowledge of how to provide sensitive care during this time.

**Keywords:**
perinatal loss care, education, healthcare professionals, blended learning, evaluation research

***IZVLEČEK***

***Uvod:*** *Delo z žalujočimi starši predstavlja neverjeten izziv za strokovnjake na področju perinatalne nege in zahteva visoko raven znanja in sposobnosti. Prispevek ocenjuje učinkovitost izobraževalnega programa Nege ob perinatalni izgubi.*

***Metode:*** *Z uporabo vprašalnika se je izvajalo ocenjevalno poročilo za zbiranje podatkov pred in po izvajanju programa. Sodelujoči so zdravstveni strokovnjaki in strokovnjaki s področja zdravstvene nege (n = 200), ki so v programu sodelovali prostovoljno (skupina zdravstvenih strokovnjakov/motiviranih in skupina ostalih) ali so jih izbrali njihovi nadrejeni, njihovo sodelovanje pa je bilo obvezno (skupina zdravstvenih strokovnjakov/nemotiviranih).*

***Rezultati:*** *Dojemanje sodelujočih o svojem lastnem znanju in razumevanje nege ob perinatalni izgubi je bilo po končanem izobraževalnem programu značilno višje, kar dokazuje njegovo učinkovitost. Podan je tudi statistično značilen učinek na splošen izid posameznih skupin anketirancev ter na celoten set ($p < 0,001$) z višjimi rezultati po izvedbi od rezultatov pred izvedbo izobraževanja. Pri splošnem rezultatu ni zaznati statistično pomembnih razlik pred sodelovanjem v izobraževalnem programu v posameznih skupinah ($p = 0,204$). Sodelujoči iz skupine zdravstvenih strokovnjakov/nemotiviranih so dosegli nižje rezultate po izvedbi v statistično pomembnem obsegu ($p < 0,05$) ter so pogosto izrazili, da je izobraževalni program »zelo zahteven« ($x2 = 20,66$, $df = 6$, $P < 0,01$) v primerjavi z drugimi skupinami.*

***Zaključek:*** *Izobraževalni program je ocenjen kot učinkovit. Nega žalujočih staršev ima posebnosti in strokovnjaki s področja zdravstvene nege potrebujejo osnovna znanja, kako v tem času ponuditi občutljivo nego.*

***Ključne besede:***
*nega ob perinatalni izgubi, izobraževanje, strokovnjaki s področja zdravstvene nege, kombinirano učenje, evalvacija programa*

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## 1 INTRODUCTION

Perinatal loss (miscarriage, stillbirth, neonatal death) is a psychologically stressful event and parents endure agonising sorrow following the death of a baby. In the Czech Republic, around 450 women and their families experience perinatal loss every year. For most women experiencing perinatal loss, the quality of care from medical professionals has a direct effect on their psychological health and the grieving process (1–3).

Medical professionals refer to stillbirth as one of the most difficult experiences in the field of obstetrics (4) and describe the support and care of bereaved parents as demanding and complicated (5, 6).

Working with bereaved parents is an immense challenge for professionals in the field of perinatal care and requires a high level of knowledge and skill. Positive attitudes in healthcare professionals toward care for parents who suffered perinatal loss are associated with previous education in the field of care for bereaved parents, support of a dedicated bereavement team, and hospital policy supporting the care for bereaved parents (7, 8).

Most professionals who deal with the experiences of parents after perinatal loss point out the need for evidence-based training in care after perinatal loss using a parent-centred integrated pathway to improve the experience of bereaved parents (3, 7, 9–11).

In the Czech Republic, however, education in this field of care is insufficient. This is why the Perinatal Loss Care (PLC) course was created. This article aims to evaluate the effectiveness of the PLC-blended educational programme in the Czech Republic.

## 2 METHODS

The PLC educational programme is intended for medical and healthcare professionals who are involved in the care of bereaved parents. It is designed to incorporate theory and practice and has a duration of 10 weeks. It is based on a holistic approach to perinatal bereavement care with an emphasis on bio-psycho-socio-spiritual elements. A blended learning approach was chosen, as is recommended by Kavanaugh et al. (12) in respect of sensitive and often emotional content associated with grieving and bereavement. The theoretical part of the programme is divided into 10 lectures available to participants in the form of e-learning. Medical professionals consider online learning opportunities as suitable for their working conditions and needs (13). Every week a new lesson of the educational programme is made available to participants. The educational goals of individual lessons are stated in Table 1.

**Table 1.** Learning objectives of the PLC educational programme.

| | |
|---|---|
| 1. | To understand the bereavement process after perinatal loss. |
| 2. | To define the principles of communicating adverse news to parents. |
| 3. | To critically evaluate the plan for the care of women during stillbirth. |
| 4. | To critically evaluate the plan for the care of parents during the death of a premature or disabled child. |
| 5. | To plan an intervention during the hospitalisation of women after perinatal loss. |
| 6. | To describe the main areas of education for women before release from hospital. |
| 7. | To understand the prospects of coping with grief after perinatal loss. |
| 8. | To distinguish normal and complex bereavement. |
| 9. | To describe the prospects of professional and non-professional help for parents after perinatal loss. |
| 10. | To apply the principles of mental hygiene. |

Training content is complemented with current research, audio-visual recordings on perinatal palliative care, references to literary resources, and the testimonies of parents who have experienced perinatal loss. During the course, participants are able to discuss individual topics with each other and with tutors. Participant involvement is supported with the allocation of tasks in an interactive online depository. At the end of the e-learning educational programme, participants take a theoretical test.

The educational programme is led by two tutors (professionals in the fields of midwifery and psychotherapy). They also participate in leading practical seminars (2x8h classroom activities), which are arranged after the 5th and 10th e-learning lessons. The seminar includes workshops, role plays to resolve model situations, communication skills training, the application of psycho-relaxing exercises, and meetings with parents who have experienced the death of a baby. During the seminars, instructors create a safe place in which participants are able to discuss sensitive topics. Participants voluntarily play various roles in model situations. Personal and professional vulnerabilities are acknowledged and, following the workshops, a clearer understanding of accessible support strategies is gained. The recommended number of participants in the programme is 20–30. Ten weeks for the educational programme was chosen intentionally, as longer educational programmes are known to have a greater chance of changing attitudes toward caring for dying patients than one-off lectures (14).

The goal of the PLC educational programme is to improve participant knowledge of PLC, therefore, an evaluation was carried out.

### 2.1 Study Design

The PLC educational programme was evaluated quantitatively using pre/post-test, three group design (divided according to occupation and motivation for participation in the educational programme; see Sample). Surveys were administered pre- and post-training to attendees in 2015–2017. These courses were always led by the two same instructors and saw a total of 242 participants. The surveys focused on the perceived level of knowledge in participants, their expectations, and perception of the difficulty of the PLC educational programme. The researchers were able to compare perceived knowledge before and after an intervention due to a baseline of target population established based on surveys (15).

### 2.2 Sample

The PLC educational programme was offered to hospitals in the Czech Republic via e-mail, and an offer of the course was available on the "Empty Cradle" website – that of a group of parents who have experienced perinatal loss. A total of two hundred participants were incorporated into the evaluation research, all of whom agreed to take part in the research and all of whom completed the pre- and post-intervention tests. For the purposes of data analysis, participants were divided into three groups. The first group (Medical Professionals/Motivated) consisted of medical professionals who chose to participate in the educational programme as a part of their lifelong education and who wanted to actively deepen their knowledge in the field of the care of bereaved parents. The second group (Medical Professionals/Non/Motivated) consisted of employees from a gynaecology-obstetrics clinic in the Czech Republic whose employer paid for the educational programme and whose attendance on the course was compulsory. The goal was a blanket training of the staff of one workplace and the seminars took place at the gynaecology-obstetrics clinic. The third group (Others) consisted of participants in the educational programme from various occupations, who were in one way or another involved in the care of bereaved parents and who were interested in obtaining new knowledge and skills in this field. Seminars for the Medical Professionals/Motivated and Others groups were held collectively (in mixed groups) at an educational centre in Prague.

### 2.3 Data Collection Tool and Process

The construction of the evaluation questionnaire was inspired by the UBET tool (16). The evaluation questionnaire that was used comprised of questions focusing on the perceived level of knowledge of the respondents before and after the completion of the educational programme (see Table 2).

**Table 2.** Pre- and post-test and points rating.

| Questions | Possibilities/ Scales | Points |
|---|---|---|
| How much do you know about the psycho-social care of parents after perinatal loss? | 1–10 | 1–10 |
| I know the rules on communicating information about the death of a baby to parents. | No – more likely no – more likely yes – yes | 0–3 |
| How would you intervene in the physical contact of a woman with her stillborn baby? | a) I would recommend the woman see and hold the baby.<br>b) I would provide information on how the woman could physically say goodbye to the baby.<br>c) I would not recommend the woman physical contact with the stillborn baby.<br>d) I would ask the woman if she wanted to see or hold her baby. | 0–3 |
| I am able to recognise cases in which the grieving process of a woman has become complex and she needs professional psychological help. | No – more likely no – more likely yes – yes | 0–3 |
| I know effective tools of mental-hygiene and I know how to use them in practice. | No – more likely no – more likely yes – yes | 0–3 |
| **Total** | | **1–22** |

The questionnaire was always completed before the start of the educational programme and, after its completion, respectively before the final practical seminar, in which further questions could be asked or further information added.

Within the framework of a mathematical-statistical analysis, the shift in the perceived level of respondent knowledge was measured using applied standard scales in a Paired T-Test. The degree of compliance was also tested using a Pearson Chi-Square test. Testing was performed using the SPSS and SASD programmes, version 1.5.6. The Medical Professionals/Motivated, Medical Professionals/Non/Motivated and Others groups were tested separately and, subsequently, the entire set together.

## 3 RESULTS

### 3.1 Demographic Data

A total of 200 participants met the criteria of the study. Their demographic characteristics are represented in Table 3. All categories were strongly dominated by women, who made up 93% in total. The first group (designated Medical Professionals/Motivated) consisted of 74 participants, of whom 53 were midwives, 9 neonatal nurses, 2 obstetricians, and 10 neonatologists. The second group (designated Medical Professionals/Non/Motivated) included 27 midwives, 51 neonatal nurses, and 9 neonatologists, with 87 participants in total. The third group (designated Others) contained 39 participants, including psychologists, social workers, doulas, counsellors, priests, crisis interveners etc.

**Table 3.** Descriptive statistics (mean and SD or relative frequency) by group.

| | Medical Professionals/ Motivated | Medical Professionals/ Non/Motivated | Others | Total |
|---|---|---|---|---|
| **Gender** (women %) | 90.54 | 95.4 | 92.31 | 93 |
| **Age** | 37.84 (8.65) | 39.13 (7.7) | 36.95 (7.64) | 38.23 (8.06) |
| **N** | 74 | 87 | 39 | 200 |

### 3.2 Evaluation

A statistically significant effect in the total score was observed in individual groups of respondents, as well as in the whole set ($p<0.001$) with post-intervention scores higher than pre-intervention scores (see Table 4).

**Table 4.** Results of pre and post-tests scores by category of attendants and in total.

| Group | Mean pre-test scores (SD) | Mean post-test scores (SD) |
|---|---|---|
| **Medical Professionals/ Motivated** | 9.76 (3.28) | 18.00 (1.90) |
| **Medical Professionals/ Non/Motivated** | 9.05 (3.20) | 17.32 (2.34) |
| **Others** | 10.05 (3.33) | 18.41 (1.81) |
| **Total** | 9.51 (3.28) | 17.79 (2.13) |

Min. 1 point, max.22 points

No statistically significant differences in total score before the completion of the educational programme in individual groups were identified ($p=0.204$). However, significant differences in total score were identified in individual groups after the course. Participants from the Medical Professionals/Non/Motivated group achieved lower scores to a significantly greater extent, and participants from the Others group achieved higher scores to a significantly greater extent ($p<0.05$).

During the analysis of individual answers from the evaluation questionnaire, some significant differences between individual groups of respondents were identified. To the question "How would you intervene in the physical contact of a woman with her stillborn baby?" a statistically significant shift in the choice of possible answer was unequivocally proven (see Table 5).

**Table 5.** The evaluation of the question "How would you intervene in the physical contact of a woman with her stillborn baby?" in pre- and post-test.

| "How would you intervene in the physical contact of a woman with her stillborn baby?" | Medical Professionals/ Motivated | | Medical Professionals/Non/ Motivated | | Others | |
|---|---|---|---|---|---|---|
| | pre-test % | post-test % | pre-test % | post-test % | pre-test % | post-test % |
| **a) I would recommend the woman see and hold the baby.** | 23.0 | 36.5 | 24.1 | 48.3 | 23.1 | 17.9 |
| **b) I would provide information on how the woman could physically say goodbye to the baby.** | 44.6 | 60.8 | 46.0 | 46.0 | 53.8 | 82.1 |
| **c) I would not recommend the woman physical contact with the stillborn baby.** | 0 | 0 | 0 | 0 | 0 | 0 |
| **d) I would ask the woman if she wanted to see or hold her baby.** | 32.4 | 2.7 | 29.9 | 5.7 | 23.1 | 0 |

In the whole set, and in the groups of medical professionals (Motivated and Non/Motivated), the shift was proven at the level of $p<0.001$, in the group of Others at the level of $p<0.05$. After completion of the course, in all cases, a statistically significant decrease was observed in the choice of answer d) "I would ask the woman if she wanted to see or hold her baby," and a statistically significant increase was observed in the choice of answer b) "I would provide information on how the woman could physically say goodbye to the baby," (with the exception of the Medical Professionals/Non/Motivated group, where the choice of answer b) did not change). The choice of answer a) "I would recommend the woman see and hold the baby," also saw a statistically significant increase, with the exception of the Others group.

Before the completion of the PLC educational programme, respondents anticipated that during the programme they would improve their knowledge and secure more assurance in the psycho-social care of bereaved parents, meaning they would, therefore, be better able to cope with the situation of perinatal loss.

Participants' expectations of the PLC educational programme were 83.8% fully met in the Medical Professionals/Motivated group, 52.9% in the Medical Professionals/Non/Motivated group, and 84.6% in the Others group. Participants mostly perceived the programme as being "moderately challenging" (58.1%). Participants from the Medical Professionals/Non/ Motivated group assessed the course as statistically significantly more often as "very challenging" ($x2=20.66$, $df=6$, $P<0.01$).

## 4 DISCUSSION

Participants' perception of their own knowledge and understanding of perinatal bereavement care was significantly higher after the completion of the PLC educational programme, proving its effectiveness. The effectiveness of the course could be affected by the combination of extremely efficient teaching methods. The blended learning method was chosen for the course, with online asynchronous e-learning on the one hand and personal meetings on the other, where elements of psycho-social training were used for the development of communication skills and the use of therapeutic techniques in the care of bereaved families. Positive effects of the course manifested in all three groups of participants (Motivated and Non/Motivated Medical professionals and Others). Each group, however, exhibited their own specific features. The Medical Professionals/ Non/Motivated group received the lowest scores in the post-test. These participants attended the course at their employer's behest; some exhibited an interest in education in this field, while others felt coerced into participating and felt that they had never encountered the situation of the death of a baby in practice. Their need for competence and autonomy, therefore, remained unfulfilled, which probably led to a negative impact on their learning experience and the satisfaction they obtained.

One question that remained unanswered in this research was whether the various medical professions benefitted from the course to the same extent. Participants in the PLC educational programme were predominantly midwives and neonatal nurses; only 2 male obstetricians were present, with no female obstetricians at all.

Therefore, they cannot be statistically compared. It can, however, be assumed that the attitude of the obstetricians toward bereavement care will differ. A qualitative study by Montero et al. (17, p. 1409) includes a statement by one of the obstetricians: "I don't believe that education is necessary, because we know intuitively how to manage these situations." In general, very little is known about obstetricians' reactions to perinatal death. Feelings of guilt and failure in obstetricians who care for women after perinatal loss (10, 17), sorrow and high emotional tension, which can lead to considerations of leaving the profession (11), are primarily mentioned. Withdrawal from the situation, "a conspiracy of silence" and denial, attention to the physical aspects of care, and immersion in administrative tasks were common reactions among healthcare personnel to perinatal death (9, 18, 19). These reactions may lead to a lower quality of care for the bereaved parents and the possibility of an avoidance of education in the field of the care of bereaved parents, or to resistance to compulsory attendance of the course. Therefore, it can be assumed that a higher attendance of obstetricians of the course could help to improve the quality of care, as well as their own well-being.

During discussions and personal meetings, participants supported each other and shared common painful stories, which in itself could have had an effect on the general sense of belonging and group support. Discussion and innovative methods during teaching tend to support the creation of opinions, attitudes and skills in the care of bereaved parents (20) and have a positive impact on the nurses' attitudes toward death by helping them better understand the significance of the experience of suffering (21). Meetings of individuals from various support and health professions also lead to an understanding of the role, as well as an appreciation of the roles of other professionals in the care of parents after perinatal loss (22).

A patriarchal approach in the field of healthcare, including care during childbirth, is still prevalent among medical professionals in the Czech Republic (23). This manifested itself in answers to the question "How would you intervene in the physical contact of a woman with her stillborn child?" Many studies state that the approach of carers and their communication with parents can have a significant effect on whether or not parents see or hold their deceased baby. Therefore, during the educational programme, great attention was paid to the rituals of bidding farewell to a deceased baby. Among other things, participants learnt that it is not recommended to ask bereaved parents the question, "Do you want to see your child?" but parents' natural compulsion to see and hold their deceased baby should be reflected (24, 25). Therefore, after the completion of the PLC course, the preference of the answer, "I would ask the woman if she wanted to see or hold her baby," significantly decreased (29.5% of respondents chose this answer in the pre-test, with only 3.5% in the post-test). The positive attitude of the respondents toward the rituals of bidding farewell to a stillborn baby (none of the respondents preferred the answer, "I would not recommend the woman physical contact with her stillborn child," in pre- nor post-test) was one positive outcome of the research. Holding and seeing a deceased baby is valuable for most but not all women (26). Who should decide what would be best for a particular woman/parent? Can the healthcare professionals recommend physical contact with a deceased baby to all women? It is currently preferred to allow the parents to decide for themselves as to which solution is the best for them. Healthcare professionals should, therefore, inform the parents verbally and in written form of the opportunities available to them to bid farewell to their deceased baby, discuss their feelings, and give them time to decide before the birth. The answer, "I would provide information on how the woman could physically say goodbye to the child," was chosen by 47% of respondents in the pre-test and 58.5% of respondents in the post-test. In our research, in the group of Medical Professionals (Motivated and Non/Motivated), the preference for the answer "I would recommend the woman see and hold the baby," increased in the post-test (compared to the pre-test). In the Others group, on the other hand, preference for this answer decreased in the post-test (compared to the pre-test). Even though some parents need increased guidance in making difficult decisions after a diagnosis of stillbirth (27), medical professionals should not take a dominant position and make the decision on the parents' behalf. It is important for them to use their communication skills to maximum effect and to further educate themselves in the field of communication with patients, principally in emotionally demanding situations.

Limitations of the study include the fact that data was only collected immediately after the educational programme. Only a brief evaluation tool was used and one which was not validated.

## 5 CONCLUSION

The PLC educational programme was evaluated as effective. Training using blended learning proved to be successful and can be recommended primarily for the education of working medical professionals who are fully experienced in practice. E-learning can be constantly updated and fine-tuned to the expectations of course participants. Workshops during personal meetings enable the development of communication skills in the care of bereaved parents, as well as self-care and mental hygiene.

These are the two areas in which participants in the PLC educational programme required the most improvement. The care of bereaved parents has its own specifics and medical professionals should possess a basic knowledge of how to provide sensitive care during this period. Not all medical professionals, however, are motivated to educate themselves further in this field. In the Czech Republic, the creation of perinatal bereavement teams, in which professionals with an empathy and deep understanding of palliative care would work, is deemed to be essential.

## CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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## ETHICAL APPROVAL

All of the respondents of the research completed the questionnaire voluntarily, were acquainted with the goals and the method of processing the questionnaire and agreed to participate in the evaluation of the educational programme. Since this study was viewed as evaluation and not specifically research, ethical approval was not formally sought nor required.

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# VALUATION OF EQ-5D-3L HEALTH STATES IN SLOVENIA: VAS BASED AND TTO BASED VALUE SETS

## VREDNOTENJE ZDRAVSTVENIH STANJ EQ-5D-3L V SLOVENIJI: VREDNOSTI ZDRAVSTVENIH STANJ, PRIDOBLJENE Z METODAMA VAS IN TTO

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**ABSTRACT**

**Introduction:** The two primary objectives of this paper were (a) to develop first logically consistent TTO based EQ-5D-3L value sets for Slovenia and (b) to revisit earlier developed VAS based EQ-5D-3L value sets.

**Methods:** Between September 2005 and April 2006, face-to-face interviews with 225 individuals in Slovenia were conducted. Protocols from the Measurement and Value of Health study were followed closely. Each respondent valued 15 health states out of a total of 23. Model selection was informed by the criteria monotonicity/logical consistency. Predictive accuracy was assessed in terms of mean square difference between out-of-sample predictions and corresponding observed means, as well as Lin's Concordance Correlation Coefficient.

**Results:** Modelling was based on 2,717 VAS and 2,831 TTO values elicited from 225 respondents. A 6-parameter constrained regression model with a supplementary power term was selected for VAS and TTO value sets, as it produces monotonic values, and proved superior in terms of out-of-sample predictive accuracy over the tested alternatives.

**Conclusion:** This is the first EQ-5D-3L TTO based value set in Slovenia and the second in Central and Eastern Europe (besides Poland). It is also the first monotonic and logically consistent VAS value set in Central and Eastern Europe. Comparisons with Polish and UK TTO values show considerable differences, mostly due to mobility with having a substantially greater weight in Slovenia. The UK value set generally produces lower values and the Polish value set higher values for mild states.

**Keywords:**
EQ-5D-3L, Slovenia, quality-adjusted life-years, social value set, utility

***IZVLEČEK***

***Uvod**: Dva osnovna cilja raziskave sta (a) prikazati prvi logično konsistentni vrednostni set EQ-5D-3L za Slovenijo, ki temelji na metodi časovne izmenjave, (b) izboljšati prejšnji vrednostni set EQ-5D-3L za Slovenijo, ki temelji na vrednostni lestvici (VAS-metodi).*

***Metode**: Od septembra 2005 do aprila 2006 je bilo opravljenih 225 osebnih intervjujev s posamezniki iz 40 slovenskih občin. Študija je natančno sledila protokolu študije MVH o merjenju in vrednotenju zdravja, ki je bila izvedena v Združenem kraljestvu. Vsak anketiranec je ocenil 15 od skupno 23 zdravstvenih stanj. Izbira modela za izračun vrednosti zdravstvenih stanj je temeljila na dveh osnovnih merilih: monotonosti in logični doslednosti vrednosti. Napovedno moč smo vrednotili s povprečno kvadrirano razliko med napovedmi izven vzorca in pripadajočimi ocenjenimi povprečji ter s pomočjo Linovega konkordančnega korelacijskega koeficienta.*

***Rezultati**: Izbrana modela temeljita na vrednostih zdravstvenih stanj 2,717 VAS in 2,831 TTO, ki smo jih pridobili v 225 osebnih intervjujih. Za oceno vrednosti VAS in TTO smo izbrali šestparametrski regresijski model z omejitvami in dodanim potenčnim faktorjem, saj se je izkazalo, da so ocenjene vrednosti na temelju tega modela monotone in imajo boljšo napovedno moč ocen izven vzorca kot vsi drugi ocenjevani modeli.*

***Zaključek**: V študiji smo prikazali prvi slovenski vrednostni set EQ-5D, ki temelji na metodi TTO, hkrati pa je to drugi set, izračunan v srednji in vzhodni Evropi (poleg Poljske). Gre tudi za prvi monotoni in logično dosledni vrednostni VAS-set tako v Sloveniji kot srednji in vzhodni Evropi. Primerjave z vrednostmi poljskega in britanskega TTO kažejo precejšnje razlike med vrednostmi posameznih zdravstvenih stanj, predvsem zaradi dimenzije pokretnosti, ki ima bistveno večjo težo v Sloveniji. Vrednosti TTO v Združenem Kraljestvu so na splošno nižje za manj težavna zdravstvena stanja, poljske vrednosti zdravstvenih stanj pa so na splošne višje.*

***Ključne besede:***
*EQ-5D-3L, Slovenija, kakovostno prilagojena leta življenja, vrednostni set VAS, koristnost*

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## 1 INTRODUCTION

Slovenia passed the regulation that required economic evaluation to inform drug and health technology reimbursement decision-making in the 1990s. Health technologies are assessed by various bodies (1, 2). The latest evaluation guidelines by the Health Insurance Institute of Slovenia recommend that the benefits of the treatment are expressed as quality-adjusted life years (QALYs).

QALY is a measure that encapsulates a treatment's impact on a patient's life length and also on their health-related quality of life (HRQOL), which is recognized as a key indicator of treatment outcomes (3). The QALY requires data that expresses health-related quality of life (HRQOL) in the form of a single value, sometimes known as a health state utility value, which is scored on a scale that assigns a value of 1 to a state equivalent to full health and 0 to a state equivalent to death (4). Weinstein and Stason (1977) connected QALYs with utilities, specifically expected utility, rather than the "weights" of the earlier literature; and this connection has remained although, not everybody agrees with the concession of the term "quality" to refer only to expected utility-based measures (5). Anyhow, in health economics, utilities (values) are typically combined with survival estimates and aggregated across individuals to generate quality-adjusted life years (QALYs) for use in cost–utility analyses of healthcare interventions (6).

There are many methods available regarding how the health states can be valued and grouped into two broad categories of measures: direct and indirect methods of measurement. The direct valuation methods include standard gamble (SG), time trade-off (TTO), DCE (discrete choice experiment), rating scales, equivalence technique, ratio scaling and person trade-off. The SG approach is the classic method of measuring preferences in economics under conditions of uncertainty, and is based on von Neumann Morgenstern utility theory (7). The theoretical underpinnings of all other methods are less clear. TTO valuation methodology does not conform to utility-under-uncertainty requirements under expected utility theory, but is still a dominant method in the valuation sets across countries (8). Regarding VAS values, there are a lot of criticisms and opposing views on their suitability for use in cost utility analysis. Mostly, criticisms consist of VAS values not being choice based and their lack of theoretical foundation (5). Due to these issues, most health economists would recommend a choice-based value set, derived from TTO or DCE data, especially for economic studies where cost-utility analysis is anticipated. If a choice-based value set is not available for the country/region, a choice-based value set can be selected from a country/region that most closely approximates the country where the study is being conducted. Alternatively, a VAS-based value set can be used if that is available for the country/region (9). Due to these issues, most health economists would recommend a choice-based value set, derived from TTO or discrete choice experiment (DCE) data to be used in studies that estimate the value of health states of any population. If a choice-based value set is not available for the country/region, a choice-based value set can be selected from a country/region that most closely approximates the country where the study is being conducted. Alternatively, a VAS-based value set can be used if that is available for the country/region (9).

Utilities (values representing preferences) for healthcare priority setting are typically obtained indirectly by asking the general population (or patients) to fill in a questionnaire and attach value to hypothetical heath state, later on converting the results to a value set for all health states, using population (or patient) values. There are at least two advantages that contributed to the popularity of the indirect methods: the pool of health states is already defined and so are their values (value set). When a patient defines his own health state in subsequent studies, a value can thus be attached to his/her health state from the value set.

Some of the established questionnaires are the Health Utility Index, the Short Form 6D, 15D instrument, Assessment of Quality of Life (AQOL) and the EuroQol 5D (EQ-5D). The EQ-5D is a prominent example of preference-based measures developed by the EuroQol Group (9). It has been suggested that these are the most widely used preference-based measures in the world (10). To improve the instrument's sensitivity and to reduce ceiling effect, EuroQoL Group developed a new version in 2009, called EQ-5D-5L. The new version kept its original 5 dimensions, but expanded the response options from 3 to 5 levels. As there are a lot of existing 3L value sets in many countries, for comparison reasons a non-parametric model was set up to transform any EQ-5D-3L values into EQ-5D-5L values. In this way, 5L values can also be used in cases when 5L preferences directly elicited from representative general population samples are not yet available (11).

The EQ-5D-3L descriptive system has been formally translated and validated into the Slovenian language in 1999/2000 (12). The two primary objectives of this paper were (a) to develop first logically consistent EQ-5D-3L TTO-based value sets for Slovenia and (b) to revisit earlier developed VAS-based EQ-5D-3L value sets for Slovenia (13). Some issues that went undetected with the previous VAS value set have been identified, and methodological advances seem to make it possible to improve on earlier modelling.

## 2 METHODS

### 2.1 Study Overview

The study was a multicentre, population-based study, using face-to-face interviews. The sample was prepared by the Statistical Office of Slovenia using the Central Population Register. In the sample, 1,000 individuals aged 18+ from 40 Slovenian municipalities were included. At the first level, 40 municipalities were randomly selected and later on 25 individuals were selected from each municipality. Each person carried a name, last name, address, house number, postcode, municipality, age and gender. The investigators started the interviews in September 2005 and finished in April 2006. Participant recruitment was conducted primarily through landline telephone numbers for each participant in the sample. 225 participants agreed to participate in the survey. Interviews were conducted by three interviewers, who underwent one-day training on the health state valuations, the purpose of the interviews and TTO procedures. To facilitate the training, the interview book prepared by Gudex (14) was translated into Slovenian language and used for training of the interviewers and in the pilot training. Each investigator conducted 5 test interviews.

### 2.2 EQ-5D

EQ-5D consists of a descriptive system and EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system consists of 5 dimensions: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD). Each dimension has 3 levels: no problems, some problems, and extreme problems (9). The respondent is asked to indicate his or her health state by ticking the box that marks the most appropriate level of problems in each dimension. A unique health state can be described by using a 5-digit vector formed according to the responses to the 5 questions. For example, no problems in MO and SC, some problems in UA and PD and extreme problems in AD can be referred to as "11223." Health states defined in this way may be converted into a single summary index by applying a formula that attaches values to each of the levels in each dimension. A total of 243 possible health states can be defined.

### 2.3 Health State Selection

In the valuation task, each investigator had 3 sets of health states, and investigators decided randomly which set to use with each respondent. The sets were named A, B and C. Each set contained 15 health states. Some health states were included in all three sets, but some were not. Health states in each set represent the complete scale of health states, from worst to best health states. Sets B and C were developed in 2000 (16). The number of all various directly valued health states in all three sets is 23 plus unconscious and dead. These states are 11211, 11111, 21111, 12111, 11112, 11121, 11122, 11113, 11131, 11133, 11312, 13311, 32211, 22222, 21232, 22323, 22233, 32223, 32313, 23232, 33321, 33323, 33333, unconscious and dead. Health states can also be divided into mild, moderate and severe states (17) in such a way that all the categories were represented in all three sets.

### 2.4 Interview Process

The questionnaire consists of four parts. In the first part, the respondent indicated his/her own health state on the day of the interview using an EQ-5D descriptive system. Furthermore, the respondent marks how good or bad his/her health state is on a visual analogue scale (VAS) from 0 to 100 (where 0 represents the worst health state imaginable and 100 represents the best health state imaginable).

The second part of the questionnaire is a valuation of the 15 selected health states. Once the respondent had familiarised himself/herself with the health states by reading them, he/she ranked the selected states from worst to best. After ranking he/she attached the value from 0 to 100 to all 15 health states.

The third part of the interview is the valuation of the same selected 15 health states using time trade off (TTO) method. The interviewers follow the adapted Measurement and Value of Health study (MVH) protocol (14). The MVH study was a large exercise, in which 3,395 respondents valued 13 different health states. Because of the limited budget, we included 23 health states altogether. Out of 23 health states, we made three different sets of 15 health states (sets A, B and C) as described in Chapter 2.3.

The objective of the TTO is to determine the length of lifetime the respondent would be willing to forego to live in a better health state (typically 'full health') and to avoid living in a bad health state. This is achieved by presenting respondents with a series of choice tasks, each involving two alternative hypothetical lives. The two lives are presented so that the respondent is forced to choose between a longer life in the health state of interest and a shorter life in better health (15).

The last part of the interview collects social demographic data: gender, age, education, work experience, smoking habits, experience with illness and postcode.

### 2.5 Preference Elicitation Techniques

In the TTO procedure, the interviewers used a TTO board and a set of health state cards. A TTO board was made of three layers of thick cardboard and incorporated a sliding scale from 0 to 10 years. Both sides of the board were used, one for states better than dead and the other for health states worse than dead. The respondent was taken through each of 15 health states to be valued,

one at a time, with the interviewer moving the scale as appropriate. The respondent needed to make a series of choices between two hypothetical lives: one involving x years of healthy life, followed by death (Life A) and the other involving t years in a worse health state (where x≤t), followed by death (Life B). Time t was fixed, whereas time x was varied until the respondent reached their point of indifference. This iterative procedure continued until the respondent was unable to choose between the two lives. In our study, the respondent started with a choice between living Life A (health state 11111) for 10 years followed by death and living Life B (worse health state) for 10 years followed by death. Life A was chosen – the next choice was between Immediate Death (x=0 for Life A) and 10 years of Life B, followed by death. In the next choice, x was set at 5 years; in case Life A was chosen, x was decreased and the opposite until the point of indifference was found. The value of Life B was calculated according to how much healthy time the respondent was willing to forgo at this point of indifference – the utility value of the health state was at this point calculated as x/10. In case of states worse than dead, the respondent was again given two alternatives, but this time Life A was a combination of health state I for y number of years followed by full health for x number of years (x+y=10), followed by death. Life B was a certain outcome of immediate death. Time x was again varied until the respondent was indifferent between both alternatives. At this point, the utility value for health state I was calculated as -x/(10-x). Respondents were allowed to trade time in months and weeks.

In VAS procedure, the respondents ranked the health states and, in the second phase, attached them a value from 0 to 100. VAS values were later rescaled using the mean observed values for state 11111 and death. Health state "Unconscious" was not used.

### 2.6 Statistical Analyses

Historically, values for EQ-5D-3L have been modelled by use of ordinary least squares (OLS) regression, using dummy variables representing the presence or absence of different levels of problems on each of the five dimensions. Built on this framework, different interaction terms have been added in different national valuation studies. More recently, the introduction of the EQ-5D-5L has resulted in a range of innovations in terms of modelling, including hybrid models combining TTO and DCE data (24), random intercept models, censored/interval regression to account for censoring at -1, and use of constrained, non-linear regression models (18, 22, 23).

For EQ-5D-3L, the standard, additive 10-parameter model, hereafter referred to as ADD10, has parameters representing levels 2 and" 3 for each dimension. Let y represent the observed disutility of a health state, represent $x_{dl}$ the dummy variable indicating the presence of problems on dimension $d$ at level l and $\beta_{dl}$ the coefficient representing the estimated disutility of having problems on dimension $d$ at level $l$ (e.g. $\beta_{MO3}$ representing the disutility of having moderate problems on mobility). The mathematical function of ADD10 is as follows:

$$y = \sum_l \sum_d \beta_{dl} x_{dl} + e = \beta_{MO2} x_{MO2} + \beta_{SC2} x_{SC2} + \beta_{UA2} x_{UA2} + \beta_{PD2} x_{PD2} + \beta_{AD2} x_{AD2} + \beta_{MO3} x_{MO3} + \beta_{SC3} x_{SC3} + \beta_{UA3} x_{UA3} + \beta_{PD3} x_{PD3} + \beta_{AD3} x_{AD3} + e \quad (1)$$

An EQ-5D-3L variant of the constrained model approach used in the Chinese and Malaysian EQ-5D-5L valuation studies employs six primary parameters: one for each dimension, representing the disutility of having problems at level 3 $(\beta_{MO}, \beta_{SC}, \beta_{UA}, \beta_{PD}, \beta_{AD})$, which for level 2 are multiplied by parameters for level 2 (L2). Thus, the disutility of having moderate problems on mobility is $\beta_{MO} \times L_2$. The mathematical function of this model, hereafter MULT6, is as follows (note that $x_{dl}$ still represents the dummy variable representing the presence of problems on dimension $d$ at level $l$):

$$y = \sum_l (\sum_d \beta_d x_{dl}) L_l + e = (\beta_{MO2} x_{MO2} + \beta_{SC2} x_{SC2} + \beta_{UA2} x_{UA2} + \beta_{PD2} x_{PD2} + \beta_{AD2} x_{AD2}) L_2 + \beta_{MO3} x_{MO3} + \beta_{SC3} x_{SC3} + \beta_{UA3} x_{UA3} + \beta_{PD3} x_{PD3} + \beta_{AD3} x_{AD3} + e \quad (2)$$

This constrained model assumes that the relative severity of level 2, "moderate problems", is similar across dimensions. This assumption reduces the number of parameters to be fitted, and thereby provides more robust results than unconstrained models, particularly with smaller samples of data.

We tested the ADD10 and MULT6 models, with and without the inclusion of a constant term (intercept) representing any deviation from full health. The model variants including intercept are denoted with an "i", e.g. ADD10i. We also tested an extension of MULT6 in which the full expression is exponentiated by a separately fitted parameter P:

$$y = ((\beta_{MO2} x_{MO2} + \beta_{SC2} x_{SC2} + \beta_{UA2} x_{UA2} + \beta_{PD2} x_{PD2} + \beta_{AD2} x_{AD2}) L_2 + \beta_{MO3} x_{MO3} + \beta_{SC3} x_{SC3} + \beta_{UA3} x_{UA3} + \beta_{PD3} x_{PD3} + \beta_{AD3} x_{AD3})^P + e \quad (3)$$

This model, hereafter MULT6P, was included under the assumption that respondents may display diminishing sensitivity to health problems when combined, so that the perceived disutility of problems on two separate dimensions at the same time may be smaller than the sum of the disutility of each problem in isolation.

Standard error estimation is non-trivial in regression models involving multiplication of two or more (presumably normally distributed) parameters. Consequently, standard errors for model parameters and modelled values were estimated for MULT6 and MULT6P using bootstrapping

(22). Briefly, 10,000 bootstrap samples were drawn (with replacement) at the level of individual study participants, each subsample of the same size as the observed data. The regression models were fitted to each bootstrap sample, and standard errors were calculated by taking the standard deviation for the resulting coefficients and the predicted health state values.

Given the limited number of valued health states, and the relatively small sample size used in this study, we were concerned that regular regression models might produce results that were highly susceptible to random error. We, therefore, tested the included model variants using penalised regression, including Lasso (20), Ridge regression (17–19), and Elastic net (21).

Model selection was informed by two primary criteria, being monotonicity/logical consistency. Modelled state values should reflect the hierarchical structure of the EQ-5D descriptive system, so that further problems on any dimension should always result in worse (lower) values. Monotonic models were compared in terms of out-of-sample predictive accuracy for observed means. This was compared using leave-out-by-state cross-validation (18, 22). Predictive accuracy was assessed in terms of mean square difference between out-of-sample predictions and corresponding observed means, as well as Lin's Concordance Correlation Coefficient.

The final Slovenian TTO model was compared visually to the Polish EQ-5D-3L value set (25) and the UK MVH value set (26), and the final VAS model was compared visually to the EU VAS value set (27).

All statistical analyses were performed in the R statistical package, version 3.3.2, in the RStudio environment, using ggplot for graphical output (28–30). Regression models were run in the xreg package (31).

## 3 RESULTS

In total, 225 respondents completed the interview, of which 126 (56%) were female. Distribution of the respondents according to social and demographic variables is shown in Table 1. The sample was well representative of the Slovenian population in terms of age, educational level and activity with students being slightly underrepresented and unemployed being slightly overrepresented. Regarding gender distribution, women were overrepresented in the sample. The majority of problems reported in the EQ-5D descriptive system were pain/discomfort, followed by problems with usual activities and mobility. A really small share of the sample had problems with self-care (9.3%). The mean health state recorded on the EQ-VAS was 72.15 (SD 20.2) and the mean estimated interview difficulty was 2.87 (1 is very easy and 5 is very difficult).

**Table 1.** Study sample characteristics compared with the Slovenian general population data 2005.

| Group | Mean pre-test scores (SD) | Mean post-test scores (SD) |
|---|---|---|
| **Age** | | |
| 18–24 | 27 (12%) | 190,239 (11.5%) |
| 25–34 | 48 (21.3%) | 300,793 (18.2%) |
| 35–44 | 43 (19.1%) | 304,490 (18.5%) |
| 45–54 | 39 (17.3%) | 310,757 (18.9%) |
| 55–64 | 28 (12.5%) | 229,580 (13.9%) |
| 65+ | 40 (17.8%) | 312,874 (19%) |
| Mean age (SD) | 45.3 (17.4) | n/a |
| **Gender** | | |
| Male | 99 (44%) | 981,465 (49%) |
| Female | 126 (56%) | 1,021,893 (51%) |
| **Educational level** | | |
| Primary | 53 (23.6%) | 494 (28.8%) |
| Secondary | 147 (65.3%) | 952 (55.5%) |
| High | 25 (11.1%) | 267 (15.6%) |
| **Work** | | |
| Employed | 111 (49.3%) | 813,100 (47.3%) |
| Retired | 62 (27.5%) | 529,622 (30.8%) |
| Housewife | 8 (3.6%) | n/a |
| Student | 20 (8.9%) | 112,228 (6.5%) |
| Unemployed | 18 (8%) | 92,575 (5.4%) |
| Other | 6 (2.7%) | n/a |
| **EQ-5D dimension problems (%)** | | n/a |
| Mobility | 68 (30.2%) | |
| Self-care | 21 (9.3%) | |
| Usual activities | 69 (30.7%) | |
| Pain/discomfort | 101 (44.9%) | |
| Anxiety/Depression | 64 (28.4%) | |
| **EQ VAS own health (SD)** | 72.15 (20.2) | n/a |

Cross-validation fit statistics can be found in Table 2. The fitted parameters of ADD10 were not monotonic. MULT6 and MULT6P with no intercept were monotonic for both VAS and TTO, while the version with an intercept was monotonic for TTO only. MULT6 displayed poor fit, both in direct estimation and in cross-validation. Ridge regression improved out-of-sample predictive accuracy for ADD10 and MULT6, but not for MULT6P. By comparison, MULT6P had substantially improved fit, outperforming all other tested variants in terms of out of sample predictive accuracy, both for VAS and TTO data. MULT6P with an intercept did not improve predictions for TTO, and did not converge for VAS. MULT6P was selected for generating VAS and TTO value sets. Coefficients and bootstrap-based SE estimates for the two models can be found in Table 3.

**Table 2.** Cross-Validation fit statistics.

| TTO | ADD10 | ADD10i | MULT6 | MULT6i | MULT6P | MULT6iP |
|---|---|---|---|---|---|---|
| **Monotonicity** | - | - | ✓ | ✓ | ✓ | ✓ |
| **R** | 0.920 | 0.941 | 0.934 | 0.930 | 0.966 | 0.966 |
| **CCC** | 0.894 | 0.938 | 0.893 | 0.929 | 0.966 | 0.966 |
| **MSE** | 0.046 | 0.022 | 0.048 | 0.024 | 0.012 | 0.012 |
| **MAE** | 0.181 | 0.114 | 0.182 | 0.126 | 0.087 | 0.087 |
| **VAS** | **ADD10** | **ADD10i** | **MULT6** | **MULT6i** | **MULT6P** | **MULT6iP** |
| **Monotonicity** | - | - | ✓ | ✓ | ✓ | - |
| **R** | 0.926 | 0.919 | 0.891 | 0.923 | 0.971 | - |
| **CCC** | 0.879 | 0.897 | 0.886 | 0.883 | 0.941 | - |
| **MSE** | 0.02 | 0.015 | 0.015 | 0.021 | 0.01 | - |
| **MAE** | 0.123 | 0.094 | 0.096 | 0.102 | 0.082 | - |

R – Pearson's correlation coefficient, CCC – concordance correlation coefficient, MSE – mean squared error, MAE – mean absolute error

**Table 3.** Coefficients and bootstrap-based SE estimates.

| | TTO | | VAS | |
|---|---|---|---|---|
| | Coefficient | SE | Coefficient | SE |
| **MO** | 0.943 | 0.126 | 0.424 | 0.070 |
| **SC** | 0.243 | 0.052 | 0.105 | 0.029 |
| **UA** | 0.202 | 0.039 | 0.103 | 0.028 |
| **PD** | 0.448 | 0.049 | 0.180 | 0.012 |
| **AD** | 0.239 | 0.037 | 0.137 | 0.021 |
| **L2** | 0.125 | 0.043 | 0.176 | 0.025 |
| **P** | 0.551 | 0.044 | 0.423 | 0.020 |

## 4 DISCUSSION

The Slovenian VAS and TTO based value sets are presented in Annex 1 and 2. The first VAS value set for Slovenia was calculated back in year 2000, however, the values of the health state were not monotonic: some of the logically superior health states displayed lower values (12). In 2012, a new improved set was published (13), however, again due to some methodological issues discovered later, it cannot be recommended for Slovenia's priority setting. With the advanced methodology, for the first time in Slovenia it was possible to obtain a logically consistent and monotonic VAS based value set as well as a 3L TTO based value set, which is also the second 3L TTO based value set in Central and Eastern Europe.

Figure 1 displays the TTO value set compared to observed mean values, along with TTO-based values from a UK MVH study and the Polish TTO-based EQ-5D-3L valuation study. Figure 2 presents the Slovenian VAS value set, observed mean values, and the EU VAS value set.

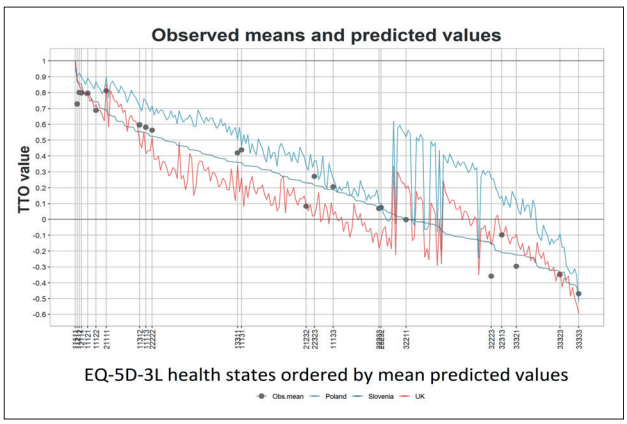


**Figure 1.** Graphical comparison of Slovenian EQ-5D-3L TTO value set versus (a) UK TTO and (b) Polish TTO value sets.

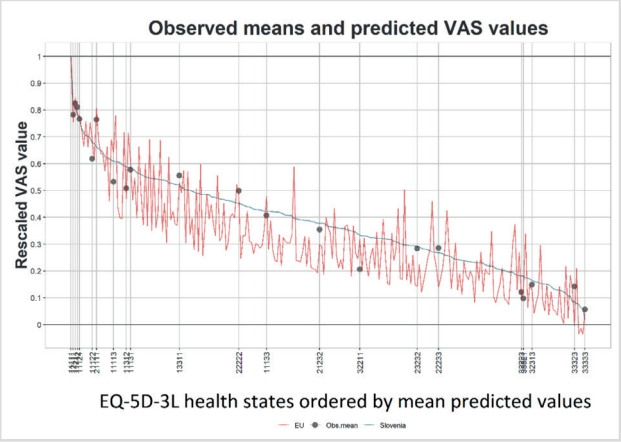


**Figure 2.** Graphical comparison of Slovenian VAS value set versus EU VAS value set.

For the TTO value set, there are two main drivers of differences between the national value sets: first, mobility has a substantially greater weight in the Slovenian value set. Second, the UK value set produces lower values for mild states, while the Polish value set produces higher values. The VAS value set is more in line with the EU VAS value set, but generally produces somewhat higher values. Due to considerable differences between TTO value sets in Slovenia in comparison to the UK and Poland, its use should be recommended for Slovenian studies.

After testing various modelling approaches, the Slovenian TTO and VAS value sets were fitted using a 6-parameter constrained regression model with a supplementary power term, which produces monotonic values and was superior in terms of out-of-sample predictive accuracy over the tested alternatives.

The Slovenian TTO-based value set, being a choice-based method, is recommended for use in all studies, including economic analysis. Systematic pairwise comparison across all conditions and value sets in previous studies (32) revealed the greatest differences between the TTO and VAS-based value sets, as well as the varying sensitivity of the disease burden evaluations of chronic disease conditions to the choice of value sets. Therefore, using a VAS value set in the presence of newly developed TTO value set in Slovenia would unnecessarily produce incomparable results. However, in order to allow for comparisons with previous studies where VAS values were used due to the absence of a TTO-based value set, it is suggested to present VAS-based results in parallel. Another option is also the presentation of the results in parallel with the UK TTO value set, given that it has been the most used value set in the region (33).

Further analysis of the differences between the first two TTO based value sets in Central and Eastern Europe (CEE) is recommended – it has always been claimed that CEE countries display more similar values of health states, which differ from value sets in Western European countries, however, the first glance at both value sets does not confirm such speculations.

The main limitation of the study is the year of the data collection: the completion of the valuation study has been substantially delayed (from the data collection in 2005), as earlier modelling attempts produced non-monotonic values. Attempts at ameliorating these modelling issues through the application of exclusion criteria failed, indicating that the observed non-monotonicities were not reflective of a small subgroup of respondents displaying conflicting preferences. The improved fit of the chosen model, which included a power term below 1, indicates that respondents display substantially diminishing sensitivity to increasing health problems. Whether or not this diminishing sensitivity is unique to this study population may warrant further investigation.

Besides the modelling issues, sample size and the low number of health states valued were additional reasons why it was difficult to obtain the monotonic value set. Currently, the EuroQol Group Association recommends the sample size of 1,000 units to complete the valuation study with sufficient statistical power. Back in 2005, such recommendations were not in place and our data collection was limited in financial terms as well as timewise.

## 5 CONCLUSION

The article presents the first TTO-based EQ-5D value set for Slovenia. There have been two previous attempts to present an EQ-5D VAS based value set in Slovenia, once in 2000 (12) and once in 2012 (13), however, those value sets either lacked logical consistency or consistent modelling techniques. The use of a constrained ordinary least squares approach built upon experiences from EQ-5D-5L valuation studies in China, but extended to handle diminishing sensitivity to increasing health problems, allowed us to generate logically consistent value sets for VAS and TTO. The two value sets presented in this paper are recommended for use in EQ-5D-3L studies in Slovenia.

## CONFLICT OF INTEREST

VPR and KR are members of the EuroQol Group, a not-for-profit organisation that develops and distributes instruments for measuring and valuing health.

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**ETHICAL APPROVAL**

Not required as the data in the study is not personal, but values of hypothetical health states.

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**Annex 1.** Slovenian EQ-5D-3L VAS value set.

| State | Utility | State | Utility | State | Utility | State | Utility |
|---|---|---|---|---|---|---|---|
| 11111 | 1 | 23131 | 0.351316 | 32222 | 0.243814 | 12313 | 0.435993 |
| 21111 | 0.6664 | 33131 | 0.135372 | 13222 | 0.51722 | 22313 | 0.371997 |
| 31111 | 0.304328 | 11231 | 0.496121 | 23222 | 0.440402 | 32313 | 0.149199 |
| 12111 | 0.81524 | 21231 | 0.423003 | 33222 | 0.19261 | 13313 | 0.362674 |
| 22111 | 0.63367 | 31231 | 0.181925 | 11322 | 0.54139 | 23313 | 0.307537 |
| 32111 | 0.291652 | 12231 | 0.476714 | 21322 | 0.45996 | 33313 | 0.105132 |
| 13111 | 0.61471 | 22231 | 0.406756 | 31322 | 0.20431 | 11123 | 0.528806 |
| 23111 | 0.51633 | 32231 | 0.171722 | 12322 | 0.519463 | 21123 | 0.44983 |
| 33111 | 0.236074 | 13231 | 0.396696 | 22322 | 0.442235 | 31123 | 0.198291 |
| 11211 | 0.817021 | 23231 | 0.337714 | 32322 | 0.19372 | 12123 | 0.507633 |
| 21211 | 0.634367 | 33231 | 0.126114 | 13322 | 0.431312 | 22123 | 0.432532 |
| 31211 | 0.291936 | 11331 | 0.414277 | 23322 | 0.367949 | 32123 | 0.187808 |
| 12211 | 0.753447 | 21331 | 0.353134 | 33322 | 0.146516 | 13123 | 0.421857 |
| 22211 | 0.605136 | 31331 | 0.136599 | 11132 | 0.489607 | 23123 | 0.359742 |
| 32211 | 0.279555 | 12331 | 0.398349 | 21132 | 0.417575 | 33123 | 0.141042 |
| 13211 | 0.587925 | 22331 | 0.339169 | 31132 | 0.17854 | 11223 | 0.508098 |
| 23211 | 0.496312 | 32331 | 0.12711 | 12132 | 0.470522 | 21223 | 0.432916 |
| 33211 | 0.22514 | 13331 | 0.330462 | 22132 | 0.401527 | 31223 | 0.188043 |
| 11311 | 0.618425 | 23331 | 0.2786 | 32132 | 0.168393 | 12223 | 0.488074 |
| 21311 | 0.519047 | 33331 | 0.084473 | 13132 | 0.391584 | 22223 | 0.416293 |
| 31311 | 0.237527 | 11112 | 0.793055 | 23132 | 0.333207 | 32223 | 0.177737 |
| 12311 | 0.590712 | 21112 | 0.624379 | 33132 | 0.123018 | 13223 | 0.406013 |
| 22311 | 0.498429 | 31112 | 0.287819 | 11232 | 0.470944 | 23223 | 0.345901 |
| 32311 | 0.226314 | 12112 | 0.73681 | 21232 | 0.401884 | 33223 | 0.131702 |
| 13311 | 0.485851 | 22112 | 0.596115 | 31232 | 0.168621 | 11323 | 0.423985 |
| 23311 | 0.414433 | 32112 | 0.275534 | 12232 | 0.452735 | 21323 | 0.361592 |
| 33311 | 0.17657 | 13112 | 0.579401 | 22232 | 0.38639 | 31323 | 0.142281 |
| 11121 | 0.767966 | 23112 | 0.489795 | 32232 | 0.158637 | 12323 | 0.407701 |
| 21121 | 0.612567 | 33112 | 0.221496 | 13232 | 0.376774 | 22323 | 0.347381 |
| 31121 | 0.282798 | 11212 | 0.737905 | 23232 | 0.320094 | 32323 | 0.132707 |
| 12121 | 0.718127 | 21212 | 0.596725 | 33232 | 0.113935 | 13323 | 0.338527 |
| 22121 | 0.58538 | 31212 | 0.275809 | 11332 | 0.393568 | 23323 | 0.285876 |
| 32121 | 0.270628 | 12212 | 0.69438 | 21332 | 0.334958 | 33323 | 0.089715 |
| 13121 | 0.569227 | 22212 | 0.570879 | 31332 | 0.124222 | 11133 | 0.384893 |
| 23121 | 0.481929 | 32212 | 0.263795 | 12332 | 0.378355 | 21133 | 0.327293 |
| 33121 | 0.217045 | 13212 | 0.555435 | 22332 | 0.321498 | 31133 | 0.118936 |
| 11221 | 0.719125 | 23212 | 0.471123 | 32332 | 0.114913 | 12133 | 0.369963 |
| 21221 | 0.585969 | 33212 | 0.210836 | 13332 | 0.313094 | 22133 | 0.314037 |
| 31221 | 0.2709 | 11312 | 0.582693 | 23332 | 0.262868 | 32133 | 0.109702 |
| 12221 | 0.678933 | 21312 | 0.49232 | 33332 | 0.073032 | 13133 | 0.305756 |
| 22221 | 0.560972 | 31312 | 0.222913 | 11113 | 0.568446 | 23133 | 0.256196 |
| 32221 | 0.258995 | 12312 | 0.557946 | 21113 | 0.481322 | 33133 | 0.068137 |
| 13221 | 0.545982 | 22312 | 0.473103 | 31113 | 0.216699 | 11233 | 0.370296 |
| 23221 | 0.463627 | 32312 | 0.211981 | 12113 | 0.544737 | 21233 | 0.314334 |
| 33221 | 0.206466 | 13312 | 0.46132 | 22113 | 0.462634 | 31233 | 0.109909 |
| 11321 | 0.572413 | 23312 | 0.393717 | 32113 | 0.205884 | 12233 | 0.355824 |
| 21321 | 0.484402 | 33312 | 0.163382 | 13113 | 0.451156 | 22233 | 0.301411 |
| 31321 | 0.218451 | 11122 | 0.705034 | 23113 | 0.385039 | 32233 | 0.100801 |
| 12321 | 0.548422 | 21122 | 0.577498 | 33113 | 0.157758 | 13233 | 0.29333 |
| 22321 | 0.465569 | 31122 | 0.266943 | 11213 | 0.545255 | 23233 | 0.244864 |
| 32321 | 0.207603 | 12122 | 0.667085 | 21213 | 0.463048 | 33233 | 0.059767 |
| 13321 | 0.454006 | 22122 | 0.553138 | 31213 | 0.206126 | 11333 | 0.307413 |
| 23321 | 0.387478 | 32122 | 0.255124 | 12213 | 0.523088 | 21333 | 0.257703 |
| 33321 | 0.159344 | 13122 | 0.538492 | 22213 | 0.445189 | 31333 | 0.069245 |
| 11131 | 0.516128 | 23122 | 0.457638 | 32213 | 0.195504 | 12333 | 0.294662 |
| 21131 | 0.439509 | 33122 | 0.202938 | 13213 | 0.434188 | 22333 | 0.24608 |
| 31131 | 0.192067 | 11222 | 0.66788 | 23213 | 0.370437 | 32333 | 0.060669 |
| 12131 | 0.49567 | 21222 | 0.55367 | 33213 | 0.148167 | 13333 | 0.238788 |
| 22131 | 0.422629 | 31222 | 0.255388 | 11313 | 0.453441 | 23333 | 0.194682 |
| 32131 | 0.181692 | 12222 | 0.634971 | 21313 | 0.386994 | 33333 | 0.021893 |
| 13131 | 0.412197 | 22222 | 0.530963 | 31313 | 0.15903 | | |

**Annex 2.** Slovenian EQ-5D-3L TTO value set.

| State | Utility | State | Utility | State | Utility | State | Utility |
|---|---|---|---|---|---|---|---|
| 11111 | 1 | 23131 | 0.128439 | 32222 | -0.03062 | 12313 | 0.34613 |
| 21111 | 0.661462 | 33131 | -0.25294 | 13222 | 0.430732 | 22313 | 0.207237 |
| 31111 | 0.130169 | 11231 | 0.389626 | 23222 | 0.282156 | 32313 | -0.18975 |
| 12111 | 0.853651 | 21231 | 0.245965 | 33222 | -0.13124 | 13313 | 0.218732 |
| 22111 | 0.606623 | 31231 | -0.1593 | 11322 | 0.46964 | 23313 | 0.091724 |
| 32111 | 0.097211 | 12231 | 0.349529 | 21322 | 0.31599 | 33313 | -0.28289 |
| 13111 | 0.623976 | 22231 | 0.210278 | 31322 | -0.10538 | 11123 | 0.49996 |
| 23111 | 0.444812 | 32231 | -0.18735 | 12322 | 0.426358 | 21123 | 0.342034 |
| 33111 | -0.01073 | 13231 | 0.221799 | 22322 | 0.278326 | 31123 | -0.08574 |
| 11211 | 0.850867 | 23231 | 0.094535 | 32322 | -0.13419 | 12123 | 0.455282 |
| 21211 | 0.60504 | 33231 | -0.28058 | 13322 | 0.290467 | 22123 | 0.303556 |
| 31211 | 0.096229 | 11331 | 0.254042 | 23322 | 0.157111 | 32123 | -0.11484 |
| 12211 | 0.770598 | 21331 | 0.124011 | 33322 | -0.22977 | 13123 | 0.315952 |
| 22211 | 0.554403 | 31331 | -0.25653 | 11132 | 0.385375 | 23123 | 0.180134 |
| 32211 | 0.063968 | 12331 | 0.218141 | 21132 | 0.242199 | 33123 | -0.21131 |
| 13211 | 0.570517 | 22331 | 0.091182 | 31132 | -0.16224 | 11223 | 0.453969 |
| 23211 | 0.401345 | 32331 | -0.28333 | 12132 | 0.34543 | 21223 | 0.302415 |
| 33211 | -0.04194 | 13331 | 0.1018 | 22132 | 0.20661 | 31223 | -0.11571 |
| 11311 | 0.616823 | 23331 | -0.01638 | 32132 | -0.19025 | 12223 | 0.411364 |
| 21311 | 0.439082 | 33331 | -0.37271 | 13132 | 0.2181 | 22223 | 0.265157 |
| 31311 | -0.0148 | 11112 | 0.841454 | 23132 | 0.091144 | 32223 | -0.14437 |
| 12311 | 0.565379 | 21112 | 0.59959 | 33132 | -0.28336 | 13223 | 0.277172 |
| 22311 | 0.397094 | 31112 | 0.092834 | 11232 | 0.344249 | 23223 | 0.145055 |
| 32311 | -0.04503 | 12112 | 0.763187 | 21232 | 0.205552 | 33223 | -0.23949 |
| 13311 | 0.410581 | 22112 | 0.549314 | 31232 | -0.19109 | 11323 | 0.310866 |
| 23311 | 0.264468 | 32112 | 0.060641 | 12232 | 0.305699 | 21323 | 0.175548 |
| 33311 | -0.1449 | 13112 | 0.565321 | 22232 | 0.170885 | 31323 | -0.21497 |
| 11121 | 0.779161 | 23112 | 0.397046 | 32232 | -0.21871 | 12323 | 0.273356 |
| 21121 | 0.560205 | 33112 | -0.04506 | 13232 | 0.182084 | 22323 | 0.141589 |
| 31121 | 0.067744 | 11212 | 0.76107 | 23232 | 0.058026 | 32323 | -0.24229 |
| 12121 | 0.711564 | 21212 | 0.54785 | 33232 | -0.31063 | 13323 | 0.152565 |
| 22121 | 0.512356 | 31212 | 0.059681 | 11332 | 0.213388 | 23323 | 0.030755 |
| 32121 | 0.03604 | 12212 | 0.69593 | 21332 | 0.086822 | 33323 | -0.33326 |
| 13121 | 0.527634 | 22212 | 0.5007 | 31332 | -0.28691 | 11133 | 0.237367 |
| 23121 | 0.365528 | 32212 | 0.028129 | 12332 | 0.17853 | 21133 | 0.108786 |
| 33121 | -0.06823 | 13212 | 0.515767 | 22332 | 0.054748 | 31133 | -0.26893 |
| 11221 | 0.709673 | 23212 | 0.355487 | 32332 | -0.31335 | 12133 | 0.201903 |
| 21221 | 0.510957 | 33212 | -0.07569 | 13332 | 0.065126 | 22133 | 0.076272 |
| 31221 | 0.035094 | 11312 | 0.558733 | 23332 | -0.05061 | 32133 | -0.29558 |
| 12221 | 0.65042 | 21312 | 0.391579 | 33332 | -0.4016 | 13133 | 0.08679 |
| 22221 | 0.465742 | 31312 | -0.04905 | 11113 | 0.592636 | 23133 | -0.03037 |
| 32221 | 0.003995 | 12312 | 0.510968 | 21113 | 0.419503 | 33133 | -0.38449 |
| 13221 | 0.48022 | 22312 | 0.351413 | 31113 | -0.0288 | 11233 | 0.200849 |
| 23221 | 0.325111 | 32312 | -0.07872 | 12113 | 0.542813 | 21233 | 0.075303 |
| 33221 | -0.09848 | 13312 | 0.364335 | 22113 | 0.378293 | 31233 | -0.29638 |
| 11321 | 0.521351 | 23312 | 0.223497 | 32113 | -0.0588 | 12233 | 0.166296 |
| 21321 | 0.360218 | 33312 | -0.17692 | 13113 | 0.391539 | 22233 | 0.043453 |
| 31321 | -0.07217 | 11122 | 0.703183 | 23113 | 0.247659 | 32233 | -0.32271 |
| 12321 | 0.475612 | 21122 | 0.506132 | 33113 | -0.15798 | 13233 | 0.05376 |
| 22321 | 0.321143 | 31122 | 0.031824 | 11213 | 0.541361 | 23233 | -0.06124 |
| 32321 | -0.10148 | 12122 | 0.644578 | 21213 | 0.377075 | 33233 | -0.41062 |
| 13321 | 0.333726 | 22122 | 0.461154 | 31213 | -0.0597 | 11333 | 0.082479 |
| 23321 | 0.196118 | 32122 | 0.000785 | 12213 | 0.494567 | 21333 | -0.0344 |
| 33321 | -0.19857 | 13122 | 0.47556 | 22213 | 0.337423 | 31333 | -0.38789 |
| 11131 | 0.432582 | 23122 | 0.321098 | 32213 | -0.0892 | 12333 | 0.05049 |
| 21131 | 0.283774 | 33122 | -0.10151 | 13213 | 0.350186 | 22333 | -0.0643 |
| 31131 | -0.13 | 11222 | 0.642901 | 23213 | 0.210866 | 32333 | -0.41322 |
| 12131 | 0.390857 | 21222 | 0.459833 | 33213 | -0.18688 | 13333 | -0.05462 |
| 22131 | 0.247056 | 31222 | -0.00014 | 11313 | 0.386101 | 23333 | -0.16321 |
| 32131 | -0.15845 | 12222 | 0.589543 | 21313 | 0.242843 | 33333 | -0.498 |
| 13131 | 0.258901 | 22222 | 0.416978 | 31313 | -0.16174 | | |

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# DESCRIBING SERBIAN HOSPITAL ACTIVITY USING AUSTRALIAN REFINED DIAGNOSIS RELATED GROUPS: A CASE STUDY IN VOJVODINA PROVINCE

## OPIS SRBSKE BOLNIŠNIČNE DEJAVNOSTI Z UPORABO AVSTRALSKIH SKUPIN PRIMERLJIVIH PRIMEROV DIAGNOZ: PRIKAZ ZA VOJVODINO

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**ABSTRACT**

**Introduction:** AR-DRG system for classification hospital episodes was implemented in Serbia to improve efficiency and transparency in the health system.

**Methods:** L3H3, IQR, and 10th–95th percentile methods were used to identify outlier episodes in the classification. Classification efficiency and within-group homogeneity were measured by an adjusted reduction in variance ($R^2$) and a coefficient of variation (CV).

**Results:** There were 246,131 hospital episodes with a total 1,651,913 bed days from 14 hospitals. All episodes were classified into 652 groups of which 441 had CV lower than 100%. "Medical groups" accounted for 51% of groups and for 72% of episodes. Chemotherapy and vaginal delivery were the highest volume groups, with 5% and 4% of total episodes. Major diagnostic category 6 (MDC 6, Diseases of the digestive system) was the highest volume MDC, accounting for 11% of episodes. "Day-cases" and "prolonged hospitalisation" accounted for 21% and 3% of episodes, respectively. The average length of stay varied from 5.6 to 8.2 days. Adjusted $R^2$ was 0.3 for untrimmed data. Trimming by L3H3, IQR, and 10th–95th percentile method improved the value of adjusted $R^2$ to 0.61, 0.49, and 0.51, identifying 24%, 7%, and 7% of total cases as outliers, respectively. Mental diseases (MDC 19) remained the lowest adjusted $R^2$ in untrimmed and trimmed datasets.

**Conclusion:** A long length of stay and a small percentage of "day-cases" characterized hospital activity in Vojvodina. Trimming methods significantly improved DRG efficiency. Future studies should consider cost data.

**Keywords:**
average length of stay, outliers, reduction of variance, AR-DRG, casemix, healthcare financing, clinical coding

***IZVLEČEK***

***Uvod:*** *Klasifikacijski sistem hospitalizacij AR-DRG je bil v Srbiji vpeljan za izboljšanje učinkovitosti in preglednosti zdravstvenega sistema.*

***Metode:*** *Za prepoznavanje odstopanj v klasifikaciji so bile uporabljene metode L3H3, IQR, in 10.-95. percentila. Učinkovitost klasifikacije in homogenosti znotraj skupine primerljivih primerov diagnoz sta bili izmerjeni s prilagojenim zmanjšanjem neskladij ($R^2$) in koeficientom razlik (CV).*

***Rezultati:*** *Zabeleženih je bilo 246.131 hospitalizacij s skupnim številom 1.651.913 preležanih dni v 14 bolnišnicah. Vse hospitalizacije so bile razvrščene v 652 skupin, od tega jih je imelo 441 vrednost CV nižjo od 100 %. »Kliničnih skupin« je bilo 51 % od vseh skupin in 72 % od vseh hospitalizacij. Kemoterapija in vaginalni porod sta po obsegu največji skupini s 5 % in 4 % vseh hospitalizacij. Skupina primerljivih primerov diagnoz 6 (MDC 6, bolezni prebavnega sistema) je največja, in sicer zavzema 11 % vseh hospitalizacij. »Dnevne obravnave« obsegajo 22 % in »podaljšane hospitalizacije« 3 % hospitalizacij. Povprečno trajanje hospitalizacije se giblje med 5,6 in 8,2 dni. Prilagojeni $R^2$ se obravnava za 0,3 neprirezanih podatkov. Aplikacija metod L3H3, IQR, in 10.-95. percentila je izboljšala vrednost prilagojenega $R^2$ na 0,61, 0,49 in 0,51, esktremne vrednosti so se pojavljale v 24 %, 7 % in 7 % vseh primerov. Duševne bolezni (MDC 19) imajo najnižji prilagojen $R^2$ v neprirezanih in prirezanih podatkovnih setih.*

***Zaključek:*** *Bolnišnično dejavnost v Vojvodini označuje dolgotrajna hospitalizacija in nizek delež dnevnih obravnav. Metode prirezovanja so opazno izboljšale učinkovitost DRG. Prihodnje raziskave naj vključijo še stroškovni vidik.*

***Ključne besede:***
*povprečno trajanje hospitalizacije, odstopanja, zmanjšanje neskladij, AR-DRG, razvrščanje casemix, financiranje zdravstva, klinično kodiranje*

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## 1 INTRODUCTION

Despite decades of transition, Serbia has maintained an archaic organisation of the health system inherited from the former Yugoslavia, with national social health insurance, universal coverage, public hospitals and physicians as state employees (1). The National Health Insurance Fund collects insurance revenues and distributes them to providers according to a contract between the Fund and providers. An integral part of the contract is a business plan with the planned amount of all services based on previous-year inputs rather than service delivery. Therefore, hospitals are incited to gradually increase inputs through increasing the bed occupancy rate, performing unnecessary procedures, and employing new staff, rather than focusing on the results or the quality of care.

To increase the efficiency of hospital healthcare, the World Bank has recommended the introduction of a prospective payment system based on diagnostic-related groups (DRGs) as one of the priorities in the reform of public finances (2). The DRG is a case-mix system created at Yale University for classifying hospital episodes in groups that are relatively homogeneous with respect to resource use and clinical conditions (3). Similar to other European countries, the main arguments for the implementation of the DRG system were to improve transparency and efficiency without deterioration in the quality of care (4, 5). The system improves transparency by condensing the confusingly large number of individual patients and thousands of procedures into a manageable number of groups. This allows for group analyses for comparison between states, regions, hospitals and departments (4).

DRG systems are adopted as a reimbursement base for a prospective payment system (5, 6). The prospective payment system incites hospitals to improve efficiency, to limit the services per patient, to treat more patients and to produce sufficient services meeting patient needs. The Australian redefined version of DRG (AR-DRG 6.0) was chosen as a case-mix model for implementation in Serbia (7). Different versions of AR-DRG, in original or in modified form, have been previously implemented in Germany, Romania, Slovenia, Croatia, Ireland, New Zealand etc. (8).

The DRG-based payment system consists of the classification system and the payment formula that is a product of hospital base rate and relative weights adjusted for outliers (9). The method for determining outliers is an integral element of any payment system and can be as important as the patient classification system itself (10). Outliers are essential because they can lead healthcare providers to expensive losses. The methods for handling outliers and weights are specific for every country or even providers according to the distribution of costs, the length of stay and the type of hospital (i.e. level of care) in the data sample (11). In general, there are two types of methods for detecting outliers: parametric and non-parametric (11). Parametric methods are based on a normal distribution of episodes around arithmetic mean, whereas non-parametric are based on inter-quartile range. Standing procedure before the implementation of a certain DRG scheme involves testing several classifications during the pilot stage and subsequently adopting the most effective one according to relevant statistical parameters (12).

The study aims to describe hospital activity using the AR-DRG, to examine case-mix performances using relevant statistics and to estimate the data quality in one Serbian province. Findings could be generalised at a national level. Results will provide precious information for the creators of the new hospital payment system.

## 2 METHODS

The autonomous province Vojvodina is located in the northern part of Serbia, with a population of 1.9 million and a total area of 21,506 square kilometres (13). Demographic and clinical data has been obtained from five university hospitals and nine general hospitals in 2016. Patients with severe conditions were transported from general to university hospitals. All hospitals might be considered as part of a complete system.

The National Institute of Public Health collected hospital records that contain age, gender, admission and discharge date, discharge status, birthweight for new-borns, the principal diagnosis, secondary diagnoses and performed procedures. The International Classification of Diseases (ICD) 10th revision and the Australian Classification of Health Interventions (ACHI) 7th edition were used for coding diagnoses and procedures. The collected data was input into computer-based software named “grouper” created by Laeta (Laeta Pty Ltd, Randwick, New South Wales, Australia), which classifies patients into AR-DRG groups according to the algorithm (7).

The AR-DRG 6.0 classification system contains 698 groups with unique alphanumeric codes classified into 23 major diagnostic categories (MDCs). The AR-DRG version 6.x definitions manual contains full names for DRGs and MDCs (7). The first character in the DRGs code refers to the major diagnostic category. According to the next two characters, all groups can be separated into “surgical DRGs” (from 01 to 39), “medical DRSs” (from 60 to 99) and “other DRSs” (from 40 to 59). The last character represents the resource consumption. Cases with higher and variable costs are grouped into a pre-MDC category.

Error cases are assigned to error DRGs (960Z, 962Z and 963Z). Groups 801A, 801B and 801C, contain operating-room procedures unrelated to the principal diagnosis.

Trimming is a method of identifying cases based on the length of stay (LOS). LOS is calculated as a difference between admission and discharge date. All cases between lower and upper threshold are determined as inliers, whereas cases out of range are determined as outliers. Three trimming methods were used: L3H3, IQR and 10th–95th percentile method. The L3H3 method is based on the average length of stay (ALOS) of each DRG. In such a method, a lower threshold (L3) is ALOS divided by three, whereas an upper threshold (H3) is ALOS multiplied by three. In the interquartile range (IQR) method, the lower threshold is calculated by equation Q1-1.5*IQR, whereas the upper threshold as Q3+1.5*IQR. The IQR is a difference between the first quartile (Q1) and the third quartile (Q3) of the distribution of LOS. In the final, 10th–95th method, the lower threshold being equal to the 10th percentile of LOS and the upper threshold to the 95th percentile of LOS.

The coefficient of variation (CV) measures variation in LOS for each DRG, as the ratio of the standard deviation to the mean. The coefficient of variation below 100% reflects acceptable within-group homogeneity.

The total sum of squares (SST) of the LOS is defined as the sum of the squared deviations of each observation from the mean of all observations (6). The error sum of squares (SSE) is defined as the sum of squared deviations of each observation from the mean of the group into which the observation has been classified. The difference between SST and SSE is the regression sum of squares (SSR). SSR is a variation between the mean of each group and the mean of the observed dataset. The ratio of SSR to SST provides a measure of the reduction in variation (RIV) measured with the coefficient of multiple determination ($R^2$). $R^2$ represents the fraction of variation in LOS explained by the DRG. In other words, $R^2$ is a summary measure of the extent to which the DRG system can predict the value of an outcome variable based on the characteristics of individual patients. $R^2$ ranges between zero and one. The coefficient of multiple determination takes maximum value only if the number of hospital episodes and number of DRG groups are equal. Since the number of groups and sample size affect $R^2$, adjusted $R^2$ was used (14). The statistical significance of adjusted $R^2$ can be measured using F statistic (15).

## 3 RESULTS

Data was obtained from 14 hospitals in Vojvodina province containing 246,131 hospital discharges with 1,651,913 inpatient days. Women accounted for 56% of all episodes. The average age of hospital patient was 50 years. University hospitals recorded 100,334 (40.8%) discharges, while general hospitals recorded 145,797 (59.2%) discharges.

A classification of all discharges using AR-DRG version 6.0 resulted in 652 discrete DRG groups, of which 8.3% had five episodes or less. There were 333 “medical”, 280 “surgical” and 39 “other DRGs”, accounting for 71.7%, 25.6% and 2.7% of discharges, respectively. R63Z (chemotherapy) accounted for the majority of inpatient discharges (4.9 per cent) with ALOS of 1.3 days. E71B (respiratory neoplasms without catastrophic complication and comorbidity) accounted for the majority of bed days (2.4 per cent) with ALOS of 7.9 days. The 20 highest volume DRGs accounted for 34.1% of discharges, while 142 highest volume DRGs accounted for 79.8% of discharges (Table 1).

**Table 1.** The highest volume DRGs with the average length of stay and the coefficient of variation for untrimmed data in Vojvodina province during 2016.

| Diagnostic related group | ALOS | % of total episodes (%) | CV |
|---|---|---|---|
| R63Z | 1.31 | 4.9 | 98% |
| O60Z | 4.43 | 3.6 | 69% |
| G60B | 3.32 | 3.0 | 195% |
| E71B | 7.85 | 2.0 | 126% |
| Z64A | 7.11 | 1.9 | 139% |
| O66Z | 3.39 | 1.8 | 102% |
| J62B | 2.84 | 1.7 | 233% |
| J11Z | 2.26 | 1.7 | 172% |
| R61C | 1.00 | 1.6 | 0% |
| N09Z | 1.77 | 1.5 | 154% |
| O01B | 6.13 | 1.3 | 48% |
| G10B | 4.29 | 1.1 | 70% |
| 961Z | 10.68 | 1.1 | 101% |
| D11Z | 2.94 | 1.1 | 71% |
| G67B | 4.69 | 1.0 | 83% |
| G70B | 4.44 | 1.0 | 104% |
| C16Z | 2.52 | 1.0 | 87% |
| Q61B | 3.42 | 0.9 | 178% |
| J62A | 3.57 | 0.9 | 186% |
| K60B | 6.48 | 0.9 | 87% |

Approximately 1.1% of episodes were identified as errors into three DRGs. 961Z (unacceptable principal diagnosis), 963Z (neonatal diagnosis not consistent with age and/or weight), 960Z (ungroupable) accounted for 95.8%, 2.2% and 1.9% of errors, respectively.

Episodes with operating-room procedures unrelated to principal diagnosis were grouped into 801A, 801B and 801C DRGs. 801C (operating room procedures unrelated to the principal diagnosis without catastrophic complication and comorbidity) accounted for 61.6% of unrelated episodes, 801B (operating room procedures unrelated to the principal diagnosis with severe or moderate complication and comorbidity) for 23.9% and 801A (operating room procedures unrelated to the principal diagnosis with catastrophic complication and comorbidity) for 14.5% of unrelated episodes.

MDC 6 (diseases and disorders of the digestive system) was the highest volume MDC, accounting for 11.4% of the total number of episodes. The five highest volume MDCs accounted for 46.3% of the total number of episodes, whereas twelve MDCs accounted for 80.5% (Table 2).
The average length of stay was 6.71 days (95CI 6.67–6.75)

**Table 2.** Variance explained (adjusted $R^2$) for the length of stay and percentage of outliers for untrimmed and trimmed data in Vojvodina province during 2016.

| Major diagnostic category | Untrimmed data | | | L3H3 | | IQR | | $10^{th}$–$95^{th}$ | |
|---|---|---|---|---|---|---|---|---|---|
| | Adjusted $R^2$ | % of total episodes (%) | % of day cases within MDC (%) | Adjusted $R^2$ | % of outliers within MDC (%) | Adjusted $R^2$ | % of outliers within MDC (%) | Adjusted $R^2$ | % of outliers within MDC (%) |
| **Pre-MDC** | 0.13 | <1 | 1 | 0.31 | 23 | 0.31 | 5 | 0.33 | 11 |
| **MDC 01** | 0.13 | 5 | 6 | 0.38 | 22 | 0.27 | 6 | 0.28 | 10 |
| **MDC 02** | 0.11 | 2 | 14 | 0.46 | 18 | 0.29 | 9 | 0.23 | 5 |
| **MDC 03** | 0.15 | 4 | 4 | 0.33 | 13 | 0.23 | 7 | 0.25 | 7 |
| **MDC 04** | 0.13 | 6 | 13 | 0.31 | 29 | 0.23 | 5 | 0.26 | 9 |
| **MDC 05** | 0.14 | 9 | 5 | 0.27 | 20 | 0.25 | 5 | 0.29 | 9 |
| **MDC 06** | 0.18 | 11 | 13 | 0.47 | 30 | 0.47 | 7 | 0.47 | 7 |
| **MDC 07** | 0.17 | 3 | 7 | 0.41 | 24 | 0.32 | 5 | 0.34 | 10 |
| **MDC 08** | 0.21 | 5 | 13 | 0.44 | 33 | 0.34 | 5 | 0.37 | 8 |
| **MDC 09** | 0.15 | 8 | 41 | 0.62 | 22 | 0.53 | 11 | 0.44 | 5 |
| **MDC 10** | 0.16 | 3 | 19 | 0.45 | 31 | 0.35 | 7 | 0.32 | 6 |
| **MDC 11** | 0.37 | 5 | 27 | 0.75 | 34 | 0.68 | 7 | 0.69 | 6 |
| **MDC 12** | 0.10 | 2 | 27 | 0.46 | 37 | 0.57 | 10 | 0.46 | 6 |
| **MDC 13** | 0.19 | 5 | 37 | 0.59 | 21 | 0.49 | 8 | 0.41 | 5 |
| **MDC 14** | 0.16 | 8 | 9 | 0.30 | 10 | 0.37 | 7 | 0.36 | 6 |
| **MDC 15** | 0.37 | 2 | 11 | 0.65 | 21 | 0.54 | 3 | 0.52 | 7 |
| **MDC 16** | 0.10 | 2 | 43 | 0.40 | 57 | 0.37 | 11 | 0.25 | 5 |
| **MDC 17** | 0.27 | 10 | 77 | 0.71 | 13 | 0.37 | 7 | 0.35 | 2 |
| **MDC 18** | 0.12 | 1 | 4 | 0.34 | 18 | 0.21 | 5 | 0.20 | 10 |
| **MDC 19** | 0.09 | 1 | 2 | 0.18 | 28 | 0.16 | 5 | 0.18 | 13 |
| **MDC 20** | 0.11 | 1 | 9 | 0.31 | 44 | 0.33 | 10 | 0.32 | 10 |
| **MDC 21** | 0.16 | 1 | 21 | 0.49 | 38 | 0.39 | 7 | 0.29 | 7 |
| **MDC 22** | 0.26 | <1 | 2 | 0.68 | 33 | 0.37 | 4 | 0.43 | 11 |
| **MDC 23** | 0.19 | 4 | 17 | 0.56 | 25 | 0.52 | 6 | 0.49 | 5 |
| **Unrelated DRGs** | 0.13 | 1 | 6 | 0.29 | 30 | 0.24 | 6 | 0.29 | 8 |
| **Error DRGs** | 0.01 | 1 | 8 | 0.06 | 37 | 0.02 | 1 | 0.01 | 5 |
| **Overall DRGs** | 0.30 | 100 | 21 | 0.61 | 24 | 0.49 | 7 | 0.51 | 7 |

and the median value was 4 days (Table 3). "Day-cases", which did not require an overnight stay in the hospital, accounted for 21.4% of total episodes. R63Z with 10,696 episodes accounted for the majority of "day-cases". After excluded "day-cases", ALOS increased to 8.24 days (95CI 8.19–8.29) whereas the median value remained 4 days. There were 7,161 (2.9%) episodes lasting more than 28 days defined as "prolonged hospitalisation". Among "prolonged hospitalisation", 1,368 (19.1%) were classified in MDC 19 (mental diseases and disorders). Without "prolonged hospitalisation" ALOS dropped down to 5.56 days (95CI 5.54–5.58) with the median value of 3. ALOS amounted to 5.98 days (95CI 5.96–6.00) with the median value of 4 days, excluding "day-cases" and "prolonged hospitalisation" altogether.

**Table 3.** The average length of stay and percentage of outliers in university and general hospitals for untrimmed and trimmed data in Vojvodina province during 2016.

| Trimming method | ALOS | ALOS (university hosp.) | ALOS (general hosp.) | % of outliers (university hosp.) (%) | % of outliers (general hosp.) (%) |
|---|---|---|---|---|---|
| **Untrimmed data** | 6.71 | 6.88 | 6.59 | - | - |
| **L3H3** | 7.02 | 6.89 | 7.09 | 24 | 24 |
| **IQR** | 5.65 | 5.56 | 5.71 | 8 | 6 |
| **10th-95th** | 5.78 | 5.73 | 5.82 | 8 | 6 |

For untrimmed data, the highest ALOS was 73.3 days for L02A (operative insertion of peritoneal catheter for dialysis with catastrophic or severe complication and comorbidity). Among DRGs with more than five episodes, the highest ALOS was 52.4 days for P62Z (neonate, admission weight 750–999 g) with seven episodes.

ALOS for "surgical", "medical" and "other DRGs" was 5.94, 6.98 and 6.84 days, respectively.

The average length of stay seen in university hospitals (6.88 days) was higher than in general hospitals (6.59 days) (Table 3). Among the DRGs seen in both types of hospitals, 282 DRGs had higher ALOS in university examples, whereas 244 DRGs had higher ALOS in general examples.

Outliers accounted for 24% (H3L3 method), 7% (IQR) and 7% (10th–95th) of total episodes, covering 20.6% (H3L3), 21.7% (IQR) and 19.7% (10th–95th) of total bed days (Table 2). The H3L3 method increased ALOS to 7.02 (Table 3) with the maximum ALOS of 105.0 days for L02A group. Within DRGs with more than five episodes, the maximum ALOS was 44.25 days for P63Z (neonate, admission weight 1,000–1,249 g without significant operating room procedure) with 16 episodes.

There were 27 DRGs with CV below 20%, 70 DRGs with CV below 50%, and 441 DRGs with CV below 100% that accounted for 2.7%, 5.9% and 53.6% of total episodes, respectively. G65A (gastrointestinal obstruction with catastrophic or severe complication and comorbidity) had the highest CV of 341%. Nine more groups had CV greater than 200%. In the group of highest volume DRGs, nine groups had CV below 100% (Table 1). Trimming increased homogeneity to 91%, 95% and 100% of DRGs with CV below 100%, also reducing maxim CV in the dataset (Table 4). Maximum variation after the H3L3 trimming method was 96% for L02A. For the IQR method, the highest value for CV was 158% for I79A (pathological fracture with catastrophic complication and comorbidity), whereas for the 10th–95th method this was 153% for V60Z (alcohol intoxication and withdrawal).

**Table 4.** The total number of DRGs and the number of DRGs with CV <100% in trimmed and untrimmed data in Vojvodina province during 2016.

| Trimming method | Total number DRGs * | Number of DRGs with CV <100% | % of total episodes CV <100% (%) |
|---|---|---|---|
| **Untrimmed data** | 639 | 441 | 53.6 |
| **L3H3** | 634 | 634 | 100.0 |
| **IQR** | 639 | 607 | 94.1 |
| **$10^{th}$-$95^{th}$** | 618 | 562 | 83.1 |

*Number of DRGs after excluding DRGs with one episode

Adjusted $R^2$ for untrimmed data was 0.30 (Table 2). Exclusion of "day-cases" decreased adjusted $R^2$ to 0.27, whereas exclusion of "prolonged hospitalisation" increased adjusted $R^2$ to 0.36. Adjusted $R^2$ for untrimmed data was 0.30 after exclusion of "day-cases" and "prolonged hospitalisation" together. Data trimming increased adjusted $R^2$ to 0.61 (L3H3 method), 0.49 (IQR) and 0.51 (10th–95th percentile) (Table 2). The L3H3 trimming method resulted in the maximum adjusted $R^2$, as well as the greatest number of outliers. MDC 16 (diseases and disorders of the blood and blood-forming organs) had the highest proportion of outliers for H3L3 and IQR, with 57% and 11% of episodes (Table 2). Even after trimming, adjusted $R^2$ for some MDCs remained relatively low (less than 0.25). The lowest adjusted $R^2$, except for errors, was for MDC 19, in both untrimmed and trimmed data (Table 2). MDC 11 (diseases and disorders of the kidney and urinary tract) had the maximum value for adjusted $R^2$. The most significant improvement in adjusted $R^2$ compare to untrimmed value was for MDC 12 (diseases and disorders of the male reproductive system).

Trimming improved adjusted $R^2$ for medical rather than for "surgical DRGs". However, the adjusted $R^2$ for "surgical DRGs" remained above values for "medical" and for "other DRGs" after all trimming methods (Table 5).

## 4 DISCUSSION

The average length of stay is a standard measure of hospital activity (15). According to Eurostat, Serbian ALOS was 9.5, being among the highest in Europe (16). Some of the reasons for prolonged hospitalization are the inadequate planning of admissions and discharges, duplicate procedures to fulfil the annual plan, as well as the shortage of mental health and palliative care community centres, lack of within-hospital coordination and archaic definition of daily cases. Therefore, the second volume group and routine procedure O60Z-Vaginal delivery had ALOS of almost five days; or the C16Z-lens procedures that are usually performed during daily cases had ALOS of almost three days.

The proportion of outlier cases is a measure of classification effectiveness (3). A less effective case-mix will detect more outliers, whereas a more effective classification will allow outliers to be assigned to inliers.

The most common trimming method in Australia was H3L3 method (17). Understandable and easily computable, this method was accepted at the beginning of AR-DRG implementation in numerous countries. The H3L3 method is based on the assumption of the normal distribution of LOS. However, the distribution of LOS is right-skewed,

**Table 5.** Variance explained (adjusted R2) and the percentage of outliers within medical, surgical and others DRGs in Vojvodina province during 2016.

| Trimming method | Medical DRGs | | Surgical DRGs | | Others DRGs | |
|---|---|---|---|---|---|---|
| | Adjusted $R^2$ | % of outliers (%) | Adjusted $R^2$ | % of outliers (%) | Adjusted $R^2$ | % of outliers (%) |
| **Untrimmed data** | 0.28 | - | 0.38 | - | 0.22 | - |
| **L3H3** | 0.60 | 29 | 0.62 | 11 | 0.47 | 16 |
| **IQR** | 0.47 | 7 | 0.58 | 8 | 0.39 | 6 |
| **$10^{th}$-$95^{th}$** | 0.50 | 6 | 0.62 | 8 | 0.39 | 8 |

and the arithmetic mean might become misleading. In additional to skew, with the median higher than mean, prolonged hospitalizations pull the ALOS more to the right. In this research, the percentage of prolonged episodes was 3% of episodes, in contrast with 1% in Ireland (18). The percentile method is also very sensitive to skewed data (19). Aforementioned statistical inconveniences support some non-parametric methods based on the IQR and median value as preferable methods in this stage of implementation (20, 21). The results of the IQR method were satisfactory, classifying 7% of cases as outliers with only 5% of groups with CV above 100% and ALOS of 5.65 days.

The evidence from literature suggests great variability in the proportion of outliers, depending on the algorithm, method (parametric or non-parametric, based on LOS or cost), prior experiences etc. (22). Outliers in Ireland, Germany, Austria and France accounted for 6%, 22%, about 14% and less than 1% of total episodes, respectively (22). According to the proposal from the US, the accepting proportion of outliers should be below 10% (3). Such a proportion was reached by two of three appllied trimming methods in this case study and closed to the acceptable ratio suggested by Professor Fedler. Fedler highlighted that optimal threshold depends on providers and their willingness to take risk (23). Such risk differs between US and European hospitals. If hospitals are risk averse, the optimal threshold should be higher and with no more than 5% of total cases beyond the upper threshold; whereas different rules should be applied on the lower threshold (in an email from Fedler S, in September 2019). As outliers are somewhat inevitable, a kind of surcharge is necessary. The common surcharge for a long-stay outlier depends on the number of hospital days beyond the upper threshold adjusted for some types of patients (e.g. new-borns) or additionally paid for new technologies, expensive medications etc. (22, 24). Some countries prefer to amplify short-stay weights without the lower threshold in order to create an incentive for short-stay visits or day-cases (11). A system without the lower threshold might be implemented in Serbia later on, in order to raise the currently small percentage of daily cases (21% in Vojvodina). On the other hand, the lower threshold is an attempt at avoiding inappropriately early discharges, colloquially called “bloody discharges” (22). In conclusion, the implementation of the DRG system is a continuous process of improving (25). Eventually, the method should be chosen by the authority as the balance between efficiency and quality, and between competition and sustainability.

Joint activities of health institutions, the National Health Insurance Fund and the Ministry of Health resulted in the modification in the hospital payment system. According to the Rulebook for 2019, 4% of the hospital reimbursement should be based on DRGs performance and 1% on quality indicators. Neither of the methods for determining outliers has been included yet (26). Presumably, the authority has planned to cross a point of no return and postpone implementation of the method until stakeholders become familiar with scheme and coding. Since there is no real competition between providers, the financial effects of recent reform are not easy to predict. For instance, it is questionable how hospitals would cover a potential decrease in revenues, even for a single percent in comparison to a previous year. Should hospitals cut down expenditure for medication or for salaries that are guaranteed by the law? Considering this, general hospitals could count on more or less a similar number of patients each year, so it could be presumed that more pressure would be on university hospitals. However, Keeler suggests that large hospitals have a lower risk from prospective payment and consequence of outliers, since they can make transfers between different DRGs (27).

The pre-DRG hospital payment system in Serbia instigated providers to prolong hospitalisation. Additional to poor coding practices and insufficient planning of hospital admissions resulted in great heterogeneous data. Therefore, the implementation of the DRG system should be strengthened with the implementation of solutions in different aspects of healthcare. From a clinical perspective, the utilisation of acute beds should be a privilege for acute patients, who should continue further treatment either in primary healthcare facilities or in nursing homes, afterward. Clinical and integrative pathways in support of knowledge and judgment should be directed at the highest volume conditions and diseases (measuring by the proportion of episodes) and for conditions with insufficient within-group homogeneity in order to reduce LOS and costs. Since there is no “best trimming method”, the choice of method must be made based not only on the characteristics of the data sample at hand but also on the goals that health policymakers intend to reach, particularly regarding the announced rationalisation of public health facilities (11, 28). The publishing and comparison of data will certainly improve transparency in clinical practice and spending.

## 5 LIMITATIONS

Data quality may affect the measuring of DRG performances (3). In the Vojvodina dataset, a bit more than 1% of cases were identified as errors, which is more than in countries with longer experience in DRG implementation (29).

Episodes with the operating room (OR) procedures unrelated to the principal diagnosis were grouped into separate DRGs. Such groups accounted for around 1% of total episodes in comparison to 0.05% in Australia (30). There are no mistakes in the real sense; despite some of

them possibly being the result of miscoding. Therefore, their percentage should be under control, because they could be a result of oversight high-cost episodes. The training of clinicians on the correct usage of ICD 10 and ACHI, to avoid such errors, is necessary. Since proper coding is essential and clinicians are more focused on treatment, the authority should consider training for coders who will review, analyse and accurately assign ICD-10-AM/ACHI codes and DRGs to all inpatient episodes.

## 6 CONCLUSIONS

A long length of stay, a small percentage of daily cases and a substantial number of long-term episodes characterized hospital activity in Vojvodina with a great heterogeneity of coding practice. AR-DRG could explain 30% of variation for LOS in raw dataset, and between 49% and 61% in trimmed dataset. The percentage of outliers varied from 7% to 24%, depending on the trimming method.

Further studies should test different trimming algorithms and identify factors associated with high length of stay and low $R^2$ for some MDCs using cost data rather than LOS.

## CONFLICT OF INTEREST

The author declares that no conflict of interest exist.

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## ETHICAL APPROVAL

The study is based on the retrospective analysis of registry data and is, as such, exempt from ethical approval.

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# DEVELOPMENT OF AN ALGORITHM FOR DETERMINING OF GENETIC RISK AT THE PRIMARY HEALTHCARE LEVEL – A NEW TOOL FOR PRIMARY PREVENTION: A STUDY PROTOCOL

## RAZVOJ ALGORITMA ZA DOLOČANJE GENETSKEGA TVEGANJA NA PRIMARNI RAVNI ZDRAVSTVENEGA VARSTVA – NOVO ORODJE V PRIMARNI PREVENTIVI: PREDSTAVITEV PROTOKOLA RAZISKAVE

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**ABSTRACT**

**Introduction:** Family history (FH) is an important part of the patients' medical history during preventive management at model family medicine practices (MFMP). It currently includes a one (or two) generational inquiry, predominately in terms of cardiovascular diseases, arterial hypertension, and diabetes, but not of other diseases with a probable genetic aetiology. Beside family history, no application-based algorithm is available to determine the risk level for specific chronic diseases in Slovenia.

**Methods:** A web application-based algorithm aimed at determining the risk level for selected monogenic and polygenic diseases will be developed. The data will be collected in MFMP; approximately 40 overall with a sample including healthy preventive examination attendees (approximately 1,000). Demographic data, a three-generational FH, a medical history of acquired and congenital risk factors for the selected diseases, and other important clinical factors will be documented.

**Results:** The results will be validated by a clinical genetic approach based on family pedigrees and the next-generation genetic sequencing method. After the risk of genetic diseases in the Slovenian population has been determined, clinical pathways for acting according to the assessed risk level will be prepared.

**Conclusion:** By means of a public health tool providing an assessment of family predisposition, a contribution to the effective identification of people at increased risk of the selected monogenic and polygenic diseases is expected, lessening a significant public health burden.

**Keywords:**
family medicine, pedigree, family history, genetic predisposition, population at risk

***IZVLEČEK***

***Izhodišča:*** *Med obravnavo bolnikov v ambulanti družinske medicine (ADM) je družinska anamneza (DA) pomemben del bolnikove zdravstvene anamneze. Trenutno vsebuje poizvedbo predvsem o boleznih s kompleksno genetsko etiologijo (npr. kardiovaskularnih boleznih, arterijski hipertenziji in diabetesu). Genetski podatki ali DA o redkih boleznih niso vključeni. Zdravniki v Sloveniji poleg družinske anamneze nimajo na voljo pripomočka za določanje genetskega tveganja za kronične bolezni.*

***Metode:*** *Razvito bo spletno orodje za določanje ravni tveganja za določene monogenske in poligenske bolezni. V presečno raziskavo bodo s pomočjo namenskega vzorčenja prostovoljno vključene ADM (N = 40), ki bodo zbirale podatke med zdravimi udeleženci preventivnih pregledov (n = 1200). Vsaka ADM naj bi vključila 30 zaporednih pregledovancev. Vključitveni kriteriji bodo odsotnost kroničnih bolezni, starost med 30 in 65 let ter soglasje za sodelovanje v raziskavi, izključitveni kriteriji pa starost pod 30 ali nad 65 let in nesposobnost sodelovati v raziskavi (slepota, psiho-organska prizadetost, duševna manjrazvitost). Zbirali se bodo demografski podatki, trigeneracijska DA, osebna anamneza prirojenih in pridobljenih dejavnikov tveganja ter pomembni klinični dejavniki za izbrane bolezni, vključno s srčno-žilnimi boleznimi, hipertenzijo, diabetesom, rakom, nevrološkimi, duševnimi, senzornimi in za druge v družini prisotne bolezni z možno genetsko etiologijo. Pri pregledovancih se bodo med preventivnim pregledom zbirali podatki o prirojenem in pridobljenem tveganju za omenjene izbrane bolezni iz osebne anamneze, prehranska anamneza, podatki o telesni aktivnosti, kajenju, pitju alkohola (AUDIT-C questionnaire), zaznavanju stresa, znakih depresije (tri presejalna vprašanja za depresijo), socialnih determinantah zdravja, indeksu telesne mase, krvnem tlaku, laboratorijskih vrednostih (krvni sladkor, lipidogram) in izračunu srčno-žilnega tveganja.*

***Ključne besede:***
*družinska medicina, rodovniki, družinska anamneza, genetska predispozicija, tveganju izpostavljena populacija*

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## 1 INTRODUCTION

In family medicine (FM), family history (FH) has been a crucial part of patient management for centuries. Taking an FH provides insight into a patient's family background and helps to clarify the context of their problems (1), while offering data on genetic predisposition and reflecting interactions between genetic, environmental, cultural and lifestyle characteristics.

Traditionally, the taking of an FH focuses on symptomatic patients in order to find a possible family predisposition for a specific disease. The modern approach is to establish genetic risks for specific diseases in healthy people (1). A positive FH is crucial in determining the risk of monogenic disorders – diseases associated with mutation in a single gene. The rare monogenic diseases represent a significant burden to morbidity in the population (2) and increase the risk of chronic non-communicable diseases by two to five times (2), mostly cardiovascular diseases, diabetes and cancer in younger people. Mental diseases, especially depression, can be a risk factor for their development in descendants even beyond two generations (3). An increased risk of the development of Alzheimer's disease, the most common of all neurological diseases, continues for at least three generations (4). FH is also very important in terms of identifying rare diseases, as these are very numerous and mostly of monogenetic aetiology (5). It is estimated that 5.3% of new-borns will suffer from a genetic disorder when followed up until the age of 25 years (6).

FH data can be used in population-screening as a primary prevention tool to identify people at increased risk. The US CDC (United States of America Centre for Disease Control and Prevention) developed a structured approach to determining the risk of specific diseases based on a three-generational FH (7). It has been known for a while that, in order to assess the genetic burden, the patient's family ties, the number of relatives with the disease, their age at disease onset and, sometimes, transmission via the paternal or maternal line, are important. These are the criteria for the risk assessment, using a categorization of high, medium or low when considering the risk level for a specific disease. When there is a way to detect the disease in its asymptomatic stage, an early diagnosis can affect the course of the disease. Determining an increased risk enables healthcare workers to carry out specific measures during early diagnosis in an at-risk population: more precise screening methods, and screening performed at a younger age and at shorter intervals than usual (8, 9).
Academic literature commonly reports that an FH of early-onset coronary diseases in close relatives increases the risk of mortality, independent of other known risk factors (10).

Using FH in a primary prevention approach is recommended by the European Guidelines on Cardiovascular Disease Prevention (11). The CDC has defined five conditions, including coronary disease, for which family risk should be determined. In a randomized controlled study within the Family HealthWare project, the CDC developed a tool and intervention software for this purpose (12); the tool was a questionnaire for collecting information on the FH of coronary heart disease, diabetes, colon cancer, breast cancer and ovarian cancer, providing an individualized plan to prevent morbidity (12).

The algorithms for assessing coronary disease risk include standard risk factors, while an FH of early-onset coronary disease is known to increase the patient's risk. FH has been shown to be associated with an early onset of CVD if it spreads beyond the inner circle of relatives (10). When the researchers took into account the number of relatives with coronary disease, the family ties or relationship, and the age of relatives at onset, together with an assessment of family risk and the development of the early onset of coronary disease, hypercholesterolemia, hypertension and obesity, the FH showed an increased risk of 2.5 times for early-onset coronary disease, and a significant association with the other diseases in people with a high or medium family risk (10).

The studies investigated the contribution of FH to an increase in the previously established proportion of high-risk patients. According to Qureshi, a systematic consideration of positive family burden with CVD showed that there were 4.8% more patients at high risk of CVD (13). An FH of diabetes is associated with an increased risk of developing the condition (14, 15). This risk can be assessed in the general population, and using FH in cancer patients can identify families at increased risk of malignant diseases (16). Electronic FHx tools vary in the way in which they are organized, displayed, collected, and integrated into the clinical workflow, so it is highly likely new FHx tools will become available and that current tools will continually improve (16-19).

There are no public health tools or electronic applications available to doctors or the lay public in Slovenia to determine the risk level for specific diseases with genetic aetiology (20-22). However, there is a tool for cancer developed by the Institute of Oncology Ljubljana, which has already been studied among Slovenian GPs as well (20).

There are currently 18 family history tools reported in the literature: six generic, two on cardiovascular disease and ten on cancer (19). The six generic tools were partly tested in primary care and partly validated against a reference standard (genetic counsellor) (19). Of the five specific tools studied in primary care, none were validated (19).

In Slovenia and Europe, data concerning the prevalence of healthy people at increased risk for monogenetic and complex genetic diseases is insufficient (14, 21,22). Some algorithms have been developed, including some partly at the primary care level, but none of them have been validated (19). Family physicians in Slovenia, however, have expressed the view that it is their duty to include genetic elements in their treatment of patients (21, 22). In addition, they and their European colleagues have recognized their unique importance, as physicians of first contact, in identifying genetic risk (23).

## 2 METHODS

### 2.1 Aim and Objectives

As part of the study, we will develop a new algorithm-based tool, available as a web application to family medicine teams and appropriate clinical pathways. The burden of genetic diseases in the Slovenian population will be assessed, as well as people's quality of life.

The objectives of the project are as follows:

1. The development of an algorithm to determine the genetic risk of diseases having a significant genetic component at the primary healthcare level, based on FH.
2. An assessment of the risk present in the Slovenian population of diseases having a significant genetic component (monogenic diseases and diseases with complex aetiology).
3. The determination of Health-Related Quality of Life (HRQOL) of people/families with a significant genetic predisposition.
4. The development of clinical pathways for patients of different levels of risk of developing monogenic and complex genetic diseases.

### 2.2 Procedures

#### 2.2.1 Development of an Algorithm to Determine the Genetic Risk of Diseases Having a Significant Genetic Component at the Primary Healthcare Level, Based on FH

An algorithm will be developed for determining the genetic risk of cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology. The tool will be able to calculate average, medium or high risk for these diseases, based solely on a three-generational FH. A modified Scheuner method (7) will be used. The Scheuner method calculates the level of risk of developing diseases based on FH using data on the generation of the relatives affected by the disease, the onset of the disease in relatives, and the number of relatives affected.

The algorithm will be tested on a sample of family medicine practice attendees who will enter the data on their three-generation family history to the algorithm, allowing for validation by clinical geneticists.

#### 2.2.2 Assessment of the Risk Present in the Slovenian Population of Diseases Having a Significant Genetic Component

In a cross-sectional study, a representative sample of family practice patients will be used to assess the burden of genetic diseases in the Slovenian population, including cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology. The assessment of the burden of genetic diseases will include subjects at genetic risk of these diseases, which will be evaluated by a three-generational FH for these diseases and the presence of congenital and acquired risk factors.

#### 2.2.3 Determination of HRQOL of People/Families with a Significant Genetic Predisposition

The HRQOL of subjects at risk of cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology will be determined. The HRQOL is one of the dimensions of the Quality of Life (QoL) concept, focusing on health. For the selected subjects we will record the influence of health, diseases and their symptoms on their physical, emotional and social well-being. This will allow for the characterization of a continuum of highly complex health outcomes defined by biological/physiological factors, symptoms, the ability to function in everyday life and a general perception of health and well-being.

#### 2.2.4 Establishment of Clinical Pathways for Patients of Different Levels of Risk of Developing Monogenic and Complex Genetic Diseases

The risk assessment algorithm based on family history will classify the subjects into three groups: low-risk, medium-risk, and high-risk. For each group, a clinical pathway of action at the primary healthcare level will be developed. If a high risk for genetic disease is identified, genetic counselling will follow. In cases of medium or low risk, the patient will be managed by the family medicine team, also taking into account acquired risk factors. Clinical pathways will include a horizontal and vertical relationship between healthcare levels and will be aligned with all healthcare level providers.

### 2.3 Participants

#### 2.3.1 Participating Teams from Family Medicine Practices

The study will involve teams from FMP (family model practices), i.e. a family physician (FP), a practice nurse and a registered nurse. The participation of at least 40 FMPs is planned; selected through a purposive sampling. The teams will participate on a voluntary basis.

Before the study, the participating FMP teams will attend a short workshop to familiarize them with the methodology and implementation of the dataset.

#### 2.3.2 Participating Patients

The participants will be comprised of people who come to FMPs for a preventive check-up. Their participation in the study will be voluntary, and informed consent will be provided, i.e. the patients will sign a statement. Each FMP is expected to include 30 consecutive people. Inclusion criteria will be the age between 30 and 65 years, and informed consent for participation in the study. Exclusion criteria will be an age less than 30 or above 65 years, and an inability to participate in the study (blindness, psycho-organic impairment, intellectual disability). It is planned to gather data from at least 1,000 people.

### 3.3 Instruments and Procedures

#### 3.3.1 Instruments

During the preventive examination, the following data will be collected: medical history of the acquired and congenital risk factors for the diseases concerned, nutritional history, history of physical activity, smoking, drinking alcohol, perception of stress, signs of depression, social health determinants, body mass index, blood pressure values, laboratory test values (blood sugar, lipidogram) and cardiovascular risk, based on Framingham risk scores (24).

For assessing the HRQOL, we will use the EQ-5D scale. This consists of four parts (25). The first part is intended to familiarize the respondents with the descriptions of health states. Each health state has five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). In the first part of the questionnaire, the respondents evaluate their health state in all five dimensions on the day of the interview (25). They also mark whether they feel better, worse or equal to how they felt in the last 12 months on average (25). They will also be familiarized with the visual analogue scale (VAS), where they mark how good or bad their own health state is on a scale from 0 to 100 (where 0 represents the worst health state imaginable and 100 represents the best) (25). For assessing risky alcohol drinking, we will use the Slovenian version of AUDIT-C (26). This is a three-item alcohol screen that helps to identify people who are risky drinkers. In men, a score of six or more is considered positive, while in women the cut-off score is five.

For depression, we will use three questions for screening (27).

#### 3.3.2 Procedures

The participating FMP teams will complete a questionnaire covering the basic demographic data of the FMP team and some information related to work in the practice: the working years of the team members, the years of FMP status (the first FMPs in Slovenia were introduced in 2011, with practices gradually joining) (8), the number of registered patients, the number of preventive examinations performed per year, and quality indices associated with prevention implementation.

Each patient will complete a questionnaire covering their basic demographic data, a three-generational FH for the monogenetic and complex genetic diseases (cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology), and an EQ-5D scale (25). The determined level of genetic risk that we find as the result of the algorithm for each individual patient will be assessed (validated) by clinical geneticists; they will check the family history data and determine whether the algorithm calculated an objective genetic risk.

## 4 DISCUSSION

### 4.1 Discussion on Expected Results

The project results are expected to contribute to the development of methodologies allowing a practical risk assessment of (currently) healthy people to evaluate their genetic predisposition, primarily for monogenetic diseases, but also for diseases with complex aetiology.

In Slovenia, FPs rarely include genetic aspects when treating patients, and they do only have limited protocols to help them manage such patients and refer them to genetic assessment (20,21). The planned project will contribute to easier and, most of all, reliable identification of people and families at a high risk of monogenetic diseases.

The target diseases constitute a global public health challenge. Early identification of people at increased risk, before they develop any signs and symptoms of the disease, may contribute significantly to effective prevention of the disease and its consequences.

By use of the algorithm to determine genetic risk, the primary prevention of chronic disease and early detection of monogenetic diseases will be strengthened, resulting in longer and higher-quality lives of family practice patients.

It has already been shown that healthy people with a less optimal lifestyle should also be encouraged to improve their lifestyle as this would improve their health-related quality of life (28).

The target diseases are all extremely important health problems. They involve rare diseases (their diagnosis is supported by the European Union and the Slovenian national plan) and multifactorial diseases, which are the biggest cause of morbidity/mortality. The aim of a very early detection of people with a significant genetic predisposition is currently a highly relevant public health application of personalized medicine.

Within this project, we will also develop clinical pathways for the management of patients with low, medium or high genetic risk. Such pathways cannot be developed without also taking into account the acquired risk factors. This will be an additional value of our project.

### 4.2 Discussion on Methodology

This study will use a cross-sectional design, which is appropriate according to the purposes and aims. We will not determine any causal relationship, as this is not one of the aims of our study. The sampling of the FMPs will be purposive, and this could contribute to a selection bias. However, the fact that the FMPs will be scattered across the whole of Slovenia will lower the bias as much as possible. The sampling of the participants in each practice will be consecutive, which is appropriate according to the study aims. The study will use subjective as well as objective data; the most problematic is data from the family history, as participants are not always aware of all the information about their relatives' illnesses (29, 30). This possibility of inaccurate or incomplete data collection will be minimized by offering the participants the opportunity to think about the topic at home prior to coming to the practice.

The developed algorithm will be based on the modified Scheuner method (7) and the results obtained from the algorithm will be validated by clinical geneticists, enhancing the validity even more.

## 5 CONCLUSIONS

This project will facilitate the identification of individuals and families at increased genetic risk at a primary health level. This will contribute to a better understanding of the epidemiology and of the extent of the health problem. New possibilities in the field of primary and secondary prevention for lowering the public health burden of these diseases will evolve.

The project will contribute to the transfer and efficient use of the contemporary findings of genetic medicine in clinical practice, which will reduce the gap between basic science and applied clinical medicine. If the identification of genetic predisposition proves to be effective in preventing complex genetic diseases, it may constitute a foundation for the development of biomarkers with a great market potential in medicine.

The project's results will serve as the basis for preparing new professional guidelines for the early detection of complex-multifactorial genetic diseases in FM, the education of healthcare workers at undergraduate and postgraduate levels, and the active inclusion in top international studies on the diseases that constitute the leading global healthcare problems.

## CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

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## ETHICAL APPROVAL

The study was approved by the National Ethics Committee of the Republic of Slovenia (No. 0120-544/2016/3).

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# PREDICTING EQUATIONS AND RESTING ENERGY EXPENDITURE CHANGES IN OVERWEIGHT ADULTS

## PREDIKTIVNE ENAČBE IN SPREMEMBE V PORABI ENERGIJE V MIROVANJU PRI PREKOMERNO HRANJENIH ODRASLIH

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**ABSTRACT**

**Introduction:** The aim of the study is to show the differences between the measured and estimated values of resting energy expenditure and any changes occurring after the 6-month weight loss intervention program.

**Methods:** We included 33 healthy adults aged 25–49 years with an average body mass index 29.1±2.7 kg/m 2 for female and 29.8±2.8 kg/m 2 for male. The measured resting energy expenditure was obtained by indirect calorimeter MedGem® Microlife and estimated resting energy expenditure by the Harris–Benedict equation, the Mifflin–St Jeor equation, the Owen equation, the Wright equation, and by the Tanita body composition analyser. All measurements and calculations were carried out before and after the 6-month intervention. Results were compared using paired t-tests. P value less than 0.05 was considered statistically significant.

**Results:** A comparison of the measured resting energy expenditure of female subjects with the estimated resting energy expenditure using the Harris–Benedict equation, the Mifflin–St Jeor equation and the Wright equation showed a statistically significant difference. A comparison of the measured resting energy expenditure of male subjects with the estimated resting energy expenditure using the Harris–Benedict equation and the Wright equation showed a statistically significant difference. There was a significant difference in the measured resting energy expenditure and estimated resting energy expenditure using Tanita.

**Conclusions:** We concluded that the most comparable equation for our sample was the Owen's equation. After losing weight, the measured resting energy expenditure has decreased, which must be taken into account in further diet therapy.

**Keywords:**
resting energy expenditure, energy expenditure, obesity, indirect calorimetry, predictive equations

***IZVLEČEK***

***Uvod:*** *namen raziskave je bil prikazati razlike med merjenimi in ocenjenimi vrednostmi porabe energije v mirovanju ter spremembe v porabi energije v mirovanju po šestmesečni intervenciji za izgubo telesne mase. Vrednost porabe energije v mirovanju je pomemben podatek pri določanju energijskih in hranilnih potreb posameznika v procesu načrtovanja ustrezne prehrane. Vrednosti porabe energije v mirovanju lahko izmerimo z indirektnim kalorimetrom ali jo ocenimo z uporabo napovednih enačb. Zanimalo nas je, kakšna je razlika med merjeno in ocenjeno vrednostjo porabe energije v mirovanju ter kakšne so spremembe porabe energije v mirovanju po končani šestmesečni intervenciji za izgubo telesne mase.*

***Metode:*** *20 zdravih žensk in 13 zdravih moških, starih od 25 do 49 let, s povprečnim indeksom telesne mase 29,1 ± 2,7 v kg/m2 za ženske in 29,8 ± 2,8 v kg/m2 za moške je zaključilo meritve porabe energije v mirovanju pred intervencijo in po njej. Porabo energije v mirovanju smo izmerili z indirektnim kalorimetrom Med Gem® Microlife, ocenjene vrednosti smo dobili z uporabo Harris-Benedictove enačbe, Mifflin-St Jeorove enačbe, Ownove enačbe ter Wrightove enačbe in iz izpiska poročila telesnega analizatorja Tanita. Ocena telesne sestave je bila opravljena z uporabo bioimpedance. Primerjavo smo naredili s parnim t-testom. Pri statističnih testih smo upoštevali stopnjo tveganja, nižjo od 5 % (p < 0,05).*

***Rezultati:*** *primerjava med merjeno porabo energije v mirovanju pri ženskah in ocenjeno porabo energije v mirovanju s Harris-Benedictovo enačbo, Mifflin-St Jeorovo enačbo in Wrightovo enačbo je pokazala statistično značilne razlike, medtem ko primerjava med merjeno porabo energije v mirovanju pri ženskah in ocenjeno porabo energije v mirovanju z Ownovo enačbo ni bila statistično značilna. Ravno tako so se pri moških pokazale statistično značilne razlike med merjeno porabo energije v mirovanju in ocenjeno porabo energije v mirovanju s Harris-Benedictovo enačbo in Wrightovo enačbo. Statistično značilna razlika pri obeh spolih se je pokazala tudi pri merjeni porabi energije v mirovanju in ocenjeni porabi energije v mirovanju, pridobljeni s Tanito. Šestmesečna intervencija je vplivala na zmanjšanje porabe energije v mirovanju, vendar so bili rezultati statistično značilni le pri moških.*

***Zaključek:*** *ugotovili smo, da je bila Ownova enačba najbolj primerljiva z izmerjeno porabo energije v mirovanju (tako za moške kot tudi za ženske). Po izgubi telesne mase se poraba energije v mirovanju zmanjša, kar je treba upoštevati pri nadaljnjem načrtovanju prehranskega vnosa.*

***Ključne besede:***
*poraba energije v mirovanju, debelost, energijske potrebe, indirektna kalorimetrija, prediktivne enačbe*

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## 1 INTRODUCTION

Total energy expenditure (TEE) is the energy organisms need for daily functioning, which is largely spent on metabolic and physiological functions [1]. The assessment of TEE is one of the fundamental functions performed in studies of nutrition. The lack of balance between the energy consumed and the energy expanded causes changes in bodyweight. One of the components representing TEE is resting energy expenditure (REE). The REE is the largest component of TEE and accounts for about 60 to 75 % of total daily expenditure in individuals with a sedentary lifestyle [2–4]. Data on individual TEE is crucial in planning adequate energy and nutrient intake in weight management nutritional intervention. REE is the energy that a person needs to maintain a body at rest [4]. REE can be measured by indirect calorimetry [4–5]. This is the gold standard for REE measurement. With this method, energy expenditure is calculated from oxygen and carbon dioxide concentrations found in the expired air [4]. Energy metabolism can also be assessed by using various equations. The most widely-used equation for estimating REE is the Harris–Benedict equation (HB) [6–7]. Following the recommendations of the American Dietetic Association (ADA) [8] the Mifflin–St Jeor (MSJ) equation is more reliable, especially in obesity [9]. Both predictive equations and indirect calorimetry measurements are used to determine the REE but the most precise method is indirect calorimetry; though it is also more expensive and time-consuming. Many authors [10–12] have found that predictive equations are unsuitable for determining the REE in overweight people because it does not take into account lean body mass, metabolic imbalances or genetic factors of an individual. Extensive review of the literature has shown that the rate of errors in the application can be high, in some cases up to 20% [12].

Obesity intervention programs include physical activity to encourage energy consumption and enhance physical strength and muscles [13]. More muscle mass means higher values of REE [2, 14]. Therefore, in the process of weight management, it is important to maintain muscle mass and lose fat mass. Additionally, the rate of weight loss is also important as rapid weight loss may cause a decrease in lean body mass, which further decreases REE. This shows the importance of a good diet plan. Therefore, this paper aims to compare measured REE and the predicted REE from the selected equations in overweight adults. Additionally, we presented the changes of REE and body composition after intervention and changes in bodyweight. We were specifically interested in changes between different (measured and estimated) REE.

## 2 METHODS

### 2.1 Study Design

This retrospective study was conducted in 2012 at the Faculty of Health Sciences, University of Primorska, Izola, Slovenia. There were 33 subjects who fulfilled the following inclusion criteria and were included in the study. Inclusion criteria for participants were: (1) body mass index (BMI) higher than 25 and lower than 35; (2) aged 25–49; (3) healthy with no metabolic, cardiovascular, endocrine, and acute or chronic inflammatory diseases; (4) not taking medication for lipid metabolism; (5) reporting a stable weight within the previous 3 months.

The participants were evaluated at baseline and after a 6-month weight loss intervention program.

### 2.2 Resting Energy Expenditure (REE)

REE was measured with a hand-held indirect calorimeter MedGem Microlife (Medical Home Solutions, Inc., Golden, and CO). A selected hand-held indirect calorimeter has been clinically tested and already assessed [15–17]. It is a self-calibrating device that measures VO2 and uses a respiratory quotient of 0.85 to calculate REE. All REE measurements were performed in the morning between 7 a.m. and 8 a.m., after 8 hours of sleep. 12 hours before the REE assessments, participants were instructed not to consume any alcohol or drugs, not to consume any food or fluids (with the exception of water) and not to exercise. Measurements were carried out after auto-calibration of the device in a quiet thermo-neutral environment (20–22°C) [18].

Estimated REE was calculated from selected equations that are more detailed and described below.

### 2.3 Anthropometric Measurements

All measurements were performed between 7 a.m. and 9 a.m. in standardised conditions by the same examiner after fasting overnight. The subject height was measured to the nearest 0.1 cm in a standing position, without shoes, using the Leicester height measure (Invicta Plastics Limited, Oadby, England). The bodyweight (kg) of the participants was measured with a 0.1 kg precision. BMI was calculated using the following formula: weight (kg)/ height (m2). Body composition, total body fat mass and fat free mass were assessed by using bioelectrical impedance analysis (BIA) Tanita BC 418MA (Tanita Corporation, Arlington Heights, IL) and data analysed with the software GMON Pro 3.2.1, provided by the same producer. From the bioelectrical impedance analysis of Tanita we also obtained information about an individual's minimum level of energy needs. BIA Tanita is using Tanita multiple regression analysis model, which includes adjusted Harris-Benedict equation and measured fat fee mass [19–20].

### 2.4 Predicted REE Calculation

REE was calculated using the Mifflin–St Jeor (MSJ)[9], the Harris–Benedict (HB)[19], the Owen (O) [21–22] and the Wright (W) [23] Equation (Table 1). Height, weight and age were used for the equations, calculated in kcal per day, and then expressed in kJ.

**Table 1.** Predictive equations for estimating the REE.

| Reference | Female | Male |
|---|---|---|
| **Mifflin-St Jeor [9]** | (9.99 x w) + (6.25 x H) - (4.92 x A) - 161 | (9.99 x W) + (6.25 x H) - (4.92 x A) + 5 |
| **Harris-Benedict [19]** | 655.09 + (9.56 x W) + (1.84 x H) - (4.67 x A) | 66.47 + (13.75 x W) + (5 x H) - (6.75 x A) |
| **Owen et al. [21], Owen et al. [22]** | (7.18 x W) + 795 | (10.2 x W) + 879 |
| **Wright et al. [23]** | (9.02 x W) + (5.88 x H) – 7.47 x A + 110.76 | (9.27 x W) + (4.58 x H) – (6.53 x A) + 451.44 |
| **Harris-Benedict adjusted from Tanita Corporation** | 655.10 + (9.56 x W) + (1.85 x H) – (4.68 x A) | 66.47 + (13.75 x W) + (5 x H) - (6.76 x A) |

Legend: A, age in years; H, height in cm; W, weight in kg

### 2.5 Intervention Program

To estimate TEE, individual REE (or a person's REE) (REE measured from indirect calorimetry) was multiplied by the appropriate activity factor (from 1.3 to 1.6) [24], then a reduction of 2,100 kJ (500 kcal) for all the participants was made. All subjects attended two educational sessions (2 h) about a healthy diet, nutritional composition, the correct timing of eating and the beneficial effects of daily intake of vegetables and fruit. Each group included 6–7 subjects. In addition, all subjects attended two sessions of one-on-one training about their prescribed individual diet plan (each subject was given a personalised diet). The diet plan consisted of 15–17% of energy from protein, 25–30% from fat and more than 50% from carbohydrates. Dietary fat composition was <10% of saturated fatty acid, at least 10% of monounsaturated fatty acid and 5% of polyunsaturated fatty acid. Subjects also received a list of food for each meal and the quantity of food in grams to choose from. Within the intervention, subjects were invited to attend a guided exercise program that included exercises for improving muscle function and strength and a Nordic walking course. The subjects also received a brochure with detailed instructions and recommendations for daily physical activity of moderate intensity. Intervention lasted six months. Measurements had been made before and after 6-month intervention.

### 2.6 Statistical Analyses

All analyses were carried out using the SPSS statistics version 23.0 (IBM, Chicago, IL). Means and standard deviation of the mean were determined at both baseline and after 6 months of intervention for all parameters. Using a paired t-test, we determined any statistical differences in the pre- and post-intervention period. We also conducted one sample t-test to evaluate the difference between the mREE and different eREE. Pearson's correlation coefficients were calculated to assess the relationships between the estimated REE and measured REE. Statistical significance was defined as $p<0.05$. We compared different results of selected predictive equations with measured REE with accuracy level ±10% of measured REE. This included predicted values of REE between 90% and 110% of measured REE.

## 3 RESULTS

Thirty-three individuals (20 female and 13 male), aged 39.5±6.5 years, completed the whole intervention program. Table 2 presents participant characteristics.

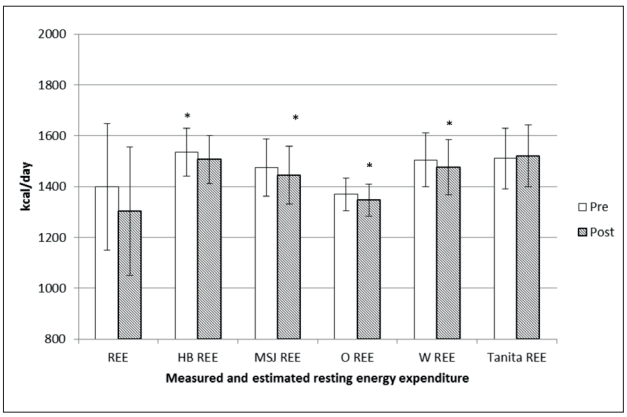
**Table 2.** Characteristics of the participants.

| Characteristic | Mean±SD | | |
|---|---|---|---|
| | Female (n=20) | Male (n=13) | Total (n=33) |
| **Age** | 40.5±6.4 | 37.92±6.6 | 39.5±6.5 |
| **Height** | 165.7±5.2 | 180.0±6.5 | 171.3±9.1 |
| **Weight (kg)** | 80.1±9.1 | 96.4±8.1 | 86.5±11.8 |
| **Fat mass (%)** | 38.2±3.1 | 24.2±3.5 | 32.7±7.6 |
| **Fat-free mass (kg)** | 49.3±4.0 | 72.6±4.5 | 58.5±12.3 |

Legend: n, the number of subjects

For the comparison of different predictive equations, we used equations from Table 1. Weight, BMI, fat mass and fat free mass were statistically significantly, reduced after 6 months in both genders (Table 3 and Table 4). Mean and standard deviations of REE, weight, body mass index, fat free mass and total fat of the female are summarised in Table 3.

All estimated REE were significantly lower after the intervention (with the exception of mean estimated REE by Tanita). REE by Tanita in female predicted a higher REE after the intervention (but that was not significant) by one percentage point. The mean measured REE was lower after the intervention, but it was not statistically significant (Table 3 and Figure 1).




Legend: REE, measured resting energy expenditure; HB, Harris-Benedict's method; MSJ, Mifflin-St Jeor's method; O, Owen's method; W, Wright's method.* The difference before and after the intervention was statistically significant in females at the level of $p<0.05$.

**Figure 1.** Comparison of different methods for determining female subjects' REE before and after the 6-month intervention.

**Table 3.** Female subject's characteristics comparison, before and after 6-month intervention.

| Female (n=20) | Mean±SD | | R |
|---|---|---|---|
| | Before intervention | After intervention | % |
| **REE (kcal/day)** | 1400±256 | 1305±260 | -7 |
| **REE (kJ/day)** | 5864±1072 | 5465±1089 | -7 |
| **HB REE (kcal/day)** | 1536 ±95 | 1507±95* | -2 |
| **MSJ REE (kcal/day)** | 1475±115 | 1445±116* | -2 |
| **O REE (kcal/day)** | 1370±65 | 1348±64* | -2 |
| **W REE (kcal/day)** | 1505±110 | 1477±111* | -2 |
| **Tanita REE (kcal/day)** | 1511±122 | 1520±124 | +1 |
| **Weight (kg)** | 80.1±9.1 | 77.0±9,0* | -4 |
| **BMI (kg/ m2)** | 29.1±2.7 | 28.0±2.6* | -4 |
| **Fat free mass (kg)** | 49.3±4.0 | 48.3±3.9* | -2 |
| **Total fat (kg)** | 30.8±5.6 | 28.7±5.8* | -7 |

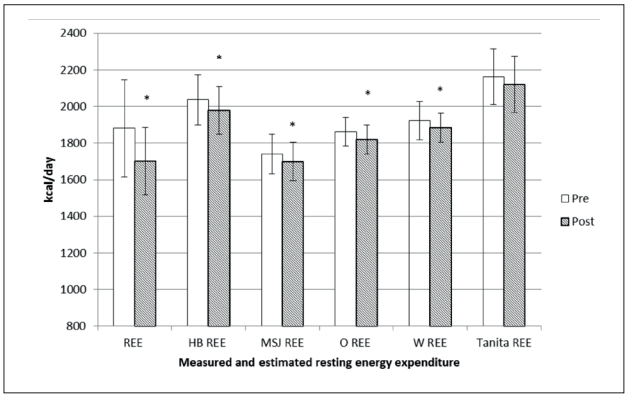
Legend: n, the number of subjects; BMI, body mass index; R, the difference in percentage points.*
The difference before and after the intervention was statistically significant in females at the level of $p<0.05$.

Mean and standard deviations of REE, weight, body mass index, fat free mass and total fat of the male are summarised in Table 4. Estimated REE (except results obtained from the Tanita scale) were significantly lower after the intervention. However, again the results we obtained from Tanita did not show any statistically significant difference (Figure 2).

**Table 4.** Male subjects' characteristics comparison, before and after 6-month intervention.

| Male (n=13) | Mean±SD | | R |
|---|---|---|---|
| | Before intervention | After intervention | % |
| **REE (kcal/day)** | 1882±275 | 1700±191* | -10 |
| **REE (kJ/day)** | 7884±1154 | 7123±801* | -10 |
| **HB REE (kcal/day)** | 2036±144 | 1979±136* | -3 |
| **MSJ REE (kcal/day)** | 1740±114 | 1699±110* | -2 |
| **O REE (kcal/day)** | 1862±82 | 1820±83* | -2 |
| **W REE (kcal/day)** | 1922±109 | 1884±102* | -2 |
| **Tanita REE (kcal/day)** | 2161±158 | 2120±160 | -2 |
| **Weight (kg)** | 96.4±8.1 | 92.3±8.1* | -4 |
| **BMI (kg/ m2)** | 29.8±2.8 | 28.5±2.6* | -4 |
| **Fat free mass (kg)** | 72.6±4.5 | 71.0±4.4* | -2 |
| **Total fat (kg)** | 23.5±4.9 | 21.3±5.7* | -10 |

Legend: n, the number of subjects; BMI, body mass index; R, the difference in percentage points.*
The difference before and after the intervention was statistically significant in males at the level of $p<0.05$.




Legend: REE, measured resting energy expenditure; HB, Harris-Benedict's method; MSJ, Mifflin-St Jeor's method; O, Owen's method; W, Wright's method.* The difference before and after the intervention was statistically significant in males at the level of $p<0.05$.

**Figure 2.** Comparison of different methods for determining male subjects' REE before and after the 6-month intervention.

We also compared the measured REE with different REE assessments (Table 5 and Table 6). Using the Pearson's correlation coefficient, we demonstrated a significantly moderate relationship between the measured REE and selected REE assessment methods for female subjects.

**Table 5.** Comparison of measured REE and estimated REE in females.

| Measured REE vs. Method comparison | Mean difference±SD | t(p) | Pearson r (p) |
|---|---|---|---|
| **Tanita** | -215.9±214.7 | -4.5 (0.000)* | 0.571 (0.009)** |
| **HB** | -202.9±218.6 | -4.1 (0.001)* | 0.582 (0.007)** |
| **MSJ** | -140.5±211.2 | -3.0 (0.008)* | 0.604 (0.005)** |
| **O** | -43.6±226.1 | -0.86 (0.399) | 0.614 (0.004)** |
| **W** | -173.0±218.1 | -3.5 (0.002)* | 0.559 (0.010)* |

Legend: HB, Harris-Benedict's method; MSJ, Mifflin-St Jeor's method; O, Owen's method; W, Wright's method.** Correlation is significant at the 0.01 (2-tailed),* correlation is significant at the 0.05 level (2-tailed).

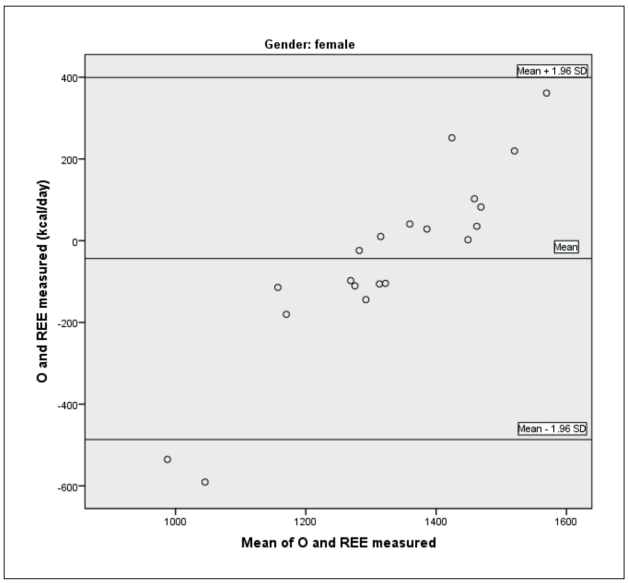



**Figure 3.** Bland-Altman plot showing the agreement between predicted REE with Owen (O) equation and measured REE for female.

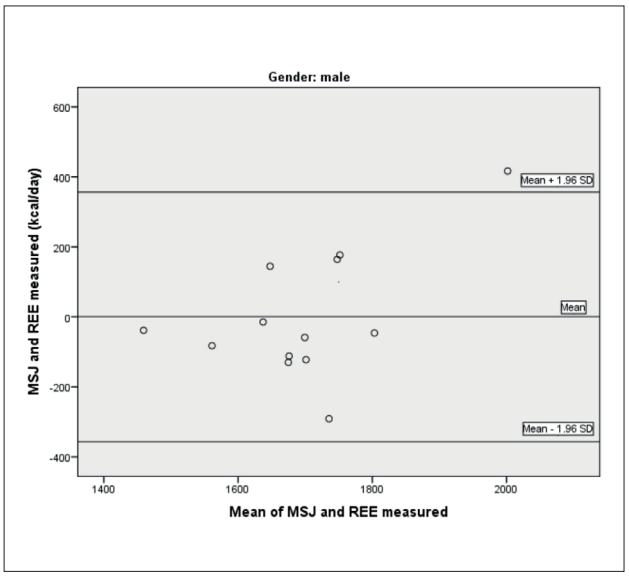



**Figure 4.** Bland-Altman plot showing the agreement between predicted REE with Mifflin-St Jeor (MSJ) equation and measured REE for male.

**Table 6.** Comparison of measured REE and estimated REE in male.

| Measured REE vs. Method comparison | Mean difference±SD | t(p) | Pearson r (p) |
|---|---|---|---|
| **Tanita** | -419.9±218.5 * | -6.9 (0.000)* | 0.235 (0.440) |
| **HB** | -297.4±195.9* | -5.1 (0.000)* | 0.322 (0.284) |
| **MSJ** | 0.553±181.7 | 0.011 (0.991) | 0.373 (0.210) |
| **O** | -120.5±201.2 | -2.2 (0.052) | 0.094 (0.761) |
| **W** | -183.8±179.8* | -3.7 (0.003)* | 0.377 (0.205) |

Legend: HB, Harris-Benedict's method; MSJ, Mifflin-St Jeor's method; O, Owen's method; W, Wright's method.** Correlation is significant at the 0.01 (2-tailed),* correlation is significant at the 0.05 level (2-tailed).

## 4 DISCUSSION

The present study compared the different methods for obtaining REE in overweight subjects. The commonly used predictive equations are less appropriate in comparison to a hand-held calorimeter [17, 25]. In comparison to a hand-held calorimeter, predictive equations do not account for differences in body composition and other conditions that also affect REE. Furthermore, a hand-held calorimeter can be more practical for use in a clinical environment. However, some authors reported that a hand-held calorimeter could be less accurate in determining REE than predictive equations in healthy people [26].

Following the recommendations of the American Dietetic Association (ADA) [8] and the Dietitians of Canada [27], the Mifflin–St Jeor (MSJ) equation is considered more reliable, especially in obesity. We were interested in the results of comparisons between measured and different predictive equations for estimating the REE.

Our results have shown statistically significant differences in a few of the observed parameters between, before and after intervention (Table 3 and Table 4). There was a statistically significant difference in the predicted REE values before and after intervention calculated with the Harris–Benedict equation, the Mifflin–St Jeor equation, the Owen equation and the Wright equation both in females and males. However, we could not find any significant changes in the measured REE in females; other studies also support these findings [28–29]. Furthermore, the results we obtained from the Tanita scale did not show any statistically significant differences in REE values before and after the intervention (in females and males). A possible reason for this could be that the Tanita scale was calibrated for a normal, healthy population (and not for overweight adults), therefore, this could be a reason for results that are different from others. After a 6-month intervention and significantly lower bodyweight, the REE was not statistically different in women. On the other hand, the measured REE in male participants was statistically different after intervention.

The comparison of the measured REE and the selected predictive equations (Table 5 and Table 6) showed different results for females and males. The one-sample t-test that was conducted in female REE showed a statistically significant difference between the measured REE and four out of five selected predictive equations (Table 5). All the selected equations have overestimated measured REE. Furthermore, all the selected equations (with the exception of Owen's equation) showed a significant difference with the measured REE. The results that we obtained from the Owen's equation are also considered as accurate predicted values because they were within ±10% of the value of the measured REE. A correlation analysis conducted between indirect calorimetry and predicted equations showed the strongest correlation with the Owen equation ($r=0.614$, $p<0.005$); all other correlations were strong and significant. Our findings are inconsistent with other studies, which found that HB and MSJ equations are a reliable tool for predicting REE [30–31]. In male participants (Table 6) the difference was significant between the measured and predicted REE with Tanita, Harris–Benedict and Wright equations. The most suitable one for male participants was the MJS equation (the calculated value of REE was -1%) and the Owen equation (the calculated value of REE was +7%). The values fell within ±10% of the value of the measured REE. Although other authors [32–33] demonstrated great accuracy also for the HB equation, we could not confirm this (percent of predicted REE was not within ±10% of the measured REE neither for females nor males). Recently published studies that compare different predictive equations and measured REE on healthy adults also came to the conclusion that the most suitable predictive equation for overweight Caucasian adults would be Owen's equation [23, 34].

Other authors [6, 31] demonstrated that the HB predicted REE was higher than the measured REE; the same results were obtained in our study. The correlation between the predicted Harris–Benedict equation and the measured REE in females was 0.58. On the other hand, there are a few studies concluding that the equations (by HB, O and MJS) underestimated the REE measured with indirect calorimetry [7, 10, 35].

The present study has limitations. This is a study with a small sample, because it's an intervention-based study on human subjects. This diminishes the strength of conclusions, which is usual for such studies. For this reason, we rely on clear statistical tests. Another limitation of the study is the fact that we did not use any gold standard method to measure REE. Usually, such methods are not available to dietitians in practice and, consequently, not in line with the study purpose. The strength of the study is that it takes account of real problems and limitations, so the results could provide a rationale for developing better prediction equations and for validating other portable indirect calorimeters to use in practice.

## 5 CONCLUSION

With the development of a practical and simple device for indirect calorimetry the necessity for using indirect calorimetry in obesity prevention has emerged.

One of the most important outcomes of the nutritional intervention is weight loss [13]. Since obesity intervention programs include physical activity that increase muscle mass, it can be assumed that the REE also increases. But

this is not so. The results after our intervention program showed reduced fat mass, fat-free mass and REE. Reduced REE occurred despite the fact that we added physical activity to our intervention [13, 36]. Not only is the degree of energy deficit important, but the distribution of macronutrients and the amount of protein per kilogram of bodyweight is also of great importance in determining fuel substrate utilisation [36]. We were interested in the various predicted equations so that we could find the most suitable one to use when indirect calorimetry is not available. We have demonstrated that the most comparable equation for our participants was the Owen equation (both for females and males). This equation gave us the most comparable results with the measured REE. According to our data, which is also confirmed by some studies [23, 34], Owen's equation can be used in predicting REE in overweight adults. This protocol can be used in clinical and non-clinical environments, in environments that can't afford handheld calorimeters, and where the predictive equation is the only way to estimate REE.

In conclusion, the energy deficit, macronutrient distribution and the rate of weight loss may be key factors in the retention of fat-free mass and REE. Dietary information should be prescribed and described on an individual basis. Because of the differences that occur in the literature, there is plenty of space for further research.

## CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

## FUNDING

There is no financial interest or risk.

## ETHICAL APROVAL

The protocols and procedures of this study were in agreement with the ethical guidelines on biomedical research on human subjects and the study was approved by the Republic of Slovenia National Medical Ethics Committee on 6.1.2012 (No.: 56/08/11 bus). Written consent was obtained from all the subjects.

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# SAFETY CULTURE AT PRIMARY HEALTHCARE LEVEL: A CROSS-SECTIONAL STUDY AMONG EMPLOYEES WITH A LEADERSHIP ROLE

## KULTURA VARNOSTI NA OSNOVNI RAVNI ZDRAVSTVENEGA VARSTVA: PRESEČNA RAZISKAVA MED ZAPOSLENIMI Z VODSTVENO FUNKCIJO

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**ABSTRACT**

**Introduction:** An effective leadership is critical to the development of a safety culture within an organization. With this study, the authors wanted to assess the self-perceived level of safety culture among the employees with a leadership function in the Ljubljana Community Health Centre.

**Methods:** This was a cross-sectional study in the largest community health centre in Slovenia. We sent an invitation to all employees with a leadership role (N=211). The Slovenian version of the SAQ – Short Form as a measurement of a safety culture was used. The data on demographic characteristics (gender, age, role, work experience, working hours, and location of work) were also collected. An electronic survey was used.

**Results:** The final sample consisted of 154 (69.7%) participants, out of which 136 (88.3%) were women. The mean age and standard deviation of the sample was 46.2±10.5 years. The average scores for the safety culture domains on a scale from 1 to 5 were 4.1±0.6 for Teamwork Climate, Safety Climate, and Working Conditions and Satisfaction, 3.7±0.5 for Perception of Management, 3.6±0.4 for Communication, and 3.5±0.6 for Stress Recognition.

**Conclusion:** The safety culture among leaders in primary healthcare organizations in Slovenia is perceived as positive. There is also a strong organizational culture. Certain improvements are needed, especially in the field of communication and stress recognition with regards to safety culture.

**Keywords:**
safety culture, primary healthcare, organizational culture

***IZVLEČEK***

***Uvod**: učinkovito vodenje je ključnega pomena za razvoj kulture varnosti v organizaciji. S to raziskavo so avtorji želeli oceniti zaznano raven kulture varnosti med zaposlenimi z vodilno funkcijo v ljubljanskem zdravstvenem domu.*

***Metode**: to je bila presečna študija v največjem zdravstvenem domu v Sloveniji. Vsem zaposlenim z vodilno vlogo (N = 211) smo poslali povabilo. Za oceno kulture varnosti je bila uporabljena slovenska različica lestvice SAQ - Short Form. Zbrani so bili tudi podatki o demografskih značilnostih (spol, starost, vloga, delovne izkušnje, delovni čas in lokacija dela). Uporabljena je bila elektronska anketa.*

***Rezultati**: končni vzorec je sestavljalo 154 (69,7 %) udeležencev, od tega 136 (88,3 %) žensk. Povprečna starost in standardni odklon vzorca sta bila 46,2 ± 10,5 let. Povprečne ocene za področja kulture varnosti na lestvici od 1 do 5 je bilo 4,1 ± 0,6 za timsko delo, klimo varnosti in delovne pogoje ter zadovoljstvo. Za področje dojemanja vodstva je bila ocena 3,7 ± 0,5, za področje komunikacije 3,6 ± 0,4 in za področje prepoznavanje stresa 3,5 ± 0,6 točk.*

***Zaključek**: kultura varnosti med vodstvenim kadrom največjega zdravstvenega doma v Sloveniji je pozitivna. Obstaja tudi visoka raven organizacijske kulture. Potrebne so nekatere izboljšave, zlasti na področju komunikacije in prepoznavanja stresa v zvezi s kulturo varnosti.*

***Ključne besede**:*
*kultura varnosti, primarna zdravstvena raven, organizacijska kultura*

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## 1 INTRODUCTION

Patient safety culture is part of the patient safety concept and is defined as a product of the attitudes, values, competencies and patterns of behaviour of individuals and groups that determine healthcare in an organisation (1).

The safety of patients at the primary level of healthcare varies considerably from the safety of patients at a secondary or tertiary level. At the primary level, there is a very large amount of contact with patients, which are usually complex interactions (2), and the uncertainty that is typical of work at the primary level is very important (3). So, patient safety here should focus on accepting uncertainty, exploring probabilities, and diminishing danger. It is also important to strive for openness and transparency in the area of patient safety (4).

Although patient safety in primary care has not been explored to the same extent as in secondary and tertiary levels, recently more and more studies are emerging (5, 6). The most common theme within the topic was safety culture. Some studies used a qualitative approach followed by a survey or an audit (7, 8) while others utilized quantitative tools to assess safety culture (9–16). One study also assessed the effect of intervention on the safety culture (17). In general, studies showed that patient safety culture was perceived positively among primary care professionals (12). However, awareness of the safety problems was only raised after getting together and discussing patient safety, therefore, measuring safety culture alone was not enough (11). There seems to be some differences among different health professionals regarding the perception of safety culture (10, 18).

An effective leadership is critical to the development of a safety culture within an organization (19). Competent and thoughtful leaders contribute to improvements in safety and organisational culture. They understand that systemic flaws exist and that each step in a care process has the potential for failure simply because humans make mistakes (20–22). This commitment is needed from all organisational leaders (governing boards and clinical leaders) as well as management. Also, leadership commitment must be expressed through actions observable to employees (23).

To establish a positive safety culture in primary care, the first step is to evaluate the current patient safety culture, which will provide basic understanding to safety-related perceptions of the healthcare providers (5). Therefore, we wanted to assess the self-perceived level of safety culture among the employees in the Ljubljana Community Health Centre. We focused only on the employees with a leadership function and hypothesized that the perception of safety culture would be perceived as positive.

## 2 METHODS

### 2.1 Research Design and Setting

This was a cross-sectional study in the largest community health centre in Slovenia – Community Health Centre Ljubljana. This health centre provides healthcare services for the municipality of Ljubljana, which comprises of around 280,000 people. It consists of eight units, which are located in separate buildings in different parts of Ljubljana. It employs around 1,500 employees of different medical and non-medical backgrounds and has around 2.5 million of patient visits per year.

### 2.2 Participants

We sent an invitation to all employees with a leadership role (N=211). They come from different professional backgrounds (i.e. physicians, dentists, registered nurses, nurse assistants, administrative staff etc.). According to the governance rules in the Community Health Centre Ljubljana, a certain number of employees with a leadership function is appointed in all eight units, such as chief of nurses, chief of physicians, chief of whole units, director of health centre etc. They work mostly within their professional fields, but have a certain amount of their working time dedicated to their leadership tasks.

### 2.3 Instruments

We used the SAQ – Short Form (24), which consists of 36 items that need to be answered on a 5-point Likert scale (1 – disagree strongly, 5 – agree strongly). We were granted permission to use this questionnaire by the University of Texas at Houston-Memorial Hermann, Centre for Health Care Quality and Safety. The permission was given on June 3, 2016. There are six domains in the original SAQ – Short Form: Teamwork Climate (items 1–6), Safety Climate (items 7–13), Job Satisfaction (items 15–19) Stress Recognition (items 20–23), Perceptions of Management (items 24–28), and Working Conditions (items 29–32). Items 14 and 33–36 are not included in any of the factors. A Slovenian version of the SAQ – Short Form showed good reliability and validity characteristics, but with slightly different domains: 1) Perceptions of Management (items 1, 9, 12–14, 24–29, 31); 2) Stress recognition (items 20–23); 3) Teamwork Climate (items 6, 33–35); 4) Communication (2–4, 11, 30, 36); 5) Safety Climate (items 5, 7, 8, 10); 6), Working Conditions and Satisfaction (items 15–19, 32) (25).

We also collected data on demographic characteristics (gender, age, profile, work experience, working period at this location, and location of work).

### 2.4 Data Collection

We collected the data through an electronic survey. The link to the survey was sent to the email addresses of the participants in February 2017. The first reminder was sent after two weeks, and the second two weeks after the first. Participation was confidential, as possible identifiers such as e-mail and IP addresses were removed by the administrative coordinator in the project. It was not possible for the researchers to link the participants to their responses.

### 2.5 Statistical Analysis

In the analysis, the scores of negatively worded items were reversed so that higher scores always indicated a more positive evaluation of the safety culture. For each domain, we calculated its mean score, which ranged from a minimum 1 to a maximum 5 points. The observed variables were safety culture scores on each domain. The explanatory variables were demographic and other characteristics of the participants. Dummy explanatory variables were created for statistical analysis. To detect any significant differences, we used an independent t-test for categorical (dummy) explanatory variables and a Pearson correlation for continuous explanatory variables. A p value of $< 0.05$ was considered to be statistically significant.

## 3 RESULTS

### 3.1 Demographic Characteristics

The final sample consisted of 154 (69.7%) participants, out of which 136 (88.3% were women. The mean age and standard deviation (SD) of the sample was 46.2±10.5 years. Participants have been working in the current location for an average of 13.6±9.8 years, and their overall working period was 21.9±10.5 years. Other characteristics are presented in Table 1.

**Table 1.** Profiles of participants and Community Health Centre units they work in.

| Characteristic | Number (%) |
|---|---|
| **Profile** | |
| Physician, dentist | 54 (35.1) |
| Registered nurse | 36 (23.4) |
| Manager | 28 (18.2) |
| Nurse assistant | 18 (11.7) |
| Other clinical staff | 16 (10.4) |
| Administrative staff | 2 (1.3) |
| **Community Health Centre unit** | |
| Unit Sentvid | 41 (26.6) |
| Unit Center | 24 (15.6) |
| Unit Vic Rudnik | 23 (14.9) |
| Unit Moste Polje | 19 (12.3) |
| Unit Bezigrad | 19 (12.3) |
| Unit Siska | 16 (10.4) |
| Administrative Unit | 8 (5.2) |
| Unit Emergency services | 4 (2.6) |

**Table 2.** Safety culture scores.

| Characteristic | Number (%) |
|---|---|
| Perception of management | 3.7 (0.5) |
| Stress recognition | 3.5 (0.9) |
| Teamwork climate | 4.1 (0.6) |
| Communication | 3.6 (0.4) |
| Safety climate | 4.1 (0.6) |
| Working conditions and satisfaction | 4.1 (0.6) |

### 3.2 Safety Culture

The domains “Teamwork Climate”, “Safety Climate”, and “Working Conditions and Satisfaction” scored highest and the domain “Stress recognition” scored lowest (Table 2).

Participants from Unit Center scored significantly higher in the domain “Communication” than participants from other units (3.7±0.2 vs. 3.5±0.4, $p<0.001$). Participants from Administrative Unit scored significantly lower in the domain “Teamwork climate” than participants from other units (3.8±1.8 vs. 4.1±0.6, $p=0.001$). Other significant differences were not observed.

## 4 DISCUSSION

This study showed that patient safety culture was, on average, perceived positively by the employees with a leadership function in the largest community health centre in Slovenia.

Previous studies in patient safety culture at the primary healthcare level in Slovenia showed that it was perceived positively but there was still a lot of room for improvement (16). For example, more attention should be devoted to improving team collaboration with a clearer description of professional team roles (18). A study on safety culture in Slovenian hospitals using a different instrument showed that the unit-level dimensions of patient safety were perceived better than the dimensions at the hospital-

level. This study also showed a raising awareness of problems of patient safety among stuff (26). This was also confirmed in our study demonstrating that patient safety is universal.

In primary care, providers with different professional backgrounds are involved in the management of patients. A good team leader is very important, not only for an effective team management and function but also for a safety culture. Namely, the role of leadership is critical to facilitate or constrain a positive safety culture. They can crucially affect a positive interdisciplinary action team, and a positive learning culture but, on the other hand, diminish a punitive culture (27). Leaders are in a position to enable a culture of safety (28, 29). Therefore, our study focused only on the employees with a leadership function.

The finding that the participants with a leadership function perceived a safety culture positively can be a good sign, indicating an actual positive safety culture in the organization. However, studies showed that there were differences in the perception of a safety culture between healthcare leaders and staff. Probably, frontline staff may be more aware of actual safety challenges than the leaders (30) and it is possible that, if frontline staff were included in the study, the safety culture would have been perceived less positively.

The perceptions of different domains were relatively homogenous. Some domains, such as Teamwork Climate, Safety Climate, and Working Conditions and Satisfaction were scored slightly higher and some, such as Stress Recognition, slightly lower. Teamwork Climate was perceived positively also by other studies in Slovenia and abroad (10, 16, 18). The domain Stress Recognition includes items through which the employees indicate that they are aware of the fact that fatigue and high workload affect a safety culture in a negative way. In Slovenia, workloads at the primary care level are high (31). But, according to the results of the present study, this is only partly recognized by the leaders as an issue that can affect a safety culture.

The second domain that scored lowest was Communication. This domain covers the items such as the effect of communication on the management of patients and communication about safety issues. This domain was also perceived as low by other studies in Slovenian primary care (16). It seems that this safety culture domain needs improvement.

There were no large differences in a safety culture perception regarding the characteristics of the participants. It is especially important that no differences were observed between different units. The degree to which staff share the perceptions within the same unit is a validity criterion for measurements of organisational climate (32). The degree of consensus amongst staff in a unit is a measure of the organisational climate's strength (1, 32). Organizational climates with diverging perceptions amongst staff are regarded as weak, with limited power to predict staff practices (33). Since no significant variations were found in the present study, we can say that organisational climate is strong in the Community Health Centre Ljubljana. It also can indicate that leaders act as a unified community with common goals and leadership methods.

Our study has some methodological consideration that we should mention. The response rate was considerably high but we have no information on the non-respondents so this could be a source of a bias. Also, we used a Slovenian version of the SAQ-AV – Short Form, in which domains are slightly different than in the original version so a direct comparison to other studies that used the same questionnaire is limited. We studied only the leaders in one (albeit the largest) primary health organization in Slovenia, so the results cannot be generalized to the whole population. Also, the questionnaire was self-administered so a certain level of social desirability by the respondents must be taken into account, i.e. answering the questions in such a way that would show the situation in a desirable way, not in an actual way.

## 5 CONCLUSIONS

The safety culture among leaders in primary healthcare organizations in Slovenia is perceived as positive. There is also a strong organizational culture. Certain improvements are needed, especially in the field of communication and stress recognition with regards to safety culture. The results could help the management of the healthcare centres to introduce a system approach to patient safety, to tackle the weak points and improve them, to initiate a continuous assessment of safety culture, and to increase awareness of a no-blame culture. Additional studies are needed to determine a safety culture in all employees of the primary healthcare organizations in Slovenia, with a special emphasis on the differences between leaders and other staff.

## CONFLICT OF INTEREST

The authors declare that no conflicts of interest exist.

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## ETHICAL APPROVAL

The study was approved by the Slovenian National Ethics Committee (No. 107/07/16).

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# GENDER DIFFERENCES IN PREDICTORS OF SELF-MEDICATION WITH TRANQUILLIZERS AND SLEEPING PILLS: RESULTS OF THE POPULATION-BASED STUDY IN SERBIA

## RAZLIKE MED SPOLOMA PRI KAZALNIKIH SAMOZDRAVLJENJA S POMIRJEVALI IN ZDRAVILI ZA SPANJE: REZULTATI POPULACIJSKE ŠTUDIJE V SRBIJI

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**ABSTRACT**

**Background:** Previous studies among the Serbian population concluded that the trend of self-medication with tranquillizers and sleeping pills requires deeper study. The objective is to identify gender differences in socio-demographic, health, and health service predictors of self-medication with tranquillizers and sleeping pills in a Serbian population of 15 years old and above.

**Methods:** This was a population-based, cross-sectional study. Data was extracted from the most recently available results of the Serbian National Health Survey of 2013. Multivariate logistic regression was used to determine independent self-medication predictors.

**Results:** The study included 14,623 participants, of which 51.77% were female. While 5.6% of the females reported self-medication with tranquillizers and sleeping pills, only 2.2% of males reported such practice ($p<0.001$). The presence of chronic disease, stress, and physical pain in the last month before the interview was significantly associated with an increased likelihood of self-medication with observed drugs in both genders. Age was the most significant socio-demographic predictor of self-medication in females, while in males it was unemployment. Women of 55–65 years of age showed a greater risk from self-medication with tranquillizers and sleeping pills in comparison to women of 15–24 years of age (aOR=4.75, 95% CI: 1.83–12.33). Unemployed males showed a greater tendency for such practice in comparison to employed (aOR=1.86, 95% CI: 1.19–2.91).

**Conclusion:** The findings highlighted predictors of self-medication with tranquillizers and sleeping pills and important differences between genders, which may contribute to the design of gender-sensitive surveillance, identification, and the prevention of such undesirable practices through evidence-based and appropriately tailored public health actions.

**Keywords:**
self-medication, unmet needs, tranquillizers and sleeping pills, predictors, prevalence, gender

***IZVLEČEK***

***Ozadje:*** *Prejšnje raziskave srbskega prebivalstva ugotavljajo, da trend samozdravljenja s pomirjevali in zdravili za spanje potrebuje poglobljeno raziskavo. Cilj: Prepoznati razlike med spoloma pri socialnih, demografskih, zdravstvenih kazalnikih ter kazalnikih zdravstvenih storitev samozdravljenja s pomirjevali in zdravili za spanje pri srbskem prebivalstvu od 15. leta starosti.*

***Metode:*** *Medsektorska raziskava na podlagi prebivalstva. Podatki so bili zbrani iz najnovejših razpoložljivih rezultatov Srbske nacionalne zdravstvene ankete iz leta 2013. Za določanje neodvisnih kazalnikov samozdravljenja je bila uporabljena multivariantna logistična regresija.*

***Rezultati:*** *Raziskava vključuje 14.623 sodelujočih, od tega 51,77 % žensk. Medtem ko je 5,6 % žensk poročalo o samozdravljenju s pomirjevali in zdravili za spanje, je le 2,2 % moških poročalo o tovrstni praksi ($p < 0,001$). Prisotnost kronične bolezni, stresa ali fizične bolečine v zadnjem mesecu pred intervjujem je značilno povezana s povečanjem verjetnosti samozdravljenja s proučevanimi zdravili pri obeh spolih. Starost je najbolj pomemben socialni in demografski kazalnik samozdravljenja pri ženskah, pri moških pa nezaposlenost. Ženske, stare med 55 in 65 let, izkazujejo večje tveganje za samozdravljenje s pomirjevali in zdravili za spanje v primerjavi z ženskami, starimi med 15 in 24 let (aOR = 4,75, 95 % CI: 1,83–12,33). Nezaposlene ženske so prikazale večjo naklonjenost tovrstni praksi v primerjavi z zaposlenimi (aOR = 1,86, 95 % CI: 1,19–2,91).*

***Zaključek:*** *Ugotovitve izpostavljajo kazalnike samozdravljenja s pomirjevali in zdravili za spanje in pomembne razlike med spoloma, kar lahko prispeva k oblikovanju nadzora na podlagi spola ter prepoznavanje in preprečevanje tovrstnih neželenih praks z ustrezno prilagojenimi promocijami javnega zdravja.*

***Ključne besede:***
*samozdravljenje, nepotešene potrebe, pomirjevala in zdravila za spanje, razširjenost, spol*

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## 1 INTRODUCTION

The World Health Organization (WHO) has defined the term 'responsible self-medication' as a practice in which individuals treat their illnesses and conditions with medicines that have been approved for use and are available without a prescription, but are also safe and effective when used as directed (1). In spite of the many benefits of responsible self-medication, actual practice in medication use provides opportunities for improper use of medicines, e.g. self-medication with drugs approved as prescription drugs. This practice was recognized as a typical example of drug misuse by the WHO (2). Accordingly, preventative actions are of high importance as they align with potential risks at the individual and community level, where such practice induces a higher prevalence of drug-induced diseases and subsequent increases in public expenditure (3–5).

It was recorded that the practice of self-medication in Serbia includes not only over-the-counter medicines but also prescription medicines. Luković et al. reported that medical students used sedatives (13%) and antidepressants (2%) without a doctor's prescription in the year previous to the study taking place (6). This practice is very worrying as it correlates to a wide range of adverse effects such as changes in blood pressure, heart rate, sweating, insomnia (7), sedation (8), and sexual dysfunction (9). Moreover, benzodiazepines are identified as a contributing factor in suicides and poisoning deaths, while withdrawal and dependence of benzodiazepines have raised particular concerns (8, 10). Since self-medication with sedatives and antidepressants could be a threat to both individual and public health, this phenomenon should be investigated in detail to reveal the most common causes and strategies for reducing such practice.

Studies on predictors of self-medication with tranquillizers and sleeping pills are rare and commonly associated with the investigation of alcohol and opioid abuse (11–13). It was shown that self-medication of anxiety disorders was associated with lower mental health-related quality of life and a higher use of health services (14). The timely screening and treatment of mental health problems are well-recognised preventive factors for substance-use disorders (15). Additionally, the lack of medicines was revealed as primary unmet healthcare needs among patients with mental health problems (16). It was also shown that adolescents who were prescribed anxiolytics during their lifetime were 12 times more likely to use another's anxiolytic medication, which was recognized as a risk factor with significant implication to later substance-use problems (17). The abuse of tranquillizers or sedatives in adults was shown to be directly associated with a higher prevalence of substance use disorder later on (18). Female gender was a well-confirmed risk factor for self-medication in general (19–24). Up-to-date research suggests that females also seem to be at a higher risk from self-medication with tranquillizers and sleeping pills, but such studies are rare (25). Studies that investigated predictors of self-medication with tranquillizers and sleeping pills only in males are missing. Highlighting the prevalence, determinants and gender differences in self-medication with tranquillizers and sleeping pills could be very useful in the creation of targeted interventions and prevention of such addictive disorders. The aim of the current analysis is to identify gender-related socio-demographic, health and health service associated predictors in self-medication with tranquillizers and sleeping pills in the Serbian population.

## 2 METHODS

### 2.1 Study Design, Sample, and Setting

This was a population-based, cross-sectional study. A study sample was generated from the Serbian population aged 15 years and above through the Serbian National Health Survey 2013, conducted during the period from October 7th to December 30th, 2013. Sampling methodology along with the study protocol was in line with the European Health Interview Survey (EHIS wave 2) Methodological Manual instructions and is described in detail elsewhere (26). Out of 16,474 registered household members aged 15 years and above, 14,623 accepted to be interviewed, which created the response rate of 88.9% (26).

The survey was approved by the Ethical Board of the National Institute of Public Health of the Republic of Serbia and the Ministry of Health. Specially trained interviewers were obliged to provide the survey participants with a printed document informing them about the survey (Information about the Survey).

### 2.2 Data Source and Variables

A face-to-face self-reported questionnaire was used for data collection. From the pool of data of the National Health Survey 2013, the data related to self-medication with tranquillizers and sleeping pills was extracted. Self-medication was presented to respondents as the usage of drugs not prescribed by the doctor, meaning that the respondent used the medicine on his/her own initiative or in consultation with the doctor but did not receive a prescription in the two weeks before the interview. The dependent variable, "self-medication with tranquillizers and sleeping pills", was defined as a dichotomous variable with two potential answers, "no" and "yes", where "no" was observed as a reference category within the statistical analysis. Benzodiazepine drugs, anxiolytics (e.g. diazepam, bromazepam, lorazepam, prazemap, alprazolam) and hypnotics (e.g. nitrazepam) were considered as mostly used tranquillizers and sleeping pills.

The study had the following three sets of independent variables, which were mostly measured by the multiple choice questions; (i) socio-demographic characteristics (age, gender [male/female]), level of education (no formal education/primary school/secondary school/ undergraduate studies/postgraduate studies), employment status (employed/unemployed, including house wife activities and working inability/pupil or student/retiree), (ii) health-related characteristics (self-perceived general health (very good/good/fair/poor/very poor), presence of chronic disease (yes/no), physical pain and its intensity in the last four weeks prior to the interview (no/yes, not more than others/yes, more than others/yes, unbearable), stress exposure in the last four weeks (no/very mild/mild/moderate/severe[very severe]), and (iii) healthcare system-related characteristics (unmet healthcare needs in the past 12 months due to the long waiting time for health service and distance or transportation barriers (no/no need for healthcare/yes), satisfaction with public healthcare service and satisfaction with private healthcare service (very satisfied/satisfied/neither satisfied nor dissatisfied/dissatisfied/very dissatisfied).

### 2.3 Statistical Analysis

Descriptive statistics were used to analyse study sample characteristics. The prevalence and 95% confidence interval (CI) of self-medication among males and females was calculated separately. The crude odds ratio (OR) with 95% confidence interval (CI) was used to analyse univariate associations between the independent (potential explanatory) variables with the dependent variable ("self-medication with tranquillizers and sleeping pills"). Variables found to be significantly associated with self-medication in the univariate analysis were included in the multivariate logistic regression models.

The multivariate logistic regression analysis identified potential, gender-related, predictors of self-medication with tranquillizers and sleeping pill using an adjusted odds ratio (aOR) with 95% CI.

Statistical significance in all analyses was deemed likely if the computed probability value was <0.05. Data analysis was performed by using Statistical Package for Social Sciences (SPSS) software (SPSS 18.0 for Windows, SPSS Inc., Chicago, IL, USA).

## 3 RESULTS

Females and males have been almost equally distributed in the study sample; 7,570 (51.77%) and 7,053 (48.23%), respectively. In sum, 579 (4%; 95% CI: 3.6–4.3) of the study population reported self-medication with tranquillizers and sleeping pills. While 421 of the female population (5.6%, 95% CI: 5.0–6.1), only 158 of the male population (2.2%, 95% CI: 1.9–2.6) reported such self-medication practice (p<0.001).

Further analysis has shown that self-medication with selected drugs among females (Table 1) and males (Table 2) was significantly associated with investigated socio-demographic and health-related characteristics, as well as unmet healthcare needs in the past 12 months due to the long waiting time for health service, distance or transportation barriers. However, it was not associated with the satisfaction with public and private health service among females, and with education and satisfaction with private healthcare service among males (p>0.05).

**Table 1.** Prevalence of self-medication with tranquillizers and sleeping pills in the Serbian female population and association with selected socio-demographic, health, and healthcare system characteristics, n=7,570.

| Female population characteristics | Prevalence of TSP self-medication, (%) | 95% CI | Crude OR | 95% CI |
|---|---|---|---|---|
| **Female TSP users** | 5.6 | 5.0-6.1 | | |
| **Age (years)** | | | | |
| 15-24 | 1.0 | 0.4-1.7 | - | |
| 25-34 | 2.4 | 1.5-3.2 | **2.20** | **1.07-4.54** |
| 35-44 | 4.0 | 2.9-5.1 | **3.85** | **1.96-7.60** |
| 45-54 | 6.6 | 5.2-8.0 | **6.51** | **3.40-12.49** |
| 55-64 | 10.2 | 8.6-11.8 | **10.43** | **5.53-19.67** |
| 65-74 | 7.0 | 5.3-8.7 | **6.94** | **3.58-13.44** |
| ≥75 | 6.6 | 4.9-8.3 | **6.53** | **3.34-12.76** |
| **Employment status** | | | | |
| Employed | 4.1 | 3.2-4.9 | - | |
| Unemployed | 6.0 | 5.1-6.9 | **1.49** | **1.14-1.96** |
| Pupil/Student | 1.1 | 0.4-1.9 | **0.28** | **0.14-0.57** |
| Retiree | 7.9 | 6.7-9.0 | **2.01** | **1.53-2.63** |
| **Education** | | | | |
| No formal education/ Primary school | 6.6 | 5.7-7.5 | - | |
| Secondary school | 5.3 | 4.6-6.0 | **0.79** | **0.64-0.97** |
| Undergraduate/Postgraduate studies | 3.9 | 2.8-5.0 | **0.58** | **0.42-0.80** |
| **Self-assessment of health status** | | | | |
| Very good/Good/Fair | 4.6 | 4.1-5.1 | - | |
| Poor/Very poor | 9.5 | 8.0-11.0 | **2.16** | **1.75-2.67** |
| **Presence of chronic disease** | | | | |
| No | 1.8 | 1.3-2.2 | - | |
| Yes | 8.2 | 7.4-9.0 | **4.98** | **3.74-6.64** |
| **Exposure to stress during four weeks prior to the interview** | | | | |
| No/Yes, not more than others | 4.3 | 3.8-4.8 | - | |
| Yes, more than others/Yes, unbearable | 13.4 | 11.4-15.4 | **3.48** | **2.81-4.30** |
| **Physical pain during four weeks prior to the interview** | | | | |
| No/Very mild | 3.4 | 2.8-3.9 | - | |
| Mild/Moderate | 7.3 | 6.2-8.4 | **2.26** | **1.79-2.85** |
| Severe/Very severe | 9.4 | 7.8-11.0 | **2.97** | **2.30-3.83** |
| **Unmet healthcare needs in the past 12 months due to a long waiting time for health service** | | | | |
| No | 5.9 | 5.2-6.6 | - | |
| No need for healthcare | 2.5 | 1.7-3.3 | **0.41** | **0.30-0.57** |
| Yes | 8.6 | 6.9-10.2 | **1.49** | **1.17-1.91** |
| **Unmet healthcare needs in the past 12 months due to distance or transportation barriers** | | | | |
| No | 6.1 | 5.4-6.7 | - | |
| No need for healthcare | 2.7 | 2.0-3.5 | **0.44** | **0.32-0.60** |
| Yes | 10.6 | 7.5-13.7 | **1.83** | **1.30-2.58** |
| **Satisfaction with public health service** | | | | |
| Very satisfied/Satisfied | 5.3 | 4.6-6.0 | - | |
| Neither satisfied nor dissatisfied | 5.8 | 4.8-6.9 | 1.11 | 0.88-1.41 |
| Dissatisfied/Very dissatisfied | 6.3 | 5.1-7.5 | 1.21 | 0.94-1.56 |
| **Satisfaction with private health service** | | | | |
| Very satisfied/Satisfied | 4.7 | 4.0-5.5 | - | |
| Neither satisfied nor dissatisfied | 5.6 | 4.2-7.0 | 1.20 | 0.87-1.64 |
| Dissatisfied/Very dissatisfied | 7.1 | 4.3-9.9 | 1.55 | 0.98-2.43 |

Notes: significant findings where $p<0.05$ are marked in bold: Abbreviations: TSP- tranquillizers and sleeping pills, CI- Confidence Interval, OR- Odds Ratio

**Table 2.** Prevalence of self-medication with tranquillizers and sleeping pills in the Serbian male population and association with selected socio-demographic, health, and healthcare system characteristics, n=7,053.

| Female population characteristics | Prevalence of TSP self-medication, (%) | 95% CI | Crude OR | 95% CI |
|---|---|---|---|---|
| **Female TSP users** | 2.2 | 1.9-2.6 | | |
| **Age (years)** | | | | |
| 15-24 | 0.4 | 0.1-0.7 | - | - |
| 25-34 | 0.9 | 0.4-1.5 | 2.72 | 0.82-9.04 |
| 35-44 | 2.0 | 1.2-2.8 | **5.86** | **1.91-18.07** |
| 45-54 | 2.8 | 1.8-3.7 | **8.31** | **2.77-24.99** |
| 55-64 | 3.1 | 2.2-4.1 | **9.34** | **3.14-27.78** |
| 65-74 | 4.1 | 2.7-5.6 | **12.54** | **4.15-37.86** |
| ≥75 | 3.3 | 1.8-4.9 | **10.09** | **3.20-31.80** |
| **Employment status** | | | | |
| Employed | 1.4 | 1.0-1.8 | - | - |
| Unemployed | 2.9 | 2.1-3.7 | **2.08** | **1.37-3.16** |
| Pupil/Student | 0.5 | 0.1-0.9 | **0.29** | **0.09-1.00** |
| Retiree | 3.6 | 2.7-4.5 | **2.63** | **1.76-3.91** |
| **Education** | | | | |
| No formal education/ Primary school | 2.0 | 1.3-2.6 | - | - |
| Secondary school | 2.4 | 2.0-2.9 | 1.25 | 0.84-1.87 |
| Undergraduate/Postgraduate studies | 2.0 | 1.2-2.8 | 1.00 | 0.58-1.72 |
| **Self-assessment of health status** | | | | |
| Very good/Good/Fair | 1.6 | 1.3-1.9 | - | |
| Poor/Very poor | 6.9 | 5.1-8.6 | **4.52** | **3.24-6.30** |
| **Presence of chronic disease** | | | | |
| No | 0.6 | 0.3-0.9 | - | |
| Yes | 4.0 | 3.3-4.7 | **6.73** | **4.30-10.53** |
| **Exposure to stress during four weeks prior to the interview** | | | | |
| No/Yes, not more than others | 1.5 | 1.2-1.8 | - | |
| Yes, more than others/Yes, unbearable | 8.5 | 6.4-10.6 | **6.03** | **4.32-8.40** |
| **Physical pain during four weeks prior to the interview** | | | | |
| No/Very mild | 1.0 | 0.7-1.2 | - | |
| Mild/Moderate | 5.2 | 4.0-6.3 | **5.57** | **3.87-8.03** |
| Severe/Very severe | 5.7 | 3.8-7.6 | **6.18** | **3.95-9.66** |
| **Unmet healthcare needs in the past 12 months due to a long waiting time for health service** | | | | |
| No | 2.5 | 2.0-3.0 | - | |
| No need for healthcare | 0.7 | 0.3-1.0 | **0.27** | **0.16-0.45** |
| Yes | 6.4 | 4.6-8.3 | **2.72** | **1.89-3.92** |
| **Unmet healthcare needs in the past 12 months due to distance or transportation barriers** | | | | |
| No | 2.8 | 2.3-3.3 | - | |
| No need for healthcare | 0.6 | 0.3-0.9 | **0.22** | **0.13-0.38** |
| Yes | 10.2 | 6.1-14.4 | **4.00** | **2.48-6.47** |
| **Satisfaction with public health service** | | | | |
| Very satisfied/Satisfied | 2.0 | 1.5-2.5 | - | |
| Neither satisfied nor dissatisfied | 2.5 | 1.8-3.2 | 1.25 | 0.86-1.82 |
| Dissatisfied/Very dissatisfied | 3.4 | 2.3-4.4 | **1.68** | **1.13-2.50** |
| **Satisfaction with private health service** | | | | |
| Very satisfied/Satisfied | 2.6 | 2.0-3.3 | - | |
| Neither satisfied nor dissatisfied | 2.2 | 1.3-3.1 | 0.82 | 0.51-1.33 |
| Dissatisfied/Very dissatisfied | 4.0 | 1.9-6.1 | 1.53 | 0.85-2.77 |

Notes: significant findings where $p<0.05$ are marked in bold: Abbreviations: TSP- tranquillizers and sleeping pills, CI- Confidence Interval, OR- Odds Ratio

### 3.1 Predictors of Self-Medication with Tranquillizers and Sleeping Pills

Multivariate analysis revealed several independent predictors of self-medication with tranquillizers and sleeping pills common for females and males. In both populations, health-related characteristics, including the presence of chronic disease, stress exposure and the presence of physical pain in the four weeks prior to the interview, were significantly associated with an increased likelihood of the use of tranquillizers and sleeping pills without a doctors' prescription (Table 3 and Table 4).

However, significant differences in socio-demographic predictors between females and males were shown. The age categories of 45–54, 55–64 and 65–74 years were independent predictors of a higher likelihood for self-medication with tranquillizers and sleeping pills among females, versus males. Concurrently, unemployment status was revealed as an independent predictor of such practices for males, whereas employment was not significantly associated with self-medication with tranquillizers and sleeping pills in females (Table 3, Table 4).

**Table 3.** Potential predictors of self-medication with tranquillizers and sleeping pills among selected socio-demographic, health, and healthcare system characteristics in the Serbian female population, n=7,570.

| Female population characteristics | Adjusted OR | 95% CI |
|---|---|---|
| **Age (years)** | | |
| 15–24 | - | |
| 25–34 | 1.86 | 0.71–4.84 |
| 35–44 | 2.63 | 1.00–6.88* |
| 45–54 | **3.37** | **1.30–8.72** |
| 55–64 | **4.75** | **1.83–12.33** |
| 65–74 | **2.96** | **1.10–7.97** |
| ≥75 | 2.62 | 0.96–7.14 |
| **Employment status** | | |
| Employed | - | |
| Unemployed | 1.14 | 0.84–1.55 |
| Pupil/Student | 1.13 | 0.40–3.25 |
| Retiree | 1.03 | 0.72–1.48 |
| **Education** | | |
| No formal education/Primary school | - | |
| Secondary school | 1.06 | 0.83–1.35 |
| Undergraduate/Postgraduate studies | 0.84 | 0.58–1.21 |
| **Self-assessment of health status** | | |
| Very good/Good/Fair | - | |
| Poor/Very poor | 0.87 | 0.67–1.13 |
| **Presence of chronic disease** | | |
| No | - | |
| Yes | **2.57** | **1.83–3.61** |
| **Exposure to stress in the four weeks prior to interview** | | |
| No/Yes, not more than others | - | |
| Yes, more than others/Yes, unbearable | **2.51** | **1.99–3.16** |
| **Physical pain in the four weeks prior to interview** | | |
| No/Very mild | - | |
| Mild/Moderate | **1.43** | **1.11–1.83** |
| Severe/Very severe | **1.49** | **1.12–1.99** |
| **Unmet healthcare needs in the past 12 months due to a long waiting time for health service** | | |
| No | - | |
| No need for healthcare | 0.69 | 0.33–1.43 |
| Yes | 1.09 | 0.82–1.44 |
| **Unmet healthcare needs in the past 12 months due to distance or transportation barriers** | | |
| No | - | |
| No need for healthcare | 1.15 | 0.78–1.71 |
| Yes | 1.07 | 0.54–2.13 |

Notes: *p=0.05; significant findings where p<0.05 are marked in bold; all variables significantly associated in univariate analysis were included in multivariate analysis. Abbreviations: OR- Odds Ratio; CI- Confidence Interval

**Table 4.** Potential predictors of self-medication with tranquillizers and sleeping pills among selected socio-demographic, health, and healthcare system characteristics in the Serbian male population, n=7,053.

| Male population characteristics | Adjusted OR | 95% CI |
|---|---|---|
| **Age (years)** | | |
| 15–24 | - | |
| 25–34 | 2.36 | 0.53–10.56 |
| 35–44 | 3.62 | 0.81–16.27 |
| 45–54 | 3.66 | 0.82–16.31 |
| 55–64 | 3.08 | 0.68–13.85 |
| 65–74 | 3.95 | 0.80–19.40 |
| ≥75 | 3.17 | 0.62–16.17 |
| **Employment status** | | |
| Employed | - | |
| Unemployed | **1.86** | **1.19–2.91** |
| Pupil/Student | 1.65 | 0.31–8.81 |
| Retiree | 1.30 | 0.69–2.46 |
| **Self-assessment of health status** | | |
| Very good/Good/Fair | - | |
| Poor/Very poor | 1.09 | 0.72–1.64 |
| **Presence of chronic disease** | | |
| No | - | |
| Yes | **2.32** | **1.38–3.90** |
| **Exposure to stress in the four weeks prior to interview** | | |
| No/Yes, not more than others | - | |
| Yes, more than others/Yes, unbearable | **3.25** | **2.24–4.73** |
| **Physical pain in the four weeks prior to the interview** | | |
| No/Very mild | - | |
| Mild/Moderate | **2.68** | **1.81–3.99** |
| Severe/Very severe | **1.85** | **1.10–3.12** |
| **Unmet healthcare needs in the past 12 months due to the long waiting time for health service** | | |
| No | - | |
| No need for healthcare | 1.94 | 0.52–7.25 |
| Yes | 1.43 | 0.93–2.18 |
| **Unmet healthcare needs in the past 12 months due to distance or transportation barriers** | | |
| No | - | |
| No need for healthcare | 0.28 | 0.08–1.06 |
| Yes | 1.55 | 0.87–2.76 |
| **Satisfaction with public health service** | | |
| Very satisfied/Satisfied | - | |
| Neither satisfied nor dissatisfied | 1.09 | 0.73–1.63 |
| Dissatisfied/Very dissatisfied | 0.99 | 0.64–1.54 |

Notes: significant findings where $p<0.05$ are marked in bold; all variables significantly associated in univariate analysis were included in multivariate analysis. Abbreviations: OR- Odds Ratio; CI- Confidence Interval

## 4 DISCUSSION

Based on our knowledge, this is a rare study highlighting gender differences in predictors of self-medication with tranquillizers and sleeping pills controlled for socio-demographic factors, health status and satisfaction with the healthcare system. Our study has shown that self-medication is a more frequent practice among the female population compared to males in cases of self-medication with tranquillizers and sleeping pills. Health-related factors (chronic disease and physical pain) and environmental stress were revealed as independent predictors of self-medication with observed drugs in both men and women. However, gender differences have been shown through two discriminatory factors, age, and employment status. While an age of above 45 years has been revealed as a strong predictor of self-medication with tranquillizers and sleeping pills in women, a similar effect was not confirmed among males. On the contrary, unemployment has been shown as a significant determinant of self-medication with tranquillizers and sleeping pills in males, but without significant influence in females.

Several previous studies investigated the determinants of regularly prescribed medication use for depression, anxiety, stress, and sleep problems in the female population (27, 28). They also found age, stress, and physical pain as predictors of regular use of hypnotics/anxiolytics/sedatives, as well as other predictors like social tension, hormone replacement therapy, headaches, palpitations, mood swings or increased muscular tension, anger, duration of symptoms lasting longer than one week, consulting a specialist, and mental health-related quality of life. In line with the abovementioned predictive factors, one potential area of intervention may be a focus on timely and proper patient education interventions by healthcare professionals with special warnings about side effects. This may aid in the prevention of future self-medication in women already prescribed drugs for depression, anxiety, stress, or sleeping problems.

This study has also shown that self-medication with tranquillizers and sleeping pills is significantly higher in males and females who have reported chronic diseases and physical pain. Since these patients are most likely already prescribed some other medicines, the possibility of drug-drug interactions is increased. This could be of particular concern if an already prescribed drug is a suppressor of the central nervous system (CNS), because of the well-known CNS suppressive effect of tranquillizers and sleeping pills (29, 30). Along with warnings about side effects, patient education interventions should include descriptions of prescribed therapy purposes, with the aim to decrease the rate of therapy duplication or harmful effects.

The results of our study have shown that the risks from self-medication in women increase significantly for those over 45 years of age, which coincides with the start of the menopause. This risk reaches a peak at 55–64 years of age when women predominantly cope with unpleasant menopausal symptoms. Additionally, many with symptoms of non-communicable diseases maintain overwhelming amounts of work and family responsibilities with little to no focus on personal health. The decline of risk starts after 65 years of age, which could be linked to the end of women's working engagement and a decrease in the level of family stress, as well as to the end of the menopause. Most middle-aged women suffer from high demands in personal and professional responsibilities and, accordingly, need specialised support. A similar phenomenon may be observed with unemployed males. In spite of Serbia's many modern ways of thinking about traditional gender roles, some traditional elements continue to dominate within Serbian society. One example is the attitude that males are consistently expected to serve as dominant breadwinners in the family. For this reason, the male population requires additional healthcare support in the effects of unstable employment status. Our study directly confirms previous data that self-medication with tranquillizers is not supported by the hypothesis of gender role convergence and expectations (11).

Environmental stress is the only modifiable factor revealed as the predictor of self-medication with tranquillizers and sleeping pills in both women and men. Although coping with stress is stressful by itself, psychotherapy, meditation, and other relaxing techniques are showed as helpful (31). However, such techniques are not yet widely accepted in the Serbian population. Concurrently, Šantrić-Milićević et al. reported that almost half of the Serbian adult population assessed their mental health as poor and 5% had diagnosed chronic anxiety or depression (32). Accordingly, well-tailored public health actions, specifically targeting middle-aged women and unemployed males and their ability to cope with stress and pressure in healthy ways, could potentially reduce the high level of self-medication with tranquillizers and sleeping tablets and prevent unwanted behaviours and consequences.

While previous studies have established the association between unmet healthcare needs and self-medication in general or with self-medication with illicit drugs, our results have not confirmed previous findings (15, 21, 23, 33). Nevertheless, a relatively high prevalence of unmet healthcare needs has been recorded. Unmet healthcare needs due to barriers related to lack of time or geographic accessibility were not potential predictors, perhaps because of the presence of chronic disease that requires continuous monitoring by health professionals. Accordingly, further research should

explore the relationship between self-medication and the kind of unmet healthcare needs (e.g. prescription of medication, check-up, consultation etc.) and concerning the type of chronic disease condition. This would be of particular benefit for well-targeted preventive measures, especially in developing countries with lower standards and rationalisations of public health expenditures within where the high impacts of unmet healthcare needs could be expected (34).

### 4.1 Strengths and Limitations

The current study has strengths and limitations. One limitation of the study was the inability to assess the cause-consequence relationship between the independent and dependent variables. Instead, we explored potential predictors for self-medication with tranquillizers and sleeping pills. Secondly, the survey data may be burdened with biases due to memory recall, which can lead to an over or underestimation of the study findings. In order to maximise the validity of the findings, participants were asked to give information on medication use for a short period of only two weeks prior to the interview, and for a particular disease out of 17 listed conditions or some other. Additionally, the data was collected in 2013, and it may be that the survey results do not reflect actual practices. However, since that time, there has been no national campaign or other similar public health initiatives with regards to decreasing the use of prescription drug use without a prescription, except in the case of antibiotics. Accordingly, we do not currently expect substitutional differences in the practice of tranquillizers and sleeping pills use. Conducting similar analyses of data from the upcoming National Health Survey will be useful since it will reveal the trend of tranquilizers and sleeping pill use and the subpopulations particularly jeopardised by this behaviour. In the representative sample of the Serbian population of 15 years and above, we were able to determine gender differences in the prevalence and predictors of self-medication with tranquillizers and sleeping pills. The data for the survey was extracted from a sample of the general population. Data related to concrete drugs used in self-medication practices were not collected, which left room for participants to potentially misinterpret tranquillizers and sleeping pills. Additionally, the absence of data related to the exact names of drugs made it impossible to conduct a deeper analysis of particular drugs and drug group usage. The results of this study may be utilised to inform the creation of the survey instrument, which sets out to specifically examine illicit/non-prescription drug and drug groups use. Study findings should be interpreted with these limitations and advantages in mind.

## 5 CONCLUSION

The study findings highlighted different predictors of self-medication with tranquillizers and sleeping pills for men and women. Gender-related socio-demographic differences in predictors were shown (higher age in females and unemployment in males), while the same health-related characteristics were shown as predictors in both genders (presence of chronic disease, physical pain, exposure to stress). While revealed practices and predictors may be useful in improving healthcare professionals' consulting practice, observed gender differences may be utilised to inform the design of gender-sensitive surveillance, identification, and prevention of such undesirable practice through well-tailored public health actions.

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## CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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## ETHICAL APPROVAL

The Serbian National Health Survey 2013 was approved by the Ethical Board of the National Institute of Public Health of the Republic of Serbia and the Ministry of Health.

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# NAVODILA AVTORJEM

Revija: **Zdravstveno varstvo (ZV)** ISSN 0351-0026 (tiskana izdaja) / **Slovenian Journal of Public Health (SJPH)** ISSN 1854-2476 (elektronska izdaja)

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10. Sugden K, Kirk R, Barry HC, Hickner J, Ebell MH, Ettenhofer T, et al. Suicides and non-suicidal deaths in Slovenia: molecular genetic investigation. In: 9th European Symposium on Suicide and Suicidal Behaviour. Warwick: University of Oxford, 2002:76.

primer za magistrske naloge, doktorske disertacije in Prešernove nagrade:

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## TABELE

Tabele v angleškem jeziku naj bodo v besedilu prispevka na mestu, kamor sodijo. Tabele naj sestavljajo vrstice in stolpci, ki se sekajo v poljih. Tabele oštevilčite po vrstnem redu, vsaka tabela mora biti citirana v besedilu. Tabela naj bo opremljena s kratkim angleškim naslovom. V legendi naj bodo pojasnjene vse kratice, okrajšave in nestandardne enote, ki se pojavljajo v tabeli.

## SLIKE

Slike morajo biti profesionalno izdelane. Pri pripravi slik upoštevajte, da gre za črno-beli tisk. Slikovno gradivo naj bo pripravljeno:

- črno-belo (ne v barvah!);
- brez polnih površin, namesto tega je treba izbrati šrafure (če gre za stolpce, t. i. tortice ali zemljevide);
- v linijskih grafih naj se posamezne linije prav tako ločijo med samo z različnim črtkanjem ali različnim označevanjem (s trikotniki, z zvezdicami...), ne pa z barvo;
- v grafih naj bo ozadje belo (tj. brez ozadja).

Črke, številke ali simboli na sliki morajo biti jasni, enotni in dovolj veliki, da so berljivi tudi na pomanjšani sliki.

Ročno ali na pisalni stroj izpisano besedilo v sliki je nedopustno.

Vsaka slika mora biti navedena v besedilu. Besedilo k sliki naj vsebuje naslov slike in potrebno razlago vsebine. Slika naj bo razumljiva tudi brez branja ostalega besedila. Pojasniti morate vse okrajšave v sliki. Uporaba okrajšav v besedilu k sliki je nedopustna. Besedila k slikam naj bodo napisana na mestu pojavljanja v besedilu.

Fotografijam, na katerih se lahko prepozna identiteta bolnika, priložite pisno dovoljenje bolnika.

## MERSKE ENOTE

Naj bodo v skladu z mednarodnim sistemom enot (SI).

## KRATICE IN OKRAJŠAVE

Kraticam in okrajšavam se izogibajte, izjema so mednarodno veljavne oznake merskih enot. V naslovih in izvlečku naj ne bo kratic. Na mestu, kjer se kratica prvič pojavi v besedilu, naj bo izraz, ki ga nadomešča, polno izpisan, v nadaljnjem besedilu uporabljano kratico navajajte v oklepaju.

## UREDNIŠKO DELO

Prispelo gradivo z javnozdravstveno tematiko mednarodnega pomena posreduje uredništvo po tehnični brezhibnosti v strokovno recenzijo trem mednarodno priznanim strokovnjakom. Recenzijski postopek je dvojno slep. Po končanem uredniškem delu vrnemo prispevek korespondenčnemu avtorju, da popravke odobri in upošteva. Popravljen čistopis vrne v uredništvo po spletni aplikaciji Editorial Manager. Uredništvo dopušča obravnavo največ treh revizij. Če tretja revizija rokopisa ne upošteva vseh pripomb recenzentov, se rokopis umakne iz uredniškega postopka. Sledi jezikovna lektura, katere stroške krije založnik. Med redakcijskim postopkom je zagotovljena tajnost vsebine prispevka. Avtor dobi v pogled tudi prve, t. i. krtačne odtise, vendar na tej stopnji upoštevamo samo še popravke tiskarskih napak. Krtačne odtise je treba vrniti v treh dneh, sicer menimo, da avtor nima pripomb.

V uredništvu se trudimo za čim hitrejši uredniški postopek. Avtorji se morajo držati rokov, ki jih dobijo v dopisih, sicer se lahko zgodi, da bo članek odstranjen iz postopka.

Morebitne pritožbe avtorjev obravnava uredniški odbor revije.

Za objavo članka prenese avtor avtorske pravice na Nacionalni inštitut za javno zdravje kot založnika revije (podpiše Pogodbo o avtorstvu in avtorskih pravicah). Kršenje avtorskih in drugih sorodnih pravic je kaznivo.

Prispevkov ne honoriramo in tudi ne zaračunavamo stroškov uredniškega postopka.

Avtor dobi izvod tiskane revije, v kateri je objavljen njegov članek.