Health-related Quality of Life and Insulin Resistance: a Longitudinal Study

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Abstract

The aim of the study was to investigate insulin resistance (IR) in association with health-related quality of life (HRQoL) among citizens of Palanga in a ten years follow-up. A randomized epidemiological study was performed out for 835 subjects. All study participants were evaluated according to for socio-demographic characteristics, behavioral factors, HRQoL and self-perceived health using questionnaires. Fasting blood samples were draw from all participants and biochemical tests were performed for the glucose, insulin. IR was evaluated by the homeostasis model assessment of IR (HOMA-IR). In subjects with IR, after adjusting with various factors, logistic regression analysis showed, that within 10 years, a significantly higher chance of deteriorating HRQoL in the areas of: physical functioning (odss ratio [OR] = 1.15, $p < 0.001$), emotional role limitations (OR = 1.07, $p = 0.034$), social functioning (OR = 1.26, $p = 0.004$), pain (OR = 1.09, $p = 0.005$) and general health perception (OR = 1.07, $p = 0.022$). People with IR have a worse HRQoL and as they age, they are significantly more likely to have a deterioration in their HRQoL compared to people without IR in the areas of physical functioning, emotional role limitations, social functioning, pain and general health perception.

Introduction

Insulin resistance (IR) occurs as part of a cluster of cardiovascular-metabolic abnormalities. Given the seriousness of the cardiovascular diseases data, diabetes is becoming a greater burden[1]. Diabetes mellitus (DM) and impaired glucose tolerance have not only been associated with increased morbidity and mortality, but also with poor quality of life[2,3].

IR was found in strong correlation with an estimated measure of quality of life in patients with coronary heart disease but no known DM[4].

IR is the primary cause of metabolic syndrome, which in turn reflects a real variety of risk factors, closely linked to each other. The etiology of metabolic syndromes is complex and multifactorial. The key causes are obesity, physical inactivity, sedentary lifestyle and aging population[5–7].

IR might potentially be linked to a rise in global health problems. Using the homeostasis model assessment of IR (HOMA-IR) and the SF-36 health survey, cross-sectional data from 1212 participants in the Hertfordshire Cohort Study revealed that IR was associated with poor health-related quality of life (HRQoL) in domains of physical health but not in domains of mental health[8].

HRQoL is a multidimensional term that relates to overall satisfaction with life and is concerned with a patient's level of functioning across physical, emotional, and social domains. It represents the patient's perception of the impact of a disease and its treatment. Many variables influence HRQoL, including disease-related disability[9].

The assessment of IR indicators in everyday clinical practice is based on fasting glucose and insulin concentrations. The HOMA-IR is one of the most often used indirect indicators for characterizing this condition in the ’steady-state’[10,11].

So far, a correlation between IR and HRQoL has been receiving little attention in medical literature and because of that, is still controversial and is not well understood. It is important to examine the association with worse HRQoL in this population. HRQoL reflects how an individual views and adapts to their symptoms burden, mental distress, functional limitations, as well as how patients perceive their overall health. Thus, we aimed to investigate HRQoL in association with IR among citizens of Palanga in ten years follow-up.

Methods

Study Participants

A random sample of 2500 citizens of Palanga aged 35–74 was drawn from the National Population Register in 2002. The citizens of Palanga were chosen as an object of investigation, because there was close community with minor migration reflecting the population of West part of Lithuania. The optimal size of the sample, ensuring representativeness of the population of Palanga aged 35–74 years, was calculated (1630 ± 33 individuals). From the sample of 2500 citizens, 160 selected persons were not invited to participate in the study, because they were not found at the given addresses, 1602 persons (600 males and 1002 females) participated in the survey in 2003. The response rate for the first survey was calculated in the following: (1602/2340) × 100 = 68.5%. In the period from 2003 until 2013, 158 persons (9.9%) of those, who had participated in the first survey in 2003, died, 47 (2.9%) had changed their living address, 20 (1.2%) declined to participate, 11 (0.7%) could not participate as a result of serious health problems, and 435 (27.2%) people did not respond to the multiple invitations sent to them by post. During the second survey, data from 931 people, 322 males and 609 females, aged 45–84 years, were collected in 2013. The first and the second surveys were approved by the Ethics Committee for Biomedical Research at Lithuanian University of Health Sciences, Kaunas, Lithuania (protocol code BE-2-25 and 14 June 2012 of approval). Informed consent was obtained from all participants during both surveys. However, blood samples were collected from only 850 subjects and fifteen (1.8%) subjects, whose blood tests showed severe thyroid dysfunction, were excluded from the analysis. The final study cohort consisted of 835 subjects: 300 (35.9%) men and 535 (64.1%) women. The mean age of the study subjects was 63.5 ± 10.3 years. The original source of method descriptions is described elsewhere[12].

Study procedure

All study participants were evaluated according to for socio-demographic characteristics (i.e., age, sex, height, weight, education and marital status), behavioral factors, HRQoL and self-perceived health using questionnaires. Fasting blood samples were draw from all participants and biochemical tests were performed for the glucose and insulin. The IR was calculated according to the formula HOMA-IR (HOMA-IR = (fasting plasma insulin [μIU/ml]) × (fasting plasma glucose [mmol/l])/22.5); normal rate of HOMA = ≤ 2.7.

Measures

WHO-5 wellbeing test

The WHO-5 Well-being Index[13] questionnaire consisted of 5 questions reflecting the well-being of a person during the last 2 weeks: I feel cheerful and in good spirits; I feel calm and relaxed; I feel active and vigorous; I

wake up feeling fresh and rested; my daily life is filled with things that interest me. The raw score is calculated by totaling the figures of the five answers. The raw score ranges from 0 to 25; 0 representing the worst possible and 25 representing the best possible quality of life, Cronbach α = 0.876. The respondents who scored 50 and more did not have depressive mood. For the respondents who scored less than 50, depressive mood was identified, and they were ascribed to the group of an increased risk of depression.

The questionnaire on general data, behavioral factors and self-perceived health

The questionnaire on general data[14] was used to collect the information about the marital status, education, employment and income of respondents. The questionnaire on behavioral factors[14] consisted of questions about smoking, alcohol consumption, and physical activity during the last year. The self-perceived health questionnaire[14] consisted of questions about complaints and diagnosed diseases, medications used during the last year, frequency of stress events, and visits to any doctor.

Objective Investigation

Arterial blood pressure (mmHg) was measured twice with a quicksilver sphygmomanometer on the right hand while a person was sitting, with the precision of 2 mm according to the methodological guidelines[15]. The average of two measurements was used for the analysis. If the participants' systolic blood pressure was greater than 140 mmHg and/or their diastolic arterial blood pressure was greater than 90 mmHg in the previous two weeks, they were graded as hypertensive.

Body height was measured in stocking feet (without shoes) with a medical height rod. Body weight was measured without shoes using a medical scale. Body mass index (BMI) was calculated according to the following formula: BMI = body mass (kg)/height (m) ^{2} using the data of height and weight measurement. Overweight was diagnosed when BMI was 25.0–29.9 kg/m^2, obesity when BMI was 30.0 kg/m^2 and more.

36-Item Short Form Medical Outcome Questionnaire (SF-36)

The 36-item Short Form Medical Outcome Questionnaire (SF-36) consists of 8 multi-item subscales that assess HRQoL on 8 domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, pain, and general health perception. Each of the 8 SF-36 domains is scored on scales from 0 to 100, with higher scores indicating better HRQoL[16]. Internal reliability (α coefficients) of 8 subscales has been found to range between 0.71 and 0.85.

Statistical analysis

The clinical and the sociodemographic characteristics were reported by frequencies and percentages for the categorical variables, and with means and standard deviations for the continuous variables. Variable distribution of similarity to normal was assessed visually and using the Kolmogorov-Smirnov and Shapiro-Wilk'o tests. The data characteristics were compared between groups without IR and with IR were using Fisher's χ^2 test, for the parametric two-tailed Student's t-test test or nonparametric Mann-Whitney U test. A logistic regression analysis using an enter method was used to investigate if 10-year follow-up period (time),

sex, age, IR were related to different areas of quality of life (Model 1) and additionally adjusted by family status; education; employment; self-perceived health; frequent stressful events; depression mood; alcohol used; smoking; illness during past 12 month; and obesity (Model 2). Statistical analyses were performed with the Statistical Package for the Science Software v.22 (SPSS, Chicago, IL). The level of significance was set at $p < 0.05$.

Results

Baseline characteristics

Table 1 lists the participants' socio-demographic characteristics of all participants are stratified into groups without IR (HOMA-IR ≤ 2.7 and with IR (HOMA-IR > 2.7) in the survey in 2003 and 2013 years follow up. As it is demonstrated in Table 1, significant differences of sex, education, BMI and self-related health were found between the study groups, both in the first survey in 2003 and the same in the second survey in 2013. Participants with IR were more likely to be male, with higher BMI, had lower than higher education, and with moderate self-related health. However, there were significantly fewer smokers in both groups after ten years.

Table 1
The sociodemographic characteristics of subjects' groups without and with insulin resistance in the survey in 2003 and 2013.

Baseline characteristics	**2003**		**p-value**	**2013**		**p-value**	**2003:2013**	**2003:2013**
	Without IR group	**With IR group**		**Without IR group**	**With IR group**		**Without IR group**	**With IR group**
	n = 557	n = 278		n = 557	n = 278			
Age, years; mean ± SD	53.1 ± 10.6	54.9 ± 9.9	**0.016**	63.0 ± 10.5	64.8 ± 9.7	**0.015**		
Sex; n (%)			**0.003**			**0.003**	–	–
Male	181 (32.5)	119 (42.8)		181 (32.5)	119 (42.8)			
Female	376 (67.5)	159 (57.2)		376 (67.5)	159 (57.2)			
BMI, kg/m2; mean ± SD	26.0 ± 4.3	30.0 ± 4.5	**< 0.001**	26.6 ± 4.1	31.0 ± 4.7	**0.002**	**0.013**	**0.005**
Marital status; n (%)			0.932			0.533	**0.004**	**0.007**
Married	420 (75.4)	211 (75.9)		376 (67.5)	181 (65.1)			
Alone	137 (24.6)	67 (24.1)		181 (32.5)	97 (34.9)			
Education; n (%)			**0.001**			**0.001**	0.287	0.839
Less than higher	369 (66.2)	217 (78.1)		351 (63.0)	214 (77.0)			
Higher	188 (33.8)	61 (21.9)		206 (37.0)	64 (23.0)			
Employment; n (%)			0.281			0.142	**< 0.001**	**< 0.001**
Employed	369(66.2)	173 (62.2)		277 (49.7)	123 (44.2)			
No employed	188 (33.8)	105 (38.8)		280 (50.3)	155 (55.8)			
Self-rated health			**0.014**			**0.018**	0.083	0.277

Note: BMI – body mass index; IR – insulin resistance; p-value of probability for comparison between groups (bolded numbers indicate significant differences, **p < 0.05**); data presented as n (%), mean ± SD.

Baseline characteristics	2003		p-value	2013		p-value	2003:2013	2003:2013
	Without IR group	With IR group		Without IR group	With IR group		Without IR group	With IR group
Good health	178 (32.1)	63 (22.7)		203 (36.4)	76 (27.3)			
Moderate	344 (62.0)	192 (69.1)		334 (60.0)	186 (66.9)			
Poor health	33 (5.9)	23 (8.3)		20 (3.6)	16 (5.8)			
Smoking regular; n (%)	198 (35.5)	112 (40.3)	0.182	85 (15.3)	38 (13.7)	0.541	**< 0.001**	**< 0.001**

Note: BMI – body mass index; IR – insulin resistance; p-value of probability for comparison between groups (bolded numbers indicate significant differences, **p < 0.05**); data presented as n (%), mean ± SD.

Comparison of Health-related quality of life scores according to the presence of IR in the survey in 2003 and 2013

The HRQoL scores of questionnaire SF-36 of study (2003 and 2013) population according to the presence of IR are shown in Table 2. HRQoL according to the physical functioning subscale was statistically significantly lower in the first study and after ten years in subjects with IR compared to subjects without IR. Also, after ten years, HRQoL in physical function subscale decreased significantly in both study groups according to the presence of IR, but the decrease in HRQoL was statistically significantly greater in the IR group. Physical role limitations subscale scores did not differ between groups in the first study, but ten years later the difference was already significant. Significantly lower physical role limitations were found in IR individuals, although HRQoL under this subscale decreased significantly with age in both groups. Social function subscale scores were the same in both with IR and without IR groups in the first study and did not change after 10 years in the group without IR, and decreased significantly in the IR group, so the difference of HRQoL according social function is statistically significant worse in subjects with IR.

Table 2
Health-related quality of life scores of subjects' groups without and with insulin resistance in the survey in 2003 and 2013.

	2003			**2013**			**2003:2013**	**2003:2013**
SF-36 domain scores, mean (95% CI)	**Without IR**	**With IR**	**p-value**	**Without IR**	**With IR**	**p-value**	**Without IR**	**With IR**
	n = 557	n = 278		n = 557	n = 278			
Physical functioning	78.5 (77.1–79.9)	75.5 (73.6–77.3)	**0.009**	75.4 (73.6–77.1)	65.4 (62.5–68.3)	**< 0.001**	**< 0.001**	**< 0.001**
Physical role limitations	66.9 (64.2–69.5)	64.9 (61.3–68.4)	0.388	60.5 (57.3–63.7)	53.2 (48.4–58.0)	**0.014**	**< 0.001**	**< 0.001**
Emotional role limitations	67.4 (64.7–70.1)	69.0 (61.3–68.4)	0.480	66.6 (63.4–69.9)	64.8 (60.0–69.5)	0.515	0.687	0.125
Social functioning	75.4 (73.9–77.0)	75.4 (73.3–77.6)	0.998	76.5 (74.6–78.4)	69.7 (66.8–72.7)	**< 0.001**	0.304	**0.001**
Mental health	64.4 (63.0–65.8)	66.3 (64.7–67.9)	0.079	68.6 (67.1–70.0)	68.4 (66.–70.5)	0.911	**< 0.001**	**0.005**
Energy-vitality	60.3 (58.9–61.7)	61.1 (59.4–62.8)	0.477	61.5 (60.0–63.0)	60.0 (57.8–62.2)	0.254	0.147	0.351
Pain	68.7 67.1–70.4)	67.8 (65.6–70.1)	0.516	69.3 (67.3–71.2)	65.2 (62.3–68.1)	**0.019**	0.636	0.093
General health perception	50.0 (48.8–51.2)	49.3 (47.9–50.8)	0.504	52.5 (51.1–53.9)	49.2 (47.2–51.1)	**0.007**	**< 0.001**	0.860

Note: IR – insulin resistance p-value of probability for comparison between groups (bolded numbers indicate significant differences, **p < 0.05**).

Mental health subscale scores decreased significantly with age in both groups, but we did not find a significant difference in the groups according to the presence of IR. The Pain subscale scores did not significantly change with age in both groups, but after 10 years, the difference in HRQoL between groups became statistically significantly different with worse HRQoL in the IR group. No differences were found in the HRQoL in energy-vitality and emotional role limitations subscales when evaluating the data in the groups according to IR over 10 years. HRQoL in the general health perception in the IR group did not change

with age, and without IR in the group it improved significantly and so after 10 years the differences between the groups became significant.

In the IR group the HRQoL become significantly worse compared with the without IR group.

The change in health-related quality of life in ten years follow up

Table 3 lists the participants' change in SF-36 subscales scores between study groups in the period from 2003 until 2013 years. As it is demonstrated in Table 3, significant differences of SF-36 subscales of physical functioning, social functioning and general health perception were found between the IR. Participants with IR had significant decrease in domains of the SF-36 subscales of physical functioning, social functioning and general health perception showing their worse HRQoL in ten years period.

Table 3
Change in Health-related quality of life scores of subjects' groups without and with insulin resistance in the period from 2003 until 2013.

SF-36 domain scores, mean (95% CI)	Without IR	With IR	p-value
ΔPhysical functioning	−3.1 (−4.7 to − 1.6)	−10.1 (−12.9 to − 7.2)	**< 0.001**
ΔPhysical role limitations	−6.4 (−9.8 to − 2.9)	−11.6 (−17.0 to − 6.3)	0.092
ΔEmotional role limitations	−0.75 (−4.4 to 2.9)	−4.3 (−9.7 to 1.2)	0.283
ΔSocial functioning	1.1 (−0.98 to 3.1)	−5.7 (−8.9 to − 2.5)	**0.001**
ΔMental health	4.2 (2.6 to 5.8)	2.1 (−0.04 to 4.3)	0.132
ΔEnergy-vitality	1.2 (−0.43 to 2.9)	−1.1 (−3.5 to 1.2)	0.110
ΔPain	0.51 (1.6 to 2.6)	−2.6 (−2.5 to − 0.01)	0.098
ΔGeneral health perception	2.5 (1.2 to 3.8)	−0.19 (−2.3 to 1.9)	**0.033**

Note: IR – insulin resistance SF-36 – The 36-item Short Form Medical Outcome Questionnaire; p-value of probability for comparison between groups (bolded numbers indicate significant differences, **p < 0.05**).

Logistic regression models

After logistic regression analysis and adjusting with various factors, we found, that within 10 years, subjects with IR have a significantly higher chance of deteriorating HRQoL in the areas of: physical functioning, emotional role limitations, social functioning, pain and general health perception, as seen in both Model 1 and Model 2 (Table 4).

Table 4
Results from regression analyses in which year, sex, age, insulin resistance are regressed on SF-36 subscales.

Independent variable	Model 1 OR (95% CI)		p-value	Model 2 OR (95% CI)		p-value
	Physical functioning					
Time	0.61	(0.49–0.76))	0.067	0.59	(0.47–0.75))	**< 0.001**
Sex: Males (1)/ Females	1.29	(1.04–1.59)	**0.018**	1.22	(0.96–1.54)	0.104
Age	1.04	(1.04–1.06)	**< 0.001**	1.04	(1.02–1.05)	**< 0.001**
IR without (1)/ with (2)	1.36	(1.10–1.68)	**0.005**	1.15	(1.07–1.23)	**< 0.001**
	Physical role limitations					
Time	0.34	(0.51–0.80)	**< 0.001**	0.64	(0.51–0.82)	**< 0.001**
Sex: Males (1)/ Females	1.32	(1.07–1.63)	**0.010**	1.15	(0.91–1.46)	**0.246**
Age	1.05	(1.04–1.06)	**< 0.001**	1.04	(1.02–1.05)	**< 0.001**
IR without (1)/ with (2)	1.17	(0.95–1.45)	0.150	1.04	(0.82–1.44)	0.253
	Emotional role limitations					
Time	0.70	(0.56–0.88)	**0.002**	0.65	(0.51–0.83)	**0.001**
Sex: Males (1)/ Females	1.09	(0.88–1.45)	0.427	1.07	(0.84–1.36)	0.600
Age	1.04	(1.03–1.05)	**< 0.001**	1.03	(1.02–1.05)	**< 0.001**
IR without (1)/ with (2)	1.11	(0.90–1.38)	0.332	1.07	(1.01–1.38)	**0.034**
	Social functioning					
Time	0.72	(0.57–0.89)	**0.003**	0.64	(0.51–0.82)	**< 0.001**
Sex: Males (1)/ Females	1.55	(1.26–1.92)	**< 0.001**	1.47	(1.16–1.87)	**0.002**
Age	1.04	(1.03–1.05)	**< 0.001**	1.03	(1.02–1.05)	**< 0.001**
IR without (1)/ with (2)	1.70	(1.37–2.10)	**< 0.001**	1.260	(1.03–1.17)	**0.004**
	Mental health					
Time	1.06	(0.85–1.31)	0.629	1.01	(0.83–1.27)	0.933
Sex: Males (1)/ Females	1.09	(0.89–1.34)	0.408	1.03	(0.82–1.29)	0.822

Note: IR – insulin resistance; OR, odds ratio; CI, confidence interval;

Model 1 – Adjusted by year, sex, age, insulin resistance;

Model 2 – Adjusted by year, sex, age, insulin resistance, marital status; education, employment, self-perceived health; frequent stressful events; depression mood; alcohol used; smoking; illness during past 12 months, body mass index. Bolded numbers indicate significant **$p < 0.05$.**

Independent variable	Model 1 OR (95% CI)		p-value	Model 2 OR (95% CI)		p-value
Age	0.99	(0.99–1.00)	0.262	1.00	(0.98–1.01)	0.711
IR without (1)/ with (2)	1.32	(1.07–1.63)	**0.008**	1.06	(0.99–1.23)	0.054
	Energy-vitality					
Time	0.89	(0.72–1.10)	0.273	0.83	(0.66–1.04)	0.107
Sex: Males (1)/ Females	1.11	(0.91–1.36)	0.316	0.97	(0.77–1.22)	0.801
Age	1.01	(1.00–1.02)	**0.011**	1.01	(0.99–1.02)	0.386
IR without (1)/ with (2)	1.40	(1.14–1.71)	**0.002**	1.03	(0.97–1.09)	0.370
	Pain					
Time	0.87	(0.71–1.09)	0.223	0.82	(0.65–1.04)	0.101
Sex: Males (1)/ Females	1.45	(1.18–1.78)	**< 0.001**	1.43	(1.13–1.80)	**0.003**
Age	1.01	(1.00–1.02)	**0.005**	1.01	(0.99–1.02)	0.327
IR without (1)/ with (2)	1.28	(1.04–1.58)	**0.018**	1.09	(1.03–1.16)	**0.005**
	General health perception					
Time	0.92	(0.74–1.15)	0.465	0.88	(0.70–1.12)	0.297
Sex: Males (1)/ Females	1.30	(1.06–1.60)	**0.014**	1.21	(0.96–1.53)	0.106
Age	1.01	(0.99–1.02)	0.090	1.00	(0.98–1.01)	0.580
IR without (1)/ with (2)	1.40	(1.13–1.72)	**0.002**	1.07	(1.01–1.14)	**0.022**
Note: IR – insulin resistance; OR, odds ratio; CI, confidence interval;						
Model 1 – Adjusted by year, sex, age, insulin resistance;						
Model 2 – Adjusted by year, sex, age, insulin resistance, marital status; education, employment, self-perceived health; frequent stressful events; depression mood; alcohol used; smoking; illness during past 12 months, body mass index. Bolded numbers indicate significant **p < 0.05.**						

Discussion

This longitudinal study regarding HRQoL of the population of West part of Lithuania indicated that the impairment of HRQoL was significantly related to IR evaluated by HOMA-IR. The major finding in the present study is that subjects both with IR and without IR reported lower SF-36 scores in domains of physical functioning, physical role limitations and mental health after ten years. Over the course of 10 years, significant changes were observed in domains of the SF-36 subscales of physical functioning, social functioning and general health perception showing worse HRQoL in subjects with IR. Furthermore, results of this study provide evidence of the need for future research to be conducted with people who have IR. It is a cause for concern that within 10 years, subjects with IR have a significantly higher chance of deteriorating

HRQoL in the areas of the five of the eight subscales: physical functioning, emotional role limitations, social functioning, pain and general health perception.

To our knowledge, ours was the first study assessing the associations of IR with HRQoL in ten years follow up. IR is an important factor that needs to be investigated to a more precise identification of the HRQoL domains that are more affected by the presence of IR. Based on the Schlotz et al. findings, IR and its related measures are associated with poor HRQoL in the domains of physical health but not in domains of mental health[8]. According to Sayer et al., glucose intolerance or an elevated plasma glucose level may induce poor muscle control and hinder physical activity[17], so it's likely that physical disability affects IR. The study by Agewall et al. showed that an estimated measure of quality of life was significantly and independently associated with IR in patients with coronary heart disease and without known DM[4].

Together, the data from these studies and our data suggest that IR seems to be one of the most important factors determining the HRQoL in healthy people. This is a potentially modifiable situation which could be changed with dietary and lifestyle improvement. As a result, we agree that more HRQoL research is needed, especially in the area of sexuality[18], to support as well as investigate the health problems related to aging in order to improve HRQoL.

There is a growing body of evidence that shows a connection between metabolic syndrome and deterioration in HRQoL[5,19–21]. Unfortunately, there is still little evidence examining IR as the primary cause of metabolic syndrome in association with HRQoL.

The contribution of the present study was to draw attention to the effects that the IR can have on HRQoL, considering the fact that IR is still an important public health issue, which in turn reflecting a real variety of risk factors.

Conclusions

The results of this study suggest that people with IR have a worse HRQoL and as they age, they are significantly more likely to have deterioration in their HRQoL compared to people without IR in the areas of physical functioning, emotional role limitations, social functioning, pain and general health perception after ten years period.

Declarations

Contributions

N.K.: conceptualization; A.P., G.V., N.M.: methodology; N.K., A.P., G.V., N.M.: validation; N.K.: formal analysis; G.V., N.M.: investigation; A.P.: data curation; N.K.: writing-original draft preparation; G.V., N.M.: writing-review and editing; N.M.: supervision; N.M.: project administration. All authors have read and agreed to the published version of the manuscript.

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Ethical approval

All procedures in our study were approved by the Ethics Committee for Biomedical Research at Lithuanian University of Health Sciences, Kaunas, Lithuania (protocol code BE-2-25 and 14 June 2012 of approval) and conforming to the principles outlined in the Declaration of Helsinki.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability

The datasets analysed during the current study are available from the corresponding author upon request.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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