ANNOTATION

of the dissertation work of Saruarov Yerbolat Galymzhanuly on the topic **«Assessment of the level of quality of life of Turkistans' residents in accordance with the risks of cardiovascular diseases»** submitted for the degree of Doctor of Philosophy (PhD) in the educational program 8D10110-«Medicine»

Research relevance:

Cardiovascular pathologies are a component of the group of diseases that affect the components of quality of life. Identifying any evidence of elevated cardiovascular disease (CVD) risk factors in healthy individuals and initiating treatment to prevent dyslipidemia or hypertension is an important step in reducing CVD morbidity and mortality. To reduce the incidence and mortality rates of CVD, it is extremely important to identify any signs of increased risk factors for cardiovascular pathologies in healthy people and to start treatment in a timely manner to prevent dyslipidemia or hypertension. Findings that accurate predictions improve clinical decisions and outcomes are sometimes questionable. Without formal impact analysis, physicians cannot determine how safe or harmful risk assessment criteria are based on their applicability. Therefore, it is important to evaluate the effectiveness of the SCORE, PROCAM and Framingham risk scales, as well as to identify their advantages and disadvantages. In addition, assessing the quality of life of patients with CVD is one of the priorities in the global health system.

Clustering of CVD risk factors is associated with increased risk of cardiovascular pathologies. Such risk factors include high blood pressure, elevated cholesterol and triglyceride levels, obesity, low physical activity or smoking, and a high incidence of type II diabetes has been identified. It is known that people with type II diabetes have a higher risk of cardiovascular disease. The results of this study confirm the high frequency of prediabetes and undiagnosed diabetes in Kazakhstan, the prevalence of β-cell dysfunction in these populations and their relationship with indicators available in clinical practice. Our data indicate the need to pay more attention to subjects with obesity, dyslipidemia and hypertension.

Research purpose:

Determination of the relationship between the level of assessment of the quality of life in prediabetes and undiagnosed diabetes with the risk indicators of cardiovascular diseases among the population of the city of Turkistan.

Research objectives:

1. Validation of the Kazakh version of the SF-36 questionnaire for assessing the level of quality of life;
2. Identification of the CVD risk index using the SCORE, PROCAM and Framingham scales, as well as an assessment of their diagnostic accuracy among the population of the city of Turkistan;
3. Assessment of quality of life depending on the risk of cardiovascular diseases and indicators of key behavioural risk factors;
4. Conducting a cluster analysis of cardiovascular disease risk factors in individuals with prediabetes and undiagnosed diabetes.

Research scientific novelty:

For the first time in Kazakhstan, a Kazakh version of the SF-36 (Short Form-36) quality of life questionnaire was developed, which was adapted and tested for reliability (validation) for the Kazakh population.

For the first time in Kazakhstan, an analysis of the diagnostic value of the international risk scales SCORE, PROCAM and Framingham used to determine the risk of cardiovascular diseases was conducted based on 10-year dynamics.

The first study in Kazakhstan on the use of cluster analysis to assess insulin resistance and β-cell dysfunction in individuals with undiagnosed diabetes and prediabetes, which are risk factors for cardiovascular disease.

Research theoretical significance:

The theoretical significance of the research work is the determination of the degree of risk of CVD using available scales, and a systematic assessment of the relationship between the identified risk indicators and quality of life, as well as an analysis of the validity of the tools used. In addition, to assess the quality of scientifically proven methods used to determine the cluster concentration of risk factors leading to CVD in prediabetes and undiagnosed diabetes mellitus.

Research practical significance:

1. Inclusion in the list of complex treatment and preventive measures with the expansion of the scope of application of the SF-36 questionnaire, which determines the level of quality of life of patients seeking medical care (screening, dynamic monitoring, planned hospitalization, etc.), and medical consultation, depending on variables based on the component of quality of life (physical and mental) in primary health care institutions.

2. Based on the results obtained during the study, the status of internationally recognized risk scales SCORE, PROCAM and Framingham was determined by categories of diagnostic value in determining the risk of CVD, as auxiliary tools that can be used in algorithms, protocols, and preventive measures in the field of healthcare.

3. Based on the results of the study, the main risk factors for CVD and risk indicators according to the Framingham scale, by creating simple methods for clustering prediabetes and undiagnosed diabetes, it is possible to determine the composition of clusters and use them as methodological aids for the purpose of optimizing the processes of organizing treatment and preventive measures.

Publication of the results of the dissertation work:

Publication of 3 articles in scientific journals proposed by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan; in publications included in the Web of Science or Scopus database – 2 articles; 3 abstracts published in the materials of foreign conferences, and 1 author's certificate received.

Provisions submitted for defence:

1. In Kazakhstan, the incidence of cardiovascular diseases tends to increase. Determining the “most accurate” tool by comparing scales such as PROCAM and Framingham, as well as the SCORE risk scale used in the treatment and diagnostic protocols of the Republic of Kazakhstan, by assessing its diagnostic efficiency, optimizes the work carried out in this direction.

2. Determining the quality of life of the population, including patients with chronic cardiovascular diseases (CVD), is the main focus of modern healthcare. In this regard, smoking, physical inactivity, obesity and hyperglycaemia were predominant among the risk factors leading to the development of cardiovascular pathology; they showed a low level of quality of life in the population.

3. In the ten-year dynamic indicators of the studied population, along with cardiovascular pathology, a high increase in the incidence of diabetes mellitus was also observed. It was found that the prevalence of prediabetes and undiagnosed cases of diabetes, which are classified by the values of the hyperglycaemic index, is associated with risk factors causing cardiovascular pathology, according to the principle of "clustering" as follows: 1) prediabetes - age and BMI indicators; 2) undiagnosed diabetes - age indicators, blood pressure, total cholesterol and low-density lipoprotein indicators.

4. A number of problems aimed at optimizing and increasing the efficiency of providing care to patients with CVD require management decisions: 1) determination of the regulatory independence of CVD risk assessment scales and expansion of their scope of application; 2) by creating a population database characterized by CVD and diabetes status, the association patterns of risk factors are continually assessed using cluster analysis; 3) organizing the preparation of electronic versions of questionnaires and risk scales, which are directed at developing digital health platforms.

Research materials and methods:

The study involved 632 residents of the city of Turkistan (average age - 51.19±11.65). Of these, 190 were men (mean age - 52.12±13.59) and 442 were women (mean age - 50.80±10.69). Each

subject participating in the study signed a consent form in which they gave their consent to participate in the study. The sampling type is a pre-targeted non-random sample. This is due to the fact that the main criterion for selecting subjects taken for the study was that these patients had undergone examination at the Clinical-Diagnostic Center of the Khoja Akhmet Yassawi International Kazakh-Turkish University 10 years ago in the period from 2012 to 2014 (a total of 660 respondents participated, of which 28 died). The age of the study participants ranged from 27 to 89 years, with a mean age of 51.2 ± 11.7 years. Inclusion criteria: the staff of the Khoja Akhmet Yassawi International Kazakh-Turkish University registered in the old database (2012-2014). Exclusion criteria: individuals who moved to another location or refused to re-participate in the study.

General clinical research methods: questionnaire method (Fagerstrom test, AUDIT, iPAQ, PSQ, SF-36 questionnaires), anthropometric studies; laboratory methods: fasting glucose level, 2-hour oral glucose tolerance test (GTT), triglycerides (TG), total cholesterol (TC), high-density lipoproteins (HDL) and determination of low-density lipoprotein (LDL) levels. Biochemical studies were performed on a biochemical analyzer Cobas Integra-400 from Roche (Basel, Switzerland). These laboratory studies were conducted in the laboratory of the Clinical-Diagnostic Center of the Khoja Akhmet Yassawi International Kazakh-Turkish University. Statistical data were processed using licensed versions of SPSS 29.0, STATA, Python and MATLAB software packages.

Research results:

According to Chapter I, the average scores for the Kazakh version of the SF-36 questionnaire ranged from 66.6 to 82.2. The highest and lowest scores were observed for the “physical functioning” PF (82.2) and “vitality” VT (66.6) scales, respectively. The scores for the scale of the Kazakh version of the SF-36 questionnaire showed negative asymmetry from 1.37 to -0.18. The correlation (discriminant validity) between each parameter and its supposed scale was greater than 0.50. The correlation coefficients between the scales and the remaining subscales ranged from 0.576 to 0.932, and all of them showed higher scores than the other scales. All scales of the SF-36 questionnaire showed promising indicators of scaling success. Internal consistency, measured by Cronbach's α coefficient, exceeded 0.7 for all eight scales. In addition, the intraclass correlation (ICC) of scores on the Kazakhstan version of the SF-36 questionnaire in two cases, i.e. test-retest reliability (n=100) for scales ranged from 0.593 to 0.888, fully preserving the statistical confidence interval.

Based on the results of Chapter II, the accuracy of the models of the main CVD risk prediction scales (SCORE, PROCAM, Framingham) was assessed by using ROC values and calculating the area under the curve (AUC). Thus, if at the beginning of the study period, that is, in 2012, the AUC value of the SCORE indicators was 0.88 (95% CI, 0.22 - 0.94), then in 2020, this value increased to 0.92 (95% CI, 0.19 - 0.94). Similarly, the 2012 and 2020 ROC/AUC values were compared for both the PROCAM and Framingham risk score models, ranging from 0.63 in 2012 for PROCAM to 0.85 in 2020, and for the Framingham score, a value of 0.95 (95% CI, 0.12-0.97) in 2012 compared to a value of 0.97 (95% CI, 0.03-0.99) in 2020. The level of Pearson correlation coefficients between the indicators of the three scales used to determine the risk of CVD was in the range of 0.996-0.999 for all scales, and the p-value was ≤ 0.05. Also, from 2012 to 2020, there was a transition trend from a low-risk level to a medium-risk level and from a medium-risk level to a high-risk level. In particular, according to the SCORE scale, the proportion of the neglected high-risks of CVD increased from 2.5% in 2012 to 4.4% by 2020. A similar trend was observed for the PROCAM and Framingham risk scales. Also, alcohol consumption, smoking status, history of cardiovascular disease and BMI are the major risk factors for cardiovascular disease, their association with SCORE, PROCAM and Framingham scores was calculated using adjusted R^2, with the strongest association found between alcohol consumption and risk score among the PROCAM scales. BMI scores were the weakest among these four major risk factors.

According to Chapter III, the main behavioural risk factors, main variables of the metabolic syndrome and level of quality of life assessment were differentiated depending on the level of CVD risk. The study found that in the sample determined by smoking, the level of quality of life was significantly higher on the scale of "social functioning" SF ($p = 0.022$) of the SF-36 questionnaire. Also, in the group of people engaged in an average level of physical activity, the average scores on

the scales of "pain intensity" BP (p = 0.017) and "social functioning" SF (p = 0.008) maintained the interval of statistical significance. The results of comparing the parameters of quality of life associated with alcohol consumption, BMI and stress indicators did not show statistical significance. However, among the main variables of metabolic syndrome, intervals of statistical significance associated with obesity and hyperglycaemic indices (prediabetes/undiagnosed diabetes) remained. Moreover, low degrees of quality of life were determined by the following indices: in sample groups with obesity - by the scales of "role functioning due to physical condition" RP, "pain intensity" BP, "social functioning" SF and "role functioning due to emotional state" RE; and hyperglycemic state (prediabetes/undiagnosed diabetes) by the scales of "physical functioning" PF, "role functioning due to physical condition" RP and "general health" GH among samples. At the same time, among the scales predicting the degree of risk of CVD, the PROCAM indicators and the SF-36 survey scales include “role functioning due to physical condition” RP (p=0.043), “pain intensity” BP (p=0.041), “general health” GH (p=0.001) and “life activity” VT (p=0.046) retained the interval of statistical significance. The same comparisons were made with the Framingham risk scale, while the interval of statistical significance was maintained between the scale “role functioning due to physical condition” RP (p=0.011) and the scale “role functioning due to emotional state” RE (p=0.002) within the parameters of the SF-36 questionnaire.

In Chapter IV, the initial data were collected from 632 participants; the final sample size was 476 after excluding cases with missing values. The prevalence of prediabetes and undiagnosed diabetes in this sample was 38.24% and 11.97%, respectively. Prevalence rates for all comparison groups stratified by age, gender, and BMI, as well as other characteristics: β-cell deficiency was also more common in participants with prediabetes (47.8%) and undiagnosed diabetes (87.72%) than insulin resistance (IR) (31.87% vs. 43.86%). The proportion of men and women did not differ significantly across groups; however, the proportion of older participants with prediabetes and undiagnosed diabetes was significant. They also showed lower values for almost all categories of CVD risk factors, with the exception of smoking and alcohol consumption. The highest mean Framingham risk score corresponded to undiagnosed diabetes, whereas the lowest score was detected for normoglycemia. Although the results of multivariable logistic regression models showing the association of individual CVD risk factors with prediabetes and undiagnosed diabetes showed favourable predictive power for prediabetes (AUC = 0.68), this value was relatively “good” for undiagnosed diabetes (0.81). The prediabetes model included such variables as age and hip circumference, while systolic blood pressure, age, total cholesterol, and HDL were included for undiagnosed diabetes. Factor 1, which accounts for the greatest variability, was closely associated with obesity-related factors (BMI, abdominal obesity, waist circumference, hip circumference, systolic and diastolic blood pressure). Factors 2 and 3, which belong to the second principal components, include variables associated with dyslipidaemia (total cholesterol, HDL, triglycerides) and lifestyle (smoking, alcohol consumption). The main outcome of the study was the high prevalence of prediabetes (38.24% 95% CI 33.96–42.70%) and undiagnosed diabetes (11.97% 95% CI 9.34–15.22%). Systematic reviews and meta-analyses of prediabetes report a pooled prevalence of 7–15%, while the prevalence of undiagnosed diabetes is 5–6%. These differences can be explained by differences in the composition of the study populations, as well as in the study design. Our study outcomes indicate statistically significant associations of CVD risk factors (age, obesity, blood pressure, lipid changes) with undiagnosed diabetes, whereas only the hip circumference measurement was associated with prediabetes. The third result of our study was the high prevalence of β-cell deficiency in both prediabetes and undiagnosed diabetes. Therefore, an analysis of CVD risk factor clusters was performed in relation to undiagnosed diabetes and prediabetes status. It was found that undiagnosed diabetes was often associated with age, blood pressure, total cholesterol and HDL from CVD risk factor clusters, and prediabetes was often associated with age and BMI values.

Conclusion:

1. The Kazakh version of the SF-36 quality of life questionnaire was validated - the Cronbach's α coefficient for all scales of the SF-36 questionnaire exceeded 0,7.

2. The risk indicators for cardiovascular diseases were determined using the SCORE, PROCAM and Framingham scales, and the diagnostic significance was assessed - according to the results of the ROC/AUC parameters, the Framingham scale showed the highest value (0,97).

3. The level of quality of life of the studied sample was determined depending on the presence of the main behavioral factors and indicators of cardiovascular disease risk: lower parameters of quality of life were found in smokers on the scale of "social activity" (SF), in individuals with low physical activity on the scales of "physical pain" (BP) and "social activity" (SF). In the study participants with high cardiovascular risk on the PROCAM scale, low indicators of quality of life were found on the scales of "role-physical activity" (RP), "physical pain" (BP), "general health" (GH), "vitality" (VT), and on the Framingham scale - in the scale of "emotional state" (RE) a lower quality of life was determined.

4. As a result of clustering of cardiovascular disease risk factors in relation to undiagnosed diabetes and prediabetes, it was found that clusters of undiagnosed diabetes risk factors causing CVD are associated with age, high blood pressure, total cholesterol and low-density lipoprotein levels, and prediabetes is associated with age and BMI.