PUBLIC HEALTH

DIABETES IN THE REPUBLIC OF NORTH MACEDONIA: EPIDEMIOLOGY AND ECONOMIC BURDEN, 2018-2021 - CORRECTED VERSION

Vjosa Recica[1], Zorica Naumovska[2]

[1] *Institute of Public Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia*

[2] *Faculty of Pharmacy, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia*

Citation: Recica V, Naumovska Z. Diabetes in the Republic of North Macedonia: epidemiology and economic burden, 2018-2021 - Corrected version. Arch Pub Health 2024; 16(1).

doi.org/10.3889/aph.2024.6117

Key words: diabetes, mortality, morbidity, health care costs

***Correspondence:** Vjosa Recica, Institute of Public Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia.

E-mail: vjosa.recica@gmail.com

Received: 15-Dec-2024; **Revised:** 13-Mar-2024; **Accepted:** 2-Apr-2024; **Published:** 15-Apr-2024

This online publication has been corrected. The corrected version was published at https://journals.mk/aph on 25-Aug- 2025

Copyright:© 2025. Vjosa Recica, Zorica Naumovska. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Competing Interests: The author have declared that no competing interests

Abstract

Diabetes is a chronic, metabolic disease with hyperglycemia caused by defects in insulin secretion, insulin action, or both, results in dysfunction and failure of various organs, reduced quality of life, increased medical costs, reduced productivity and premature mortality in diabetic patients. The main goal of the study is presentation of epidemiological data for diabetes, evaluation of complications associated with the disease and economic burden of diabetes in the Republic of North Macedonia. Materials and methods: A retrospective epidemiological study based on prevalence data from the Diabetes Registry in the Republic of North Macedonia, as well as data from primary and specialized healthcare centers was conducted. It combined population demographics in our country in 2021 with epidemiological data for diabetes, as well as healthcare costs associated with diabetes obtained from WHO, Institute of Health Metrics and Evaluation and National Health Insurance Fund. Results: The incidence rate of type 1 diabetes (T1DM) in the Republic of North Macedonia was presented with 1.21‰ newly diagnosed in 2018 and 2.8‰ in 2021 with is highest rate in the age group of youths from 10-14 (12.4‰) in 2021. In time period 2018-2021, the incidence rate of patients with type 2 diabetes (T2DM) also enlarged from 323.3‰ to 355.5‰, while the prevalence rate increased from 5554.4‰ to 6549.3‰. The highest prevalence rates for T2DM analyzed by age were observed in age groups between 55 and 79 years. The highest rate of diabetes-associated complications in North Macedonia are complication on peripheral circulation, followed by ketoacidosis, neurological complications, ophthalmic complication, diabetic coma and multiple complications. The percentage of prescriptions for blood glucose lowering drugs (excluding insulin) in our country rose form 7.3% in 2018 up to 7.6% in 2020, whereas the cost of provision of diabetes treatment supplies in 2021 for patients on insulin amounted to approximately 13,457,508,62 USD. The calculated burden of diabetes mellitus and diabetic complications in the Republic of North Macedonia amounted to 42,806.59 disability-adjusted life-years (DALYs). Conclusions: Diabetes rates are increasing worldwide and in the Republic of North Macedonia, too. This epidemiological study is a solid base for implementation of the national strategy for diabetes and will contribute in effective planning and evaluation of all aspects of diabetes control in the Republic of North Macedonia.

ЈАВНО ЗДРАВЈЕ

ДИЈАБЕТЕС ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА: ЕПИДЕМИОЛОГИЈА И ЕКОНОМСКО ОПТОВАРУВАЊЕ, 2018-2021 - КОРЕГИРАНА ВЕРЗИЈА

Вјоса Речица[1], Зорица Наумовска[2]

[1] *Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија*

[2] *Фармацевтски факултет, Универзитет "Св. Кирил и Методиј" во Скопје, Република Северна Македонија*

Цитирање: Речица В, Наумовска З. Дијабетес во Република Северна Македонија: епидемиологија и економско оптоварување, 2018-2021 - корегирана верзија. Арх Ј Здравје 2024;16(1) doi. org/10.3889/aph.2024.6117

Клучни зборови: дијабетес, морталитет, морбидитет, трошоци за здравствена заштита

***Кореспонденција:** Вјоса Речица, Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија.

E-mail: vjosa.recica@gmail.com

Примено: 15-дек-2023; **Ревидирано:** 13-мар-2024; **Прифатено:** 2-апр-2024; **Објавено:** 15-апр-2024

Оваа публикација е корегирана и корегираната верзија е објавена на https://journals.mk/aph на 25-авг-2025.

Печатарски права: ©2025 Вјоса Речица, Зорица Наумовска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Дијабетесот е хронична, метаболична болест со хипергликемија предизвикана од промени во инсулинската секреција, дејството на инсулинот или и на двата фактора, што резултира со нарушување на физиолошката функција на многу органи и нивно потенцијално откажување, што, пак, резултира со намалување на квалитетот на животот на пациентите, зголемување на медицинските трошоци, намалување на продуктивноста и прерана смртност кај пациентите со дијабетес. Главна цел на студијата е презентација на епидемиолошки податоци за дијабетесот, евалуација на компликации поврзани со болеста и економско оптоварување од дијабетесот во Република Северна Македонија. Материјали и методи: Спроведена е ретроспективна епидемиолошка студија базирана на податоци за преваленција од Регистарот за дијабетес во Република Северна Македонија, како и податоци од примарни и специјализирани здравствени центри. Ги комбинира демографијата на населението во нашата земја во 2021 година со епидемиолошки податоци за дијабетес, како и трошоци за здравствена заштита поврзани со дијабетес добиени од СЗО, Институтот за здравствена метрика и евалуација и Националниот фонд за здравствено осигурување. Резултати: Стапката на инциденција на дијабетес тип 1 (Т1ДМ) во Република Северна Македонија е претставена со 1,21‰ новодијагностицирани во 2018 година и 2,8‰ во 2021 година со највисока утврдена стапка кај возрасната група на млади од 10-14 години (12,4‰) во 2021 година. Во временскиот период 2018-2021 година, стапката на инциденција на пациенти со дијабет тип 2 (Т2ДМ) исто така се зголемила од 323,3‰ на 355,5‰, додека стапката на преваленција се зголемила од 5554,4‰ на 6549,3‰. Највисоките стапки на преваленција за T2DM анализирани според возраста беа забележани во возрасните групи помеѓу 55 и 79 години. Највисока стапка на компликации поврзани со дијабетес во Северна Македонија се компликации на периферната циркулација, по што следуваат кетоацидоза, невролошки компликации, офталмолошки компликации, дијабетична кома и повеќекратни компликации. Процентот на рецепти за лекови за намалување на гликозата во крвта (кај пациенти што не се на инсулин) во нашата земја се зголемил од 7,3% во 2018 година на 7,6% во 2020 година, додека трошоците за обезбедување средства за третман на дијабетес во 2021 година за пациенти на инсулинска терапија изнесувале приближно 13.457.50 ,62 американски долари. Пресметаниот товар на дијабетес мелитус и дијабетични компликации во Република Северна Македонија изнесува 42.806,59 disability-adjusted life-years (години на животот приспособени на неспособност/попреченост) (DALYs). Заклучоци: Стапките на дијабетес се зголемуваат во светот, како и во Република Северна Македонија. Оваа епидемиолошка студија е солидна основа за имплементација на националната стратегија за дијабетес и ќе придонесе во ефективно планирање и евалуација на сите аспекти на контролата на дијабетесот во Република Северна Македонија.

Introduction

Diabetes is a chronic, metabolic disease characterized by hyperglycemia caused by defects in insulin secretion, insulin action, or both, which leads over time to serious damage, dysfunction and failure of various organs[1]. Several pathogenic processes that destroy pancreatic beta cells with subsequent insulin deficiency, and others that result in resistance to insulin action are involved in the development of diabetes[2].

Diabetes mellitus can be categorized into the following main types:

a) Type 1 diabetes (T1DM), caused by the autoimmune destruction of beta cells, leading to an absolute insulin deficiency, including latent autoimmune diabetes in adulthood.

The etiology of T1DM has still not been fully understood although several factors have been identified such as genetic factors, environmental factors, and viral infections. Type 1 diabetes mellitus is considered as a cell-mediated autoimmune destruction of insulin-secreting cells in the pancreas. Although the autoimmune process begins many years before clinical detection and presentation, the destruction remains undetected because 10-20% of beta-cell volume is sufficient to cover the clinical symptoms. The rate of beta-cell destruction varies significantly, being rapid in some individuals (mainly infants and children) and typically slow in adults[3].

b) Type 2 diabetes (T2DM), characterized by the progressive loss of suitable insulin secretion from beta cells, which could result in complete lack of insulin production, often accompanied with insulin resistance[4]. A pre-diabetic stage characterized with high blood glucose levels is a common stage in patients before the diagnosis of T2DM. Recent studies have shown that certain long-term damages to the body, particularly the heart and circulatory system, may already occur during this stage[5].

c) Specific types of diabetes due to other causes, such as monogenic diabetes syndromes (including neonatal diabetes and maturity-onset diabetes in the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug-induced or chemical diabetes (as seen with the use of glucocorticoids, in HIV/AIDS treatment, or after organ transplantation), etc.[6].

d) Gestational diabetes mellitus: diagnosed in the second or third trimester of pregnancy, which was not clearly present before pregnancy[7].

Risk factors for T1DM include family history, race, and certain viral infections in childhood. The incidence rate of T1DM varies significantly worldwide and depends on the interaction between genetic susceptibility and specific environmental factors. Recently, it has been proven that low socioeconomic status is associated with higher rates of morbidity and mortality in patients with T1DM[8].

Risk factors for T2DM are diverse, with some being modifiable, while others are not. Non-modifiable risk factors for T2DM include age, race or ethnic background, family history (genetic predisposition), history of gestational diabetes, and low birth weight. The incidence and prevalence of diabetes increase with age.

Modifiable risk factors or lifestyle factors that contribute to onset of T2DM include increased body mass index (BMI), physical inactivity, poor diet, and hypertension, smoking, and alcohol consumption, among others[9]. Increased BMI, as well as an increased waist-to-hip ratio are recognized as high risk factors for diabetes[10]. Additionally, it is well-established that obesity is a major contributor to insulin resistance and T2DM[11]. Increased demand for insulin can be copped by improving the release activity of the pancreatic beta cells. However, when release capacity of beta cells is not modified, progressive deficiency of insulin and insulin resistance occur, leading to T2DM and abnormalities in carbohydrate, protein, and fat metabolism[12-14].

High morbidity and mortality in diabetic patients are presented in many cross-sectional studies and are a result of common microvascular and macrovascular complications identified in patients with T1DM or T2DM[15,16]. Microvascular complications include peripheral neuropathy with a risk of foot ulcers, amputations, and joint problems; autonomic neuropathy can cause gastrointestinal, genitourinary, cardiovascular symptoms, sexual dysfunction and retinopathy, with the potential of vision loss; nephropathy that can cause renal insufficiency, while macrovascular complications consist of cardiovascular diseases, stroke, cerebrovascular diseases and peripheral arterial disease[17]. There are other complications of diabetes that cannot be included in the aforementioned categories, such as dental diseases, decreased resistance to infections, and complications during childbirth in women with gestational diabetes[18].

Chronic complications are the primary outcome of the progression of T2DM, reducing patients' quality of life, burdening healthcare systems, and increasing mortality among diabetics[19]. After adjusting for age, the mortality rate among people with T2DM is approximately twice that of their non-diabetic peers[20,21]. Approximately 50-80% of all individuals with diabetes die from cardiovascular diseases, cerebrovascular diseases, and renal insufficiency, which are leading causes of death[22,23].

The economic burden of diabetes mellitus is enormous having a significant impact on patients, healthcare providers and national healthcare systems, particularly in low and middle-income countries[24,25]. The estimated total cost of diagnosed diabetes in 2017 was 327 billion dollars, including 237 billion US dollars in direct medical costs and 90 billion dollars in reduced productivity. The largest components of direct medical costs are hospital inpatient care (30% of total medical costs), prescription medications for diabetes complications (30%), antidiabetic agents, and diabetes supplies (15%), and physician visits (13%). Indirect costs include increased absenteeism from work (3.3 billion dollars), reduced productivity at work (26.9 billion dollars) for employed individuals, reduced productivity for those not in the workforce (2.3 billion dollars), work disability due to disease-related disability (37.5 billion dollars), and lost productive capacity due to premature mortality (19.9 billion dollars)[26,27]. The poor disease management usually results

in increased hospital admissions, accounting for over 40% of the costs attributed to diabetes[28].

Collection of relevant epidemiological data, identification of specific risk factors for increased morbidity and mortality in diabetes patients, evaluation of national economic burden of the disease and implementation of appropriate strategy for prevention, treatment and improved quality of life for patients with diabetes is a challenging process and strategic approach is inevitable[29]. The main goal of the study is presentation of epidemiological data for diabetes, evaluation of complications associated with the disease and economic burden of diabetes in the Republic of North Macedonia. These data are a solid base for implementation of national strategy for diabetes and will help in designing of educational programs/interventions for improved prevention and treatment strategies for diabetes in our country.

Materials and methods

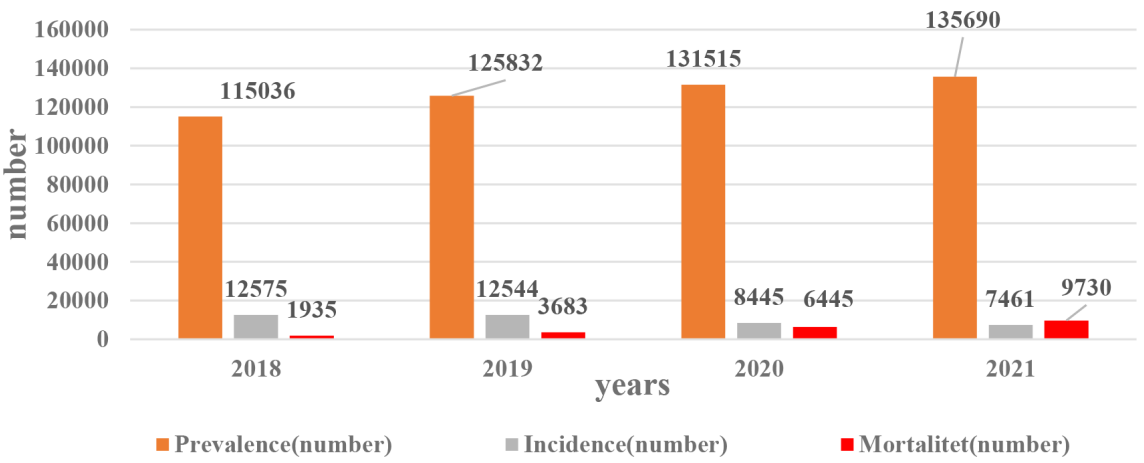
The study employed a retrospective epidemiological approach based on prevalence data taken from the Diabetes Registry of the Institute of Public Health of the Republic of North Macedonia, as well as data from primary healthcare centers and specialized services. It combined population demographics in our country in 2021 with epidemiological data for diabetes, as well as healthcare costs associated with diabetes obtained from WHO, Institute of Health Metrics and Evaluation and National Health Insurance Fund.

Results

Published data by Smokovski et al., suggest that national prevalence in North Macedonia in 2015 among people aged 20 to 79 years was 11.44% or 180.180 patients with diagnosed and undiagnosed diabetes mellitus, 46.9% patients with diagnosed diabetes out of whom 43.8% on insulin therapy.[30] According to the International Diabetes Federation (IDF) Diabetes Atlas, 9th edition (2019), the estimated prevalence of diabetes in North Macedonia was 11.2%, which was higher than the global average of 9.3%. This percentage corresponded to approximately 175,100 adults aged 20–79, indicating that about one in every nine adults in the country had diabetes at that time.[31] In contrast, the IDF Diabetes Atlas, 10th edition (2021) reported a national prevalence of 7.4% in North Macedonia, which was lower than the global average of 10.5%. This figure corresponded to an estimated 116,100 adults aged 20–79 living with diabetes.[32]

The analysis of the individual record from the National Register for Diabetes Mellitus confirmed increase of number of diabetic patients from 115,036 in 2018 up to 135,690 in 2021 presenting 6.6% of population. The mortality increased in the same period and was presented with 1,935 deaths vs. 9,730 in 2018 and 2021, respectively (Figure 1).

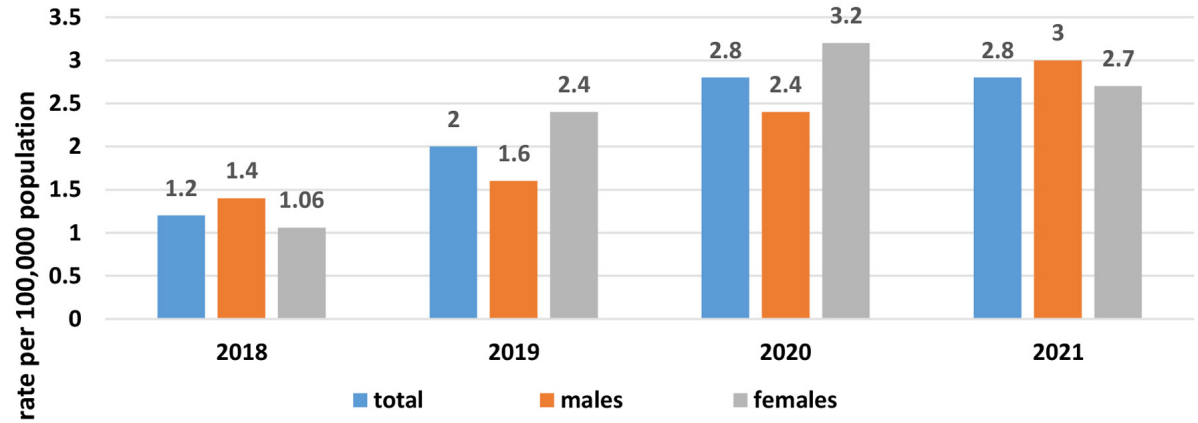
Figure 1: Incidence, prevalence and mortality of diabetes in the Republic of North Macedonia, 2018-2021



The official date suggests that the rate of newly diagnosed cases of diabetes (all diagnoses) in 2021 was 406.1, compared to 684.65 in 2018 per 100,000 population. Out of 135,690 patients with diabetes registered in 2021, 75,820 were male and 59,870 females.

The incidence rate of newly diagnosed patients with T1DM in 2018 was 1.21%ooo, presented with 1.4%ooo in males and 1.06% in females, while in 2021 the incidence rate of T1DM increased up to 2.8%ooo (3%ooo in males and 2.7%ooo in females) (Figure 2).

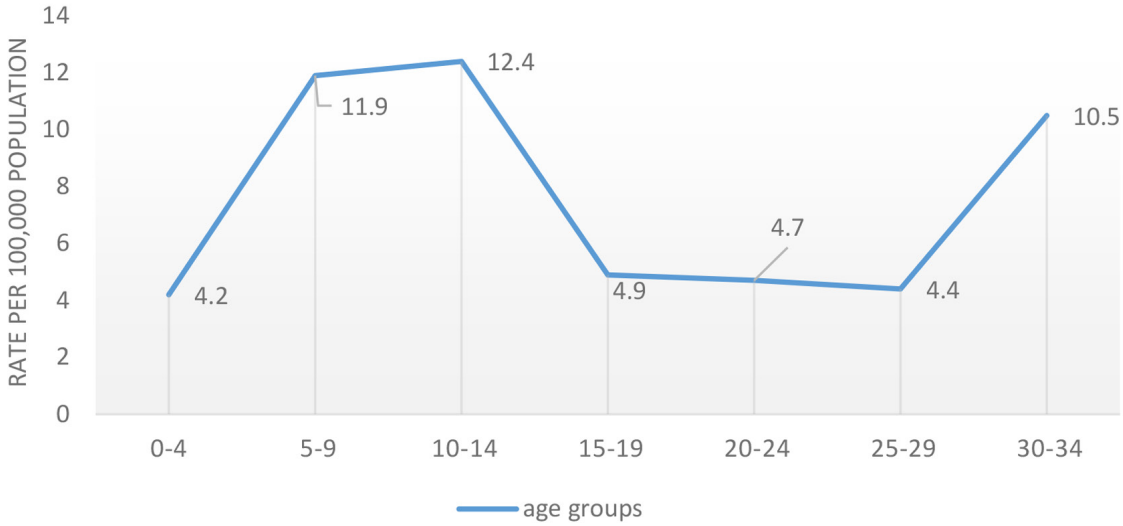
Figure 2: Incidence rate of T1DM per 100,000 population, analyzed by gender



The rate of new cases of T1DM in North Macedonia in youths younger than 20 years was highest in the age groups from 10-14 (12.4%ooo). The total number of children aged 0–14 years diagnosed with T1DM in this period was 45, of which 25 (61.4%) were boys, and 15 (49.6%) were girls.

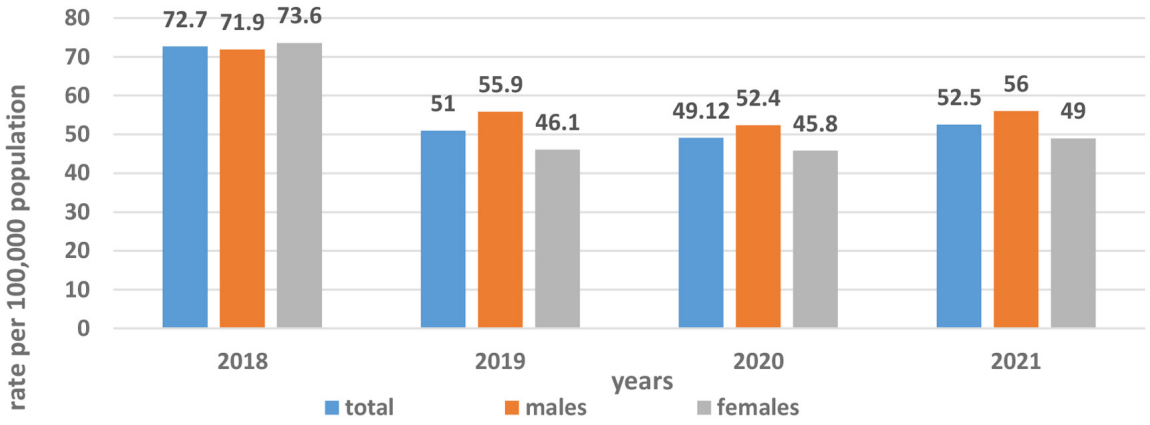
The average age at which diabetes mellitus was diagnosed was 7.8 years.

Figure 3: Incidence rate of DMTB1 per 100,000 population, analyzed by age in 2021



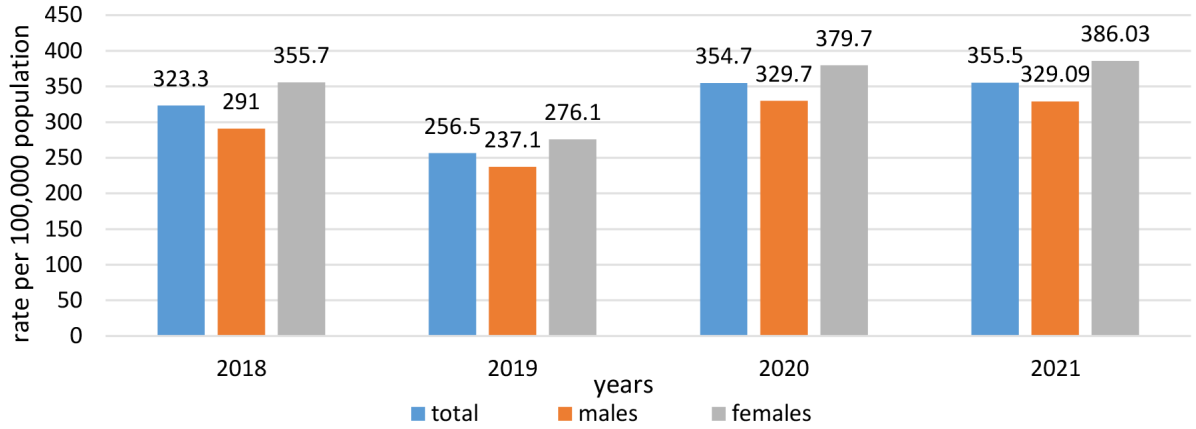
In 2018 the prevalence of diagnosed T1DM in the Republic of North Macedonia was 72%ooo presented with higher rate of 73.6%ooo in females and 71.9%ooo in males. In the period from 2018 to 2021 the prevalence rate decreased for 19.5%ooo and in 2021 it was 52.5%ooo in the total population (56%ooo in females and 49%ooo in males).

Figure 4: Prevalence rate per 100,000 population of T1DM, analyzed by gender



The incidence rate of T2DM was higher in women in the evaluated period compared to men. The Incidence rate of T2DM in 2018 in the total population was 323.3%ooo, with a higher rate in females (355.7%ooo) than in males (291%ooo), rising up the rate of 355.5%ooo (386.03%ooo female vs. 329.09%ooo male) in 2021.

Figure 5: Incidence rate per 100,000 population of T2DM, analyzed by gender



The highest incidence of diabetes mellitus in the period 2018-2021 was found in people aged between 55-74 years, and the incidence was approximately 8% higher in males compared to females (Figure 6).

Figure 6: Incidence rate per 100,000 population of T2DM, analyzed by age

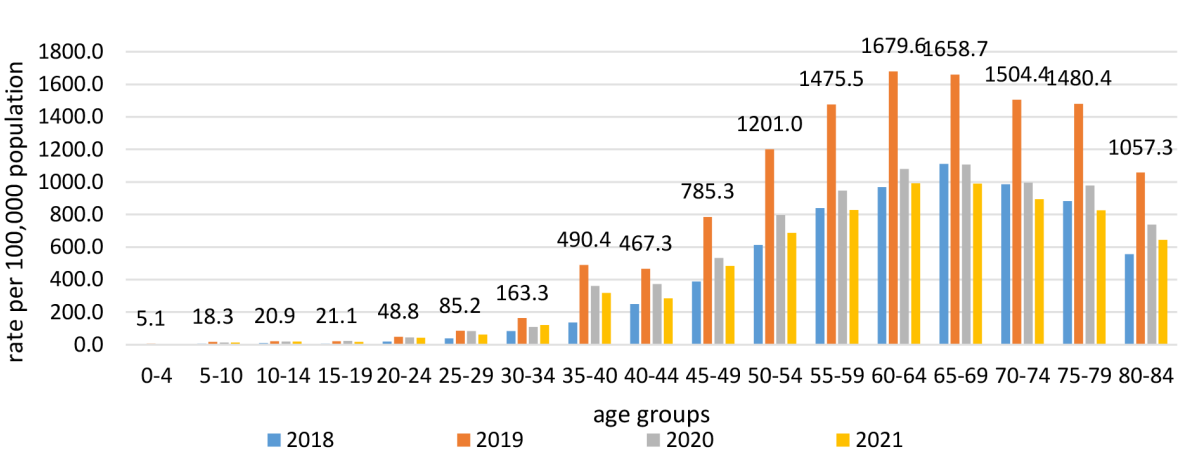
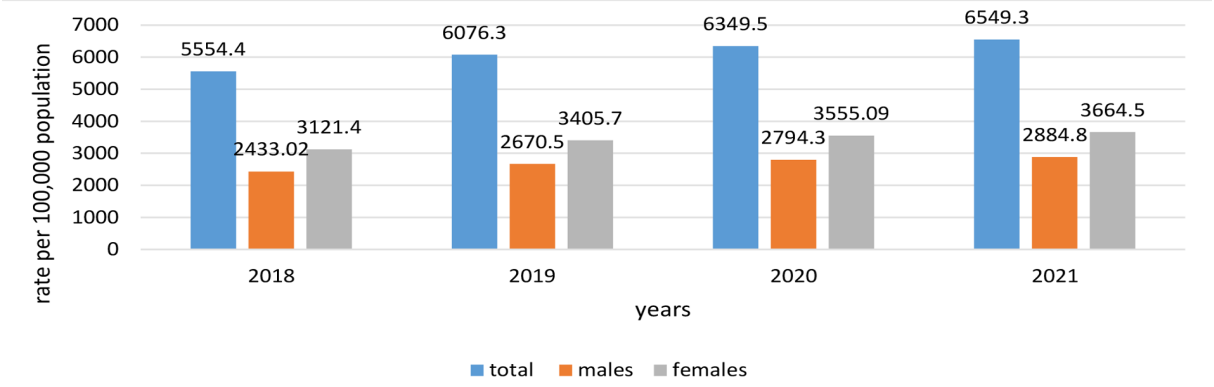


Figure 6 presents incidence rates for T2DM analyzed by age, with higher rates seen in age groups from 55-79, (1475.5 per 100,000 in 55-59), (1679.6 per 100,000, in 60-64), (1658.7 per 100,000, in 65-69), (1504.4 per 100,000, in 70-74) and (1480.4 per 100,000 in 75-79). Higher prevalence rate was found in women compared to men.

The reported prevalence of diagnosed diabetes in 2018 was approximately 5554.4‰, with 3121.4‰ in females (56.2%) and 2433.03‰ in males (44.8%). In the evaluated period (2018-2021) prevalence rate increased by 8.4%, rising up to 6549.3‰ in 2021 in the total population, presented with 3664.5 in females (55.9%) and 2884.8‰ (44.1%) in males (Figure 7). The average prevalence rate in the four-year period was 6132.1‰.

Figure 7: Prevalence rate per 100,000 population of T2DM, analyzed by gender



The highest prevalence rates for T2DM analyzed by age were observed in the age groups 50-59, 70-79, and 80 years and older (10721.3 per 100,000 - 55+), (27520.1 per 100,000 75-79), (33760.7 per 100,000 - 80+), respectively (Figure 8).

Figure 8: Prevalence rate per 100,000 population of T2DM, analyzed by age

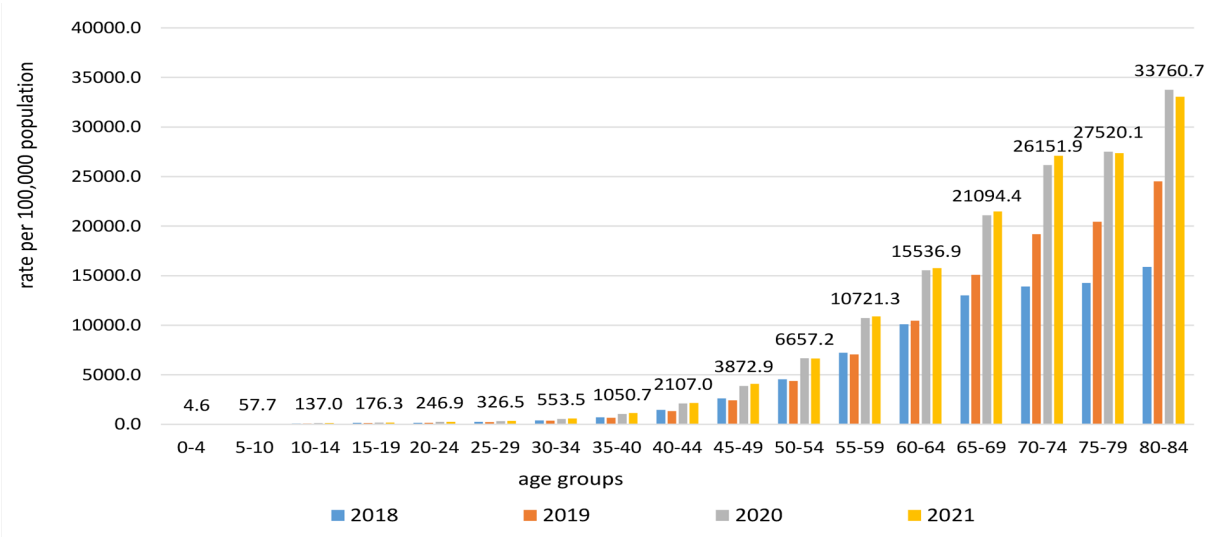


Figure 9: Complication prevalence rates related to diabetes mellitus per 100,000 population

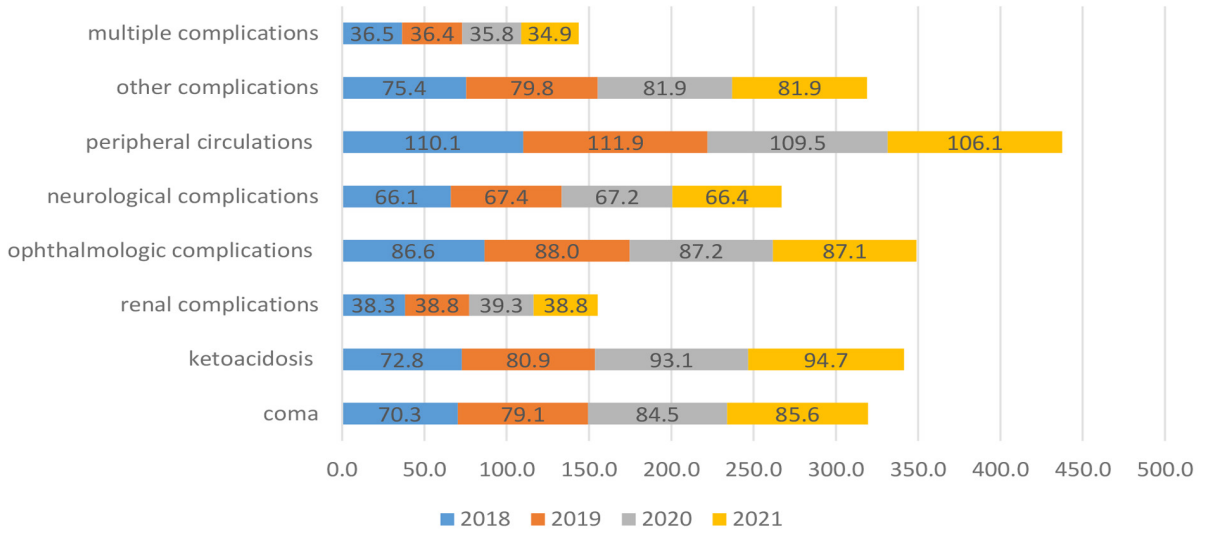
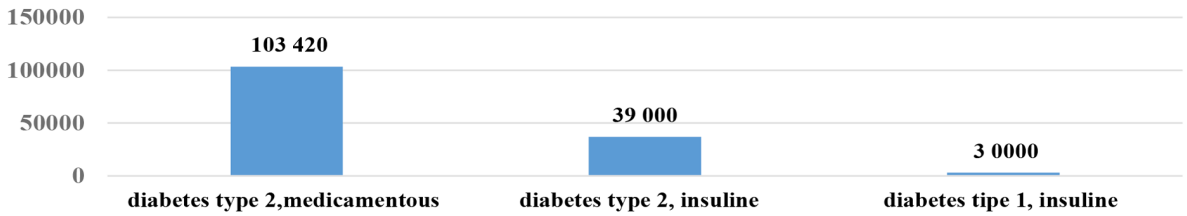


Figure 9 presents the results of complication rates associated with diabetes including peripheral complications, ophthalmologic complications, renal complications, ketoacidosis, coma, and multiple complications. The highest rate of diabetes-associated complications in the Republic of North Macedonia were complications of the peripheral circulation (110.1‰ in 2018 and 106.1‰ in 2021). In the evaluated 4-year period, complications related to ketoacidosis raised from 72.8‰ in 2018 to 85.6‰ in 2021.

The official data from the Ministry of Health in the Republic of North Macedonia in 2021 show that approximately 103,420 patients were on non-insulin antidiabetic treatment and 42,000 (3,000 with T1DM and 39,000 with T2DM) were on insulin therapy (Figure 10).

Figure 10: Registered number of patients diagnosed with diabetes mellitus on antidiabetic treatment and on insulins



Source: Ministry of Health, 2021

Based on the provided data from the National Insurance Fund of North Macedonia, in 2018 there were 1.735.520 prescriptions for blood glucose lowering drugs (excluding insulin) released, accounting for 7.3% of the total number of prescriptions. In 2020, the number of prescriptions for blood glucose lowering drugs (excluding insulin) rose to 1.836.037, accounting for 7.6% of the total number of prescriptions. This indicates a significant increase in the number of prescriptions for blood glucose lowering drugs over the evaluated period, which may reflect an increase in the prevalence or management of diabetes in North Macedonia during that time[33].

The cost of provision of diabetes treatment supplies in 2021, including insulins, glucagon, insulin pumps, glucometers, and other consumables related to insulin treatment of patients on insulin in 2021 amounted to 759,655,000.00 denars, which is approximately 13.457.508,62 USD.

The Global Burden of Diseases (GBD), Injuries and Risk Factors Study generates publicly available estimates of total diabetes deaths, prevalence, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) at the global, super-region, region, and country and territory levels. The calculated burden of diabetes mellitus and diabetic complications in the Republic of North Macedonia amounts to 42,806.59 DALYs. This includes 20,671.47 DALYs for males and 22,135.12 DALYs for females. Out of the total DALYs, 20,453.71 are years of healthy life lost due to premature death (YLLs), and another 22,135.12 are years of healthy life lost due to disability (YLDs) caused by diabetes and its complications. The most vul-

nerable age groups are adults aged 45 to 79 years, which collectively account for 86.46% of the burden. Percentage change in DALYs count was 153.4% (116.8 to 190.3). In 2021 age standardized DALYs rate (per 100,000) for North Macedonia was 1268.1 highest for 28% compared to Global range (915.0).

Table 1: Disability-adjusted life years (DALYs) globally and in North Macedonia

Country	**DALY count in 2021 (thousands)**	Percentage change in DALY count, 1990–2021 (%)	Age-standardised DALY rate in 2021 (per 100,000)	Percentage change in age-standardised DALY rate, 1990–2021 (%)
Global	79 200 (67 800 to 92 500)	189.8% (171.1 to 203.4)	915.0 (782.6 to 1067.4)	38.6% (29.7 to 45.3)
Central Europe	1550 (1250 to 1890)	73.7% (63.6 to 82.0)	748.1 (598.1 to 913·2)	23.0% (15.3 to 29.4)
Albania	17.8 (13.7 to 23.2)	147.8% (119.1 to 175.6)	417.5 (323.5 to 544.8)	26.9% (12.3 to 40·5)
Bosnia and Herzegovina	75.2 (61.2 to 91.0)	171.1% (134.0 to 204.2)	1253.6 (1022.6 to 1527.9)	88.3% (62.4 to 111.5)
Bulgaria	115 (89.8 to 138)	35·5% (23.2 to 48.7)	868.1 (675.6 to 1051.7)	24.6% (13.5 to 36.2)
Croatia	62.7 (49.6 to 75.9)	73.0% (58.1 to 84.2)	743.1 (580.3 to 903·3)	29.7% (18.3 to 37.8)
Czech Republic	171 (136 to 211)	106.7% (87.4 to 125.6)	829.8 (659.6 to 1029.7)	35.7% (22.9 to 47.6)
Montenegro	8.79 (7.12 to 10.7)	118.1% (95.9 to 139.0)	896.2 (728.1 to 1091·2)	39.7% (26.3 to 52.0)
North Macedonia	41.7 (32.6 to 51.1)	153·4% (116.8 to 190.3)	1268.1 (1000.4 to 1554.4)	46·4% (26.1 to 68.5)

Source: Institute for Health Metrics and Evaluation (IHME), Seattle

Discussion

Worldwide, approximately 537 million adults (aged 20-79) live with diabetes – about 1 in 10 people. This number is projected to increase to 643 million by 2030 and 783 million by 2045. Over 3 of 4 adults with diabetes live in low and middle-income countries. The increase of number of diabetic patients was confirmed in the evaluated 2018 – 2021 period in our study and the official data suggests that in 2021 6.6% of the population in North Macedonia was living with diabetes. Diabetes was accountable for 6.7 million deaths in 2021 – 1 death every 5 seconds. The results obtained in our study also suggest huge amplification of mortality in patients with diabetes, from 1935 in 2018 to 9730 in 2021. Approximately 541 million adults worldwide have impaired glucose tolerance (IGT), putting them at high risk of type 2 diabetes. The percentage of people with undiagnosed diabetes (predominantly type 2) was 50.1% in 2021, or 231.9 million undiagnosed patients globally, and in North Macedonia this percentage was 39.6%[35].

The incidence rate of T1DM in the Republic of North Macedonia increased for more than 100% and was presented with 1.21%ooo newly diagnosed in 2018 and 2.8%ooo in 2021, with the highest rate in the age group

of youths from 10-14 (12.4%ooo) in 2021. In 2018, the prevalence rate in the Republic of North Macedonia was 72%ooo (73.6%ooo in females and 71.9%ooo in males). A declination of the prevalence rate of T1DM in 2021 was observed - 52.5%ooo (56%ooo in females and 49%ooo in males).

In the period 2018-2021, the incidence rate of patients with T2DM also enlarged from 323.3%ooo to 355.5%ooo, while the prevalence rate increased from 5554.4%ooo to 6549.3%ooo. Higher incidence and prevalence rate in the four-year period was confirmed in females compared to males. The prevalence of diabetes increases with age, with the highest estimated prevalence in the population aged over 65 years. The prevalence of diabetes among people aged 20 to 79 years in Europe is estimated to be 59.3 million, representing 8.9% of the population in this age group, including 24.2 million adults with undiagnosed diabetes. In 2019, there were 704.4 million people in the age groups over 65, of which 135.6 million had diabetes[36,37]. In line with all global trends, in our study the highest incidence rate was found in people aged between 55-79 years. In the evaluated subgroups of patients with T2DM, the highest incidence rate was observed in 2019. These results are due to establishment and implementation of updated protocols by National Institute of Health resulting in better statistical recording and evaluation of diabetic patients. Unfortunately, as a result of the COVID-19 pandemic and non-adherence to protocols in years 2020 and 2021 a decreased rate in subgroups of patients with diabetes was confirmed in comparison to 2019. The obtained results suggest inevitable improvement of adherence to the protocols for diabetic patients recoding in order to improve planning and implement the National strategy for diabetes in our country. The highest prevalence rates for T2DM analyzed by age were observed in the age above 50, as presented in the study (10721.3 per 100,000 - 55+), (27520.1 per 100,000 75-79) and (33760.7 per 100,000 - 80+).

The highest rate of diabetes-associated complications in North Macedonia were complications of peripheral circulation (110.1%ooo in 2018 and 106.1%ooo in 2021). In the evaluated 4-year period, the complications related to ketoacidosis raised from 72.8%ooo to 85.6%ooo in 2018 and in 2021, respectively, followed by neurological complications, ophthalmic complications, diabetic coma and multiple complications. These common microvascular and macrovascular complications in patients with diabetes type 1 or type 2 are related to the high morbidity and mortality in diabetic patients and our results are in line with the results from other cross-sectional studies[15,16].

According to WHO estimates, out of 995.2 million adults in 2030 in Europe, 195.2 million will have diabetes, and by 2045, out of 1.4 billion adults, 276.2 million are expected to have diabetes. The International Diabetes Federation (IDF) generates worldwide estimates of diabetes deaths and prevalence for type 1 diabetes in people aged 19 years or younger and for total diabetes in those aged 20–79 years, with the most recent estimates produced in 2021, and has projected the future prevalence of total diabetes through 2045. The data obtained from the International Diabe-

tes Federation, from year 2011 suggested 33.7% of people with impaired fasting glucose in North Macedonia with the estimated increase of these percentage by 36.8% in 2030[35]. Evaluation of data from the National diabetes registry have confirmed some inconveniences regarding the quality of mandatory requirements for follow up of patients with diabetes resulting in some gaps in presented analysis, which is recognized as one of the main limitations of our studies. Identification of missing data for fasting glucose levels and HbA-1c in the National diabetes registry resulted in recommendation initiated by the Institute for Public Health for inclusion of additional laboratory results in order to identify prediabetes (fasting glucose levels, HbA-1c glucose level, etc.)[38].

If diet and exercise fail to maintain HbA-1c to the target, then the treatment algorithm in the management guidelines recommends starting with monotherapy, then progressing to combination therapy (dual or triple), and eventually to insulin. The number of available options for treatment of T2DM has been continuously increasing over the last decade. These include metformin, sulfonylureas, thiazolidinediones, incretin-based therapies, sodium-glucose cotransporter 2 inhibitors and different types of insulin. Most T2DM medications effectively reduce glycated hemoglobin, with their efficacy ranging from approximately 0.8% to 1.5% reduction in HbA-1c glycated hemoglobin. In patients where diabetes standard glucose levels are not achieved, long-term complications might appear[38].

Globally, diabetes incurs at least 966 billion dollars in healthcare costs, an increase of 316% over the past 15 years. Official data suggest that the average medical costs for patients diagnosed with diabetes is 2,636 US dollars per year. This translates to a total healthcare expenditure of 980.5 million US dollars in 2021. The International Diabetes Federation projects an increase in healthcare expenditures related to diabetes treatment, estimating an average cost of 2,895 US dollars per year by the year 2030. On average, people with diagnosed diabetes have medical costs approximately 2.3 times higher compared to healthy individuals. Overall, this comment highlights the significant healthcare costs associated with diabetes treatment. In the Republic of North Macedonia approximately 103,420 patients were on non-insulin antidiabetic treatment and 42,000 were on insulin therapy in 2021. The percentage from total number of prescriptions for blood glucose lowering drugs (excluding insulin) in our country rose from 7.3% in 2018 up to 7.6% in 2020. Unfortunately, these are the only publicly available data for the drugs that are covered by health incurrence, and there is a lack of information for out-of-pocket expenditures for patients on antidiabetic, non-insulin treatment in the Republic of North Macedonia. Additionally, the cost of provision of diabetes treatment supplies in 2021, for patients on insulin amounted to 759,655,000.00 denars, which is approximately 13,457,508,62 USD. Presented data refer to all direct cost associated with diabetes, but when complications associated with diabetes are taken into account the economic burden dramatically

increases. According to the latest data from the World Health Organization (WHO), diabetes and its complications account for 3.42% of the total burden of all diseases and conditions worldwide. As presented in the results, the calculated burden of diabetes mellitus and diabetic complications in the Republic of North Macedonia amounts to 42,806.59 DALYs. Overall, this piece of information underscores the significant impact of diabetes and its complications on public health, both globally and specifically within North Macedonia, with a focus on the loss of healthy life years and the most affected age groups. Percentage change in age-standardized DALY rate in 1990-2021(%) in North Macedonia was 46.4%, with the highest value compared to global range (38.6%). Compared to neighboring countries, North Macedonia has the highest percentage of DALY from diabetes mellitus, followed by Albania (26.9%), Croatia (29.7%), Romania (18%), Central Europe (23.0%), but excluding Bosna and Hercegovina (88.3%), with the highest rate in Europe[39].

Conclusions

Diabetes is a serious medical condition that affects millions of people worldwide. In line with the global trends, the incidence and prevalence rates of diabetes in the Republic of North Macedonia increased in the evaluated period, 2018-2021. The results obtained in this study confirmed that 7.09% of the population in North Macedonia in 2021 were living with diabetes. The incidence rate of T1DM inclined from 1.21%ooo in 2018 to 2.8%ooo in 2021, while the incidence rate for T2DM raised from 323.3%ooo to 355.5%ooo in the evaluated period. The same trend was confirmed for the prevalence rate of T2DM presented with 5554.4%ooo in 2018 and 6549.3%ooo in 2021. The calculated burden of diabetes mellitus and its complications in the Republic of North Macedonia is 42,806.59 DALYs, where 20,671.47 are due to years of life lost (YLLs) and 22,135.12 are due to years lived with disability (YLDs) caused by diabetes and diabetic complications, resulting in higher costs. This epidemiological study is a solid base for implementation of the national strategy for diabetes and will contribute in effective planning and evaluation of all aspects of diabetes control in the Republic of North Macedonia.

References

1. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2014 Jan 1;37(Suppl 1):S81-S90. DOI: 10.2337/dc14-S081.
2. World Health Organization. Global Report on Diabetes; WHO: Geneva, Switzerland, 2017.
3. Report of a WHO Consultation. Geneva, Switzerland: World Health Organization; 1999.
4. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021;44(Suppl. 1): S15-S33. DOI: 10.2337/dc21-ad09.
5. Donath MY, Meier DT, Böni-Schnetzler M. Inflammation in the pathophysiology and therapy of cardiometabolic disease. Endocrine

Reviews 2019; 40(4): 1080-1091. DOI: 10.1210/er.2019-00002.

6. The Effect of Insulin on the Alpha-Cell Response to Hyperglycaemia in long-standing alloxan diabetes. PMC333086.
7. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001; 345:790–797.
8. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008; 9(5):367-77. DOI: 10.1038/nrm2391.
9. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretary dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. The Journal of Clinical Investigation 1999; 104: 787-794. DOI: 10.1172/JCI7231.
10. Spellman CW. Pathophysiology of type 2 diabetes: targeting islet cell dysfunction. J Am Osteopath Assoc 2010;110(3 Suppl 2):S2-7. PMID: 20382838.
11. Lopez J. Carl A. Burtis, Edward R. Ashwood and David E. Bruns (eds): Tietz Textbook of Clinical Chemistry and Molecular Diagnosis (5th edition): Elsevier, St. Louis, USA, 2012, 2238 pp, 909 illustrations. Indian J Clin Biochem. 2013 Jan;28(1):104–5. DOI:10.1007/s12291-012-0287-7. PMCID: PMC3547451.
12. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Committee Report 2001, American Diabetes Association.
13. Centers for Disease Control and Prevention. National Diabetes Statistics Report. Accessed in 12.06.2022.
14. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414:782–787.
15. Scott A, Chambers D, Goyder E, O'Cathain A. Socioeconomic inequalities in mortality, morbidity and diabetes management for adults with type 1 diabetes: a systematic review. PLoS One. 2017;12 (5): e0177210. DOI: 10.1371/journal.pone.0177210.
16. Mazidi M, Toth P P, Banach M. C-reactive protein is associated with prevalence of the metabolic syndrome, hypertension, and diabetes mellitus in US adults. Angiology. 2017;(article 331971772928). DOI: 10.1177/0003319717729288.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998 Jul;15(7):539-53. DOI: 10.1002/(SICI)1096-9136(199807)15:7<539:AID-DIA668>3.0.CO;2-S.
18. Deshpande A D, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Physical Therapy 2008; 88(11):1254–1264. DOI: 10.2522/ptj.20080020.
19. Tuttolomondo A, Maida C, Pinto A. Diabetic foot syndrome as a possible cardiovascular marker in diabetic patients. Journal of Diabetes Research. 2015; 2015:12. DOI: 10.1155/2015/268390.
20. Lee ET, Keen H, Bennett PH, Fuller

JH, Lu M. Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. Diabetologia. 2001;44(Suppl 2(2)):S3–13. DOI: 10.1007/PL00002936.

21. LeRoith D, Fonseca V, Vinik A. Metabolic memory in diabetes--focus on insulin. Diabetes Metab Res Rev. 2005;21(2):85–90. DOI: 10.1002/dmrr.530.
22. Solli O, Stavem K, Sonbo Kristiansen I. Health-related quality of life in diabetes: The associations of complications with EQ-5D scores. Health and Quality of Life Outcomes. 2010;8(1):18. DOI: 10.1186/1477-7525-8-18.
23. Linda SG, William HH, Smith PJ. National Diabetes Data Group. Diabetes in America. Bethesda. 2. 1995. Mortality in Non-Insulin-Dependent Diabetes[A] NIH Publication NO.9521468.
24. International Diabetes Federation. Diabetes Atlas. 2. Brussels.
25. Available at https://fzo.org.mk/. Accessed in 10.11.2022.
26. International Diabetes Federation. Available at: https://idf.org/about-diabetes/what-is-diabetes/facts-figures.html.
27. Deshpande A D, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Physical Therapy 2008; 88(11):1254–1264. DOI: 10.2522/ptj.20080020.
28. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. Diabetes Care 2008; 31:596–615.
29. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. Nat Rev Endocrinol 2012;8(4):228–36.
30. Smokovski I, Milenkovic T, Trapp C, Mitov A. Diabetes care in Republic of Macedonia: challenges and opportunities. Annals of Global Health. 2015 Nov 1;81(6):792-802.
31. International Diabetes Federation. International Diabetes Atlas 2019 9th edition. Available at https://diabetesatlas.org/.
32. International Diabetes Federation. International Diabetes Atlas 2021 109th edition. Available at https://diabetesatlas.org
33. Available at https://fzo.org.mk/izvestai-potrosuvacka-lekovi-pzz. Accessed in 13.10.2023.
34. Afroz A, Alramadan MJ, Hossain MN. et al. Cost-of-illness of type 2 diabetes mellitus in low and lower-middle income countries: a systematic review. BMC Health Serv Res 2018; 18: 972. DOI: 10.1186/s12913-018-3772-8.
35. International Diabetes Federation. International Diabetes Atlas. Available at https://diabetesatlas.org/.
36. American Diabetes Association. The cost of Diabetes. Available at: https://diabetes.org/about-us/statistics/cost-diabetes.
37. www.iph.mk. Accessed in 12.12.2022.
38. Mata-Cases M, Benito-Badorrey B, Roura-Olmeda P, Franch-Nadal J, Pepió-Vilaubí JM, Saez M, Coll-de-Tuero G, GEDAPS (Primary Care Group for the study of Diabetes) of the Catalonian Society of Family and Community Medicine. Clinical inertia in the treatment of hyperglycemia in type 2 diabetes pa-

tients in primary care. Curr Med Res Opin 2013; 29:1495–502.

39. “Global Burden of Disease Study 2019 (GBD 2019) Covariates 1980-2019.” 03 Mar.2023, https://ghdx.h