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Public health challenges in post-soviet countries during and beyond COVID-19

Edited by
Yuliya Semenova, Natalya Glushkova and
Antonio Sarría-Santamera

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Public health challenges in post-soviet countries during and beyond COVID-19

Topic editors
Yuliya Semenova — Nazarbayev University, Kazakhstan
Natalya Glushkova — Al-Farabi Kazakh National University, Kazakhstan
Antonio Sarría-Santamera — Nazarbayev University, Kazakhstan

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Anshuman Mishra,
IAAM, Sweden

*CORRESPONDENCE
Yuliya Semenova
✉ yuliya.semenova@nu.edu.kz

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Editorial: Public health challenges in post-Soviet countries during and beyond COVID-19

Natalya Glushkova[1], Yuliya Semenova[2]* and Antonio Sarria-Santamera[2]

[1]Department of Epidemiology, Biostatistics and Evidence Based Medicine, Al-Farabi Kazakh National University, Almaty, Kazakhstan, [2]School of Medicine, Nazarbayev University School of Medicine, Astana, Kazakhstan

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Editorial on the Research Topic
Public health challenges in post-Soviet countries during and beyond COVID-19

The dissolution of the Union of Soviet Socialist Republics (USSR) on December 25, 1991, marked a monumental event in the latter half of the 20th century. It led to the emergence of fifteen former socialist republics—Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan—as independent nations, breaking away from the former union. This significant dissolution triggered a profound socio-economic crisis, the repercussions of which endured for many years. In fact, some of these independent states have yet to fully recover their pre-dissolution levels of socio-economic development, even as of today (1). Currently, the wealthiest post-Soviet states are those that possess ample natural resources, such as Russia, Kazakhstan, Uzbekistan, Turkmenistan, and Azerbaijan, and those like the three Baltic states that successfully transitioned to market-oriented economies and established stable political systems. The objective of this paper is to describe the public health situation in those countries.

During the Soviet era, the Semashko model proved to be both cost-effective and well-structured, significantly contributing to the overall health improvement of the Soviet population. This centralized, all-encompassing healthcare model featured a hierarchical structure, with the state funding and providing healthcare services to its citizens free of charge. It placed a particular emphasis on controlling communicable diseases such as typhus and tuberculosis, with primary and hospital care as its cornerstones. The Semashko model led to several improvements, ensuring the availability of essential vaccines and achieving high vaccination coverage rates, as well as low rates of infant and maternal mortality (2).

However, in the 1980s, the collapse of oil prices, upon which the USSR's economy heavily relied, initiated a decline in healthcare quality due to insufficient investment and mismanagement. By the time of the USSR's dissolution, the healthcare system was grappling with shortages of basic equipment, medications, and modern technologies, despite having an abundant supply of healthcare professionals. Consequently, the former Soviet republics inherited an underfunded and inefficient healthcare system, compelling them to confront the numerous challenges arising from the union's dissolution (3). Following the disintegration of the USSR, the newly independent nations were compelled to undertake comprehensive reforms of their public systems, including healthcare, which had long adhered to the Semashko system.

After the dissolution of the USSR, many countries initiated healthcare system reforms that led to the privatization of state-owned health facilities. The empirical evidence of the impact of those reforms is very limited, but seems that has not contributed to an improvement in outcomes (4). However, due to chronic underfunding and a lack of political commitment, post-Soviet countries generally retain many aspects of the Semashko model, resulting in shared similarities in the overall structure and governance of healthcare systems, characterized by a strong vertical hierarchy (3).

National Ministries of Health (MoH) play a central role in healthcare governance. They are responsible for designing and implementing health policies and introducing legislative changes. These MoHs not only handle planning but also oversee healthcare provision, with minimal delegation of decision-making to subnational health authorities. Public involvement in health policy formulation is lacking, and patient rights remain inadequately protected. Moreover, there is still over-reliance on large hospitals, and the allocation of health resources lacks transparency (5). Only a few countries have introduced mandatory health insurance, with more planning to implement it in the future. However, private and voluntary health insurance is largely non-existent, primarily due to the low-income levels in the general population, making it challenging for many to afford such coverage. Furthermore, out-of-pocket payments constitute a significant share of healthcare expenditures, exceeding 60% in Armenia, Tajikistan, and Turkmenistan (6), which is well-above the level recommended by the World Health Organization (WHO) of 20% (7). This predisposes people to catastrophic health expenditures in a situation of a public health emergency.

Given that the majority of healthcare professionals were (and still are) low-paid salaried employees, and due to the shortage of funds in the healthcare sector, and insufficient regulatory oversight, medical corruption became a matter of concern. Meanwhile, corruption has a significant negative impact on healthcare systems and the health outcomes of the population. As such, it was estimated that countries with high levels of corruption in the healthcare sector have twice as high childhood and infant mortality rates as compared to the countries with low rates of medical corruption (8).

The trend of underfunding in healthcare persists to this day. According to World Bank data from 2020, only Armenia allocated healthcare expenditures at a level typical of many developed nations, at 12.24% of the Gross Domestic Product (GDP). In contrast, other former Soviet countries allocated significantly less, with Kazakhstan, one of the region's industrial leaders, spending only 3.79% of GDP on healthcare (6).

Many national governments implemented a series of health plans aimed at strengthening primary healthcare, improving the accessibility of medical services, and modernizing hospital infrastructure. These plans placed significant emphasis on the control of both infectious and non-communicable diseases (NCDs). Similar to many other nations, NCDs are the leading cause of mortality, significantly contributing to lower life expectancy compared to European Union (EU) levels. Premature mortality is a significant factor, with the highest rates observed in men, often exceeding a 10-year gender gap. Cardiovascular disease (CVD) ranks as the primary cause of death, followed by oncological and digestive system disorders. Several factors contribute to this high rate of premature mortality, including excessive alcohol consumption, smoking, and an unhealthy diet. Poor control of arterial hypertension and dyslipidemia further contributes to premature mortality from conditions like ischemic heart disease, stroke, and hypertensive heart disease (Azfar et al.). In some countries, governments have made significant investments in tertiary prevention of CVD, making it accessible and affordable. However, secondary prevention is suboptimal, and primary prevention strategies are lacking. To bridge these gaps, a multi-pronged approach is necessary. There is a need for the prioritization of primary CVD prevention with a focus on the reduction of modifiable risk factors and the promotion of healthier foods, as well as encouraging more regular physical exercise, given the shift toward a more sedentary lifestyle in many post-Soviet nations. Concurrently, efforts to enhance the management of arterial hypertension and dyslipidemia for secondary prevention should be intensified.

When it comes to cancer, the second most common cause of mortality among NCDs, lung cancer takes the top spot in the majority of post-Soviet nations. This prevalence is attributed to the high rates of smoking and ambient air pollution resulting from industrial and traffic emissions (Zhylkybekova et al.). In contrast, stomach cancer is the primary cause of cancer-related mortality in post-Soviet countries with lower levels of economic development, such as Tajikistan, Kyrgyzstan, and Uzbekistan. This can be attributed to factors such as a high prevalence of Helicobacter pylori infection, overcrowded living conditions, and the influence of certain environmental factors (Albuquerque et al.). Furthermore, there is a growing trend of breast cancer, which has become the most common cancer site among females (Midlenko et al.). Addressing this trend requires the implementation of public health strategies for control and prevention. There is a need to make cancer screening programs accessible and affordable for the people, as well as to implement the "best-buy" campaigns to increase the uptake of the existing cancer screening programs.

Historically, the USSR had robust infection control services, including disease surveillance. However, after its dissolution, infection control significantly deteriorated, especially during the early transition period. As a result, new challenges like HIV/AIDS and multidrug-resistant tuberculosis (MDR-TB), have emerged. During the 1990s and early 2000s, there was a significant increase in TB incidence and mortality, which started declining only in the second half of the 2000s. By the end of the 2010s, most post-Soviet nations achieved a substantial decline in TB mortality, except for Russia, where it remains elevated due to high rates of heavy alcohol intake, incarceration, and the burden of HIV/AIDS (9). In general, during the 1990s and early 2000s, post-Soviet nations bore witness to one of the world's most rapidly expanding HIV/AIDS epidemics, along with a surge in cases of viral hepatitis B and C, primarily due to the widespread use of injection drugs. While the prevalence of injection drug use has decreased over the past decade, several post-Soviet countries, including Russia and Turkmenistan, continue to prohibit buprenorphine or methadone substitution therapy, despite its effectiveness. This presents a persistent challenge in managing the HIV epidemic in these regions. Moreover, with evolving patterns of HIV transmission, the coverage of anti-HIV programs remains inadequate, and there is a notable deficiency in the availability of antiviral treatments, which heavily relies on external funding sources (Gabdullina et al.).

Another pressing public health concern in the region is antibiotic resistance, highlighting the imperative need for action (10).

The COVID-19 pandemic exposed the existing gaps in infection control. Despite the fact that many post-Soviet countries share borders with China, the first cases of COVID-19 were not registered until February-March of 2020. Following these initial cases, countries immediately implemented strict measures, including lockdowns, curfews, and border closures between regions. As the COVID-19 epidemic progressed, countries faced a severe shortage of hospital infrastructure and medical professionals (Gazezova et al.). The rapid initial increase in the number of COVID-19 cases overwhelmed the healthcare system, leading to waiting lists for emergency hospitalization. This was partly due to a previous reduction in the number of hospital beds (11). Countries with significant financial resources were able to mobilize them in an effort to contain the epidemic. However, even these resources were insufficient to meet the rapidly growing demands for medicines, equipment, diagnostic tests, and hospital facilities.

With the introduction of the Sputnik-V vaccine in 2020, Russia has emerged as a significant COVID vaccine producer. Consequently, the geopolitical affiliations of this major country within the post-Soviet space exert an influence on public health dynamics and contribute to enhanced healthcare management in affiliated countries. Despite the early availability of anti-COVID-19 vaccines, post-Soviet countries have exhibited some of the lowest vaccination rates due to a high prevalence of vaccine hesitancy (Peshkovskaya et al.). This reluctance to get vaccinated can be attributed to the tense relations between governments and citizens, a common feature of the former USSR. As a result, the general public lacks trust in state institutions, including the healthcare system and science. It was surprising to observe that many healthcare professionals shared these views, occasionally discouraging patients from getting vaccinated and assisting them in avoiding vaccination (Adambekov et al.). To address the issue of vaccine hesitancy, special strategies need to be devised, focusing on immunization policy, capacity building, addressing population fears, and promoting positive behavior change.

Although the health of the population in post-Soviet countries began to improve at the beginning of the 21st century, the COVID-19 crisis resulted in excess mortality, a decrease in average life expectancy, and exposed many unresolved issues in healthcare system management and financing (12). To address these existing gaps, further healthcare reforms need to be planned. For these reforms to succeed, the participation of all major stakeholders is necessary, including government officials, the medical community, and patient representatives (13). Additionally, decentralization of government structures is required to enhance governance effectiveness. This process must be accompanied by the allocation of sufficient resources and an increase in healthcare system financing. The allocation of healthcare resources should be fair and transparent, with efforts made to involve the population in healthcare management. There is a need to increase the professionalism and improve qualification of healthcare managers and administrators (14).

Given that the former Soviet Union represents one of the world's largest geographical regions with low population density, its public health challenges differ from those in other regions. Therefore, the introduction of biomedical technologies related to digitalization, biosensors, and similar advancements might offer greater cost-effectiveness. Importantly, the process of digitizing the healthcare system must continue, as many post-Soviet countries currently lack comprehensive health information systems (15). Additionally, there is a need to shift focus from administratively monitoring outputs to identifying relevant outcomes, analyzing potential origins or impacts of poor performance, and implementing ambitious quality improvement programs (16). Aside from the introduction of advanced technologies, political stability could substantially contribute to a better healthcare model.

Academic institutions can play a pivotal role by providing education to strengthen the public health workforce and conducting research to generate new evidence. In addition, academia can serve as a cornerstone for reform and improvement, actively engaging with governments in the formulation of policies, providing expert insights, and addressing healthcare challenges. Academic institutions can promote public awareness and participation by organizing public health campaigns, disseminating health information, and involving the community in healthcare decision-making. Collaboration between academia, government, and healthcare organizations is essential to achieve sustainable and positive change in the healthcare landscape of post-Soviet nations.

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A Review of Rare Disease Policies and Orphan Drug Reimbursement Systems in 12 Eurasian Countries

Marcin Czech[1], Aleksandra Baran-Kooiker[2]*, Kagan Atikeler[3,4], Maria Demirtshyan[5], Kamilla Gaitova[6], Malwina Holownia-Voloskova[7,8], Adina Turcu-Stiolica[9], Coen Kooiker[10], Oresta Piniazhko[11], Natella Konstandyan[12], Olha Zalis'ka[11] and Jolanta Sykut-Cegielska[13]

[1] Department of Pharmacoeconomics, The Institute of Mother and Child, Warsaw, Poland, [2] Department of Pharmacoeconomics, Faculty of Pharmacy, Medical University of Warsaw, Warsaw, Poland, [3] Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands, [4] Unit of Health Technology Assessments, Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency, Ankara, Turkey, [5] Ascent Global Market Solutions (Non-profit), Walnut Creek, CA, United States, [6] Center for Economics and Health Technology Assessment, Republican Center for Health Development, Ministry of Health, Nur-Sultan, Kazakhstan, [7] State Budgetary Institution Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department, Moscow, Russia, [8] Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland, [9] Department of Pharmacoeconomics, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Craiova, Romania, [10] Independent Researcher, Warsaw, Poland, [11] Department of Management and Economy of Pharmacy, Medicine Technology and Pharmacoeconomics, Postgraduate Faculty, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine, [12] Republican Center of Medical Genetics, Yerevan State Medical University, Yerevan, Armenia, [13] Department of Inborn Errors of Metabolism and Paediatrics, The Institute of Mother and Child, Warsaw, Poland

Edited by:
Piotr Romaniuk,
Medical University of Silesia, Poland

Reviewed by:
Stephen Groft,
National Center for Advancing Translational Sciences (NCATS), United States
Agnieszka Zimmermann,
Medical University of Gdansk, Poland

***Correspondence:**
Aleksandra Baran-Kooiker
aleksandra.baran@gmail.com

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Background: Despite international initiatives on collaboration within the field of rare diseases, patient access to orphan medicinal products (OMPs) and healthcare services differ greatly between countries. This study aimed to create a comprehensive and in-depth overview of rare diseases policies and reimbursement of OMPs in a selection of 12 countries in the Western Eurasian region: Armenia, France, Germany, Kazakhstan, Latvia, The Netherlands, Poland, Romania, Russia, Turkey, Ukraine, and the United Kingdom.

Methods: A systematic literature review was performed and an analysis of publicly available legislative and rare disease health policy data was undertaken in five focus areas: rare disease definition, newborn screening, registries, national plans, access to/reimbursement of OMPs.

Results: Screening programs are broadly implemented but the number of screened diseases differs significantly (2–35 diseases), either between EU and non-EU countries, between EU member states and sometimes even within a single country. In most countries rare disease registries are operating with regional, national, European or worldwide coverage. The number of rare disease registries is growing, as a result of the National Plans (EU) and increased international scientific cooperation. France, Russia, and Poland have a centrally acting registry. National plans are present in all EU countries but implementation varies and is ongoing. The number of reimbursed OMPs in the selected countries ranges from nearly all available OMPs in the Netherlands, Germany, and France to zero in Armenia. Reimbursement rules differ considerably regionally and a trend is observed of reimbursement conditions getting stricter for expensive (orphan) drugs.

Discussion: Inequality in patient access to new OMPs still exists due to variations in national policies, healthcare budgets, health insurance, and reimbursement systems. The observed differences are challenging for rare disease patients, health authorities and manufacturers alike. Progress can be seen, however, and international cooperation and harmonization is slowly but steadily expanding in the rare disease arena.

Keywords: rare diseases, newborn screening, national plan, patient registries, reimbursement, policy

INTRODUCTION

Between 6,000 and 8,000 rare diseases have been identified, most of genetic origin and with severe clinical manifestations. Due to insufficient knowledge on disease pathology, diagnosis is frequently delayed, often resulting in early and irreversible complications. Thirty percent of rare disease patients die before the age of five[1]. Pharmacotherapy, known as orphan drugs or Orphan Medicinal Products (OMPs), exists for <3% of rare diseases[2] (1–3). Registration and reimbursement are the two main policy hurdles before a drug can reach a patient. Regulatory legislation for OMPs has been harmonized across the European Union (EU), with simultaneous regulatory approval for OMPs across 28 member states (4). However, differences remain in reimbursement and pricing systems in member states, based on factors such as healthcare budget (related to a country's GDP), type of healthcare and health insurance system, patient co-payment rules, reimbursement timelines and evidence requirements (i.e., type, level, and presentation). Consequently, patient access is often unpredictable and restricted while reimbursement strategies for manufacturers are fragmented and complex. The high prices of many orphan drugs, often combined with a limited amount of clinical evidence (mainly due to small patient populations), can lead to Incremental Cost-Effectiveness Ratios (ICER) that exceed "willingness to pay" levels (5). Budget restriction measures, especially around "expensive drugs" (which OMPs often are), are increasingly common. Reference pricing methods (i.e., HTA agencies comparing and referencing to drug prices in other countries or regions) can influence manufacturers to postpone or even avoid entering certain markets due to a possible cascading price-drop effect elsewhere (6). These are a few of the factors that can cause inequality in patient access to new medical technologies and treatments (7). A 2017 survey by EURORDIS confirmed that 24% of rare disease patients did not receive treatment because of no drug availability in their country (vs. 7% of the general population) and 15% due to inability to pay for treatment (vs. 6%) (8).

A recent step toward HTA harmonization between EU member states is the official proposal of the EU Health Technology Assessment (HTA) Regulation in 2018, which has been planned to be adopted in 2019. A pivotal component of this regulation is a centralized Joint Clinical Assessment (JCA) at the European level, which is aimed at establishing the (clinical) value of the treatment for HTA purposes (9). Such a central assessment would reduce HTA workload in the individual member states, promote the sharing of knowledge and leverage the expertise of rare disease experts and patient representatives in the EU. In essence, the JCA resembles the shared regulatory assessment done by the European Medicines Agency (EMA) in the Centralized Procedure (9). The JCA could improve the quality and speed of HTA for OMPs at the national level and promote further HTA harmonization. However, details on implementation, member state representation and how the joint clinical assessment will be legally binding (for national HTA purposes) is still under discussion and some concerns are already being voiced (10). The final HTA decision making, which depends on country specific factors such as the structure of the healthcare system, reimbursement factors and budgeting aspects, will likely remain at the national level.

Rare disease policies are a high focus area, given the medical need surrounding rare diseases and the relatively large impact these diseases and their treatment potentially have on healthcare budgets. The reimbursement status of orphan drugs in Eastern Europe has been described by several authors recently (11–15). There have been multiple publications describing OMP policies in Central and Eastern Europe in single countries (16–18) or covering a larger number of countries in Europe (5, 19–22). Pejcic et al. focused on HTA and pricing as well as rare disease policies in 14 Eastern European countries (23). In 2015 Gammie et al. presented a comprehensive review of legislations, regulations and policies in 35 countries describing in detail the national orphan drug policies, orphan drug marketing authorization processes (and accelerated procedures), incentives, marketing exclusivity, pricing, and reimbursement (2015) (24). Dharssi et al. evaluated key patient-needs across five dimensions: improving coordination of care, diagnostic resources, access to treatment, patient awareness and support, and promoting innovative research in 11 EU and non-EU countries (25).

However, there is still little comprehensive and in-depth information available in the English literature on orphan drug policies and HTA processes within the European Commonwealth of Independent States (CIS), such as in Russia, Armenia, and Kazakhstan in comparison to European Union countries. This field is rapidly evolving due to implementation of national plans for rare diseases in some European countries and HTA developments. Therefore, the aim of this article is to bridge the identified gaps by presenting an overview and comparison of current rare disease policies, HTA and reimbursement processes for orphan drugs in a broader range of Eurasian countries.

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[1] https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf (accessed September 18, 2019).

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/12/WC500240710.pdf (accessed September 18, 2019).

MATERIALS AND METHODS

For this publication an analysis of rare disease policies was undertaken, focused on the following topics, including several "core areas" as defined by the EU (Council Recommendations of 2009) (26):

- Rare disease definition,
- Newborn screening (NBS) for rare diseases,
- National plans (NP) for rare diseases,
- Rare disease registries (central vs. disease-specific),
- Reimbursement and HTA approaches for orphan drugs, including access to orphan drugs (measured by the number of reimbursed OMPs) and availability of early access methods (e.g., compassionate use, named patient-programs, conditional reimbursement).

Other aspects mentioned in the 2009 EU Council Recommendation such as research on rare diseases empowerment of patient organizations, and sustainability were not researched as they are difficult to quantify and assess in an objective manner. Codification and inventorying of rare diseases were excluded as well in this paper, as these have little direct impact on treatment. In addition, the authors decided to include newborn screening, reimbursement (incl. early access programmes) and HTA processes, in order to present a more holistic overview of rare disease policies in each country.

The 12 countries included in this study were selected to be diverse from a geographical and socio-economical viewpoint and represent a wide range of rare disease policy development across the western Eurasian region: Armenia (AM), France (FR), Germany (DE), Kazakhstan (KZ), Latvia (LV), The Netherlands (NL), Poland (PL), Romania (RO), Russia (RU), Turkey (TR), Ukraine (UA), and the United Kingdom (UK).

A systematic literature review was performed to identify previous research and relevant publications, using the following keywords: rare disease, rare disorder, orphan drug, orphan medicinal product, health policy, reimbursement, HTA, health technology assessment, newborn screening, patient registry, national plan, legislation, access, Poland, Germany, Netherlands, Holland, Kazakhstan, Russia, Ukraine, Turkey, Armenia, France, UK, United Kingdom, England, Scotland, Northern Ireland, Wales, Romania, Latvia. Articles published from 2017 to 2019 were included. The review resulted in 681 publications that were screened by title/abstract, 610 publications were excluded due to insufficient relevance to the selected focus areas, 71 full-text articles were assessed for eligibility, of which 10 were included. All steps of the literature review (identification, screening, eligibility, inclusion, and data extraction) were performed by two independent researchers, according to PRISMA methodology (please refer to **Figure 1**).

In order to gather further information in the scope of the article, an explorative internet search (gray literature review) was done of publicly listed policies, legislations, guidelines, governmental publications and other sources of relevant orphan drug HTA information. This was done by searching the websites of local Health Authorities, e.g., the Ministry of Health and HTA agency. The most up-to-date data the authors could find was included. Experts from all countries were interviewed to confirm the obtained information or in case public information was insufficient, unclear, contradictory or lacking. The authors' intention was to select a fair representation of different types of stakeholders involved in market access processes of orphan drugs. Public institution representatives, payers, scientists, clinicians, and commercial entity representatives from the countries were interviewed. Their number was dependent on the quality of information available from public sources and the willingness of stakeholders to provide additional data as well as a degree of involvement in the study. A list of questions was sent to the experts by email and followed up by phone interviews. Approval by an ethics committee was not required for this research.

Definition of Rare Disorders, Orphan Drugs and Epidemiology

The EU has officially defined rare diseases as being rare when they affect fewer than 1 in 2000 (i.e., a prevalence of 5 or less per 10,000) (28) and in most of the selected countries this definition is used [FR, DE, LV, NL, PL, RO, UK, and UA (29, 30)]. In Russia the maximum prevalence for a rare disease is defined as 1 in 10,000 (31). There is no data available on the maximum prevalence for a rare disease in Kazakhstan (32). Some countries use additional definitions in situations where a condition is not officially defined as rare, such as in the UK, where the National Health Service (NHS) classifies all conditions that require specialized medical care also as rare if they occur in <500 citizens yearly (29)[3]. Turkey defines a rare disease when they affect no more than 1 in 100,000, which is 50 times less frequent than the European Union definition (33, 34). There is no specific definition for "rare disease" in Armenian legislation, only "levels of disability" which define whether the patient will receive the necessary medicines for free or not[4].

The Netherlands defines the classification "orphan drug" as either having an official EU orphan designation or if it targets a disease with a prevalence of <1 in 150,000 and shows a clinically proven therapeutic benefit and no other registered medicine exists[5].

France introduced an extra definition of "rare cancer" if the cancer occurs in <6 in 100,000 per year or requires specialized treatment due to untypical tumor location or complex disease characteristics (29, 35). Effective from October 2018, Scotland has introduced a new definition for ultra-orphan drugs: "medicines that are used to treat a condition with a prevalence of 1 in 50,000 or less or around 100 people in Scotland," which will mostly be used to facilitate early access programs and reimbursement processes[6].

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[3] https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/ (accessed September 18, 2019).

[4] Interview with Armenian key opinion leader (accessed September 5, 2019).

[5] https://www.nza.nl/regelgeving/beleidsregels/BR_CU_2018__Weesgeneesmiddelen (accessed September 18, 2019).

[6] https://news.gov.scot/news/treatments-for-rare-conditions (accessed September 18, 2019).

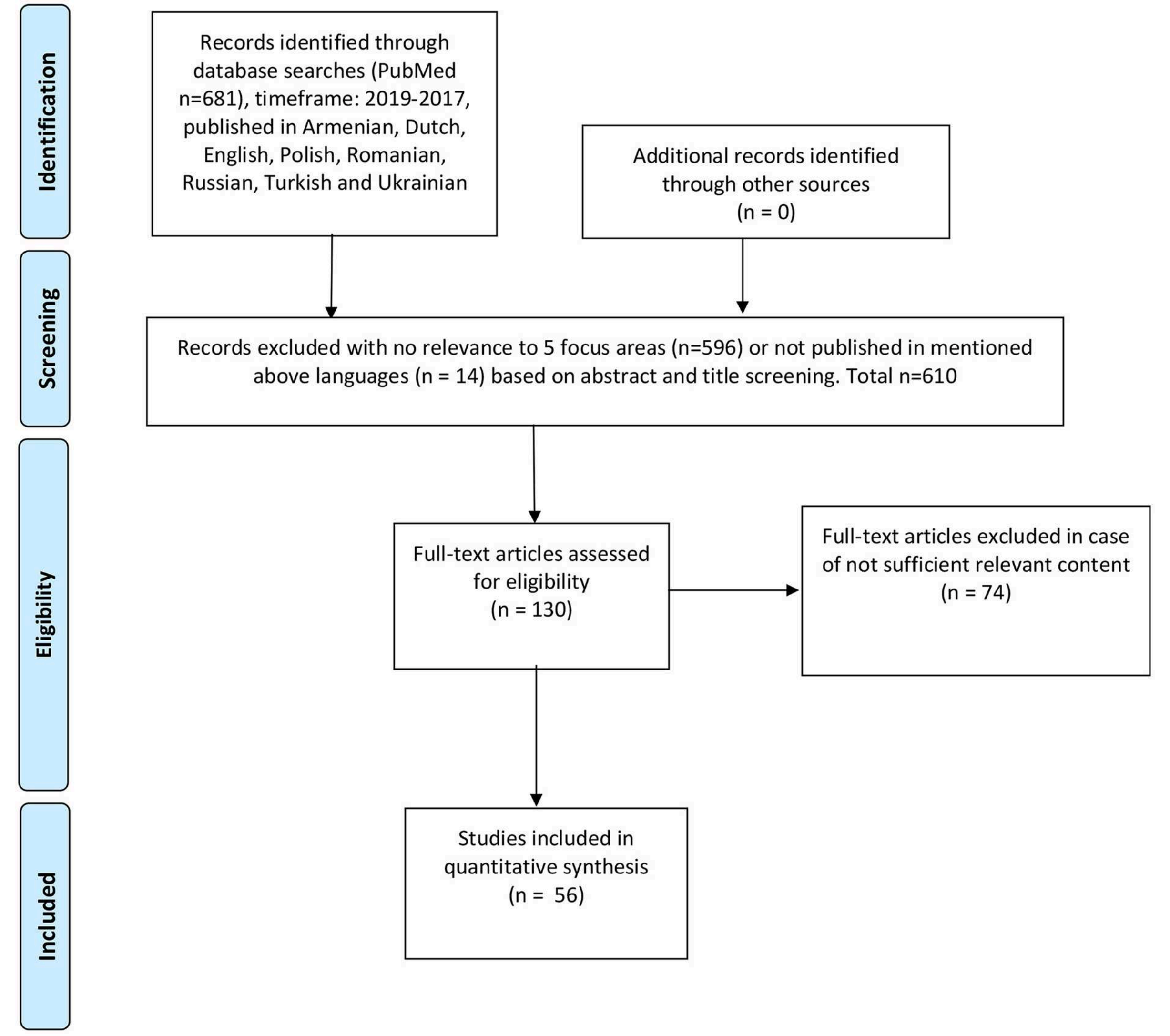

FIGURE 1 | Reproduced with permission from PRISMA 2009 flow diagram (27).

Newborn Screening

Newborn screening (NBS) is used to identify and effectively treat certain rare disorders at an early stage and to prevent irreversible damage. NBS is performed in all countries selected for this review. There is, however, a lack of uniformity between screening programs, mainly in the number of screened disorders, ranging from 2 to 35 (see **Table 1**). Poland currently screens for 28 rare diseases (36), The Netherlands 20 (37, 38), Germany 15[7,8] (39), France and Russia 5 and (N.B.: 35 in Moscow) (29)[9], Ukraine 4 (41), Turkey 6 (40, 42)[10]. Armenia[4], Kazakhstan[11] (43), Latvia and Romania[12] (44, 45), only screen for phenylketonuria and congenital hypothyroidism. England, Scotland, and Wales screen for nine diseases, whereas Northern Ireland (part of the UK as well) screens only for 5 (29)[13,14]. In several countries the number of screened diseases is being expanded or planned to

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[7] https://www.g-ba.de/informationen/richtlinien/15/ (accessed September 18, 2019).

[8] https://muko.info/ueber-mukoviszidose/neugeborenen-screening.html (accessed September 18, 2019).

[9] https://mosgorzdrav.ru/ru-RU/news/default/card-print/1802.html (accessed September 18, 2019).

[10] https://dosyaism.saglik.gov.tr/Eklenti/11173,259822214447pdf.pdf?0 (accessed September 18, 2019).

[11] https://newjournal.ssmu.kz/publication/249/realizatsiya-skriningovykh-programm-vkazakhstane-na-sovremennom-etape/ (accessed September 18, 2019).

[12] Order of Romanian MoH no. 387/2015 regarding the change and completion of the Order of the MoH no. 861/2014 for approving the criteria and methodology for health technology assessment, Ordinul nr. 387/2015 privind modificarea şi completarea Ordinului ministrului *sănătăţii* nr. 861/2014 pentru aprobarea criteriilor şi metodologiei de evaluare a tehnologiilor medicale.

[13] http://www.nhs.uk/Conditions/pregnancy-and-baby/Pages/newborn-blood-spot-test.aspx (accessed September 18, 2019).

[14] http://www.gov.scot/Topics/Health/Services/Screening/Newborn (accessed September 18, 2019).

TABLE 1 | New born screening of rare diseases per country (29)[4], (36–38)[7,8], (39)[9], (40–42)[10,11], (43)[12], (44, 45)[13,14].

	AR (4)	**DE (15)**	**FR (5)**	**KZ (2)**	**LV (2)**	**NL (20)**	**PL (28)**	**RO (2)**	**RU (5)**	**TR (6)**	**UA (4)**	**UK: NI (5)**	**UK: ENG/WAL/SCO (9)**
Argininemia							X						
Argininosuccinic aciduria (ASA)							X						
Alfa –Thalassemia/HbH disease						X				P			
Beta-Thalassemia						X							
Beta-ketothiolase deficiency						P	X						
Biotinidase deficiency (BIO)		X				X	X			X			
Carnitine-acylcarnitine translocase deficiency (CACT)		X				P	X						
Carnitine transporter deficiency (OCTN2)						X	X						
Carnitine palmitoyltransferase deficiency type I & II (CPT-1, CPT-2)		X				P	X						
Congenital adrenal hyperplasia (CAH) or Adrenogenital syndrome (AGS)		X	X			X	X		X		X		
Congenital hypothyroidism (CH)	X	X	X	X	X	X	X	X	X	X	X	X	X
Cystic fibrosis (CF)		X	X			X	X		X	X	X	X	X
Citrullinemia type I & II							X						
Developmental hip dysplasia	X									X			
Galactosemia (GAL)		X				X			X	X			
Galactokinase deficiency (GALK)						P							
Guanidinoacetate methyltransferase deficiency (GAMT)						P							
Glutaric acidemia type 1 (GA-1)		X				X	X						X
Glutaric acidemia type 2							X						
HMG-CoA-lyase deficiency (HMG)						X	X						
Homocystinuria (HCU)							X						X
Isovaleric acidemia		X				X	X						X
Long Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD)		X				X	X						
Maple syrup urine disease (MSUD)		X				X	X						X
Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)		X				X	X					X	X
3-Methylcrotonyl-CoA carboxylase deficiency (3-MCC) (3-methylcrotonylglycinuria)						X	X						
Methylmalonic academia (MMA)						P	X						
Mitochondrial trifunctional protein deficiency							X						
Mucopolysaccharidosis type 1 (MPS I)						P							
Multiple CoA carboxylase deficiency (MCD)						X	X						
Phenylketonuria/hyperphenylalaninemia (PKU)	X	X	X	X	X	X	X	X	X	X	X	X	X
Propionic acidemia (PA)						P	X						
Retinopathy of prematurity	X												
Severe combined immune deficiency (SCID)						P							
Sickle Cell Disorder (bearer)		P	X			X						X	X
Tyrosinemia type 1 (TYR-1)		X				X	X						
Tyrosinemia type 2 (TYR-2)							X						
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)		X				X	X						
X-linked adrenoleukodystrophy (X-ALD)						P							

X, newborn screening performed; P, Pilot or planned to be extended (newborn hearing test not included).

be expanded, notably in Turkey (going from 6 to 10 screened diseases)[11] and the Netherlands (from 20 to 32) (37), but without specific timelines.

National Plans for Rare Diseases

In 2009 the European Council issued the recommendation for EU member states to create and adopt a plan focused on rare disorders by the end of 2013, with the goal to have an overall Community strategy for "ensuring effective and efficient recognition, prevention, diagnosis, treatment, care, and research for rare diseases in Europe" (46). For this purpose, the European Project for Rare Diseases National Plans Development (EUROPLAN) was introduced to promote and help EU members with the construction and implementation of their national plans[15,16].

NL, DE, UK, LV have created a national plan within the timelines defined by European Commission but in most of these EU countries the implementation is in progress (16, 29)[17,18,19,20]. In Poland and Romania, a National Plan for RDs was developed but has never been implemented[21,22]. The most recent version of Polish Plan for RDs for 2017–2019, was written under the auspices of the Polish MoH and was planned to be approved in the 3rd quarter of 2019[22,23]. France was a forerunner in introducing a National Plan in 2004, with an assigned budget of €100 M for implementation over 2005–2008 (29). The 3rd French national plan has been created for 2018–2022. Rare disorder patients in France can also receive support from the so-called Cancer Plan (latest version 2014–2019, in case of rare oncological diseases, and the National Plan for Rare Handicaps (2014–2018), addressing rare physical disabilities (29, 47–49).

In Russia a special program exists (on the federal level) for financing 12 high-cost diseases: hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, lymphoid malignant neoplasms, hematopoietic and related tissues, multiple sclerosis, hemolytic-uremic syndrome, juvenile arthritis with systemic onset, mucopolysaccharidosis type I, II, and VI[24] (50).

Both Kazakhstan and Turkey have national programmes for rare diseases, but they are undergoing implementation. In the non-EU countries in this review (KZ, TR) (40, 51–53) a national strategy targeting rare diseases was not adopted and, in some cases there is even a complete lack of legislation that addresses the needs of rare disease patients and orphan drug topics (e.g., AM)[4]. **Table 2** describes the most important characteristics of the national plans and their status at the time of writing.

Disease Registries

A limited number of registries for rare disorders exist in most of the selected countries, even though it is a focus topic in many of the national plans. The first outcomes of implementing rare disease registries are already visible and resulted in scientific collaboration such as the Network dedicated to Rare Adult Cancer (RAC), through which knowledge on epidemiology, survival prognosis, prevalence, burden of rare cancers is shared. Registries are either public or private non-profit or for profit (54–56)[25].

France implemented a central registry (fr. Banque Nationale de Données Maladies Rares, BNDMR) that collects data for all rare disorders, next to 12 other rare disorder registries. The central registry gathers epidemiological data in order to optimize clinical practice and healthcare policies. It also serves to facilitate patients to therapeutic programs and clinical trials. Rather uniquely, data on patients' family members is also collected. The epidemiological data is aggregated within the centers for rare diseases (Centres des maladies rares) CEMARA program (replaced by the BaMaRa application in 2017) which has identified more than 380,000 patients and 4,200 rare disorders (29, 57–59). Since 2017 109 CRMRs (multi-site reference centers) were created, 387 reference centers and 1,757 competence centers identified, as well as 83 resource and competence centers (CRCs) (67). Up to May 2019 there were 143 RD registries in France (60). Poland has a Central Registry for Inherited Disorders which is obligatory to report birth defects to since 2014 as well as 10 disease specific registries[26].

Germany has acted on the NP recommendation to create disease registries such as the Open Source Registry System for Rare Diseases (Open-Source-Registersystem für Seltene Erkrankungen) (29, 61)[25]. Currently in Germany there are 149 RD registries (13 regional, 94 national, 18 European, and 24 global)[25] and a central portal (61, 62).

The UK has 74 functioning registries under control (incl. 12 global, 13 European), also by public or private institutions (29)[25].

Latvia has one registry for multiple diseases, called the "Registry for Certain Diseases," which include rare cancers, hereditary disorders, managed by the Centre for Disease Prevention and Control. There are plans to implement a central registry for rare disorders within the national plan (16, 29)[25].

Until May 2019 32 RD registries in The Netherlands existed, however, the national plan led to appointing around 350

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[15] https://ec.europa.eu/health/rare_diseases/national_plans/detailed_en (accessed September 18, 2019).

[16] http://www.europlanproject.eu/NationalPlans?idMap=1 (accessed September 18, 2019).

[17] Dutch National Plan Rare Diseases. http://www.nfu.nl/img/pdf/nationaal-plan-zeldzame-ziekten.pdf (accessed September 18, 2019).

[18] https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/N/NAMSE/National_Plan_of_Action.pdf (accessed September 18, 2019).

[19] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684461/Rare_Disease_Policy_Board_-_Second_Progress_Report_2016-2018.pdf (accessed September 18, 2019).

[20] https://www.england.nhs.uk/wp-content/uploads/2018/01/implementation-plan-uk-strategy-for-rare-diseases.pdf (accessed September 18, 2019).

[21] Interview with Romanian key opinion leader (accessed August 11, 2019).

[22] Interview with Polish and Romanian key opinion leader (accessed August 13, 2019).

[23] https://bip.kprm.gov.pl/kpr/bip-rady-ministrow/prace-legislacyjne-rm-i/prace-legislacyjne-rady/wykaz-prac-legislacyjny/r32597703041012,Narodowy-Plan-dla-Chorob-Rzadkich.html (accessed September 18, 2019).

[24] Interview with Russian key opinion leader (accessed September 1, 2019).

[25] https://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf (accessed September 18, 2019).

[26] http://www.rejestrwad.pl/o-rejestrze/historia-prwwr (accessed September 18, 2019).

TABLE 2 | Description of National Plan for Rare Diseases per country (16, 29)[4], (54–64)[25,26], (65)[27], (66)[28,29].

Country	Characteristics of the national plans
AR	No NP or special legislation for rare diseases.
DE	NP developed and implemented: 7 focus areas, 52 proposed solutions, implemented in 2013. Twenty-eight rare disease institutions have been working together under the name NAMSE since 2009. In 2015 an online information portal (project ZIPSE) has been created, and an interactive map for patients to find centers of expertise.
FR	NP developed and implemented. 1st Ed. 2005–2008: 10 priority areas, budget €100 M. 2nd Ed.: 2011–2014 (budget €180 M), extended to 2016. Focus areas: improve quality of care for RD patients, more international collaboration and French research. Forty-seven specific steps for plan realization, incl. an audit. 3rd Ed. Cancer Plan 2014–2019 (incl. rare cancers). Definition of rare cancer introduced <6/100,000 per year or specialized treatment required due to atypical tumor location or cancer complexity. 2nd edition Cancer Plan structured functions among cancer centers. The NP for "Rare Handicaps" 2009–2013 was created by CNSA (National Solidarity Fund for Autonomy), which financially supports elderly frail and disabled people. The plan focuses on improving access to information on rare disabilities, having unified diagnostic and disease qualification processes, reference centers and introducing specialized care for rare disabilities. The 2nd Edition (2014–2018) has four priorities: support societal integration processes, improve quality of life, ensure age-independent medical care, and support clinical trials. CNSA is responsible for implementation.
KAZ	No NP.
LV	NP developed and implemented. Created for 2013–2015 by a working group consisting of representatives of HCPs, MoH, and patients organizations. The NP was accepted in 2013 but without any budget. Main priorities: access to information on rare diseases and registry creation. Due to lack of resources, the NP only has an organizational and structural role, but not practical.
NL	NP developed and implemented (NPZZ), but has not come to full fruition yet (2017). The plan contains observed hurdles (awareness, organization, research, role of patient organizations, need for coordination), several recommendations (education of HCP's, information management, healthcare organization and access to treatment, scientific research, appointment of a RD coordinator), and both short and long-term priorities within these areas The ZonMW institute has reviewed development/implementation of the NP since 2015, to structure and prioritize the multitude of observations and recommendations. The final recommendation to the MoH was given by ZonMW in February in 2017, with a large focus on creating 300 reference centers (completed) and their role in coordinating healthcare access and expertise down to local healthcare providers.
PL	First draft of an NP was developed by the National Forum for Rare Disorders with the Team for Rare Disorders in 2012, but not implemented (2017). The draft describes in detail screening, diagnostic and genetic tests, reference centers, multidisciplinary care, integrated social support systems for patients and families, education on rare diseases, sources of information, access to orphan drugs and a central registry of rare disorders. A new Plan for Rare Diseases was created in 2017 under leadership of the Polish Ministry of Health with an intention to be implemented in the near future.
RU	No NP.
RO	The MoH, National House for Health Insurance with the National Alliance for Rare Diseases (RONARD) started working on the NP in 2008 and it was proposed in the National Health Program. The draft of Romanian national plan was never adopted as a separate policy document with an allocated budget. Eight priorities were emphasized in this plan: - Establishing legal, social, economic norms and principles - Developing a network/chain of centers involved in diagnosis, treatment, rehabilitation and prevention - Facilitating access to the newest medicinal products and technologies - Improving access to information on rare diseases - Educating doctors - Involvement in clinical trials on rare disorders - Empowerment of patients' organizations and strengthening their role - Development of cooperation with other European countries. The MoH appointed the National Council for Rare Diseases, which has a consultative role and coordinates the implementation of the NP. Due to economic reasons, the implementation period has been extended to 2020.
UA	No NP exists, but legislative amendments concerning rare diseases have been introduced in 2014 (approved in 2015), via which the official list of rare diseases (256 diseases) has been published and rules for reimbursement of OMP's (by state and local budget) were defined and disease registries were introduced. In addition, the "National Action Plan to implement the UN Convention on the Rights of the Child" (August 2016) includes prioritization of pediatric rare disorders.
UK	NP developed and implemented. The National Strategy for rare diseases has been accepted by the MoH in 2013, incorporating 51 commitments for patients with rare disorders to be fulfilled by 2020. Commitments are broad and concern diagnostics, access to information, improvement of healthcare, creation of disease registries, clinical trials. Implementation has started in regions and progress is monitored.
TR	No NP.

reference centers that are able to comply with the EU standards, including 5 of the 24 new European Reference Networks (ERN) (65)[27]. The large number of centers will be working together in clusters, to prevent fragmentation (66).

Romania has two disease registries (biliary atresia and cystic fibrosis), both contributing to European registries[28].

Turkey has five working registries, one for oral ulcers in Behcet disease, cystic fibrosis (contributing to EUROCARE

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[27] European Reference Networks. https://ec.europa.eu/health/ern/networks_en (accessed September 18, 2019).

[28] http://www.anm.ro/_/ORDINE/ORDIN%20%20%20Nr%20387_2015_modif%20si%20complet%20OMS%20861_2014.pdf (accessed September 18, 2019).

cystic fibrosis registry), Duchenne, Becker, and spinal muscular dystrophy (contributing to TREAT-NMD), pediatric atypical hemolytic uremic syndrome, severe chronic neutropenia (contributing the SCN international registry) (40, 63). A registry for rare pediatric metabolic disorders is financed by Hacettepe University Hospital and the Metabolic Disease Foundation (METVAK). Turkey participates in European registries E-IMD (40, 64).

Russia is the only non-EU country in this review having a central rare disorder registry (31). There are no official rare disease registries in Kazakhstan, but work is underway to establish a national rare disease registry to help identify common genetic mutations within the Kazakh population, which is intended to collaborate internationally (51)[29]. Armenia has no registries[4] and is also the only country that does not have patient organizations gathering data. Disease registries are under development in Ukraine, which currently has one, for spinal muscular atrophy[24].

Rare Disease Policies and Access to Orphan Drugs

Although the European Commission has granted 2121 "Orphan Designations" from 2000 until 2019, "only" 164 orphan drug marketing applications were approved via EMA's centralized procedure in this period (1–3).

In contrast to the regulatory process, which is performed centrally and leads to a simultaneous drug approval for all 28 EU members, health technology assessment, pricing, and reimbursement are still executed on the national level. This can lead to differences in patient access, as illustrated below. Data from 2015 shows that the Netherlands reimbursed all OMPs registered in the EU except 3 (Ceplene®, Mepact®, and Bronchitol®) (68). In Germany the total number of reimbursed OMPs was 133[30]. Since the 2011 introduction of legislation aiming at controlling prices of patented pharmaceuticals and to curb spending (Act to Reorganize the Pharmaceuticals' Market in the Statutory Health Insurance System, AMNOG) until March 1st 2017, 51 orphan drug reimbursement procedures have been finalized by Germany's Federal Joint Committee (Gemeinsame Bundesausschuss, G-BA)[31]. OMPs are most widely accessible in Germany and France (69).

France reimburses 116 orphan drugs, England 68, Scotland 55, and Wales 47 (65). England, <50% of centrally authorized OMPs are routinely funded by the NHS, with one-third of these recommended by NICE (69).

Latvia reimburses 25 orphan drugs, 21 via three reimbursement pathways (the reimbursement list, individual reimbursement and the CCUH program "Medicinal treatment for children with rare diseases") and 4 through multiple reimbursement mechanisms (15).

Poland reimburses 48, the vast majority of which within so-called "Drug Programs" (DPs), introduced by the MoH in 2012 for expensive medical technologies (replacing previous "therapeutical programs") (11, 70–72). DPs are mainly designed to control consumption of the most expensive drugs[22].

Romania has 70 reimbursed OMPs[21,32]. Russia has been reimbursing 27 high-cost drugs for orphan diseases on the federal level and 43 in the Moscow region (73–75)[33], which is an example of regional differences in patient access. Ukraine reimburses 23 active substances for 7 diseases approved for state procurement based on the national drug program inclusion criteria (76, 77), 12 diseases for children and adults, covering 65 INNSs.

In Turkey currently 43 orphan drugs are reimbursed but 22 of them are not currently marketed in Turkey, for this reason, Social Security Institutions use direct importation for those products (78, 79).

Kazakhstan has 42 reimbursed OMPs at the country level and 2 reimbursed rare disease funds. However, according to the Kazakh definition of orphan drugs/rare diseases there are 150 orphan drugs for 50 disease classes (80, 81).

In Armenia there is no reimbursement as seen in the other countries: many medicines are given via donations[4]. Medicines are distributed free of charge from the MoH warehouse to polyclinics and hospitals nationwide. All medicines are obtained through tenders posted by the Armenian MoH. When a rare disease does not cause physical or mental disability, all costs for required medicines or medical nutrition are borne by the patient[4].

Early Access (Compassionate Use, Named Patient Programme, Conditional Reimbursement)

According to Balasubramanian et al., 20 out of 28 EU member states had an established compassionate use programme (CUP) (82). A CUP exists in all EU countries selected for this review, except Poland (work on implementation of a national CUP is ongoing)[23] (82).

In the EU it is also possible to request a CUP centrally via the EMA Committee for Medicinal Products for Human Use (CHMP) when adequate clinical evidence exists on safety and efficacy, but most CUPs are executed on the country level via the local regulatory authority. Only 5 CUPs have been granted through the CHMP so far[34].

Early access programs are not offered in Kazakhstan, Armenia, Russia, and Ukraine (51)[4,24,35].

France makes extensive use of CUPs for rare diseases, with 70% of the currently reimbursed orphan drugs having had early access before the marketing authorization (59). France is also unique in the fact that it has a legal framework for

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[29] https://www.zakon.kz/4777791-nacionalnyjj-reestr-redkikh.html (accessed September 18, 2019).

[30] https://www.slideshare.net/OHENews/access-to-orphan-drugs-in-the-uk-and-other-european-countries (accessed September 18, 2019).

[31] http://skc-beratung.de/wp-content/uploads/2017/03/White_Paper_SKC.pdf (accessed September 18, 2019).

[32] https://www.cnas.ro/page/listamedicamentelor-2019.html (accessed September 18, 2019).

[33] http://www.iokpb1.ru/perechen-7-nozologii-2019.pdf (accessed September 18, 2019).

[34] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c (accessed September 18, 2019).

[35] Interview with Ukrainian key opinion leader (accessed September 5, 2019).

"early access" for already registered drugs for which a new (medical need) indication is still under assessment, called RTU (Recommendation for Temporary Use) (83, 84). Sixteen products have received an RTU in France so far (83). RTU allows for a more flexible access approach than many other countries, such as the Netherlands, that only allows non-registered drugs for a CUP, regardless of whether the (orphan) indication is approved or not[36].

In Turkey exist three well-established processes to get access to unapproved drugs, e.g., approved off label-use of registered drugs (e.g., different indication/dosage, or non-approved patient subgroups), Named Patient Imports and CUPs (33, 34). A CUP is acceptable for products that have entered a phase-III clinical program and in case of serious or life-threatening conditions, but only if patients cannot enroll in a clinical trial in Turkey. The Medicines and Medical Devices Agency supervises these programs (33, 34). Scotland has a two-tier program for access to non-routine drugs (i.e., drugs normally not available in the Scottish healthcare system) called PACS, with tier 1 reserved for ultra-orphan drugs and tier 2 for other non-routine drugs (not approved by the Scottish Medicine Consortium). Cost-effectiveness is explicitly excluded from any argumentation for access[37].

HTA and Reimbursement Processes for Orphan Drugs

Rare disease populations are small and often show large disease heterogeneity, which leads to difficulties in generating well-powered and controlled randomized clinical trials and useful outcomes. This makes the generation of (high quality) evidence on clinical efficacy and cost-effectiveness troublesome. In turn, HTA assessment processes are usually not tailored to deal with these rare diseases and orphan drugs characteristics. Many countries still reimburse OMP's despite a lower quality of evidence and accept higher prices, often because of societal/compassion-related arguments and the limited total budget impact of the rare disease treatment. Some countries have reduced requirements for evidence and other waivers for rare disease treatments. For example, in France a cost-effectiveness analysis is not required. The Haute Autorité de Santé (HAS) assesses therapeutic benefit, calculated as Service Medical Rendu (SMR), which takes into account: clinical effectiveness, safety of alternatives, clinical relevance in overall treatment strategy, disease severity, population size, and indication (for chronic and preventable diseases) (29).

Similarly, in Turkey orphan drugs are exempt from submitting pharmacoeconomic analyses, which allows OMPs to enter the market faster (if budget impact is within limits) (33, 34). In Romania OMPs receive additional value points (55) during the HTA process, which increases chances for reimbursement (29)[12].

Since 2012 a conditional reimbursement has been possible in the Netherlands, in cases of discussion/doubt over a therapeutic benefit, cost-effectiveness, or the predicted budget impact of a medical intervention (only available for outpatient drugs)[38]. These conditional approvals were intended to ensure patients could get early access to innovative medicines while maintaining budget control. This program came with the requirement to provide additional scientific data within 4 or 7 years (in exceptional cases), for which a subsidy could be requested with a maximum of 400,000 €. However, the number of products that applied for conditional reimbursement up to 2017 turned out to be low. Therefore, the conditional reimbursement program has been replaced by a more general subsidy program, focused at supporting small and medium manufacturers[38].

Romania also has a conditional reimbursement program, which aims to allow patient access to new drugs quickly, while still keeping a focus on evidence-based medicine and budget control[39].

In the UK, NICE performs an HTA assessment using incremental cost-effectiveness ratios which are usually implemented by the regions, although a re-assessment or a purely regional HTA can also be done in Scotland, Wales, and Northern-Ireland. The NICE HTA process is based on a threshold level per ICER, with increasing evidence requirements if certain ICER levels are exceeded. Orphan and ultra-orphan drugs can get higher limits[40,41,42,43,44,45,46].

The Act to Reorganize the Pharmaceuticals' Market in the Statutory Health Insurance System (AMNOG), introduced in Germany in 2011, changed reimbursement of new innovative drugs considerably[31]. Manufacturers are allowed to set prices freely during the first year after marketing authorization, with a mandatory 7% discount to statutory health insurances. An "early benefit assessment" is done after 12 months, after which reimbursement will be recalculated, taking into account the perceived additional benefit of the medicine[47] (85). Lower evidence thresholds for OMPs were applied within the process and an automatic "additional benefit" for OMPs was assumed, with no necessary comparison against alternative therapies. This

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[36] https://www.cbg-meb.nl/mensen/voor-handelsvergunninghouders/inhoud/voor-aanvraag-handelsvergunning/compassionate-use-programma (accessed September 18, 2019).

[37] https://www.gov.scot/news/reforming-access-to-new-medicines/ (accessed September 18, 2019).

[38] Letter of the Healthcare Minister on restructuring of the conditional reimbursement ruling https://www.rijksoverheid.nl/documenten/kamerstukken/2017/02/21/kamerbrief-over-herinrichting-van-de-regeling-voor-voorwaardelijke-pakkettoelating (accessed September 18, 2019).

[39] http://www.cnas.ro/casbr/page/contracte-cost-volum-cost-volum-rezultat.html (accessed September 18, 2019).

[40] https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf (accessed September 18, 2019).

[41] http://gov.wales/newsroom/health-and-social-services/2017/170110fund/?lang=en (accessed September 18, 2019)

[42] https://www.scottishmedicines.org.uk/About_SMC/Policy_statements/A_Guide_to_Quality_Adjusted_Life_Years (accessed September 18, 2019).

[43] http://www.bbc.com/news/uk-scotland-scotland-politics-32761132 (accessed September 18, 2019).

[44] https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf (accessed September 18, 2019).

[45] https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making (accessed September 18, 2019).

[46] The interview with British key opinion leader (accessed July 14, 2019).

[47] The interview with German key opinion leader (July 5, 2019).

streamlined and simplified the reimbursement process for OMPs considerably. The "Legislation for more safety in the supply of pharmaceuticals" (GSAV) introduced in 2019 changed several parameters for OMP reimbursement in Germany, by removing several benefits for OMPs and increasing the likelihood of price reductions for OMPs (67, 86). Under GSAV, OMP manufacturers are more likely to have to invest in data collection activities (e.g., patient registries) and perform comparative analyses. The automatic added benefit clause is removed for OMPs with an annual revenue >€50 M. In this case, a comparative analysis will have to be provided. GSAV now includes both hospital as outpatient costs in the revenue calculations, increasing the likelihood of exceeding the threshold. G-BA will be authorized to perform periodic re-evaluation of the drug's benefits (and conduct price negotiations if deemed necessary). The actual impact of GSAV on orphan drugs, i.e., availability/patient access, pricing, time to market, and disease/drug understanding, remains to be seen. GSAV legislation might lead to more structured, approach toward Real World Evidence (RWE) creation in the rare disease/orphan drug field. It is possible that Germany will push these topics onto the EU agenda during its co-presidency in 2020/2021 (67, 86).

Some countries are looking at novel and alternative methods of assessing orphan drugs, such as Poland who is considering to use MCDA (Multi-criteria decision analysis) in its HTA policies[48].

A detailed overview of HTA and reimbursement processes is presented in **Table 3**.

DISCUSSION

Limitations of the Study

In order to get a complete overview of the Eurasian region, many more countries would have to be included, however, this went beyond the scope of this article and would overly enlarge it. This overview presents the most recent information that was possible to retrieve at the time of writing, but policies and regulations are continuously changing. Sometimes new information is difficult to find and only available in local languages. The politicization of the (orphan) drug price debate results in shifting political viewpoints highly dynamic healthcare policies. Not all country data is comparable, i.e., mismatches exist in definitions, different aspects of rare disease policies that are covered and the level of detail, on top of structural differences in healthcare systems. To keep this information relevant and up-to-date, research should be done periodically to expand and include the latest information. The German GSAV shows that new and extensive policies can be introduced quickly, especially in an era of rising cost-awareness. Sharing scientific progress and relevant policy developments in a collaborative manner is very relevant in the orphan drug arena, where knowledge and experience are often scarce. A publicly accessible "policy repository" could be a useful tool for researchers and policy makers to share best practices and combine efforts, but which would require continuous input and resources.

This study shows that large differences exist between selected countries with regard to orphan drug policies, solutions, available healthcare budgets, and the level of patient access. This applies to EU vs. non-EU countries, EU member states, and even within a single country. Despite these variations that make it difficult to create a comprehensive overview of policies or generate a clear-cut conclusion, the authors have attempted to capture a representative picture.

Newborn Screening

Good examples of intra-country differences are newborn screening and orphan drug reimbursement between the regions of the UK (i.e., Northern Ireland vs. Scotland, England, and Wales) and in Moscow vs. the rest of Russia. Newborn children are screened for the highest number of rare disorders in Poland (28), followed by The Netherlands (20). On the lower end of the scale, Kazakhstan, Latvia, Romania screen for only two diseases. Russia has the region with the broadest newborn screening in this review (35 RD's in Moscow), although large parts of the country have a much smaller program[9]. Aggregation of data concerning newborn screening is not always straightforward, since many rare metabolic disorders have different names or subtypes which can be considered either as one disease or as separate rare conditions, depending on publications and local guidelines. Disease carriership is sometimes counted as a separate condition (e.g., sickle cell disease and sickle cell carriership in the Netherlands). Overall though, the national plans have led to expansion of the amount of screened diseases. Implementing a new screened disease requires testing and validation of new technology, so the implementation status is sometimes not clear to the public.

Despite the wide international consensus on the efficiency of NBS for phenylketonuria in terms of costs and effectiveness, this consensus is challenged as new disorders are proposed to be included in a NBS program (93). NBS programs might be relatively inexpensive, even when the confirmatory diagnostic tests for both the true and false positives and the follow-up and treatment costs of affected children are included. However, the high heterogeneity of the disorders potentially detected by screening, and the lack of robust and long-term scientific evidence on the effectiveness of the treatments and the natural history of the disorders, pose a number of methodological difficulties that limit the applicability of standard pharmacoeconomic evaluation methods to prove its cost-effectiveness.

Disease Registries, National Plans for Rare Diseases

The national plans have stimulated the creation of registries as scientific centers, but implementation varies per region. Government publications have been reviewed to assess the availability of patient/disease registries, but whether the mentioned registries are operational, being implemented or merely announced is sometimes not transparent. Reorganization, grouping, and renaming of registries is common. Other

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[48] https://www.gov.pl/web/zdrowie/rada-ministrow-przyjela-dokument-polityka-lekowa-panstwa-20182022 (accessed September 18, 2019).

TABLE 3 | Comparison of reimbursement systems of orphan drugs and rare diseases policies (15, 16, 29, 70–72)[4,24], (68)[30,31], (11, 69)[32], (73–75)[33], (76–84)[34,35,36,37,38,39,40,41,42,43,44,45,46,47], (67, 85, 86)[1,48], (87)[2,3], (88, 89)[4,5], (90, 91)[6,7,8,9], (92, 93).

Country	Reimbursement/HTA process
AR	No specific reimbursement process for OMP's. No defined HTA process.
DE	The AMNOG Act requires manufacturers to send in a dossier at the time of regulatory approval (and <1 month after indication change) to the Federal Joint Committee (FJC), the decision-making body of the joint healthcare representatives—HCP's, hospital association, and sickness funds) to demonstrate additional benefit of the drug over a comparator drug. After the additional benefit is granted by the G-BA, a reimbursement price is negotiated between manufacturer and GKV-SV (National Association of Statutory Health Insurance Funds). A budget cap of €50 M per active substance was introduced in 2016. After 12 months, practical benefit was assessed and reimbursement adjusted accordingly. Reimbursement prices that are negotiated on the national level are published. Afterwards, the more than 100 health insurances further negotiate discounts with the manufacturer, which are not publicly available. Except for OMPs, G-BA lets IQWiG (Institute for quality and science in healthcare) assess the proposed additional benefit with the dossier submission at the time of marketing authorization, with five benefit categories: major, considerable, minor, non-quantifiable, no additional benefit. Evidence quality is taken into account, based on the number of studies, evidential certainty and clinical outcomes, resulting in three possible scores: proof, indication or hint of benefit. Four clinical outcomes are measured: mortality, morbidity, adverse events, and health-related quality of life (HRQoL). Patient subgroups can be excluded in case of no added benefit. If projected sales are <€1 M, no full dossier is needed. Until 2019, OMPs with an EMA marketing authorization were viewed as automatically having an established additional benefit over existing therapies (i.e., the 'no additional benefit' score was excluded from OMP benefit scores). After 12 months, an early benefit assessment is performed after which prices can be renegotiated. This changed in 2019, when the GSAV bill introduced a new clause for OMPs that exceed the 50 M annual revenue threshold: in this case drug manufacturers need to perform a comparative analysis with an appropriate comparator drug within 3 months. (Hospital) Inpatient costs are now also to be included in the 50 M budget vs. only outpatient cost before 2019, increasing the likelihood for OMPs to exceed the threshold. Under G-BA can require drug manufacturers to setup data collection programs (patient registry data) according to G-BA rules, as well as require physicians and hospitals to provide OMP administration data to registries in order to be allowed to prescribe these drugs. The costs of these observational data collection activities would have to be covered by drug manufacturers. GSAV authorizes G-BA to perform periodic reassessment of the benefit analysis with new (registry) data. GSAV can lead to an increased number of price-renegotiations/reductions. Arbitration procedures can be started in case of conflicting views between manufacturer and IQWiG/GBA.
FR	No specific reimbursement criteria exist for rare diseases (standard HTA applies), however, a cost-effectiveness analysis is not needed. HAS assesses therapeutic benefit, calculated as Service Medical Rendu (SMR), which takes into account: clinical effectiveness, safety of alternatives, clinical relevance in overall treatment strategy, disease severity, population size, indication (for chronic and preventable diseases). The SMR defines the drug reimbursement level for drugs (three levels exist). The MoH is responsible for final reimbursement. For drugs which HAS considers irreplaceable, reimbursement is set at 100%. HAS also assesses the ASMR indicator (Amelioration du Service Medical Rendu), i.e., therapeutic improvement in comparison to other available treatments and sets the price level based on this value (five possible levels). No specific reimbursement criteria exist for rare diseases. The SMR defines three reimbursement levels for drugs. The MoH is a decision maker. For drugs which HAS considers irreplaceable, reimbursement is set at 100%. HAS also assesses the ASMR indicator (Amelioration du Service Medical Rendu), i.e., therapeutic improvement in comparison to available treatments and sets the price level based on this value (five levels exist). Standard HTA process applies to OMPs, however, a cost-effectiveness analysis is not required. HAS assesses therapeutic benefit, calculated as Service Medical Rendu (SMR), which into account: clinical effectiveness, safety of alternatives, clinical relevance in overall treatment strategy, disease severity, population size, indication (for chronic and preventable diseases).
KAZ	Healthcare is generally funded by the State and is free for all citizens. Treatment of rare diseases is covered within the national healthcare budget, and no special reimbursement rules exist for OMP's. However, OMP funding needs to be applied for by the regions, after which budget is granted by the State, based on individual patient characteristics (e.g., body mass/dosing). OMP's need to be registered in Kazakhstan or elsewhere and be on the official orphan drug list to be eligible for reimbursement. All medical interventions are monitored under supervision of the MoH. No specific HTA process for OMPs.
LV	Drugs listed on the national reimbursement drug list are reimbursed, based although individual patient reimbursement decisions can be made a by the medical council (limit: 14,229 Euro per patient/year). The national reimbursement list has three sections: List A with therapeutically equivalent drugs (generic drugs); List B with drugs without therapeutic equivalent; List C with drugs costing more than 4,269 Euro per patient per year. The manufacturer must reimburse at least 10% of the costs of drugs on list C for a defined number of patients. Other OMP's can be reimbursed on an individual basis in medical need (life-threatening situations) if costs are <€14,229 per year, which is assessed by the National Drug Agency. Co-payment is needed in case of additional costs, by patient or manufacturer. This does not limit access substantially. Between 2008–2011, 300+ patients had successful individual negotiations. Pediatric rare disorders can receive special reimbursement rules. The NHS evaluates therapeutic value, price, expected budget impact and cost-effectiveness for each drug before it is included in the reimbursement list. No specific HTA rules for OMPs. List C decisions are made annually, depending on budget and total budget impact of the treatment.
NL	OMP's go through the same HTA process as all other "specialist drugs," which are assessed based on the "risk" they pose to the overall Dutch basic insurance coverage, taking into account budget impact, lack of control over the use of the product, doubts on the quality of evidence, etc. If the risk is considered high, a formal HTA assessment is done. A price >€25,000 per patient per year is also defined as a risk factor, however, if total budget impact is small (<€2.5 M per year), ZiN will likely not do an assessment. Due to a frequent lack of evidence for OMP's, the rarity, severity, and societal impact of the disease will be considered. Hospital drugs (mainly specialty care) that either are expected to have a high per patient cost, or a high total budget impact, can be put into a "sluice" (waiting room) by the minister of health. This means a delay in reimbursement until a positive evaluation, restrictions for use have been put in place and/or a successful price negotiation has been done by the MoH (undisclosed).
PL	No special reimbursement rules for OMPs. A reimbursement application is sent to the MoH, which transfers it to AOTMiT for evaluation (containing clinical effectiveness, cost-effectiveness, and budget impact analyses). AOTMiT gathers and assesses information on health, social, economic, and ethical aspects of medicinal technology. The Transparency Council (part of AOTMiT) gives its recommendation on pricing and reimbursement and the final recommendation is issued by the President of AOTMiT. Final approval is given by the Healthcare Minister. Most OMPs are reimbursed within "Drug Programs" (DPs), introduced by the MoH in 2012 for expensive medical technologies replacing previous "therapeutic programs." DPs are mainly designed to control consumption of the most expensive drugs. As a tailored approach to HTA for OMPs does not currently exist in Poland, standard HTA rules for "standard" medicinal products apply, which take into account: health priorities, results of sequelae of disease, public health significance, social preferences, organizational, legal aspects, and ethical aspects. The cost-effectiveness threshold is based on an ICER (Incremental cost-effectiveness ratio) that needs to be lower or equal to 3×GDP per capita to consider a medical technology cost-effective (3 × 41.985 PLN = 125.955 PLN∼29.989 EUR in 2016, EUR rate from 16.03.2018 1EUR = 4.2PLN).

(Continued)

TABLE 3 | Continued

Country	Reimbursement/HTA process
RO	OMP's are reimbursed within the National Program for rare disorders and National Program for treatment of chronic disorders (list C2), and provided for free. HTA was introduced in 2014, with separate rules for reimbursement of OMPs. In order to be included in the reimbursement list, medicinal products need to gain a minimum of 60 points (out of 80) during HTA. Results between 60 and 79 ensure conditional reimbursement, with price negotiation and by using risk-sharing tools (agreements on cost-volume, cost-volume-outcome). Drugs with an orphan designation assigned by EMA automatically get 55 points and depending on the reimbursement status in other EU countries points are added: 0 points if the drug is reimbursed in up to 2 EU countries 10 points if the drug is reimbursed in 3–7 EU countries 20 points if the drug is reimbursed in 8–13 EU countries 25 points if the drug is reimbursed in at least 14 EU countries.
RU	The reimbursement system is quite complex, consisting of many lists, programs and levels of reimbursement. OMP's can be reimbursed on federal and regional levels. Federal reimbursement is based on the Vital and Essential Drug List (VEDL)—a list of reimbursed drugs with price limits. Federal benefits are available if rare disease patients belong to one of the "privileged categories" of citizens such as veterans, invalids or victims of the Chernobyl and Mayak disasters. Orphan drugs are mainly reimbursed within two programs, the high-cost Nosologies List and the orphan diseases list. Within the seven nosologies program, funded on the federal level, the treatment for those diseases is reimbursed: hemophilia, cystic fibrosis, pituitary nanism, Gaucher disease, lymphoid malignant neoplasms, hematopoietic and related tissues, multiple sclerosis, hemolytic-uremic syndrome, juvenile arthritis with systemic onset, mucopolysaccharidosis type I, II, and VI. Although the reimbursed treatments on the 24 orphan diseases list are defined on the federal level, funding is done regionally. If budget allows, treatment for other rare disorders (not on one of the lists) can be reimbursed. There is no special HTA for OMPs, the same rules apply as for other medicinal products.
TR	All OMP reimbursement applications are assessed by the Medical and Economic Evaluation Commission, which informs the Reimbursement Commission that will make a final decision. The TITCK, SGK, and the Ministry of Finance are part of the Medical and Economic Evaluation Commission and the Reimbursement Commission. Orphan drugs are exempt from submitting pharmacoeconomic analyses in contrast to other medicinal products, which allows OMP's to enter the market faster (if budget impact is within limits).
UA	In 2016 the new legislation on HTA was implemented. The new regulation introduced criteria (such as morbidity level, disease prevalence, evidence on comparative effectiveness, safety) which are taken into consideration in order to include medicinal products to National essential medicines list (NLEM). In addition a pharmacoeconomic analysis must be provided while applying for the reimbursement. An expert Committee on the Selection and Use of Essential Medicines was appointed by the MoH for decision making concerning the inclusion of medicinal products to NLEM. No specific reimbursement and HTA processes for OMPs exist. In January 2019 HTA Department was established at the State an Expert Centre of the MoH to prepare recommendations and inform decisions on medical technologies financed by the state funds. The main stakeholders are the central government (Cabinet of Ministers), the MoH, the Ministry of Finance and local governments. In 2019 there are 41 national programs that are approved annually for public (state) procurements for diseases, rare diseases in particular, through which OMP's are procured annually via international organizations (UNDP, Crown agents, UNICEF). Currently there are clinical protocols approved by the MoH for treatment of mucopolysaccharidosis, Gaucher disease, epidermolysis bullosa, cystic fibrosis, phenylketonuria, Wilson's disease.
UK	**England** NICE performs HTA assessment using (incremental) cost-effectiveness ratios, with thresholds for medicines (incl. orphan drugs): below the £20,000 limit NHS reimbursement is based mainly on cost-effectiveness data, between £20,000–£30,000 more data is needed e.g., degree of ICER certainty, innovativeness, whether or not the drug is life-extending at end of life, etc. Above £30,000 evidence needs to be stronger. For very rare disorders (1 < 50,000) the HST (Highly Specialized Technologies) programme is used, which uses an ICER QALY limit of £100,000. If costs remain below that the assessment will be based on standard cost-effectiveness analysis. Above the limit evidential certainty, the innovation level and actual effectiveness increase (QALY gains) will be taken into account and a QALY modifier can raise the cost limit up to £300,000 per incremental QALY. In 2017 NICE introduced a "budget impact test" with a limit of £20 million (over 3 years), set by the NHS. If the limit is exceeded a commercial negotiation is triggered, special arrangements need to be made and reimbursement can be delayed or phased in over a longer period. Expensive OMP's can also be procured via the Cancer Drug Fund (budget £340 M in 2016), a dedicated budget for innovative costly treatments too expensive for common NHS reimbursement (after NICE recommendation), and also via an Individual Funding Request to the NHS. **Wales** Wales is generally following NICE' reimbursement recommendations, but has its own agency All-Wales Medicines Strategy Group (AWMSG) which can approve drugs for reimbursement. A special treatment fund for high-cost drugs has been introduced in 2017. **Scotland** The Scottish Medicines Consortium (SMC), the Scottish equivalent of NICE, reviews all newly approved medicines, including orphan and ultra-orphan drugs. The HTA process is similar to England, with similar ICER QALY thresholds (£20 and £30 k). The Scottish NHS boards are not obliged to follow SMC's advice. A separate fund exists dedicated to funding expensive medicines, including rare disease treatments, called the New Medicines Fund. Since 2014 manufacturers can ask SMC to convene a Patient and Clinician Engagement (PACE) group, if their drug is not recommended for reimbursement by the New Drug Committee (NDC). PACE was setup after the realization that existing cost-effectiveness thresholds were not always suitable for (ultra)rare diseases and end-of-life conditions. PACE is aimed at enlarging the role of expert physicians and patients in the decision-making process. Orphan drugs for ultra-rare diseases can receive additional flexibility in the process. **Northern Ireland** The Department of Health (DH) in Northern Ireland assesses all NICE recommendations for local implementation. Very rare drugs approved via NICE HST assessment will be approved for reimbursement.

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[1] *https://www.gkv-spitzenverband.de/english/statutory_health_insurance/amnog_evaluation_of_new_pharmaceutical/amnog_english.jsp (accessed September 18, 2019).* [2] *Interview with French key opinion leader (accessed July 26, 2019).* [3] *https://www.has-sante.fr/portail/upload/docs/application/pdf/2014-03/pricing_reimbursement_of_drugs_and_hta_policies_in_france.pdf (accessed September 18, 2019).* [4] *https://www.zorginstituutnederland.nl/over-ons/programmas-en-samenwerkingsverbanden/horizonscan-geneesmiddelen/sluis-voor-dure-geneesmiddelen (accessed September 18, 2019).* [5] *http://www.korektorzdrowia.pl/wp-content/uploads/3.-wojciech-matusewicz-1.pdf (accessed September 30, 2019).* [6] *Order of MOH No. 84 dated 11.02.2016, Order of MoH No. 1050 dated 07.10.2016. Available online at: http://www.apteka.ua/article/362317 (accessed September 30, 2019).* [7] *http://www.apteka.ua/article/390509 (accessed September 30, 2019).* [8] *Order of MOH No. 778 dated 27.10.2014 http://zakon3.rada.gov.ua/laws/show/160-2015-%D0%BF (accessed September 30, 2019).* [9] *https://www.scottishmedicines.org.uk/how-we-decide/pace/ (accessed September 30, 2019).*

institutions, such as universities or patient organizations are often involved in gathering this data but they were not included in this review. The ongoing implementation of national plans in the EU since 2013 has reinforced the international recognition of rare disorders in governmental programs substantially, leading to alteration and implementation of various policies. The newly approved European Reference Networks are a good example. The results of this increased data gathering will hopefully lead to better understanding, diagnosis and treatment of rare diseases, but this will take time.

Access to Treatment

The main effect of the fragmentation of reimbursement policies is unequal access to treatment. The number of reimbursed OMPs in the selected countries ranges from 100+ OMPs in The Netherlands, Germany, France to zero in Armenia. The EU countries are leading in access to OMPs but positive developments for patients are also seen outside the EU, e.g., in Russia and Kazakhstan. Like France, Turkey also has implemented regulatory flexibility, by allowing the use and importation of drugs for non-registered orphan indications (i.e., managed off-label use).

In some countries legislation is completely lacking, leaving patients without many options to get access to any (expensive) medication, such as in Armenia. Early access programs can temporarily alleviate an urgent medical need for OMP with a low burden for society and patients, and since these are relatively easy to implement they should be introduced in all countries.

HTA and Reimbursement

No specifically tailored HTA approaches were identified for orphan drugs, although waivers and reduced data requirements are often present in some form or another. Many countries use standard HTA processes but do reimburse OMP's despite lacking evidence.

Rare diseases commonly place a large burden on family and caregivers, the impact of which is usually not taken into consideration in standard cost-effectiveness analyses (94–96). In light of the lack of appropriate HTA tools that can incorporate benefits and costs specific to rare disease treatments beyond the standard cost per QALY, e.g., socio-economic aspects, Multi-Criteria Decision Analysis (MCDA) is an approach that could be considered. MCDA can support decision-making processes by capturing and weighting a range of factors of a certain intervention, the result of which is one composite outcome score. This outcome can be used for comparison between technologies (97, 98). MCDA has been implemented in legislation in Lombardia (for diagnostics, medical devices, interventional procedures, and medicinal products including OMPs) and also in Hungary for new hospital medical technologies (99, 100). Poland is currently considering the use of MCDA for this purpose.

Researchers in the rare disease area are also looking into the use of MCDA, which has resulted in a list of scientific publications and MCDA model designs, but full consensus on MCDA is still lacking and further research is needed to support implementation in (rare disease) HTA (94, 101–116).

Reimbursement rules are harder to unify than regulatory legislation, due to regional economic and political differences, also in the EU. However, signs of international cooperation are visible, as the European Parliament Committee on Environment, Public Health and Food Safety (ENVI) is investigating shared HTA and pricing projects in the EU[49]. The European Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA) project is a step toward international harmonization and improvement of patient access to OMPs. This platform aims to facilitate an early dialogue on pricing and reimbursement already during the development phase of OMPs between pharmaceutical companies and competent authorities[50] (117). The Transparent Value Framework (TVF) which is an MCDA-like method developed by Hughes-Wilson, was also tested within this project in order to develop a coordinated mechanism between the 12 participating Member States and orphan drug developers to evaluate the value of OMPs[51].

The EU HTA Regulation that was announced builds on these earlier initiatives, centered around the concept of a centrally performed Joint Clinical Assessment (JCA) that can be used by national HTA agencies (8). Economic factors will probably still be evaluated nationally, but a central "clinical value" assessment would avoid duplication efforts, reduce workload and make the HTA process more transparent and predictable for all stakeholders. Given the pressure on costs, especially in the area of expensive medicines, sharing, and implementation of new cost-reduction policies is to be expected.

New Scientific Methodology

Several new scientific and methodological approaches are being developed to improve evidence generation and analysis for small population groups, including new trial designs and clinical endpoints such as was done in the EU FP7 framework recently and its subprograms IDEAL (Integrated DEsign and AnaLysis of small population group trials), InSPiRe (Innovative methodology for Small Populations Research) and ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence)[52]. Goal Attainment Scaling (GAS) came out as an example of a "rediscovered" endpoint that can capture individual and heterogeneous symptoms via personalized outcome parameters (118, 119). $N = 1$ trial methodology (single-subject design) allows to perform a double-blind randomized placebo-controlled trial with one single patient, via randomized treatment cycles of both drug and control. Although limitations exist (e.g., suitable for chronic conditions only), the method seems appropriate for ultra-rare diseases (120). Drug manufacturers can benefit from all these developments, e.g., with improved clinical methodology for rare diseases and clear, predictable and transparent orphan drug legislation and HTA processes that are adapted for orphan drugs. In turn, this can support regulators and payers when assessing the value and benefits of OMPs. It is not clear,

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[49] http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf (accessed September 30, 2019).

[50] https://www.eurordis.org/content/moca (accessed September 30, 2019).

however, if and how fast these new developments will result in actual benefits for rare disease patients, i.e., improved access to a wider range of drugs. International medical and scientific collaboration for rare diseases already exists for a while (e.g., Orphanet, Eurordis), but cooperation on HTA issues and patient access is still lagging behind. Unified international approaches to tackle common issues surrounding orphan drugs are being developed slowly.

This article has looked at a broad range of initiatives over a wider region, and it can be concluded that no single country in this review can be marked as having the "most optimal" rare disease solutions. A broad national newborn screening program can be accompanied by a relatively small reimbursement program in the same country. Learnings should be taken from the respective national experiences and by sharing of policy related information, which was also the aim of this publication. In order to create additional momentum, initiatives that can effectively support orphan drug access should be prioritized and placed on the public agenda, preferably supported by strong political entities. The rarity and complexity of the rare disease/orphan drug arena makes collaboration and harmonization essential. Only in this way the 350 million people suffering from rare disorders around the world can hope to expect fair and equal access to treatments in the future[53]. Continuous research and sharing of information is highly recommended to identify and promote best practices in the rare disease policy field.

AUTHOR CONTRIBUTIONS

MC coordinated the group of researchers in gathering and unifying information and provided information about Poland. AB-K performed data analysis, data gathering, wrote the publication, and provided information about Poland, Latvia, France, United Kingdom. KA provided information about Turkey. MD editorial changes and provided information about Armenia. KG provided information about Kazakhstan. MH-V provided information about Russia. AT-S provided information about Romania. CK proofread and provided information about The Netherlands and Germany. OP and OZ provided information about Ukraine. NK provided information about Armenia. JS-C provided information about Poland.

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[51] Hughes-Wilson W. *MoCA Concept and Pilot Project, Feedback From the Process Around the First Pilot Project*. Berlin: ECRD. Available online at: http://download2.eurordis.org.s3.amazonaws.com/moca/presentations/PRES-2014-05%20MoCA%20Concept%20and%20Pilot%20Project%20(Hughes-Wilson).pdf (accessed September 30, 2019).

[52] https://ec.europa.eu/research/fp7/index_en.cfm (accessed September 30, 2019).

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Comparison of Cardiovascular Medicines Prices in Four European Countries

Zornitsa Mitkova[1]*, **Mariya Vasileva**[2], **Alexandra Savova**[1,2], **Manoela Manova**[1,2], **Silvia Terezova**[2,3] and **Guenka Petrova**[1]

[1] Faculty of Pharmacy Bulgaria, Medical University of Sofia, Sofia, Bulgaria, [2] National Council on Pricing and Reimbursement of Medicinal Products, Sofia, Bulgaria, [3] Economics of Infrastructure Faculty, University of National and World Economy, Sofia, Bulgaria

The aim of the current study was to compare pricing methodologies at the manufacturer, wholesale, and retail levels, and to estimate the price differences of AT1-receptor blockers (sartans), Angiotensin-converting enzyme (ACE)—inhibitors, and their fixed-dose combinations (FDCs) in four countries using similar methodologies: Slovakia, Greece, Bulgaria, and Romania (SK, GR, BG, and RO, respectively). The methodologies for manufacturer, wholesale, and retail price establishment have been compared using nationally implemented rules. Overlapping trademarks were established retrospectively on the manufacturer and retail levels in November 2017. The average price per tablet, percentage of price deviation, and statistically significant differences were calculated. The selected countries apply external reference pricing at the manufacturer level. A wide variation in the number of referent countries was observed (from 12 to 27). Despite the use of a regressive scale for price calculation, large variations between margins and value-added tax (VAT) are established, thus leading to different final medicine prices. This study found that medicine prices were lower in RO than in other selected countries. It was caused by the fact that 15 products had the lowest manufacturer price and 14 products had the lowest retail price in RO. Results of Kruskal–Wallis test showed that there were no significant differences between prices per tablet on the manufacturer and retail levels. In the group of fixed-dose combinations, ramipril/hydrochlorothiazide, and irbesartan/hydrochlorothiazide showed more than 100% deviation. The prices of cardiovascular medicines differed within the observed countries. The differences in pricing methodologies (e.g., margins, VAT) at the national level did not significantly affect retail prices, as a low manufacturer price usually leads to a low retail price.

Keywords: ACE- inhibitors, AT1-receptor blockers, manufacturer price, retail price, price difference

Edited by:
Nemanja Rancic,
Faculty of Medicine, Military Medical Academy, Serbia

Reviewed by:
Stefano Omboni,
Istituto Italiano di Telemedicina, Italy
Simon Grima,
University of Malta, Malta
Svetlana Radevic,
University of Kragujevac, Serbia

***Correspondence:**
Zornitsa Mitkova
sppmitkova@mail.bg

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INTRODUCTION

Reference pricing is used as a method for price regulation in many European countries. Pharmaceuticals prices can be regulated, or can be a result of the market environment (1). The application of external reference pricing (ERP) started in the early the 90's (2), and is now the most commonly used price control measure in Europe (3).

In each country, it is applied differently, usually in combination with other pharmaceutical policy measures. The size of the reference basket and the applied rules for a price calculation influence the price level and supply of medicines (4). Pricing criteria implemented in the CEE countries are similar and external reference pricing methodology is common in this region (5).

ERP is applied mainly to reimbursable medicines. The number of countries used as references ranges from three in Portugal to 30 in Poland. The pricing criteria used for medicinal products in the central and eastern European (CEE) countries are quite similar. Slovakia is the most frequently referenced country, whereas Cyprus, Iceland, Malta, Luxembourg, and Norway are not as frequently used as reference countries (6).

The methods for defining reference countries vary. Sometimes, the countries should be similar in terms of some characteristics, such as economic or geographical similarity and health system funding. Studies showed that at the national level, after ERP implementation, health expenditures decreased in the short term, as the prices are more likely to decline (7, 8). At the international level, ERP methodology can affect prices in other European countries, resulting in price fluctuations, delay launches, and manufacturers' withdrawal from markets where the price is low (9). Large launch delay to 3 years on average in Eastern Europe is found (10). Pharmaceutical pricing experts from Russia, Asia, Middle East, and South Africa confirm that ERP could be used for pricing decisions, but not as the only mechanism for price regulation (11).

Recent studies have shown that price differences exist across countries (12, 13). In countries with lower gross domestic product (GDP), where the resources are limited, the payers cannot effectively control the prices if ERP is used only as a cost containment measure (14). Studies show that the introduction of generic products with focus only on prices is not as effective as implementing other policies (15). The medicines are unaffordable for many European Union (EU) citizens. This may contribute to non-compliance, adherence, and rising direct and indirect costs (16–18).

In CEE countries, cardiovascular diseases (CVDs) prevalence is higher than in Western, Northern, and Southern European countries. The data showed that in the EU healthcare for CVDs is 53% (€111 billion), productivity loss is 26% (€54 billion), and informal care of people with CVDs is ∼21% (€45 billion) of the total costs (19). Adequate access to cardiovascular (CV) medicines benefits the treatment of CVDs and could lead to decreased morbidity and mortality.

The main objectives of the study were as follows: [1] to explore the methodology of price calculation in four East European countries—Slovakia, Greece, Bulgaria, and Romania (SK, GR,BG, and RO, respectively) at the manufacturer, wholesale, and retail levels. [2] To compare prices between overlapping medicinal products from the therapeutic groups of AT1-receptor blockers (sartans), ACE inhibitor groups, and their fixed-dose combinations (FDCs) at the manufacturer and retail levels. [3] To calculate the price deviations from the lowest priced medicinal products to evaluate the overall effect of a market environment and country policy on medicine prices.

MATERIALS AND METHODS

Within the international cooperation for prices comparison EURIPID the RO, BG, GR, and SK are considered as countries that manage to maintain the lowest possible prices (https://www.euripid.eu/aboutus). This is one of the reasons for their selection (12, 20, 21). The second reason is that they all apply ERP for the regulation of medicine prices. The third reason is that they refer one to another and always are included in their national baskets despite the regulatory changes. The similar methodology for manufacturer price setting and variation in pricing methodology makes them an attractive for comparison.

The choice of therapeutic groups was determined by their importance in CVD therapy as a first-line recommended therapy in many guidelines (22, 23).

Comparative analysis between the methodologies for manufacturer and retail price establishment was performed among countries under consideration. Regulatory acts were used as a source of information and published scientific papers (24–27).

The manufacturer and retail prices of overlapping trademarks (produced by the same marketing authorization holder) of AT1-receptor blockers, ACE inhibitors, and their FDCs were collected from the official registers of the observed countries in November 2017 (28–31). Thirty-four overlapping trade names belonging to seven international non-proprietary names (INNs) and 9FDCsare considered for the price comparison analysis.

Price per tablet was calculated for each trademark. All prices were converted in Euro at the exchange rate of 1 euro = 1.956 BGN (Bulgarian Leva) and 1 euro =4.42 RON (Romanian Lei).

The average price per tablet was calculated at the manufacturer and retail levels between the four countries. The difference in the average and lowest prices was determined by deducting the lowest price from the average.

The statistical significance of price differences on the manufacturer and retail levels was examined using the Kruskal–Wallis test.

The percentage of deviation of medicines prices compared with the lowest one was calculated using the formula:

$$Ip_{ij} = \frac{p_{ij}}{p_{imin}} \times 100$$

$$Ip_{ij} - price\ index\ of\ product\ i\ in\ a\ country\ j$$

Abbreviations: ACE, inhibitors: Angiotensin-converting enzyme inhibitors; AT1, receptor blockers, sartans: Angiotensin II type 1 receptor blockers; CEE, countries: Central and Eastern European countries; CVD, cardiovascular diseases; ERP, external reference pricing; EU, European Union; FDCs, fixed-dose combinations; INN, International non-proprietary name; PDL, Positive Drug List; VAT, value-added tax.

TABLE 1 | Comparison of price establishment methodologies.

	Slovakia		**Greece**		**Romania**		**Bulgaria**	
Reference countries for calculation of manufacturer price	All EU countries (27)		All EU countries (27)		AT, BE, BG, CZ, DE, EL, ES, HU, IT, LT, PL, SK		Main countries: RO,FR, LT, LV, GR, SK,PT, IT, SI, ES *Additional countries: BE, CZ, PL, HU, DK, FI, EE	
Pricing methodologies, applied for calculation of manufacturer price	The average of the three lowest prices of EU member states		The average of the three lowest prices of EU member states		The lowest ex-factory price for the same product out of 12 reference countries		The lowest ex-factory price for the same product out of 10 +7 reference countries	
Wholesale mark up *Wholesale margin (%) over manufacturer price, EUR*	Manufacturer price	Margin	Manufacturer price	Margin	Manufacturer price	Margin	Manufacturer price	Margin
	0.00–2.66	14.10%	Ex-factory price < 200 euro	4.9%	0–11.31	14%	0–5 euro	7%
	2.67–5.31	11.10%	Ex-factory price >200 euro	1.5%	11.31–22.62	12%	5–15 euro	6%
	5.32–7.97	8.10%			22.62–67.87	10%	Over 15 euro	4% (but no more than 5 euro)
	7.98–13.28	5.10%			Over 67.87	6.78 euro		
	13.29–23.24	3.30%						
	23.25–39.83	2.70%						
	39.84–73.03	2.40%						
	73.04–165.97	2.25%						
	165.98–331.94	2.10%						
	331.95–663.88	1.95%						
	Over 663.88	1.80%						
Margins established for calculation of retail price	Wholesale price	Margin	Wholesale price	Margin	Wholesale price	Margin	Wholesale price	Margin
	0.00–2.66	32.90%	0–50	30.00%	0–5.66	24%	0–5 euro	20%
	2.67–5.31	25.90%	50.01–100	20.00%	5.66–11.31	20%	5–15 euro	18%
	5.32–7.97	18.90%	100.01–150	16.00%	11.31–22.62	16%	Over 15 euro	16% (but no more than 12.5euro)
	7.98–13.28	11.90%	150.01–200	14.00%	22.62 –67.87	12%		
	13.29–23.24	7.70%	200.01–300	12.00%	67.87	7.91 euro		
	23.25–39.83	6.30%	300.01–400	10.00%				
	39.84–73.03	5.60%	400.01–500	9.00%				
	73.04–165.97	5.25%	500.01–600	8.00%				
	165.98–331.94	4.90%	600.01–700	7.00%				
	331.95–663.88	4.55%	700.01–800	6.50%				
	Over 663.88	4.20%	800.01–900	6.00%				
			900.01–1,000	5.50%				
			1000.01–1,250	5.00%				
			1250.01–1,500	4.25%				
			1500.01–1,750	3.75%				
			1750.01–2,000	3.25%				
			2000.01–2,250	3.00%				
			2250.01–2,500	2.75%				
			2500.01–2,750	2.50%				
			2750.01–3,000	2.25%				
The mark ups are applied on the manufacturer price	Yes		No		No		Yes	
VAT,%	10		6		9		20	

p_{ij} -manufacturer/retail price per tablet of the product i in a country j:

$$p_{imin} - minimum\ price\ per\ tablet\ of\ the\ product\ i$$

$$PD_{ij} = Ip_{ij} - 100$$

$$PD_{ij} - percentage\ price\ deviation\ of\ the\ product\ i\ in\ a\ country\ j$$

Where,
Product i—compared INNs
Country j—selected countries.

RESULTS

Comparison of Methods for Price Establishment

The selected countries applied ERP at the manufacturer level, and they refer their prices one to another. At the national level, there were differences and similarities in methodologies, thus leading to differences in the final prices of products (**Table 1**).

In GR, the manufacturer prices are calculated as the average of the three lowest prices out of the other 27 EU countries in Europe. Since 2016, price revisions have been applied twice per year—May and November. Decisions for the inclusion of new products are made four times annually. The price of generic products was 65% of the price of the reference product (32) (**Table 1**).

SK applied reference pricing using prices from 27 European countries. The manufacturer price was calculated as the average of the lowest prices in three countries. In SK, the monthly ex-factory price of medicines was officially published, whereas reference price revisions were conducted every 6 months. The maximum price of the first generic product should not exceed 65% of the reference product price (5). Reimbursements list was revised four times annually (33) (**Table 1**).

In RO, a new pricing methodology has been applied since 2015. The ex-factory price should be the lowest from the 12 reference countries (where BG, SK, and GR are also included). The reference price of generics was 65% of the producer price for innovative drugs. The reference prices were updated once a year (in October) using the latest average exchange rate from RON to EUR (**Table 1**).

In BG, the ex-factory price may not be higher than the BGN equivalent of the lowest ex-factory price for the same medicinal product in the reference countries (the total number was 17: 10 main and 7 additional reference countries, **Table 1**). The Positive Drug List (PDL) was revised each month in terms of inclusion, changes, and/or exclusion of medicines. The manufacturer price of the generic products must not exceed 70% of the manufacturer price of the reference product included in the PDL (**Table 1**) (34).

Comparison of CV Medicine Prices

The number of overlapping trade names and dosage forms of AT1-receptor blockers, ACE- inhibitors, and FDCs with the lowest prices at the manufacturer and retail levels are presented in **Table 2**. It is evident that the prices of medicines were lower in RO because 15 products had the lowest manufacturer price and 14 products have the lowest retail price in RO, followed by GR.

TABLE 2 | Number of medicinal products with the lowest manufacturer and retail prices per tablet.

Number of medicinal products with the lowest:	Country			
	SK	GR	RO	BG
Manufacturer price per tablet, euro	4	9	15	6
Retail price per tablet. euro	7	12	14	1

The lowest and average price per tablet for each overlapping trademark was calculated as follows (**Table 3**):

Four INNs of ACE inhibitors and 11 FDCs could be compared in all countries, and those are not the first in the class, such as enalapril. By comparing the manufacturer and retail prices of monoproducts in the group of ACE inhibitors, we confirmed that the unit prices were the lowest in RO, followed by GR and BG. The differences between the average and the lowest prices were not significant in terms of monetary cost. Regarding the FDCs, 1 product in RO (hydrochlorothiazide/ramipril 5/25 mg), 1 in SK (quinapril/ hydrochlorothiazide 20 mg/12.5 mg), and 2 in GR possessed the lowest manufacturer and retail prices (indapamide/perindopril 2.5/0.625 mg and indapamide/ perindopril 5/1.25 mg). In the group of AT-receptor blockers, comparison between 4 INNs and 10 FDCs was possible. At the manufacturer and retail levels, the lowest price was found in one product in RO (irbesartan 150 mg). The FDC GR had the lowest manufacturer price for telmisartan/hydrochlorothiazide 80 mg/12.5 mg, and the lowest retail price for irbesartan/hydrochlorothiazide 300/12.5 mg.

Results of Kruskal–Wallis test showed that there were no significant differences between the lowest and average price per tablet on the manufacturer and retail levels ($p > 0.05$).

Table 4 presents the rate of deviation in percentage from the lowest manufacturer and retail prices in each country (**Table 4**). Where there was only one product, the rate of deviation was not calculated, which happened often in RO ($n = 14$). This could mean that in RO, fewer products per INN were reimbursed. Higher rate of deviation in GR showed a wide competition per observed INN, which was most evident for ACE inhibitors.

Within the group of monoproducts, the ACE inhibitor ramipril was the INN with a high price deviation of 241–458%, whereas in the group of AT-receptor antagonists, irbesartan had a deviation of 219–240%.

Between FDCs, prices of combinations of ramipril/hydrochlorothiazide in the group of ACE inhibitors and irbesartan/hydrochlorothiazide in the group of AT-receptor antagonists deviated by more than 100%.

DISCUSSION

The observed countries applied ERP as a methodology for the control of expenditures, but different calculation methods to compute the prices on a national level. The number of reference countries included in the basket varied from 12 to 27, but the lowest prices did not differ significantly, probably owing to simultaneous referencing at

TABLE 3 | The lowest and average price per tablet on the manufacturer and retail levels.

INN. dosage form	Manufacturer price (euro)			Difference between the average and the lowest price	Retail price (euro)			Difference between the average and the lowest price
	Country where the lowest price is found	The lowest manufacturer price per tablet, euro	Average manufacturer price per tablet, euro		Country where the lowest price is found	The lowest retail price per tablet, euro	Average retail price per tablet, euro	
ACE inhibitors and their FDCs								
Perindopril 10 mg	GR	0.1497	0.1838	0.0341	GR	0.2163	0.2769	0.0606
Perindopril 5 mg	GR	0.1313	0.1456	0.0143	GR	0.1897	0.2216	0.0319
Ramipril 2.5 mg	RO	0.0243	0.0563	0.0320	RO	0.0374	0.0839	0.0465
Ramipril 5 mg	RO	0.0350	0.0812	0.0462	RO	0.0539	0.1218	0.0679
Ramipril 5 mg	RO	0.0538	0.1021	0.0483	RO	0.0829	0.1538	0.0709
Quinapril 20 mg	RO	0.0813	0.0998	0.0185	RO	0.1253	0.1519	0.0266
Zofenopril 30 mg	BG	0.2135	0.2223	0.0088	GR	0.3086	0.3310	0.0224
Perindopril/indapamide 2.5/0.625 mg	GR	0.1497	0.1705	0.0208	GR	0.2163	0.2570	0.0407
Perindopril/indapamide 5/1.25	GR	0.1510	0.1739	0.0229	GR	0.2183	0.2604	0.0421
Perindopril/indapamide 10/2.5 mg	RO	0.2587	0.2750	0.0163	RO	0.3857	0.4062	0.0205
Hydrochlorothiazide/ ramipril 5/25 mg	RO	0.0742	0.1263	0.0521	RO	0.1143	0.1901	0.0758
Quinapril/hydrochlorothiazide 20 mg/ 12.5 mg	SK	0.1296	0.1471	0.0175	SK	0.1842	0.2178	0.0336
Amlodipine/perindopril 10/10 mg	RO	0.2587	0.2685	0.0098	RO	0.3857	0.3975	0.0118
Amlodipine/perindopril 10/5 mg	BG	0.1773	0.2423	0.0650	GR	0.3830	0.3954	0.0124
Amlodipine/perindopril 5/10 mg	RO	0.1703	0.1832	0.0129	RO	0.2539	0.2740	0.0201
Amlodipine/indapamide/perindopril 10/2.5/10 mg	RO	0.3124	0.3300	0.0176	RO	0.4658	0.4849	0.0191
Amlodipine/indapamide/perindopril 10/2.5/5 mg	RO	0.2970	0.3114	0.0144	RO	0.4428	0.4586	0.0158
Amlodipine/indapamide/perindopril 5/1.25/10 mg	RO	0.2083	0.2264	0.0181	RO	0.3105	0.3363	0.0258
Amlodipine/indapamide/perindopril 5/1.25/5 mg	RO	0.1913	0.1990	0.0077	RO	0.2853	0.2968	0.0115
AT1–receptor blockers (sartans) and their FDCs								
Valsaratan 160 mg	SK	0.105	0.135	0.03	RO	0.173	0.212	0.039
Irbesartan 150 mg	RO	0.044	0.089	0.045	RO	0.067	0.133	0.066
Candesartan 16 mg	BG	0.109	0.134	0.025	BG	0.166	0.2	0.034
Telmisartan 80 mg	SK	0.111	0.136	0.025	SK	0.177	0.206	0.029

(Continued)

TABLE 3 | Continued

INN. dosage form	Manufacturer price (euro)			Difference between the average and the lowest price	Retail price (euro)			Difference between the average and the lowest price
	Country where the lowest price is found	The lowest manufacturer price per tablet, euro	Average manufacturer price per tablet, euro		Country where the lowest price is found	The lowest retail price per tablet, euro	Average retail price per tablet, euro	
Telmisartan 80 mg	GR	0.216	0.233	0.017	GR	0.312	0.349	0.037
Irbesartan. HCTZ 300 mg/12.5 mg	GR	0.127	0.198	0.071	GR	0.184	0.301	0.117
Telmisartan/HCTZ 80 mg/12.5 mg	GR	0.158	0.159	0.001	GR	0.228	0.242	0.014
Telmisartan/HCTZ 80 mg/ 25 mg	RO	0.160	0.168	0.008	GR	0.232	0.256	0.024
Telmisartan/HCTZ 80 mg/12.5 mg	GR	0.243	0.269	0.026	GR	0.351	0.403	0.052
Telmisartan/ HCTZ 80 mg/ 25 mg	GR	0.247	0.249	0.002	GR	0.357	0.37	0.013
Amlodipín/ telmisartan 80 mg/10 mg	BG	0.514	0.539	0.025	BG	0.765	0.774	0.009
Amlodipín/ telmisartan 80 mg/5 mg	SK	0.52	0.539	0.019	SK	0.730	0.775	0.045
Valsartan/sakubitril 24 mg/26 mg	BG	2.09	2.256	0.166	SK	2.646	2.996	0.35
Valsartan/sakubitril 49 mg/51 mg	GR	2.092	2.296	0.204	SK	2.640	2.957	0.317
Valsartan/sakubitril 97 mg/103 mg	BG	2.09	2.256	0.166	SK	2.578	2.853	0.275

the manufacturing level. GR and SK used an average of three of the lowest prices, whereas BG and RO used the lowest prices from the countries in the basket. These differences in the number of referent countries, as well as the period of price revision, probably determined the differences between pharmaceuticals prices.

There are international collaborations for price comparison for the regulatory purposes as EURIPID for example but studying why some countries manage to maintain the lowest prices if beneficial for the international audience, especially for the medicines with high utilization (35). If the experience of those countries is analyzed and popularized, it will make important medicines affordable to many more citizens in Europe. This online database of EURIPID is currently exclusively available for national competent authorities for pricing and reimbursement of medicinal products that makes the scientific comparison of the methodologies and prices impossible via it.

The effectiveness of ERP measures is now widely discussed. The price revision in one country may contribute to changes in the others. A literature review showed that ERP application as a policy measure depends mainly on implementation and rules within the countries (36, 37). ERP is a well-known and widely used tool to control expenditures, but price control should be used together with other policies, especially those supporting the rational use of medicines and improving prescribing behavior (38).

A systematic review proved that reference pricing reduces pharmaceutical prices and, hence, expenditures and leads to substitution toward lower-priced drugs. This study also confirmed the need for new effective pricing policies, including value-based pricing, managed entry agreements, and health technology assessment (HTA) (39). At the analysis, BG and RO use managed entry agreements (40), whereas HTA is performed in BG, RO, and SK.

Over 2,000 drugs have disappeared from the market in the last 5 years, thus affecting patients' access to therapy and enhancing parallel exports (41, 42). Such a negative tendency can ruin the concept of ERP, which is why such studies are necessary.

A simulation of pharmaceutical prices showed a 15% reduction over 10 years. More detailed country baskets and frequent price revisions lead to higher price reductions. Revision frequencies also varied and contribute to price divergence and international price decrease (43).

The frequent price revision in BG probably led to a high rate of prices decreasing between 4 and 75.4% (44, 45). In GR, an average price decrease of 9.5% was achieved after the changes in the reference price system in 2010. Prices of ∼12,000 medicinal products were recalculated because of the new system introduced in 2010 (46). Nevertheless, the study found the most significant deviation (more than 100%) for the six products in GR, thus confirming that other factors, such as the company's policy, taxes, and country environment, also affected the final medicine prices.

The SK new reference pricing system, which was introduced in 2012, was expected to create savings estimated at € 75 million.

TABLE 4 | Percentage of deviation from the lowest manufacturer and retail price (%).

INN. dosage (mg)	Percentage price deviation of the lowest manufacturer price per tablet in selected countries (%)				Percentage price deviation of the lowest retail price per tablet in selected countries (%)			
	SK	**GR**	**RO**	**BG**	**SK**	**GR**	**RO**	**BG**
Perindopril 10 mg	13.1	–	64.9	13.1	22.4	–	70.2	19.4
Perindopril 5 mg	16.5	–	6.2	20.8	26.5	–	13.3	27.3
Ramipril 2.5 mg	32.9	458.4	–	34.6	39.8	424.1	–	32.9
Ramipril 5 mg	59.1	388.6	–	80	67	358.3	–	78.3
Ramipril 5 mg	47.4	264.3	–	47.2	54.8	241.4	–	45.7
Ramipril 20 mg	28.3	58.5	–	4.2	33	49.1	–	2.9
Zofenopril 30 mg	10.7	0.04	5.7	–	17.1	–	9	2.9
Perindopril/indapamide 2/0.625 mg**	13.1	–	29.3	13.1	22.4	–	33.5	19.4
Perindopril/indapamide 5/1.25 mg**	12.4	–	12.7	35.5	21.4	–	16.2	39.4
Indapamide/perindopril 10/2.5 mg**	14.9	6.2	–	4	14.3	3.1	–	3.8
Ramipril/hydrochlorothiazide 5/25 mg *	18.9	226.1	–	35.7	24.7	206.2	–	34.3
Quinapril/ HCTZ 20 mg/ 12.5 mg*	–	35.6	6.9	11.3	–	37.8	15.9	67.5
Amlodipín/perindopril 10/10 mg	7.3	3.7	–	4	7.7	0.7	–	3.8
Amlodipín/perindopril 10/5 mg	51.2	49.5	45.9	–	5.2	–	0.7	7
Amlodipín/perindopril 5/10 mg	8	6.1	–	16.2	12.8	2.9	–	16
Amlodipín/ind/perindopril 10/2.5/10 mg**	10.3	8.1	–	4.1	7.7	4.8	–	3.9
Amlodipín/ind/perindopril 10/2.5/5 mg**	8.5	6.7	–	4.1	6.8	3.5	–	3.9
Amlodipín/ind/perindopril 5/1.25/10 mg**	17.3	13.3	–	4.1	19.4	9.9	–	3.9
Amlodipín/ind/perindopril 5/1.25/5 mg**	6.6	5.2	–	4.2	10.2	2	–	4
Valsaratan 160 mg	–	68.8	7.3	38.3	15.6	47.6	–	27.4
Irbesartan 150 mg	68.1	240.4	–	111.3	64	218.9	–	109
Candesartan 16 mg	18.9	39.1	32.9	–	14.2	31.8	34.5	–
Telmisartan 80 mg	–	33.9	20.1	35.5	–	21.2	15.9	29.3
Telmisartan 80 mg	8.9	–	1.3	20.9	15.3	–	4.5	27.4
Irbesartan/HCTZ 300/12.5 mg*	41.1	–	11.2	169.3	52.6	–	18.6	184.1
Telmisartan/HCTZ 80/12.5 mg*	1.6	–	1.1	1.6	10.2	–	7.6	6.8
Telmisartan/HCTZ 80/ 25 mg*	17.9	0.4	–	3.6	26.7	–	6.1	8.6
Telmisartan/HCTZ 80/12.5 mg*	4.6	–	1.2	37.1	10	–	4.3	44.3
Telmisartan/HCTZ 80/25 mg*	3.4	0.5	–	0.9	8.1	–	2.6	3.4
Amlodipín/telmisartan 80/10mg	3.8	3.8	12.1	–	–	3.4	9.4	2.5
Amlodipín/telmisartan 80/5mg	–	0.1	9.9	4.5	–	3.1	11	11
Valsartan/sakubitril 24/26 mg	1.4	0.1	30.3	–	–	5.5	33.6	13.7
Valsartan/sakubitril 49/51 mg	1.4	–	30.2	7.5	–	2.2	23.2	22.7
Valsartan/sakubitril 97/103 mg	1.4	0.1	30.3	–	–	4.7	26.1	11.8

**HCTZ –hydrochlorothiazide; **indapamide; – indicated country with the lowest price.*

However, in SK, ERP resulted in higher prices compared with countries with similar income levels owing to the selection of reference countries (8).

A previous study confirmed that there is no substantial reduction in international price differences within EU countries applying EPR (47). We found that a small difference existed between the average and lowest prices, and there was a lack of significant difference in the same trademarks. However, after applying the price deviation approach, we observed large variations in prices between some of the countries. Therefore, the use of different approaches and points of view could provide more comprehensive and objective data of the existing price differences. It could be used by manufacturers and regulatory bodies when determining a price variation between countries. It is also important for receiving information on CV medicine utilization and how it is affected by price variation, a problem for which there is relatively limited information in the country (48).

The observed price deviation varied from 0.1 to 458%, thus confirming that the existing magnitude of the price difference was significant as a value. However, only six medicinal products showed more than 100% deviation from the lowest price. ACE inhibitor prices revealed the highest hesitations, whereas FDCs prices did not differ at such high degrees. Likewise, there were no products found at the same price in two or more countries. The reasons for such variance were probably more related to the health insurance environments and the country policy (49).

A price comparison of high-cost originator medicines in some European countries found lower prices in GR, Hungary, SK, and the UK. German and Swedish, Danish, and Irish prices were found at the upper end (7). Another study showed the highest prices in Germany (9), whereas one of the lowest prices is found in RO. Our study also found the lowest prices of CV medicines in RO (at the manufacturer and retail levels), despite the fact that the list of reimbursed medicines in RO was not updated between 2008 and 2015. Other factors, such as margins, VAT, or exchange rate, lead to low medicine prices.

A previous study on CV medicine prices showed that BG and RO follow the same methodology, but the differences in VAT and margins set different retail prices. The lower wholesale and retail margins in BG lead to a lower retail price, regardless of the higher VAT (20% in BG and 9% in RO). Therefore, the VAT influence is not the one factor for final retail price formation (50). The lower VAT rate has been balanced with higher margins in some countries.

The study found that differences between the prices of CV medicines existed, despite the expectation that ERP would equalize and reduce them. The differences between retail prices in the four countries under consideration were higher than those found at the manufacturer level. This was due to the established mechanisms for calculation of final medicine prices and ERP applications.

Our study confirms ERP methodology limitations and establishes price difference in reference countries, if they are compared simultaneously. This is the first study comparing prices of CV -medicines on manufacturer and retail level and provides direct data for ERP and implemented methodologies influence on final prices. The price comparison is widely discussed issue and often used from pharmaceutical companies for decision of product launches, from regulatory bodies for amendment of legislation or from other researchers reporting implemented regulatory measures for price control. The limitation of the study is a small number of overlapping trade names found (on total 34 in four countries) from overall variety of medicinal products approved in EU. This prompts the necessity for further studies exploring price differences and ERP influence on total medicines market.

Overall, the study found that lower manufacturer prices led to lower retail prices. The deviation in prices revealed their sensitivity to health policies and the market environment. It also contributed to manufacturers' decisions and therapeutic competition within a country.

In summary, the prices of CV medicines differed within the observed countries. The differences in pricing methodologies (e.g., margins, VAT) at the national level could not influence retail prices significantly, as a low manufacturer price usually led to a low retail price. From our results, we can conclude that RO was the country with the lowest prices of CV medicines (AT-receptor blockers and ACE inhibitors), followed by GR owing to financial crisis and low incomes. It could favor patients' affordability and cardiovascular therapy in those countries. Although BG had very frequent price revision as well as the lowest GDP per capita in the EU, this was not the key driver for lower prices, especially at the retail level.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: National Council on prices and reimbursement of medicinal products. Registers PDL. Annex 1 https://portal.ncpr.bg/registers/pages/register/archive.xhtml Ministerstvo zdravotníctva; Available at: http://www.health.gov.sk/?kategorizacia-a-ceny Υποϵργεί Υγείας/Ministry of health; Available at: http://www.moh.gov.gr/articles/times-farmakwn/deltia-timwn Casa Nationalâ de Asigurâri de Sânâtata/National Health Insurance Fund Available at: http://www.cnas.ro/category/lista-medicamentelor.html.

AUTHOR CONTRIBUTIONS

GP conceived and designed the investigation and collected the data. ZM, AS, and MM prepared medicine selection and price calculations. MV performed a methodology comparison. ST and MM analyzed the data and performed the deviation percentage analysis. ZM performed the statistical analysis. GP designs the result interpretation and discussion. All authors wrote and revised the manuscript, and approved its submission for publication, confirming that that the work is original.

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Cardiovascular Disease and Mental Distress Among Ethnic Groups in Kyrgyzstan

Hossain Syed Azfar[1], *Kenesh O. Dzhusupov*[2], *Hans Orru*[3,4]*, *Steven Nordin*[5], *Maria Nordin*[5] *and Kati Orru*[6]

[1] Department of Family Medicine, International School of Medicine, Bishkek, Kyrgyzstan, [2] Department of Public Health, International School of Medicine, Bishkek, Kyrgyzstan, [3] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, [4] Institute of Family Medicine and Public Health, University of Tartu, Tartu, Estonia, [5] Department of Psychology, Umeå University, Umeå, Sweden, [6] Institute of Social Studies, University of Tartu, Tartu, Estonia

The purpose of this study was to characterize different ethnic groups in Kyrgyzstan regarding cardiovascular disease (CVD) and mental distress, and to investigate the association between CVD and mental distress. The mental distress was measured in terms of sleep disturbance, burnout, and stress.

Materials and Methods: A cross-sectional study was carried out among six ethnic groups in Kyrgyzstan, aged 18 years and above. The sample was stratified for age, education, family status, and income. We used the Karolinska Sleep Questionnaire to assess sleep disturbance, the physical and emotional subscale of the Shirom Melamed Burnout Questionnaire to assess burnout, and the 10-item Perceived Stress Scale to assess perceived stress.

Results: The distribution of CVD differed significantly between the six ethnic groups, with higher prevalence among East Europeans, and Western Asians and lower among Other minorities and Central Asians. In all ethnic groups in Kyrgyzstan, individuals with CVD had increased odds of sleep disturbance and burnout. There was a significant difference in burnout and stress between persons with and without CVD in Kyrgyz and East European ethnic groups.

Conclusion: There was a significant difference in burnout and stress between persons with and without CVD in Kyrgyz and East European ethnic groups. In addition to CVD prevention, mitigating sleep disturbance and preventing burnout in the general population should be aimed at in public health measures.

Keywords: mental distress, cardiovascular disease, ethnicity, Central Asia, minority

Edited by:
Wulf Rössler,
Charité – Universitätsmedizin Berlin, Germany

Reviewed by:
Serge Brand,
University Psychiatric Clinic Basel, Switzerland
Souheil Hallit,
Holy Spirit University of Kaslik, Lebanon
Rene Schilling,
University of Basel, Switzerland

Correspondence:
Hans Orru
hans.orru@umu.se

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INTRODUCTION

Cardiovascular diseases (CVDs) are the worldwide leading cause of mortality (1, 2). Globally, the highest CVD mortality rates are found in Ukraine, Russia, and Central-Asia (63, 55, 63–42% in 2016, respectively) (3). Those post-Soviet countries like Kyrgyzstan [with a population of 6.3 million in 2018 (4)] have experienced volatile economic and political transitions that make up challenging socioeconomic conditions for health and well-being in the multi-ethnic population.

The main risk factors for CVD include physical inactivity, obesity, unhealthy diet, smoking, drug abuse, hypertension, and lipid abnormalities (5–11). Prior studies have shown lower CVD mortality attributable to dietary risk in Kyrgyzstan and among Central Asians (Kazakhs, Tajiks, and Kyrgyzs) compared to East Europeans (Russians, Ukranians, and Belorussians) and Western Asians (Georgians, Azerbaijani) (12). There are also gender differences as women have lower incidence levels and develop the disease later than men (13, 14). Their protective mechanisms against CVD are mainly associated with sex hormone (e.g., estrogen) levels as the incidence and severity of CVD increase in women during post-menopause period (15). At the same time, gender behavioral differences may play an important role. As women visit physicians more often, their diseases are registered more frequently, whereas men may not visit a physician until it may be too late (16).

Apart from those, various social factors may contribute to differences in CVD incidence. Individuals with low socioeconomic status experience higher rates of CVD burden and mortality (17–21). Low level of educational attainment is associated with high prevalence of cardiovascular risk factors, high CVD incidence, and CVD mortality (19, 22). In Kyrgyzstan, in 2017, the Gini coefficient, that is a measure of inequality among levels of income, was 26.8 (23). This reflects relatively good equality in income distribution since the country residents have a similar relatively low standard of living.

It has been indicated that socioeconomic inequalities are more prevalent among minority ethnic populations who have high prevalence of CVD and related risk factors (24), and this inequality is growing globally (25–28). Ethnic minorities also experience more barriers to access a CVD diagnosis (29), poorer recording of clinical data (30), receive lower quality of health care, and have poorer health outcomes (31). Carson and colleagues showed that ethnicity is an important predictor of hypertension (32). Kontsevaya et al. found that among Kyrgyz women, arterial hypertension prevalence was significantly lower than in their Russian peers (36.8 vs. 46.2%, respectively) (33). At the same time, among Kazakh and Kyrgyz men, systolic blood pressure was significantly higher than in Russians (33).

It is well-documented that social factors may moderate stress level (34). Chronic psychological stress is associated with a greater risk of depression, autoimmune diseases, respiratory infections as well as coronary heart disease (35, 36). Stress as a complaint is related to anxiety (37) and depression (38). Psychosocial factors such as depression and low social support are in turn established risk factors for heart disease (36, 39) and have been associated with high risk of adverse cardiovascular outcomes (35, 40–44), and mortality among patients with CVD (45, 46). Mental distress is associated to social factors (poverty and unemployment), ethnicity, gender, age, and disability (47, 48).

Stress may perpetuate sleep disturbance, as complaints in burnout (49) and symptoms of insomnia (50), may lead to poor sleep, worry, and increase of blood pressure (51, 52). Whereas, stress fluctuates strongly since it is a necessity in daily life in coping with everyday hassles, chronic stress that results in burnout may be a particular risk factor for chronic diseases (53, 54). Sleep disturbance is both an initiator and a consequence of burnout and depression (51, 55–57). As the result of long-term inflammatory processes due to mental distress, plaque formation on the vascular walls in atherosclerosis may eventually lead to a CVD event (58–60). The fact that stress also underlies burnout and sleep disturbance, highlights the importance of these conditions on persons with CVD.

The current study aimed at characterizing different ethnic groups in Kyrgyzstan with respect to CVD and the mental distress conditions including sleep disturbance, burnout, and stress, and to investigate the association between CVD and mental distress. Based on earlier evidence, we infer that some ethnic groups are more likely than other to contract CVD. The present study tested the hypotheses of the minorities, compared to dominant Kyrgyz ethnic group, being more likely to suffer from CVD and/or having higher levels of mental distress. Following Mezick et al. (61), Grandner et al. (62), Slopen et al. (63), and Johnson et al. (64), we expected ethnic-group differences also in sleep disturbance.

MATERIALS AND METHODS

Data Collection

A sample of 694 individuals aged 18 years and older visiting polyclinics (Centers of Family Medicine) and health care centers were invited to participate in a study entitled "Health status of ethnic minorities in Kyrgyzstan." We chose five polyclinics in the suburban areas, where representatives of minorities mainly reside in Bishkek. Kyrgyzs as a control group were recruited from the same facilities. We used a questionnaire with 47 questions to explore the health status, behavioral and psychological determinants and prevalence of CVD, body mass index (BMI), age, gender, education level, ethnicity, and income. Informed consent was obtained from participants after explaining the study aims, voluntariness of participation, and anonymised data processing. The respondents answered the questionnaire and could ask for assistance or explanations from the study leader.

The initial sample included 1,200 participants. With a response rate of 57.8%, this resulted in 694 respondents. We used random sampling stratified for ethnicity, age, education, and gender. Ethnicity was asked as open question: "Please, indicate your ethnicity:…" [see also Phinney and Ong (65)]. In Kyrgyzstan, the Kyrgyz comprise 73.3% of the population. Other major ethnic groups include Russians (5.6%) concentrated in the north, and Uzbeks (14.7%) living in the south. Small, but noticeable minorities include Dungans (1.1%), Uyghurs (0.9%), Tajiks (0.9%), Kazakhs (0.6%), and Koreans (0.3%). Other small ethnic minorities make up 2.6% of the population (4). Following this, the participants were divided into six groups based on their ethnicity. Kyrgyz people, (1) "Kyrgyz," functioned as a control group for comparison with the other ethnic groups. Due to their similarity in religious background and geographical origins we grouped five additional ethnic groups as follows: (2) "East Europeans": Russian, Byelorussian, and Ukrainian; (3) "Central Asians": Uzbek, Kazakh, Tatar; (4) "East Asians":

Korean; (5) "Western Asians": Georgian, Armenian, Turk, and Azerbaijan; and (6) "Other minorities": Dungan and Uyghur. In the initial sample of 1,200 participants, we aimed at ethnic group proportions of 40% Kyrgyz, 20% East Europeans, 20% Central Asians, 5% East Asians, 5% Western Asians, and 10% Other minorities. The final sample of respondents consisted of 31.3% Kyrgyz, 34.4% East Europeans, 16.4% Central Asians, 5.5% East Asians, 3.3% Western Asians, and 9.1% Other minorities. Regarding age groups, we aimed at equal proportions of age groups, resulting in 24.9% aged 18-29, 24.4% aged 30-39, 17.3% aged 40-49, 17.3% aged 50-59, and 16.1% aged $\geq$ 60 years. Regarding education, we aimed at the proportions 26% with higher education, 68% with high school education, and 5% with elementary or secondary school. In the final sample, higher education was overrepresented, 41%, and the proportions were 57.2% with high school education, and 1.6% with elementary education. In the final sample male sex are slightly under-represented (43.5%).

The 694 respondents were distributed across the ethnic groups: Kyrgyzs (control, 217 individuals, mean age = 39.2 ± 14.8), East Europeans (239 individuals, mean age = 48.5 ± 15.7), East Asians (38 individuals, mean age = 43.4 ± 20.6), Central Asians (114 individuals, mean age = 38.1 ± 14.7), Western Asians (23 individuals, mean age = 43.2 ± 13.3), and Other Minorities (63 individuals, mean age = 34.3 ± 14.3).

Questionnaire Instruments

The questionnaire used was in the Russian language. Socio-demographic variables were assessed following the Guidelines for Handling the Harmonized Questionnaire (66), and anthropometric data (e.g., height and weight) were assessed according to the WHO recommendations (67). We used the question "Do you have any CVD diagnosed by a doctor" to determine any diagnosed CVD, coded as "Any CVD." We grouped individuals according to their educational background (1 = Primary; 2 = Secondary High school, incomplete higher education, or vocational school; and 3 = University degree). Individuals were grouped according to their BMI (weight in kilograms divided by the square of height in meters) as follows: BMI < 25 kg/m² as (1) reference; BMI ≥ 25 kg/m² as (2) individuals with higher risk (68).

The Karolinska Sleep Questionnaire (KSQ) was used to assess sleep disturbance (69). The questions were: "Have you been bothered by the following complaints during the past three months": "… difficulties falling asleep," "… repeated awakenings with difficulties falling asleep again," "… premature awakenings involuntary," and "… disturbed/restless sleep." The response options throughout the KSQ are (0) never, (1) seldom (occasionally), (2) sometimes (several times per month), (3) often, (4) most of the times, or (5) always. The score can range from 0 to 20 (high score representing high level of sleep disturbance). The KSQ has good reliability, construct validity, and criterion validity (69). The internal consistency in the current study was good (Cronbach's Alfa 0.868). For further analysis, the participants were divided into groups that as far as possible constituted the first to third and the fourth quartile: 82.7% individuals with score 0-8 ("less sleep problems"); and the rest with score 9 or higher ("much sleep problems").

The physical and emotional subscale of the Shirom Melamed Burnout Questionnaire was used to measure burnout (70, 71). The subscale consists of eight items ("I feel tired," "I feel refreshed," "I feel physically exhausted," "I feel fed-up," "My batteries" are "dead", "I feel burned out," "I feel mentally fatigued," "I feel no energy for going to work in the morning"). The response scale ranges from 1—"almost never" to 7—"Almost always." The score can thus range between 7 and 56 (high score representing high level of burnout). The SMBQ has good construct validity and reliability (72). The internal consistency in the current study was good (Cronbach's Alfa 0.848). For further analysis, we divided individuals into two groups according to quartiles: 76.5% individuals with score 8-25 as "low burnout"; and the remaining with score 26 or higher as "high burnout."

The 10-item Perceived Stress Scale (PSS-10) was used to measure degree to which situations are appraised as stressful (73). The items assess how unpredictable, uncontrollable, and overloaded the respondents find their lives ("… been upset because of something that happened unexpectedly?" "…felt that you were unable to control the important things in your life?", "…felt nervous and stressed?", "…felt confident about your ability to handle your personal problems?", "…felt that things were going your way?", "…felt that you could not cope with all the things that you had to do?", "…felt you been able to control irritations in your life?", "…felt that you were on top of things?", "...how often have you been angered because of things that happened that were outside of your control?", "how often have you felt difficulties were piling up so high that you could not overcome them?"). The score can range from 0 to 40 (high score representing high stress level). The PSS-10 has good construct validity (74). The internal consistency in the current study was good (Cronbach's Alfa 0.901). For further analysis, we divided individuals into two groups according to quartiles: 75.6% individuals with score 0-21 ("low stress"); and the rest with score 22 or higher ("high stress"). Mean scores for all "mental distress factors" (sleep disturbance, burnout, perceived stress) were calculated (see **Table 1**).

Statistical Analysis

The statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Differences between ethnic groups in prevalence of CVD, socio-demographic outcomes and mental distress factor were tested with Chi-Square Test, *T*-Test, and *post-hoc* Bonferroni Test. Analyses of covariance (ANCOVAs) were conducted to study the associations between prevalence of CVD and levels of sleep disturbance, burnout, and stress. The odds for having CVD in relation to level of sleep disturbance, burnout, and stress in the various ethnic groups, with the Kyrgyz as referents, were assessed with logistic regression analysis, where also gender and BMI were considered. Confounding variables were only included in the analyses if they correlated with the analyzed variables according to Spearman correlation analysis. Since age was highly correlated with CVD (0.693, see **Appendix 1**), we removed age from further calculations. Due to multicollinearity, the independent variables

TABLE 1 | Prevalence of cardiovascular disease (CVD), socio-demographic outcomes, and mental distress factor in various ethnic groups.

	Kyrgyz	East Europeans	Central Asians	East Asians	Western Asians	Other minorities	Chi^2 (*p*)
			CVD, *n* (%)				17.29 (<0.001)
Yes	67 (30.9)	102 (42.7)	30 (26.3)	13 (34.2)	9 (39.1)	13 (20.6)	
No	150 (69.1)	137 (57.3)	84 (73.7)	25 (65.8)	14 (60.9)	50 (79.4)	
			Gender, *n* (%)				24.46 (<0.001)
Male	76 (35.0)	97 (40.6)	54 (47.4)	21 (55.3)	12 (52.2)	42 (66.7)	
Female	141 (65.0)	142 (59.4)	60 (52.6)	17 (44.7)	11 (47.8)	21 (33.3)	
			Age, *n* (%)				111.45 (<0.001)
18-29	66 (30.4)	19 (7.9)	42 (36.8)	12 (31.6)	4 (17.4)	30 (47.6)	
30-39	49 (22.6)	67 (28.0)	23 (20.2)	9 (23.7)	5 (21.7)	16 (25.4)	
40-49	37 (17.1)	46 (19.2)	22 (19.3)	2 (5.3)	6 (26.1)	7 (11.1)	
50-59	50 (23.0)	42 (17.6)	17 (14.9)	3 (7.9)	4 (17.4)	4 (6.3)	
≥60	15 (6.9)	65 (27.2)	10 (8.8)	12 (31.6)	4 (17.4)	6 (9.5)	
			Education, *n* (%)				30.03 (<0.001)
Primary	10 (4.6)	14 (5.9)	14 (12.3)	0 (0.0)	2 (9.1)	7 (11.3)	
High school	103 (47.5)	114 (47.7)	67 (58.8)	24 (63.2)	14 (63.6)	39 (62.9)	
University degree	104 (47.9)	111 (46.4)	33 (28.9)	14 (36.8)	6 (27.3)	16 (25.8)	
			Income (soms), *n* (%)				20.56 (0.15)
≤8,000	29 (22.8)	75 (39.3)	18 (25.0)	7 (35.0)	5 (26.3)	10 (23.8)	
8,001-16,000	34 (26.8)	52 (27.2)	26 (36.1)	3 (15.0)	7 (36.8)	15 (35.7)	
16,001-30,000	35 (27.6)	37 (19.4)	18 (25.0)	6 (30.0)	3 (15.8)	11 (26.2)	
≥30,001	29 (22.8)	27 (14.1)	10 (13.9)	4 (20.0)	4 (21.1)	6 (14.3)	
			BMI, *n* (%)				17.21 (0.00)
<25	124 (57.1)	99 (41.4)	61 (53.5)	25 (65.8)	11 (47.8)	37 (58.7)	
≥25	93 (42.9)	140 (58.6)	53 (46.5)	13 (34.2)	12 (52.2)	26 (41.3)	
			Mean score value (*SD*)				***P***
Sleep disturbance	4.99 (4.02)	5.44 (4.12)	5.12 (3.75)	5.23 (4.05)	5.04 (3.39)	3.82 (3.73)	0.13
Burnout	19.77 (9.69)	20.19 (8.71)	19.29 (8.73)	17.97 (9.17)	20.52 (10.59)	17.36 (8.73)	0.27
Stress	16.44 (8.86)	16.33 (7.04)	16.36 (8.79)	14.73 (6.89)	15.95 (7.58)	12.93 (9.25)	0.05

with a high bivariate correlation should not be included in multiple regression analysis (75). The α-level was set at 0.05.

Ethical Concerns

Ethical approval was received from the Research Ethics Committee of the International School of Medicine, Kyrgyzstan (Ref #10, 28.06. 2017). All study participants gave written informed consent in accordance with the Declaration of Helsinki.

RESULTS

There were significant differences in the distribution of CVD ($\chi^2 = 17.29$ at $DF = 1$, $p < 0.001$) and socio-demographic outcomes between the ethnic groups (**Table 1**). According to *post-hoc* tests, compared to Kyrgyz people (30.9%), the prevalence was significantly higher ($p < 0.05$) among East Europeans (42.7%), Western Asians (39.1%), and lower among Central Asians (26.3%) and other minorities (20.6%), in this study. Having high BMI (≥25) was more common among East Europeans and Western Asians. Among the mental distress factors, stress level showed a clear tendency to differ significantly ($p = 0.05$) between ethnic groups, whereas levels of sleep disturbance and burnout did not (**Table 1**). *Post-hoc* Bonferroni tests showed that East Asians and Other minorities had significantly lower prevalence of high stress than the Kyrgyz ($p < 0.05$). The results from the Spearman correlation analyses are given in **Appendix 1**, showing ethnic group, gender and BMI as confounding variables.

We explored the association between CVD and mental distress in all studied individuals. Income was excluded from the analyses since too many respondents had not answered that question. The ANCOVA on the associations between severity of mental distress and prevalence of CVD, showed a statistically significant difference in level of sleep disturbance between individuals with CVD ($M = 6.50$, $SD = 3.96$) and those without CVD ($M = 4.36$, $SD = 3.81$) [$F_{(47.43)}$, $DF = 1$, $p < 0.001$]. The difference remained after controlling for ethnic group, gender and BMI (F for in between group $= 23.25$, $p < 0.001$). There was also statistically significant difference in burnout score between the CVD group ($M = 21.48$, $SD = 9.43$) and the reference group ($M = 18.57$, $SD = 8.83$) [$F_{(16.06)}$, $DF = 1$, $p < 0.001$]. The difference remained after controlling for ethnic group, gender and BMI (F for in between group $= 14.81$, $p < 0.001$). The difference in stress score between the CVD group ($M = 16.79$, $SD = 7.63$) and the reference group ($M = 15.55$, $SD = 8.46$) did not show a trend [$F_{(3.54)}$, $DF = 1$, $p = 0.060$]. The difference remained insignificant after controlling for ethnic group, gender, and BMI. Thus, in this study, sleep disturbance and burnout seem to be associated with CVD, but not stress.

The logistic regression analyses (**Table 2**) indicated that compared to individuals with low levels of sleep problems, individuals with high levels of sleep problems have 2.16 (95% CI 1.4–3.34) times higher odds of having a CVD. Compared to individuals with low levels of burnout, individuals with high levels of burnout have higher (1.58 95% CI 1.07–2.33) odds of having a CVD. There was no difference in chances of having a CVD among individuals with high level of perceived stress compared to low level of perceived stress group. As for the differences in ethnic groups, in analysis of burnout and stress, compared to the majority ethnic group Kyrgyz, East Europeans had 1.55 (95% CI 1.02–2.35—for burnout) and 1.52 (1.01–2.31 for stress) times higher odds of having a CVD. Furthermore, compared to Kyrgyz, Central Asians and Other minorities had a tendency for lower odds and Western Asians and East Asians had a tendency for higher odds of having a CVD in case of all mental distress factors. However, these associations need to be considered carefully considering the small number of representatives in some minority groups.

DISCUSSION

This study addressed the differences in cardiovascular health as well as social and psychological determinants in Kyrgyzstan. As for the prevalence of CVD, the results confirm findings of earlier studies showing different CVD pattern among various ethnic groups (32, 37). Particularly, East-Europeans like Russians have been shown to have a higher prevalence of CVD compared to Central Asians (Kyrgyzs and Kazakhs) (33). This study indicated significantly higher prevalence of CVD among East Europeans (42.7%) and Western Asians (39.1%) compared to Kyrgyz people (30.9%). Furthermore, compared to these groups, the prevalence of CVD was significantly lower among Central Asians (26.3%) and Other minorities (Dungans and Uyghurs, 20.6%). This may be explained by the tendency of East Europeans and Western Asians, compared to Kyrgyzs and Central Asians (Kazakhs, Tajiks) and other minorities, showing lower CVD mortality attributable to dietary risk, including less alcohol consumption (12, 76, 77).

We also clarified the levels of mental distress factors among the ethnic groups in Kyrgyzstan. Based on studies of Salyers and Bond (78), Mezick et al. (61), Grandner et al. (62), and Slopen et al. (63), we expected ethnic differences in burnout and sleep disturbances. However, in the current study the levels of burnout or sleep disturbance did not differ among ethnic groups whereas such differences by ethnic groups have been shown in other contexts (79). *Vice versa*, in this study, the mean score value of stress was lower among East Asians ($M = 14.7$) and Other minorities (Dungans and Uygurs, $M = 12.9$) than among the Kyrgyzs, East Europeans, and Central Asians ($m > 16.3$). This suggests that the majority population, Kyrgyz, does not stand out as having particularly better mental health than the other ethnic groups. The conclusions on the ethnic differences in burnout and sleep disturbance differ from those from studies in the US (61, 79). Thus, the present finding that in Kyrgyzstan, compared to other ethnic groups, the majority of the population, Kyrgyzs do not stand out having better mental stress outcomes can be explained by the lower economic status of this group (80–82). Furthermore, the higher rate of mental stress in Kyrgyzs, East Europeans and Central Asians may be attributed to the fact that unlike these ethnic groups, East Asians (Koreans), Dungans and Uyghurs (Other minorities) have kept their religious practices (e.g., pray five times a day) throughout Soviet time till currently (83–85), and religious practices have been associated with positive mental health outcomes (86).

The ANCOVAs showed significantly higher levels of sleep disturbance and burnout in the CVD group compared to the referent group. This difference remained significant after

TABLE 2 | Association between mental distress factors and cardiovascular disease in regression analysis, odds ratios (95% CI); models adjusted for ethnicity and gender, and BMI ($n = 694$; with CVD $n = 234$).

	Sleep (much sleep problems *n* = 120)	**Burnout (high burnout *n* = 165)**	**Perceived stress (high stress *n* =169)**
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Mental distress factor	2.16 (1.4–3.34)***	1.58 (1.07–2.33)*	1.14 (0.77–1.69)
Ethnicity (ref Kyrgyz, *n* = 217**)**			
East European (239)	1.47 (0.97–2.24)	1.55 (1.02–2.35)*	1.52 (1.01–2.31)*
Central Asian (114)	0.88 (0.51–1.51)	0.80 (0.53–1.53)	0.88 (0.52–1.51)
East Asian (38)	1.59 (0.74–3.42)	1.69 (0.78–3.66)	1.59 (0.73–3.44)
Western Asia (23)	1.41 (0.53–3.73)	1.36 (0.53–3.52)	1.40 (0.54–3.60)
Other minorities (63)	0.70 (0.34–1.44)	0.70 (0.34–1.44)	0.70 (0.34–1.43)
Gender (female *n* = 392)	2.31 (1.61–3.30)***	2.32 (1.62–3.30)***	2.33 (1.63–3.34)***
BMI (BMI ≥ 25 *n* = 337)	1.14 (1.09–1.18)***	1.13 (1.09–1.18)***	1.14 (1.09–1.18)***

*$p < 0.05$; ***$p < 0.001$.

controlling for ethnic group, gender and BMI. Our regression analysis confirmed that compared to the individuals with lower levels of sleep problems and burnout, individuals with high levels of either of these mental distress factors were more likely to have CVD. Earlier studies have shown that poor sleep can lead to disease (51, 52) and cause exhaustion disorder and stress (49). Thus, our findings of associations of CVD with sleep disturbance and burnout, but not with stress, are not surprising. Stress fluctuates strongly over time to cope with everyday hassles, which compromises the sensitivity of this variable. Despite of previous reports of declining of sleep disturbance with age (79, 87), our results did not find this negative correlation.

In our logistic regression analysis for burnout and stress we could see significantly higher odds of having a CVD among East Europeans compared to Kyrgyz; and a tendency for lower odds compared to Central Asians and Other minorities compared to Kyrgyz. Thus, next to the level of mental distress, gender and BMI, specificities in ethnic groups may be associated with the higher prevalence of CVD. The mechanisms behind the effect of ethnic group for mental distress factors and CVD needs further exploration. The cross-sectional design of this study does not enable to test of such cause and effect. Whereas, ethnic group can be expected to be a cause rather than effect in this context, the associations can well be bidirectional.

We believe that some of our results may be explained by insufficient number of minority participants. Despite stratified random sampling, ethnic groups differed significantly in age, gender, and education. The invitations for participation directed at patients visiting polyclinics and health care centers cannot be expected to have resulted in a fully representative sample of participants, which compromises the representativeness of the findings, in particular regarding the prevalence rates. Since results on prospective self-reported assessment of mental distress, such as sleep disturbance and burnout, lack in consistency (88), there is a need for further assessment as well as psychophysiological evaluation. We also asked the participants about having any CVD diagnosed by a doctor rather than using hospital records. This might have caused diagnosis bias, even if we specified CVD diagnosed by a doctor.

Nevertheless, the current study is one of the very few studies of health inequality among ethnic minorities in Central Asia. The current findings add value to the existing bulk of knowledge of mechanisms mediating the relationship between cultural, mental stress factors, and CVD. The present use of self-reported CVD and mental distress may in future research be complemented by hospital records of CVD diagnosis and psychophysiological measures related to distress.

CONCLUSION

This study suggests that Kyrgyz people have lower prevalence of CVD, compared to East Europeans and Western Asians in Kyrgyzstan, and higher compared to Central Asians and Other minorities. In studied sample in Kyrgyzstan, individuals with relatively high level of sleep disturbance and burnout, more likely reported suffering from CVD. Next to the mental distress factors, gender and BMI, the characteristics of ethnic groups may be associated with the higher prevalence of CVD, as there were higher odds for CVD among East Europeans compared to Kyrgyz.

The high prevalence rates indicate the need of better diagnosis and treatment of CVD and burnout as well as improving sleep quality with public health measures, including stress management, restful environment, increased physical activity, and better nutrition. Based on the present and previous study outcomes, it can be concluded that there is a need for the development of a relevant approach in mitigating sleep disturbance and preventing burnout in the general population, not only in specific ethnic groups.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical approval was received from the Research Ethics Committee of the International School of Medicine, Kyrgyzstan (Ref #10, 28.06. 2017). All study participants gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

HA and KD contributed conception of the study and organized the data collection and analysis. KO and HO contributed design, methods of the study, and interpretation of the data. MN and SN contributed interpretation of the study findings. KO and HA performed the statistical analysis and wrote the first draft of the manuscript. HO and KD wrote sections of the manuscript. All authors contributed to the manuscript revision, read and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

TABLE A1 | Spearman correlation coefficients between cardiovascular disease and key analysis factors (n = 694).

Any CVD	**Gender**	**Age**	**Education**	**Family status**	**Ethnic group**	**Income**	**BMI**	**Sleep score**	**Burnout score**	
Gender (0 = female, 1 = male)	0.202***									
Age	0.693***	0.266***								
Education	0.058	0.093*	0.077*							
Family status	0.007	0.13	0.180***	0.086*						
Ethnic group	–0.038	-0.172**	–0.046	–0.160**	0.018					
Income	–0.233	-.149**	–0.282***	0.124**	0.130**	–0.052				
BMI	0.334***	0.03	0.449***	0.021	0.119**	0.027	–0.006			
Sleep score	0.251***	0.119**	0.275***	0.072	–0.037	–0.032	–0.058	0.067		
Burnout score	0.154***	0.111**	0.175***	0.149***	0.063	–0.054	0.071	0.113**	0.469***	
Stress score	0.061	0.176***	0.071	0.103***	0.097*	–0.090*	0.096*	0.005	0.401***	0.524***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

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How the Labor Market Affects the Self-Perceived Health of Older Workers. The Evidence From Central and Eastern European Countries (CEECs)

Paulina Ucieklak-Jeż[1] *and Agnieszka Bem*[2]*

[1] *Faculty of Law and Economics, Jan Długosz University, Czestochowa, Poland,* [2] *Department of Corporate and Public Finance, Wrocław University of Economics and Business, Wrocław, Poland*

Background: The paper aims to analyze the impact of key labor market indicators on the self-assessed health of the population of older workers (aged 55–64).

Methods: Authors build the econometric models where the dependent variable is the self-perceived health status (for women and men separately). Explanatory variables are selected key indicators of the labor market, covering unemployment, including long-term, inactivity, or under-employment. The average household income is used to control the effect of wealth. Additionally, the models incorporate the variable describing the proximity of retirement. The research sample consists of nine countries of Central and Eastern Europe: Poland, Czech Republic, Slovakia, Hungary, Lithuania, Latvia, Estonia, Bulgaria, and Romania.

Results and Conclusions: The study confirms that in the group of elderly workers, the perceived state of health is influenced by long-term unemployment, inactivity, and, in the case of women, time-related underemployment.

Keywords: social determinants of health, self-perceived health, key indicators of the labor market, unemployment, inactivity

Edited by:
Rasheda Khanam,
University of Southern Queensland, Australia

Reviewed by:
Tsangyao Chang,
Feng Chia University, Taiwan
Guvenc Kockaya,
Analysis and Consultancy Plc., Turkey

Correspondence:
Agnieszka Bem
agnieszka.bem@ue.wroc.pl

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INTRODUCTION

Rich literature describes how the social gradient affects the population's health. Social determinants of health (SDH) consist of non-medical factors deriving from the social and economic environment—these dimensions significantly affect the health state (1). The most commonly noted socio-economic factors shaping health are income, social status, social support network, education and literacy, physical environment, environmental quality. The list is still open due to the complexity of a phenomenon of health (2).

Among the determinants listed above, employment status and working conditions are perceived as crucial. As a result, several studies of SDH include more or fewer variables related to the labor market. These are, for example, the employment status (3) or occupation (4–6). From the first look, a link between good health and unemployment seems to be intuitive. There is a general assumption that employment and healthful working conditions promote good physical and mental health. However, previous studies provide inconsistent results, and the debate in this area is still open.

Importantly for further analysis, the link between health and labor market status is bidirectional. Better health promotes employment and increases income (7). Being unemployed contributes to higher mortality (8) or deteriorates the perceived health (9). As summarized by Maarten and Marcel, health and work are endogenously related because of a direct causal impact of health on work and vice versa (9).

The study aims to analyze the impact of selected labor market indicators on self-assessed health. It gives a fresh look at the decomposed problem of unemployment, including long-term unemployment or labor market inactivity, based on critical indicators of the labor market (KILM) developed by the International Labor Organization. The research focuses on the age group 55–64; this group at higher risk of unemployment or permanent inactivity. Along with age, the health status deteriorates—it is reflected both in mortality rates and subjective health state self-assessment. Additionally, the decisions of elderly workers related to their professional activity can be affected by social, cultural, and economic factors and perceived health. The choice of this age group also responds to the current demographic problems—the process of aging societies, manifested by the declining share of young workers, encourages employers to retain their employees representing older age groups. It can be one of the possible answers to the demographic problems, but only if they are ready to extend their working lives.

The research sample covers nine countries of Central and Eastern Europe (CEE). Although their demographic situation is currently relatively favorable compared to western European countries, this could change drastically in the coming decades. The fall of communism and the economic transition has dramatically declined fertility rates, which will soon affect the labor market (10). Demographic challenges, which are already apparent in developed countries of West Europe, will stoke the CEE countries, with increased force, in the perspective of 20 years.

LITERATURE CONTEXT

As previously mentioned, the labor market's impact on health status is still a vital research area. It is mainly due to previous inconsistent results. The reasons for this "inconsistency" are multiple. Most of all, the labor market is a comprehensive concept and can be analyzed from different perspectives. Finally, the researchers usually focus on two main areas: working conditions (including social factors) or a broader picture of unemployment, including losing a job, long-term unemployment, or inactivity. Different measures of health state (mortalities, morbidities, life expectancies, or self-assessment) are the next potential source of conflicting results.

Generally, the previous findings, in the area of the relationship between unemployment and health, can be split into two categories—studies that support the hypothesis of the detrimental effect of unemployment on health, mainly via a mechanism of lowered income and impaired social status, and results that suggest quite the opposite mechanism.

Many works confirm that a loss of a job, or broadly being unemployed, impacts health negatively. Brenner was the first who described this inverse relationship. Therefore, in the literature, it is often called the "Brenner hypothesis" (11, 12). This undesirable effect is mainly rooted in the loss or reduction of income, which results from lowered economic activity, sometimes leading to poverty. This situation may worsen self-persisted health individually, but it is often combined with other unfavorable factors related to the social environment (13).

Inspired by Preston's law, researchers usually accept the assumption that higher-income individuals are healthier than those with lower incomes. Several previous studies confirm this thesis (10), often demonstrated by higher mortality rates after a job loss (14) and significantly evident in the men subpopulation (14, 15). Unemployment may also sharply decrease subjective well-being (16). This effect is more apparent when the time unemployment extends to long-term one (17–20). The unemployed individuals also carry a higher burden of diseases than those who work, even if it is only a part-time job (21).

One of the recent studies by Economou et al. (22), based on European countries' data, supports the view that unemployment harms health—when the unemployment increases by 1%, the mortality rises approximately per 1.54 deaths for every 100,000 inhabitants. This finding is exciting as authors tend to control the confounding factors in the analyzed relationship. It is also in line with Crost and Friedson (23). They estimate that a 1% increase in the group-specific unemployment rate is associated with an ∼0.015% increase in the group-specific mortality rate. Additionally, Catalano et al. (24), job loss increases the risk of premature mortality, and, according to Eliason and Storrie (14), such experience rises by 44% of men's risk of death.

This relationship between job status and health has potentially many explanations. As a result of job loss, lowered income usually translates into lower availability of health services, especially in private insurance systems. Having or not having health insurance is, in several countries, strongly linked to the labor market. As confirmed by Van Doorslaer et al. (25), people with higher incomes are significantly more likely to benefit from medical consultations than people with lower incomes (26). However, the consequences of unemployment go far beyond a simple reduction of income. Several studies emphasize additional psychological factors like the stigma and isolation related to unemployment (27). This situation is comparable with the negative consequences of retirement (28), linked to lowered income and broken social networks (29).

The inverse relationship was pioneered by the works of Ruhm (30–32), Gerdtham and Ruhm (33), Neumayer (34), and Tapia Granados (35). Gerdtham and Ruhm (33) confirm that a 0.4% growth of mortality accompanies the 1% decrease in the unemployment rate. This negative relationship is confirmed by several further studies, among all by Ariizumi and Schirle (36) for middle-aged Canadians. Birgisdóttir and Ásgeirsdóttir (37) report the pro-cyclical nature of unemployment for the middle-aged Iceland population. Tapia Granados and Ionides (38) estimate that when unemployment increases by 1%, it is linked to mortality drop by 0.5%. Haaland and Telle (39) fortify this result by observing that other factors related to deteriorated health also have a pro-cyclical character. The impact of low education and poor health on unemployment varies by the work-life stage (40). Deficient health levels are observed for residents of underdeveloped areas and those at risk of poverty or unemployment (41). According to the European Commission, higher morbidity, and premature mortality rates are observed in groups of illegally employed, homeless, and single parents (42).

To summarize, earlier studies usually suggest that unemployment affects a population's health negatively. It seems that, although the evidence supporting this hypothesis is relatively new, the latest studies suggest quite remote conclusions. Tapia Granados and Ionides partially described this problem, and they found that in the second half of the twentieth century, economic growth started to affect health negatively, in contrast to earlier decades (38).

Some differences in previous results may also be rooted in analyzed countries' characteristics, as Hessel and colleagues report (43). Contextual factors, including policy responses, may have contributed to the different results. Health inequalities, by employment status, increase significantly by 72% in men and 16% in women after controlling covariates. Those trends are partly mediated by consequences of unemployment, such as income loss, income poverty, life satisfaction, and economic sorrows. Using regression models for panel data, the authors confirm that the observed increases in health inequalities at the population level also exist at the level of individuals (44).

MATERIALS AND METHODS

Source of Data

Data covering the years 2005–2018 for nine countries of Central and Eastern Europe (CEE): Poland (PL), Czech Republic (CR), Slovakia (SL), Hungary (HUN), Lithuania (LT), Latvia (LV), Estonia (EST), Bulgaria (BUL), and Romania (ROM) are investigated. This research group is consistent in terms of economic development, demography, culture, or historical baggage despite their different population potential. The data come from the following sources: EUROSTAT and LABORSTA, provided by the International Labor Organization (ILO).

Model

The very formulation of the hypothesis on the health effects of unemployment appears to be risky in the context of previous studies; hence the research bases mainly on exploratory data analysis, focusing on the effects of individual labor market characteristics on the health of older workers. Several aspects of the labor market are considered, like unemployment, including long-term and time-related underemployment, labor inactivity, and informal economy employment.

The following research questions are formulated:

1. Which characteristics of the labor market influence health status more significantly?
2. Is the strength and direction of this relationship the same for men and women subpopulations?

To answer those questions, two GMM models, separately for men and women, are calculated (45, 46). GMM models help avoid OLS method requirements, usually challenging to fulfill, like the normality of variable distributions. GMM allows estimating the non-linear parameters of the dynamic panel models. Additionally, GMM is more robust than other methods of estimation (47, 48). Such an active panel model help to address the endogeneity problem caused by reverse causality between health and its social determinants (49).

In the model based on the first differences, there are no personal effects. The assumption that there is no correlation between explanatory variables and particular outcome results is no longer required. The use of instrumental variables eliminates the problem of endogeneity of variables and estimator mismatch (50).

The Chow test examines the stability of the model parameters.

Dependent Variables

The dependent variable describes the populations' health state (variable SP18). Generally, there are two types of health state measures—objective and subjective. The most popular objective measures are mortalities or life expectancies. They are reliable as they base on actual events and public statistics. The subjective indicators require survey research where respondents are asked to assess their health state (both physical and mental), usually using the five-degree Likert scale (51).

The subjective indicators, especially self-assessed health (SAH), although biased by their subjective component, are very inclusive and capture all aspects of health (both mental and physical, including functional and well-being dimensions) not covered by other health variables (52–57). Hence, SAH is a strong predictor of mortality (52, 57, 58).

Apart from this strong advantage, SAH is also biased by socio-economic factors like gender, age, income, occupation, race, cultural background (57–61). Different age groups are governed by different factors (61, 62). Middle-aged respondents assess their health through the prism of symptoms and psychic well-being, while the elderly rather face chronic diseases (63). There are also differences rooted in gender—some studies report that SAH is a better predictor of men's mortality (64). Countries heterogeneities may also affect the results—Southern and Central and Eastern Europeans are much more likely to misreport their physical and cognitive abilities than Northern and Western Europeans.

This research bases on SAH for the population aged 55–64. The data concerning SAH comes from the European health interview survey (EHIS). Respondents assess the general perceived health by answering the question: "How is your health in general? Is it ..." Very good/Good/Fair/Bad/Very bad? It is a standardized question recommended by the World Health Organization (65).

The dependent variable (SP18) covers the percentage of respondents aged 55–64 (men and women separately) who assess their health as "good" or "very good."

TABLE 1 | Explanatory variables—selected indicators of the labor market.

	Variable	Description
1	Labor force participation rate (KILM 1)	A measure of the proportion of a country's working-age population that engages actively in the labor market, either by working or by looking for work
2	Part-time employment as a percentage of total employment (KILM 6)	A measure of employment in the informal economy as a percentage of total non-agricultural work
3	Long-term unemployment (KILM 11)	The unemployment lasting 12 months or more as a percentage of the total unemployment
4	Time-related underemployment (KILM 12)	The time-related underemployment as a percentage of total employment
5	The inactivity rate (KILM 13)	The percentage of the population that is neither working nor seeking work
6	Retirement age (RA-55)	Difference between retirement age and age 55
7	Household income (INCOME)	Mean income by household type—EU-SILC and ECHP surveys, single person household. Household income refers to the total amount of gross revenue generated by the individuals living within one particular household

Explanatory Variables

Explanatory variables are selected key indicators of the labor market (KILM) (**Table 1**), covering the different unemployment aspects. These are labor market participation (KILM1), part-time employment (KILM6), long-term unemployment (KILM11), time-related underemployment (KILM 12), and inactivity rate (KILM13) (**Table 1**).

There are also additional variables that go beyond the characteristics of the labor market. Since the test sample involves persons of pre-retirement age, the variable RA-55 describes the timespan to the retirement for persons aged 55 years (respectively, for women and men), taking into account different retirement schemes in the individual countries. We assume that the proximity of retirement benefits may affect individuals' decisions to stay active or transit into a state of inactivity. A lower value of RA-55 should contribute to higher ratios of inactivity.

The variable INCOME helps to control the impact of the financial situation on health. The level of generated income may also impact the decision to leave the labor market (**Table 1**).

RESULTS

Statistical Analysis

Tables 2–7 present the descriptive statistics for KILM 1, KILM 6, KILM 11, KILM 12, KILM 13, and SP18. Labor force participation (KILM 1) is one of the primary measures for assessing the labor market from the perspective of social conditions, including health. The value of KLIM 1 was, in 2018, the lowest (36.1%) in Romania and the highest in Estonia (74.4%) (**Table 2**).

A decreasing KILM1 disparity over time, measured by the mean share in the maximum value, can also be observed. A smaller disparity applies to the male population than to women (in 2018, 89.59% comparing to 76.16%). The concentration of KILM1 (Gini coefficient) is also minimal, which means an even distribution, especially for men. For women, we also see more significant variability between countries −23% compared to 9% for men (**Table 2**).

The more significant disparity of KILM6, measured by the average at the maximum value, affects men rather than women. The share of the average maximum in 2018 is 61.89% for men. The Gini coefficient for men and women adopts similar values does not exceed 0.21. Right-hand asymmetry (1.24) for women means that part-time work as a percentage of women's total employment is below average in most countries. For men, we observe a moderate left side asymmetry (0.47) (**Table 3**).

About half of unemployed people were unemployed for more than 12 months. The long-term unemployment rate in 2008 for women was the lowest in Hungary (43.4%) and the highest (79.1%) in Slovakia. In 2018 KILM11 was the lowest for Poland, compared with the other surveyed countries −33.9%. The KILM11 disparity, measured by the mean's share in the maximum, is similar for men and women. The concentration measured with the Gini coefficient is low both for the men and women population. Distributions are characterized by right-sided strong asymmetry in women's cases (**Table 4**).

KILM 12 describes the problem of underemployment as a percentage of workers who would like to extend the number of working hours. In 2008 the lowest value of KILM 12 for women was reported in Estonia (1%) and the highest in Poland (14.2%). On average, 4.31% of women and 5.07% of men would like to work longer in 2018. The KILM12 disparity, measured by the share of mean in the maximum value, is high for both women and men. The concentration is high, especially for men—an uneven distribution is observed. Right-side asymmetry is extreme for both sexes, and values are characterized by very high volatility. In Poland, 15.9% of employed women and 16.4% of working men would like to extend their working hours. These values stand out from other countries (**Table 5**).

The inactivity rate is the proportion of the working-age population excluded from the labor force. The KILM13 rate for women was the lowest in 2008 in Estonia (38.6%) and the highest in Poland −78.6%. In the period 2008–2018, there is a clear positive tendency for female and male populations. In the case of women, the inactivity rate dropped from 60.6 to 43.33% during the years 2008–2018. The lower disparity, measured by the share of mean in the maximum value, applies to men. Men's and women's concentration coefficients are low with weak right-side asymmetry for both subpopulations (2018) (**Table 6**).

To summarize, the preliminary analysis of variables indicates a vital gender gap. 43.3% of women aged 55–64 are inactive—women do not look for employment for various reasons. It is significantly higher than for men (31.73%). Simultaneously, the number of inactive women decreased substantially between 2008 and 2018 (from 60.6 to 43.33). The reasons may be related to reforms in the area of retirement policy aiming to increase the

TABLE 2 | KILM 1—descriptive statistics for the years 2008 and 2018.

	Women		Men	
	2008	**2018**	**2008**	**2018**
Average value	39.4	56.67	57.98	68.27
Average value/maximum value (%)	64.17	76.16	85.77	89.59
Kurtosis	1.11	−1.29	0.12	−1.42
Gini coefficient	0.19	0.13	0.08	0.05
Skewness	0.44	−0.20	−0.99	−0.20
Standard dev.	13.38	12.99	8.82	5.92
Volatility (%)	34	23	15	9

TABLE 3 | KILM 6—descriptive statistics for the years 2008 and 2018.

	Women		Men	
	2008	**2018**	**2008**	**2018**
Average value	15.14	15.93	6.91	7.92
Average value/maximum value (%)	51.76	51.40	62.21	61.89
Kurtosis	2.87	3.63	−0.75	−0.85
Gini coefficient	0.20	0.19	0.21	0.21
Skewness	1.24	1.65	−0.07	0.47
Standard dev.	6.08	6.16	2.58	2.94
Volatility (%)	40	39	37	37

TABLE 4 | KILM 11—descriptive statistics for the years 2008 and 2018.

	Women		Men	
	2008	**2018**	**2008**	**2018**
Average	56.73	47.87	52.48	52.93
Average value/maximum value (%)	71.72	61.85	64.08	72.12
Kurtosis	2.04	2.68	1.02	−1.12
Gini coefficient	0.09	0.13	0.15	0.14
Skewness	0.90	1.66	0.48	0.06
Standard dev.	10.43	2.98	14.19	12.84
Volatility (%)	18	27	27	24

TABLE 5 | KILM 12—descriptive statistics for the years 2008 and 2018.

	Women		Men	
	2008	**2018**	**2008**	**2018**
Average	4.01	4.31	3.67	5.07
Average value/maximum value (%)	28.25	27.11	22.22	30.90
Kurtosis	6.28	7.78	4.98	0.94
Gini coefficient	0.42	0.40	0.61	0.53
Skewness	2.41	2.71	2.23	1.47
Standard dev.	3.82	4.20	4.98	5.34
Volatility (%)	95	98	136	105

TABLE 6 | KILM 13—descriptive statistics for the years 2008 and 2018.

	Women		Men	
	2008	**2018**	**2008**	**2018**
Average	60.60	43.33	42.02	31.73
Average value/maximum value (%)	77.10	67.81	70.39	77.59
Kurtosis	−1.11	−1.29	0.12	−1.42
Gini coefficient	0.12	0.17	0.11	0.11
Skewness	−0.44	0.20	0.99	0.20
Standard dev.	13.38	12.99	8.82	5.92
Volatility (%)	22	30	21	19

TABLE 7 | Retirement age in analyzed countries (in 2008 and 2018).

	Women		Men	
	2008	**2018**	**2008**	**2018**
Bulgaria	60	61.17	60	61.17
Czechia	59.33	62.67	59.33	62.67
Estonia	60.5	63.25	60.5	63.25
Hungary	61	63.25	61	63.25
Latvia	61.5	63.25	61.5	63.25
Lithuania	60	62.33	60	62.33
Poland	60	60	60	60
Romania	58.42	60.92	58.42	60.92
Slovakia	62	62.42	62	62.42

retirement age, especially for women, and equalize retirement age for both sexes (**Table 6**). This change had a significant positive impact on the activity of this age group increasing participation rates—from 39.4 to 56.67 for women and from 57.98 to 68.27 for men. However, in many CEE countries, women still retire earlier than men, which usually means passing into a state of inactivity.

About half of unemployed people are unemployed for more than 12 months, both women and men. Only a tiny proportion of those who work (4.31% of women and 5.07% of men) would like to do more, although the situation is sharply different between countries. This need for extra hours of work is evident in Poland and Romania.

The variable SP18 describes the percentage of persons who assess their health as "*good*" and "*very good.*" We observe that this percentage for women significantly increases between 2008 and 2018, while for men slightly decreases. The disparity of the variable SP18 is high both for men and women. A moderate left side asymmetry similar for both men and women can be observed.

Some analyzed variables show very high volatility or inequality between countries. Hence, in the next step, we test the significance of differences between means of selected variables for women (**Table 8**) and men (**Table 9**) subpopulations. The vast majority of differences between means are statistically significant (statistically significant differences are marked as gray areas). In particular, there are no significant differences for Latvia (LV).

TABLE 8 | SP18—descriptive statistics for the years 2008 and 2018.

	Women		Men	
	2008	**2018**	**2008**	**2018**
Average value	27.06	40.51	45.89	45.58
Average value/maximum value (%)	75.38	73.39	76.74	72.69
Kurtosis	−0.72	−0.70	−0.83	0.05
Gini coefficient	0.13	0.13	0.10	0.13
Skewness	−0.59	−0.26	0.48	−0.46
Standard dev.	6.82	9.54	8.48	10.70
Volatility (%)	25	24	18	23

GMM Model

Separate models for men and women due to the significant variation in variable values are estimated. Models 1 and 2 explain the self-perceived health for women and men, respectively. Both models are estimated using explanatory variables number 1–5 (**Tables 10**, **11**).

The general form of the model 1and 2 are as follow:

$$
\begin{aligned}
\mathrm{SP18} = {} & a_0 + a_1\boldsymbol{KILM1} + a_2\boldsymbol{KILM6} + a_3\boldsymbol{KILM11} + a_4 KILM12 \\
& + a_5\boldsymbol{KILM13} + \beta_1\mathrm{BUL} + \beta_2\mathrm{CR} + \beta_3\mathrm{EST} + \beta_4\mathrm{LV} \\
& + \beta_5\mathrm{LT} + \beta_6\mathrm{HUN} + \beta_7\mathrm{PL} + \beta_8\mathrm{ROM} + \beta_9\mathrm{SL} + \varepsilon_i
\end{aligned}
$$

The models do not contain any structural changes. The Chow test, in both cases, confirms the stability of the parameters. The null hypothesis assumes the absence of structural changes. For the male model, $F_{(5,\,97)} = 0.59331$, with p-value 0.7051, and for women, $F_{(3,\,113)} = 2.48539$ with p-value 0.0643.

In model 1, estimated for women aged 55–64, three variables explain the self-perceived health—long-term unemployment (KILM11), time-related underemployment (KILM12), and inactivity rate (KILM13). Other variables did not enter the model. For KILM 11, the partial regression coefficient is −0.0540644 with an error of ±0.0298267, which allows the following interpretation: when the long-term unemployment rate increases by 1 (%), health perception decreases by 0.054 (%), provided that the values of other variables do not change. When the time-related underemployment (KILM12) increases by 1%, the self-perceived health decreases by 0.0742690 (%). Analogically, the partial regression coefficient for KILM13 in (%) is −0.764447, with an error of 0.0358556. Hence, if the inactivity rate increases by 1 (%) on average, the perception of health decreases by 0.764447 (%), provided that the size of other variables does not change (**Table 11**).

The dependent variable's [SP18(f)] arithmetic mean is 31.45357 and the standard deviation of the dependent variable is 10.89073. GMM criterion: Q = 1.69439e-022 (TQ = 1.89772e-020).

The self-perceived health of men aged 55–64 (model 2) is explained by only two variables: long-term unemployment (KILM11) and inactivity rate (KILM13).

The partial regression coefficient for KILM 11 is −0.112940 with an error of ±0.0422647, which allows the following interpretation: as the long-term unemployment rate increases by 1 (%), health perception decreases by 0.112 (%), provided that the values of other variables do not change. Analogically, the partial regression coefficient for KILM13 in (%) is −0.608790, with the error of 0.0722067. Hence, if the inactivity rate increases by 1 (%) on average, the perception of health decreases by 0.609 (%), provided that the size of other variables does not change (**Table 12**).

Models 3 (for women) and 4 (for men) are estimated using all explanatory variables. It allows for analyzing the potential effect of retirement age and income.

The general form of the model 3 and 4 are as follow:

$$
\begin{aligned}
\mathrm{SP18} = {} & \alpha_0 + \alpha_1\mathbf{KILM1} + \alpha_2\mathbf{KILM6} + \alpha_3\mathbf{KILM11} + \alpha_4 KILM12 \\
& + \alpha_5\mathbf{KILM13} + \alpha_6\mathrm{INCOME} + \alpha_7\ \mathrm{RA} - 55 + \beta_1\mathrm{BUL} \\
& + \beta_2\mathrm{CR} + \beta_3\mathrm{EST} + \beta_4\mathrm{LV} + \beta_5\mathrm{LT} + \beta_6\mathrm{HUN} + \beta_7\mathrm{PL} \\
& + \beta_8\mathrm{ROM} + \beta_9\mathrm{SL} + \varepsilon_i
\end{aligned}
$$

The models do not contain any structural changes. The Chow test in both cases confirms the stability of the parameters. The null hypothesis is the absence of structural breaks in a time series. In the male model (model 4), this is a low value [$F_{(4,111)} = 7.10122$, p-value = 3.96467e-005], and for women (model 3), it is indisputable [$F_{(6,\,93)} = 1.38501$, p-value = 0.228855].

When the additional variables (INCOME, RA-55) are included, the long-term unemployment ratio does not enter the model. The partial regression coefficient for KILM 12 is −0.187317 with an error of ±0.0623989, which allows the following interpretation: as the time-related underemployment rate increases by 1 (%), health perception decreases by 0.187317 (%), provided that the values of other variables do not change. Analogically, the partial regression coefficient for KILM13 is −0.695259, with an error of 0.0544718. Hence, when the inactivity rate increases by 1 (%) on average, the perception of health decreases by 0.695259 (%), provided that other variables do not change (**Table 13**).

This model also includes the impact of household income and retirement age. When the household income increases by 1 (%), the perceived health very slightly increases by 0.00215923 (with the error of 0.000419313). In the case of RA-55, the strength of the relationship is significantly higher. When RA-55 increases by 1 (%), the perceived health decreases by 2.19702 (with the error of 0.467027). It can be interpreted as follow: women who expect a more extended period of work until retirement assess their health state as worse.

The dependent variable's [SP18(f)] arithmetic mean is 31.45357 and the standard deviation of the dependent variable is 10.89073. GMM criterion: Q = 6.8816e-024 (TQ = 7.70739e-022).

Model 4 also includes additional variables (INCOME, RA-55). In this case, only one variable describing the labor market enters the model (the long-term unemployment ratio). The partial regression coefficient for KILM 11 is −0.0744426 with an error of ±0.0298090, which allows the following interpretation: as the long-term unemployment rate increases by 1 (%), health perception decreases by 0.0744426 (%), provided that the values of other variables do not change (**Table 14**).

TABLE 9 | Test for significance of mean differences for women (statistically significant differences market as gray areas).

Variable	Country	LV	HUN	PL	LIT	EST	SL	CR	ROM	BUL
KILM11	LV	56.771	47.718	49.979	54.200	52.578	74.736	48.993	–	63.500
	HUN		8.373	6.318	2.521	3.722	−19.131	7.576	–	−7.480
	PL			−1.947	−5.839	−4.021	−26.078	−1.142	–	−15.776
	LIT				−3.823	−2.161	−24.044	0.888	–	−13.606
	EST					1.405	−21.127	4.927	–	−9.958
	SL						−20.457	3.091	–	−10.411
	CR							26.299	–	13.303
	ROM								–	−15.416
	BUL									–
KILM12	LV	4.957	4.544	19.339	3.200	1.254	2.032	2.071	3.651	4.545
	HUN		0.899	−17.992	4.289	9.546	6.869	7.332	2.895	0.770
	PL			−18.518	3.287	8.498	5.909	6.295	1.982	−0.001
	LIT				20.922	23.793	22.185	22.631	19.754	17.502
	EST					5.961	3.151	3.388	−1.130	−2.726
	SL						−2.246	−2.672	−6.357	−6.921
	CR							−0.111	−3.893	−4.957
	ROM								−4.126	−5.152
	BUL									−1.691
KILM13	LV	40.379	65.350	70.071	43.593	34.364	63.871	57.264	65.771	54.286
	HUN		−25.666	−29.408	−3.112	6.735	−20.486	−16.524	−35.723	−13.295
	PL			−4.511	20.351	33.160	1.254	7.640	−0.553	10.228
	LIT				24.014	36.712	5.125	11.726	5.317	14.159
	EST					9.258	−16.494	−12.274	−26.478	−9.412
	SL						−26.481	−23.242	−47.796	−19.717
	CR							5.415	−1.950	7.728
	ROM								−10.326	2.645
	BUL									13.455
SP18	LV	17.907	20.307	29.979	30.371	33.286	34.564	41.064	42.428	44.150
	HUN		−2.851	−13.604	−13.032	−20.101	−15.695	−27.569	−31.122	−25.914
	PL			−10.542	−10.223	−16.229	−13.121	−23.813	−26.924	−22.945
	LIT				−0.384	−3.902	−4.086	−12.105	−14.338	−13.165
	EST					−3.169	−3.560	−10.879	−12.843	−12.150
	SL						−1.243	−9.749	−12.307	−11.108
	CR							−5.990	−7.522	−7.833
	ROM								−1.664	−2.974
	BUL									−1.729

For women, the household income impacts self-perceived health marginally. When the household income increases by 1 (%), the perceived health very slightly increases by 0.00302122 (with the error of 0.000459543). In the case of RA-55, a healthy relationship but in a different direction is observed. When RA-55 increases by 1 (%), the perceived health increases by 2.30497% (with the error of 0.489014). Hence, men who expect to work for a longer time assess their health state as better.

The dependent variable's [SP18(f)] arithmetic mean is 31.45357 and the standard deviation of the dependent variable is 10.89073. GMM criterion: Q = 6.8816e-024 (TQ = 7.70739e-022).

To summarize, the labor market characteristics which influence the perceived health are, depending on the model, long-term unemployment (KILM 11), time-related underemployment (KILM 12), and inactivity rate (KILM 13). All those factors affect perceived health negatively. When we include income, we observe a positive relationship; however, it is relatively feeble. It seems that the retirement age plays an important role. Estimated models suggest that women who expect a longer timespan of work perceive their health as worse. This relationship is relatively high and statistically significant. For men, and the opposite relationship is detected—men who expect to work up to longer age assess their health as better. It

TABLE 10 | Test for significance of mean differences for men (statistically significant differences market as gray areas).

Variable	Country	LV	HUN	PL	LIT	EST	SL	CR	ROM	BUL
KILM11	LV	57.907	48.250	54.709	52.893	49.207	74.450	47.393	62.843	49.193
	HUN		3.028	0.814	2.794	2.815	−6.385	4.500	−2.656	2.997
	PL			−1.356	−1.434	−0.233	−7.010	0.240	−4.460	−0.238
	LIT				0.458	1.171	−4.500	1.725	−2.034	1.204
	EST					1.174	−8.136	2.290	−5.131	1.250
	SL						−6.909	0.522	−4.293	0.004
	CR							8.893	4.311	7.215
	ROM								−6.309	−0.543
	BUL									4.551
KILM13	LV	34.9	50.407	33.386	33.493	47.971	41.393	33.871	40.586	46.107
	HUN		−5.651	1.094	0.848	−6.067	−5.692	0.651	−3.344	−9.226
	PL			6.265	5.902	0.766	3.466	5.861	3.398	1.632
	LIT				−0.066	−6.881	−7.457	−0.317	−4.347	−11.043
	EST					−6.273	−5.605	−0.212	−3.751	−8.582
	SL						3.341	6.261	3.159	0.926
	CR							5.717	0.553	−5.590
	ROM								−3.684	−8.864
	BUL									−3.640
SP18	LV	22.821	23.586	30.314	32.114	33.229	38.136	44.507	51.364	52.616
	HUN		−0.503	−6.312	−4.118	−6.419	−5.522	−14.404	−16.386	−18.701
	PL			−4.791	−3.586	−5.398	−5.064	−12.438	−14.647	−16.486
	LIT				−0.825	−1.924	−2.884	−10.212	−12.813	−15.025
	EST					−0.456	−1.812	−5.230	−7.620	−8.450
	SL						−1.676	−6.354	−9.161	−10.479
	CR							−2.223	−4.414	−4.971
	ROM								−3.636	−4.635
	BUL									−0.640

TABLE 11 | GMM model 1, dependent variable—SP18(f).

Variable	Coefficient	Standard error	*t*-ratio	*p*-value
Const	87.6358***	2.58565	33.89	< 0.0001
KILM11	−0.0540644*	0.0298267	−1.813	0.0699
KILM12	−0.0742690**	0.0344980	−2.153	0.0313
KILM13	−0.764447***	0.0358556	−21.32	< 0.0001
Latvia	−35.4239***	1.20294	−29.45	< 0.0001
Hungary	−14.4547***	1.09374	−13.22	< 0.0001
Lithuania	−20.7720***	1.33958	−15.51	< 0.0001
Estonia	−25.1447***	1.19975	−20.96	< 0.0001
Bulgaria	1.78340	1.16948	1.525	0.1273

**significance level $\alpha = 0.1$, **significance level $\alpha = 0.05$, and ***significance level $\alpha = 0.01$.*

TABLE 12 | GMM model 2, dependent variable—SP18 (m).

Variable	Coefficient	Standard error	*z*	*p*-value
Const	71.1119	3.25845	21.82	< 0.0001
KILM11	−0.112940***	0.0422647	−2.672	0.0075
KILM13	−0.608790***	0.0722067	−8.431	< 0.0001
Latvia	−20.5037***	1.29170	−15.87	< 0.0001
Hungary	−11.3895***	2.18675	−5.208	< 0.0001
Estonia	−14.2939***	1.11234	−12.85	< 0.0001
Lithuania	−12.6338***	1.61623	−7.817	< 0.0001
Poland	−3.12142**	1.30629	−2.390	0.0169
Bulgaria	12.0580***	1.54434	7.808	< 0.0001
Romania	15.1295***	1.53300	9.869	< 0.0001

**significance level $\alpha = 0.1$, **significance level $\alpha = 0.05$, and ***significance level $\alpha = 0.01$.*

is potentially an exciting finding but, in our opinion, requires further research.

DISCUSSION

The research involves people aged 55–64. It is a period in life when health progressively deteriorates. Lack of success in the labor market, like losing a job, can also contribute to the deterioration of health. Previous studies do not expressly answer the link between employment and health.

As summarized in section Literature Context, several studies confirm the detrimental impact of unemployment on health outcomes, regardless of the dependent variables. The negative

TABLE 13 | GMM model 3, dependant variable—SP18(f).

Variable	Coefficient	Standard error	*z*	*p*-value
Const	89, 3495	4, 49566	19.87	< 0.0001
KILM12	−0.187317***	0.0623989	−3.002	0.0027
KILM13	−0.695259***	0.0544718	−12.76	< 0.0001
INCOME	0.00215923***	0.000419313	5.149	< 0.0001
RA-55	−2.19702***	0.467027	−4.704	< 0.0001
Latvia	−36.2116***	1.22729	−29.51	< 0.0001
Hungary	−17.3224***	1.84488	−9.389	< 0.0001
Poland	−6.51857***	2.24979	−2.897	0.0038
Lithuania	−24.5082***	1.23516	−19.84	< 0.0001
Estonia	−30.2173***	1.25956	−23.99	< 0.0001
Slovakia	−5.80266***	1.86952	−3.104	0.0019
Czechia	−9.90302***	1.95995	−5.053	< 0.0001

**significance level α = 0.1, **significance level α = 0.05, and ***significance level α = 0.01.*

TABLE 14 | GMM model 4, dependant variable—SP18(m).

Variable	Coefficient	Standard error	*z*	*p*-value
Const	29.2000	4.04098	7.226	< 0.0001
KILM11	−0.0744426**	0.0298090	−2.497	0.0125
INCOME	0.00302122***	0.000459543	6.574	< 0.0001
RA-55	2.30497***	0.489014	4.714	< 0.0001
Latvia	−31.3491***	1.74868	−17.93	< 0.0001
Hungary	−31.0303***	2.25511	−13.76	< 0.0001
Estonia	−30.4854***	2.57825	−11.82	< 0.0001
Lithuania	−23.4199***	1.63270	−14.34	< 0.0001
Poland	−30.7461***	1.22612	−25.08	< 0.0001
Slovakia	−17.5330***	2.81387	−6.231	< 0.0001
Czechia	−17.3291***	2.58550	−6.702	< 0.0001

**significance level α = 0.1, **significance level α = 0.05, and ***significance level α = 0.01.*

effect of being unemployed is reflected in higher mortality and morbidity rates or lower health state self-assessment (13, 17, 22–24, 29, 44, 66–68). This relationship is perceived as being bidirectional. Hence the willingness to seek a job is also influenced by the health state (49). Lower self-assessed health may result from depression symptoms that often accompany unemployment or inactivity (69). According to Krug and Eberl, workers, who enter unemployment with lower health, assess their health as worse (29).

The impact of unemployment on health is evident in various health indicators—the authors usually analyze health in the context of mortality, maturity, and self-health (SAH). If mortality is examined, most studies, especially earlier ones, suggest a negative impact. In one of earlier studies, Brenner, based on British data, concludes that a negative impact of unemployment is expressed by slowing the decline in mortality (11). Also, Wilson and Walke demonstrable an adverse effect on health by increased mortality experience of Britain unemployed (8). Morris and colleagues estimate that unemployed middle-aged British men were twice as likely to die in the following 5.5 years as those who remained continuously employed (70). Similar dependencies confirm, in Finland, Martikainen and Valkonen (71), Tapia Granados in Spain (72), Crost and Friedson in the USA (23), in Sweden: Eliason and Storrie in Sweden (14) and Garcy and Vågerö (19). Ariizumi and Schirle confirm, using Canadian data, that a one p.p. increase in the unemployment rate lowers the predicted mortality rate by nearly 2%. Zagozdzon et al. find that the Polish unemployed are at greater risk of death than the overall population (73).

Panel studies in this area are not so consistent. Based on data from 13 European Union countries, Economou et al. confirm a strong, positive relationship between adverse economic conditions, including unemployment and mortality (22). On the other hand, Tapia Granados et al. find, using data from 27 European countries with over one million citizens, that an increase of one percentage point in the unemployment rate is associated with a reduction of 0.5% in the rate of age-adjusted mortality (38). Gerdtham and Ruhm, using a fix-effect panel with 23 OECD countries, including countries of CEE, confirm that one p.p. decrease in the unemployment rate is associated with the growth of 0.4% in total mortality (33).

When morbidities describe a health state, results are, by far, more consistent. They usually indicate a higher risk of heart disease (70, 74–81). Individual studies conducted in different countries, including CEE countries, examine this adverse effect in more detail and identify various causes of increased risk, but are most often associated with stress associated with job loss, lifestyle changes, and different physical activity patterns.

From the point of view of this research, the most interesting are the studies in which respondents assess their health independently (SAH). Binder and Coad conclude that unemployment cause a substantial decrease in subjective well-being in the UK population (16). László et al., using data from 3 population-based studies (16 countries including CEE countries), find that job insecurity was significantly associated with an increased risk of poor health in the Czech Republic, Denmark, Germany, Greece, Hungary, Israel, the Netherlands, Poland, and Russia. In contrast, this relationship is statistically insignificant in other countries analyzed countries (82). Based on Spanish data, Urbanos-Garrido and Lopez-Valcarcel confirm the detrimental impact on unemployment on SAH.

By contrast to that, Tøge and Blekesaune, using data from 28 European Countries, including CEE ones, suggest that unemployment and health are partly due to decreased self-rated health as people enter unemployment. This study also emphasizes the detrimental impact on older workers' health (83). Against this background, Krug and Eberl get exciting results. Based on data for Germany, they find exciting time-lags related to the relationship between unemployment and SAH. During the first year of unemployment, SAH is significantly lower than 2 or more years before entering unemployment and when the period of unemployment is longer than 1 year (29).

In light of the presented findings, only long-term unemployment impacts health detrimentally. The constant lack of professional activity has a similar influence. Additionally, women's self-assessed health suffers from time-related underemployment. Previous studies show that women are at higher risk of underemployment as underemployment is most common in women's professions (84).

This study also confirms that among the group of elderly workers, the perceived state of health is affected not simply by unemployment but primarily by its structure. Short-term unemployment is often perceived as desirable—it allows job seekers to find suitable employment. It can be a time of relief from a daily routine for stressed workers, especially when social support schemes offer satisfying financial security levels. However, in light of those findings, long-term unemployment harms self-assessment health. However, this effect is more substantial for men. This negative impact is possibly rooted not only in lower economic status but social factors that may also contribute to lower perceived health status (26). Those results contrast with the findings of Kostrzewski and Worach-Kardas, who investigated a group of 454 Polish unemployed aged 45 years and older—they conclude that a period of unemployment did not significantly contribute to the self-rated health (85).

In contrast to many earlier studies, significant gender differences are not observed, which is a little bit puzzling in the context of research suggesting that unemployment has a more substantial impact on men's health (16, 44, 86–88). For example, Eliason and Storrie find that the overall men's mortality is 44% higher, while there is no impact on female mortality (14).

Women are also at higher risk of underemployment due to the structure of jobs they usually take (84). To a more significant extent, women are permanently excluded from longer working-hour (89). According to obtained results, this need for extra working hours harms their health assessment. It is in line with previous studies. Friedland and Price found that underemployed workers report lower health and well-being (90).

Apart from the problem of unemployment, presented findings highlight the importance of labor market inactivity. Three of four estimated models suggest the negative impact of inactivity on health—this impact is more substantial compared to other characteristics of the labor market. At the age of about 60 years, both women and men usually decide when to retire. From the labor market perspective, it means a transition into a state of inactivity or significantly reduced working hours. According to Eurostat, 15.9% of unemployed aged 55–64 who left the labor market chose early retirement, while 15.8% were forced to retire due to illness or disability (91). It indicates the bidirectional relationship between inactivity and health; as French reports, unhealthy people retire earlier (92). Also, Disney concludes that poor health is a predictor of individual retirement behavior among workers aged 50 until state pension age (93). Men in poor health are expected to retire 1–2 years earlier—this effect is visible after correcting potential endogeneity of self-rated health problems (94).

The lack of activity, rather than unemployment, might be a source of health state deprivation. Inactivity has a significant negative impact on both sexes' perceived state of health (95). Hence, social and economic consequences of inaction are often related to retirement and adversely affect well-being (96), especially in a group of older employees. This detrimental impact is reported in earlier studies—Behncke concludes that retirement significantly increases the risk of being diagnosed with a chronic condition, increased risk factors, or physical activity problems (97). Retirement may also be related to a decrease in cognitive skills (98). According to Dave, retirement cause an increase in difficulties associated with mobility, daily activities, illness conditions, and a decline in mental health (99).

There is a group of researchers that reports a positive impact of retirement on health. Che concludes that the probability of "fair" or "poor" self-reported health among white-collar workers decreases substantially after retirement (100, 101). Some studies suggest that retirement improves subjective health status and mental health due to lower stress and a better lifestyle (102, 103). While researchers often report a positive impact on mental health, at the same time, perceived general health, and physical health may suffer (104, 105). It seems that for better-educated workers, the decision to retire is more beneficial (100, 104, 106, 106).

The results also suggest that the retirement age influences importantly perceived health, but this relationship's direction is damaging for women and positive for men. It contrasts with studies suggesting that the statutory retirement age is unrelated to an individual's health (101). Although the study confirms that the retirement age affects perceived health, the differences between women and men require further research.

LIMITATIONS OF THE STUDY

As previously mentioned, CEE countries form a homogenous group in terms of economy, demography, and social systems, including retirement schemes, making the estimation results more reliable. The research results generally confirm the relationship revealed in previous studies, both on the direction and strength of the dependencies. However, there are a few limitations to consider. Firstly, the previous findings are significantly inconsistent, so it is difficult to identify some universal conclusions.

Secondly, most studies in this area cover data from highly developed countries—the US and Western Europe. Research in developing countries is relatively scarce and most often points to a positive link between unemployment and health (68, 107, 108). However, comparisons with developing countries do not appear to be justified, as there are characterized by very restricted social policy, which plays an essential role in the consequences of unemployment. Moreover, while there are still some development differences between eastern and western Europe, CEE countries are very close to Western European neighbors when it comes to social security systems. Unfortunately, previous studies on CEE countries usually cover individual populations (Poland, Czech Republic) and are usually based on mortality rates. In panel studies, CEE countries appear as part of a larger research sample covering European or OECD countries.

Therefore, it is justified to conduct further comparative studies to capture possible differences between Western Europe countries and CEE countries. Although the microeconomic structure of unemployment in the nations of eastern Europe appears to be similar to the industrialized west (109)—some studies suggest that populations of CEE can be more sensitive to business cycle fluctuations, independent of gender (110). At the same time, Bambra and Eikemo report the minor relative inequalities between employed and unemployed in the Southern and Eastern welfare states (111). That suggests the potential direction of further research.

CONCLUSIONS

The process of demographic change is an undeniable fact. In the coming years, pre-retirement age employees will form a significant group in the labor market. This part of the population is, by nature, at higher risk of health state deterioration, as a part of the aging process. Any difficulties in the labor market may boost these problems and push workers out of the labor market, as we remember the bidirectional relationship between health and its socio-economic determinants. Taking into account the potential shortage of workers, it may pose severe problems for the economy.

Unemployment, especially when it has a long-term character, harms the health of employers from the older age groups—unemployed assess their health state as worse than those who have a job. Interestingly, the impact of labor inactivity is, importantly, more wasting than an unemployed status. Although this effect's mechanism requires further studies, we presume that permanent resignation from job-seeking reinforces the social gradient's detrimental impact, leading to a worsen economic situation or deepen social isolation.

Apart from long-term unemployment, women also suffer from time-related underemployment. It suggests that public politics promoting employment should concentrate not only on unemployed but also part-time workers.

Being inactive is a natural consequence of taking retirement. In this context, the problem of retirement age plays an important role. All CEE countries, except Poland, gradually increase the statutory retirement age, especially for women. It can be a source of, on average, lower perceived health status (compared to men).

To conclude, there are several advantages of an active senior policy aimed at galvanizing older workers' activities, promoting employment, and gaining new competencies. This tailor-made policy should address the identified determinants of labor inactivity to prevent early retirement.

This study has several advantages comparing to the existing literature: firstly, to our best knowledge, this is the first study on this group of countries, which may open the discussion on potential differences between European countries. Secondly, the analysis covers diverse aspects of unemployment (overall unemployment, long-term unemployment, underemployment, and inactivity), catching the most critical dependencies. Thirdly, the research includes the variable describing the proximity of retirement to control potential differences of retirement schemes, which plays a crucial role in studies on older workers.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://ilostat.ilo.org/.

AUTHOR CONTRIBUTIONS

PU-J and AB: conceptualization and writing—original draft preparation. PU-J: data curation, formal analysis, methodology, resources, and visualization. AB: investigation and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Health Information Systems in the COVID-19 Pandemic: A Short Survey of Experiences and Lessons Learned From the European Region

*Elsa Negro-Calduch, Natasha Azzopardi-Muscat, Dorit Nitzan, Richard Pebody, Pernille Jorgensen and David Novillo-Ortiz**

World Health Organization, Regional Office for Europe, Copenhagen, Denmark

Edited by:
Andreea Molnar,
Swinburne University of Technology, Australia

Reviewed by:
Angelo D'Ambrosio,
Freiburg University Medical Center, Germany
Anthony Bokolo Jr.,
Norwegian University of Science and Technology, Norway

****Correspondence:***
David Novillo-Ortiz
dnovillo@who.int

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Introduction: The COVID-19 crisis provides an opportunity to reflect on what worked during the pandemic, what could have been done differently, and what innovations should become part of an enhanced health information system in the future.

Methods: An online qualitative survey was designed and administered online in November 2020 to all the 37 Member States that are part of the WHO European Health Information Initiative and the WHO Central Asian Republics Information Network.

Results: Nineteen countries responded to the survey (Austria, Belgium, Croatia, Czech Republic, Finland, Greece, Iceland, Ireland, Israel, Italy, Kazakhstan, Latvia, Lithuania, Romania, Russian Federation, Sweden, Turkey, United Kingdom, and Uzbekistan). The COVID-19 pandemic required health information systems (HIS) to rapidly adapt to identify, collect, store, manage, and transmit accurate and timely COVID-19 related data. HIS stakeholders have been put to the test, and valuable experience has been gained. Despite critical gaps such as under-resourced public health services, obsolete health information technologies, and lack of interoperability, most countries believed that their information systems had worked reasonably well in addressing the needs arising during the COVID-19 pandemic.

Conclusion: Strong enabling environments and advanced and digitized health information systems are vital to controlling epidemics. Sustainable finance and government support are required for the continued implementation and enhancement of HIS. It is important to promote digital solutions beyond the COVID-19 pandemic. Now is the time to discuss potential solutions to obtain timely, accurate, and reliable health information and steer policy-making while protecting privacy rights and meeting the highest ethical standards.

Keywords: data, health information system, COVID – 19, lessons learned, health data

INTRODUCTION

Health information systems (HIS) are systems that incorporate information generated by both population-based and institution-based data sources to provide information to support decision-making (1). The operational response to the COVID-19 pandemic required the rapid adaptation and leveraging of the capabilities of existing HIS to collect, transmit and analyze key health data in real-time that allowed to understand the epidemiological situation and craft appropriate control measures (2). Due to the unprecedented nature of the pandemic in severity and scale, HIS capabilities in many countries were overwhelmed by the information demands and the challenges encountered. Multiple technological gaps were exposed, especially in low and middle-income countries (3, 4). Initial challenges ranged from new demands on key contributors at each health system level, who were already overburdened by the pandemic, to the urgency in determining how to effectively document seamless, continuous COVID-19 processes in electronic health record-embedded (EHR) databases (5).

The WHO Regional Office for Europe (WHO/Europe) unit on Data, Metrics, and Analytics within the Division of Country Health Policies and Systems (WHO/EURO/CPS/DMA) provides the Member States with guidance, tools, and examples of good practices for HIS based on what has worked in the past (6). The COVID-19 pandemic has provided a valuable opportunity to identify the strengths and weaknesses of existing HIS in the context of a global health emergency. Thus, the (WHO/EURO/CPS/DMA) conducted a short qualitative survey to assess Member States' experiences regarding the performance of their national HIS, intending to offer a snapshot of specific concerns, corrective measures adopted, and lessons learned throughout the COVID-19 pandemic.

METHODS

In November 2020, the (WHO/EURO/CPS/DMA) designed and administered an online qualitative survey to assess lessons learned and experiences implementing health information systems (HIS) in the context of the COVID-19 pandemic.

The objectives were to identify experiences, capture valuable insights, and identify issues to be explored further within individual countries. Specifically, we aimed at assessing (1) which components of the HIS worked well, (2) which components of the HIS did not work well, (3) any practical workarounds or solutions, and (4) lessons learned.

The questionnaire included five open-ended questions, one rating scale question, and one yes/no question (**Table 1**). Open-ended questions were used to gain deeper insights into specific issues and capture responses that would not have been well represented with quantitative data.

The questionnaire, available in English and Russian, was administered to all the WHO National Focal Points (NFPs) of the 37 Member States of the WHO European Health Information Initiative (EHII) and the WHO Central Asian Republics Information Network (CARINFONET) via a secure internet-based system. The completion time was approximately 10 min to motivate respondents during this busy time and achieve a high response rate. The responses to each question were entered into a Microsoft Excel spreadsheet, combining the datasets from each language. Qualitative data analysis was performed, extracting common traits from the open-ended questions. Where possible, a summary analysis of the quantitative findings of the survey is offered. Results are presented in an aggregated and anonymized format.

RESULTS

Completed questionnaires were received from 19 out of 37 Member States contacted (51.3% response rate), namely, Austria, Belgium, Croatia, Czech Republic, Finland, Greece, Iceland, Ireland, Israel, Italy, Kazakhstan, Latvia, Lithuania, Romania, Russian Federation, Sweden, Turkey, United Kingdom, and Uzbekistan.

Participants were prompted to rate the HIS COVID-19 response using a 0-to-10 point scale (Question 7). Scores ranged from 2 to 10 with a median score of 8 (interquartile range [25, 75%]: 7, 8). Only two of the 19 countries gave a score below 5 (**Figure 1**). The median value among all respondents indicates that most respondents felt that the HIS in their countries worked reasonably well and addressed the needs that arose during the COVID-19 pandemic to a satisfactory degree.

Participants were asked to comment on which components of the HIS had worked well (Question 5). The majority (89.4%) indicated that a secure infrastructure for the electronic transmission of health data, already in place, had provided the foundation. In addition, dedicated disease registries, hospital statistics, and mortality registries, maintained over the years, had proven to be valuable data sources for monitoring population health and healthcare provision during the pandemic. Only 11% ($n = 2$) mentioned that the linking of case-based data had been possible. One country indicated that:

> *"A National patient portal was already in place and was relatively easy to enhance to provide services to citizens."*

Others ($n = 2$) commented that reporting to the supranational level had been diligent and in compliance with international standards:

> *"The mandatory reporting of clinical cases of some communicable diseases and deaths to a national register, and to the international level (ECDC and WHO) (. . .) worked well."*

At the same time, 36.8% ($n = 7$) of participants indicated that HIS had been adapted rapidly:

> *"The teams understood the sense of urgency and put everything in place to make things work."*
>
> *"Within a very short time, a series of surveys and panel studies were established to collect up-to-date data during the crisis."*

TABLE 1 | Survey questions.

No.	Question	Type
Q1	Name of the country	Identification
Q2	Name of the person and organization responding to this survey	Identification
Q3	Did existing HIS elements before COVID19 have to be modified to respond to COVID-19 information needs (i.e., clinical case management, public health, and scientific research, etc.)?	Yes/No
Q4	Please comment briefly about the adjustments/modifications/solutions developed.	Open-ended
Q5	Which components of the Health Information System (HIS) for COVID19 have worked well?	Open-ended
Q6	Which components of the HIS for COVID19 do not work so well or had unintended consequences and why?	Open-ended
Q7	Is the country expected to perform any further adjustments to the HIS?	Open-ended
Q8	Has the Health Information System (HIS) in your country responded well to the needs of the COVID19 pandemic (data capture, coding, data use, data analysis, interoperability, etc.)?	0-to-10 rating scale
Q9	What were the lessons learned during the COVID19 pandemic as regards Health Information Systems in your country?	Open-ended

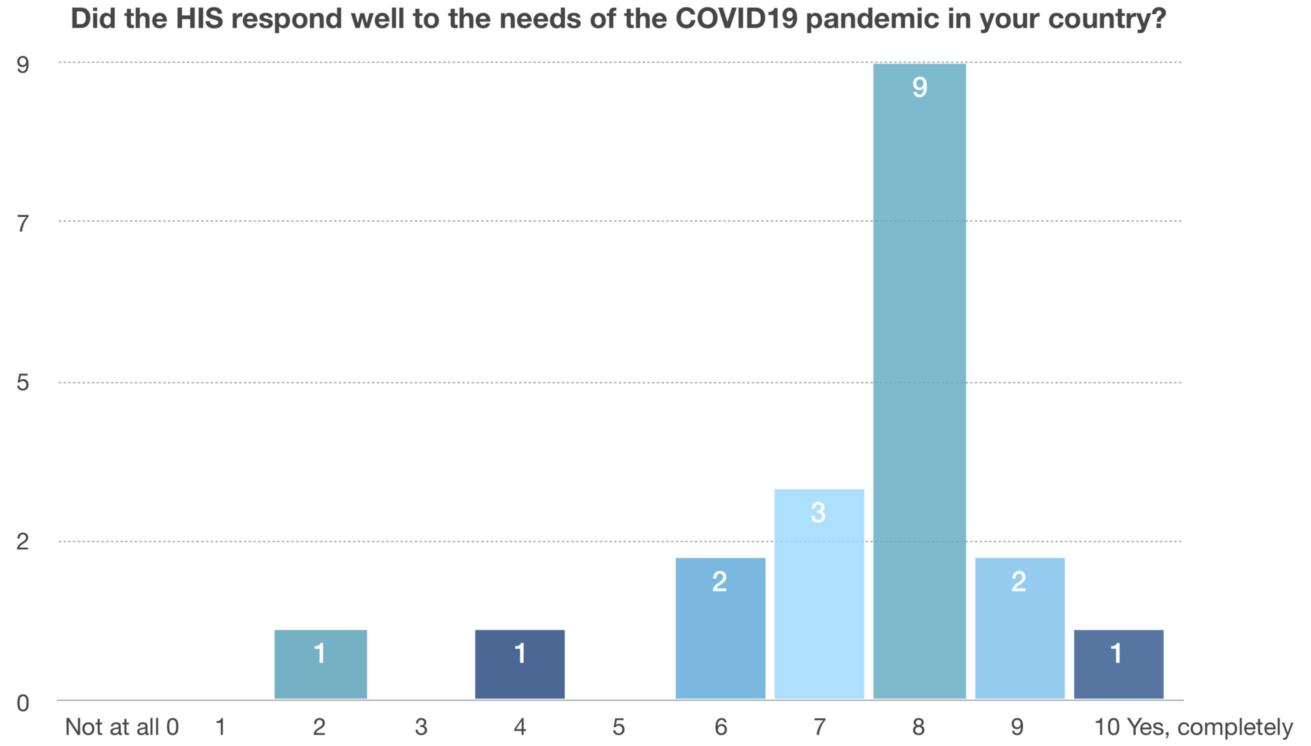

FIGURE 1 | HIS rating scores.

Some countries possessed an existing telemedicine infrastructure before the COVID-19 outbreak, while others developed it during the pandemic to avoid unnecessary patient and staff exposure:

> *"e-Prescribing has become more feasible and comprehensive, generating a better capture of patterns and trends and even informing on prescribing patterns and epidemiological data."*

Two countries set up online workshops to train healthcare workers on COVID-19 clinical information and other instructions, speeding up the implementation of guidelines and protocols.

Regarding adjustments and solutions developed to adapt their HIS to respond to COVID-19 data requirements (Questions 3 and 4), all countries indicated that the existing disease surveillance systems had provided a foundation but needed to be upgraded and reorganized to keep pace with the dynamics of the pandemic. Novel screening processes, hospital-based and ambulatory testing, reporting and analytics tools were all developed or upgraded accordingly to inform public health decision-making:

> *"There was an urgent need to develop a system to collect new information - from an emergency preparedness perspective (. . .). This system was designed specifically as decision support in an emergency and not to collect data for statistics."*
>
> *"Another main solution developed very quickly was a database containing data on covid-19 patients."*
>
> *"New dashboards and data pipelines were established to publish updated statistics on cases, deaths, health care and testing."*
>
> *"The hospital discharge registry was modified to include COVID-19 variables."*
>
> *"New information systems had to be set up rapidly, e.g., contact tracing information systems and ICU information systems."*
>
> *"A Public Health Management System (. . .) was integrated with the entire health system (. . .) and used at the border gates. Citizens brought to our country from abroad were recorded in this system."*
>
> *"First rollout of a, albeit temporary, unique patient identifier. The first in the country to be used."*

Increased reporting frequency (i.e., hospital statistics, prescribed drugs) was cited by 21% ($n = 4$). Twenty-six percent ($n = 5$) mentioned the establishment of new death registration systems to allow for timely calculation of excess mortality:

> *"We moved to an electronic and more timely death registration system."*

Sixteen percent ($n = 3$) of respondents explained that their national version of ICD-10/11 had been quickly updated as soon as COVID-19 coding advice (1) and WHO/ECDC case definitions and recommendations were available (2, 3):

> *"We were successful to quickly update the (. . .) version of ICD-10 when WHO issued coding and terminology recommendations for covid-19 early 2020, and to spread instructions to health care facilities through well-established networks."*

Eleven percent ($n = 2$) indicated that they were exploring ways to facilitate access and usability of data for research purposes.

The majority of the countries (89%) reported that further adjustments to the HIS were still expected (Question 7). In this regard, two countries specified that additional improvements were anticipated to support the rollout of vaccination programs by setting up national electronic immunization registries.

Most respondents (89.5%) believed that the main issues were the lack of the required data infrastructure for effective information management and accurate reporting on relevant COVID-19 data (Question 6). Dedicated HIS components needed to be upgraded or set up from scratch, often in an uncoordinated manner due to the urgency, imposing a heavy burden on those involved:

> *"Covid-19 imposed a heavy burden on both data providers and producers of statistics."*
>
> *"Increased reporting frequency (i.e., hospital statistics) brought the downside of allowing less data quality control compared to working on a more spaced basis."*

A transition period was necessary to achieve well-functioning operational processes because of the consequent technical glitches and delays in data reporting. There were instances of suboptimal data capture, poor timeliness, and limited use of information for action by decision-makers:

> *"The lack of interoperability and a comprehensive EHR (. . .) did not allow for sound planning in terms of resources allocation."*
>
> *"Huge engagement for establishing timeliness, limited use of data at the decision-making level, insufficient interoperability between health care providers and public health authorities"*

Apart from delays related to upgrading HIS components to respond to COVID-19, 31.5% ($n = 6$) of respondents mentioned that a significant factor impacting timeliness, quality, and completeness of data was related to poor interoperability, as well as (in some cases) decentralized HIS operating in different regions or states. These led to problems in coordination, data exchange, and linkage of data:

> *"The coordination between agencies and regional/local health authorities could be improved."*
>
> *"The number of tests, cases in long term care and infected staff were only available on a provincial level."*
>
> *"The lack of information from primary care settings and municipal health care had a negative impact on our ability to fully assess the interventions during the pandemic."*
>
> *"It was very difficult to obtain data from the residential and nursing homes, especially from the private ones."*
>
> *"Existing problems such as the fragmentation of data in several data silos led to problems during the pandemic."*
>
> *"Largest problems were timeliness and linkage of data."*

Registration delays on mortality statistics were also reported to have biased the results of excess mortality analyses. For example, one country mentioned that the usual time between a death occurring and being available for excess mortality analysis was three months at the beginning of the pandemic:

> *"The national health registries, the causes of death registry, and other individual based registries (. . .) were not primarily designed to fulfill the more acute needs of emergency surveillance during a pandemic."*
>
> *"Time lags in mortality data (. . .) hampered estimates of excess deaths early in the pandemic."*

Furthermore, one country noted that a large amount of health data was being captured in unstructured clinical notes, making it much more difficult to process and analyze. Thirty-seven percent ($n = 7$) of respondents noted that critical IT infrastructure and labor for effective contact-tracing were insufficient or non-existent before COVID-19. Tools for cluster identification and geo-localization, interpretation, and application of the General Data Protection Regulation (GDPR) were not in place. These were also deemed an important barrier for implementation:

> *"The legal aspects and GDPR (interpretation/application) have been a barrier."*
>
> *"There were some challenges to balance the demand for timely HIS information vs. the need to prevent unauthorized access to confidential information."*

BOX 1 | Lessons learned: comments from survey respondents.

- *"The timeliness aspect is central, and the demand for rapid data capture, analysis and response is quite different in an emergency scenario such as the covid-19-pandemic, compared to the general health system monitoring"*
- *"There is still a lot of work to do to improve data capture, timeliness and interoperability of different information systems"*
- *"The dashboard has been especially successful as a transparency tool"*
- *"Coordinated communication efforts to the political level, the general public and media are essential as the final output from any surveillance system"*
- *"Development of information systems needs good coordination to ensure good interoperability across the health sector"*
- *"Planning and systematic approach in building Health Information Systems were far from desired"*
- *"Advanced HIS is a fundamental component for both expertise advise/evidence, policy development and political action"*
- *"Strong and competent legal teams are needed to quickly assess new situations and to support actions in any area, including information management"*
- *"There is a need for clarifying the application and limits of existing laws governing privacy during the emergency"*
- *"Constant investment and funding will be required for the health information system going into the future"*
- *"Underinvestment in public health administration and in public health research has a negative effect on pro-active interventions"*
- *"Better use of health data for secondary purposes, linkage, sharing and accessing will become the norm due to COVID"*

One NFP reported that resources had been primarily allocated to COVID data collection, negatively impacting effective information management for other diseases:

> *"The IT resources allocated to COVID data collection had a negative impact on other data collections."*

Another respondent mentioned that due to the dramatic increase in the general public and media interest in COVID-19 epidemiology, HIS professionals had to communicate more clearly and widely about data collection specifications, data analysis, and interpretation for different purposes.

Finally, NFPs were asked to elaborate on experiences and lessons learned throughout the COVID-19 pandemic (Question 9). The consensus across the sample was that information needs in an emergency vs. general public health or health system monitoring were very different, and the existing HIS processes and protocols had been developed to serve the latter. Comments from survey respondents are shown in **Box 1**.

DISCUSSION

This brief qualitative research describes how countries in the WHO European Region experienced HIS challenges brought by the pandemic. The limitations of this research relate to the lack of a quantitative approach that would have allowed the measurement of HIS performance by quantifying the distributions of given variables. We preferred a qualitative approach which allowed us to explore the countries' experiences, perceptions, and understanding and determine divergent and common traits from COVID-19 responders at a national level. The survey was designed to be responded in a few minutes to encourage participation, considering COVID-19 priorities. We also hypothesized that providing response options in a more structured questionnaire could have led to acquiescence bias; that is why many of the questions were open-ended. Furthermore, the COVID-19 pandemic is ongoing, and consequently, our assessment captured respondents' perceptions at a single point in time. Although only a bit more than half of the countries (51.3 percent) chose to participate, those which responded represented a wide geographical and economic range.

Information needs during public health emergencies are different from routine health monitoring, and existing HIS were developed to serve the latter (7). The pandemic prompted a greater need for accurate and timely epidemiological data on various topics to understand the impact and plan for an adequate response (8). The capabilities of HIS in every country underwent corrections and enhancements to collect these COVID-19-related data. Typically, HIS upgrades encompass budgeting, planning, design, project oversight, pretesting, communication with end-users, and, finally, implementation (9). However, due to the urgency of the situation, insufficient material and human resources, and lack of proper strategic planning, these stages were improvised or completely skipped, resulting, in some cases, in inadequate data for the COVID-19 information needs and implementation delays. These challenges forced countries to face the limitations of their HIS, raising awareness of the relevance of such systems in public health emergencies. In any case, overall, countries reported satisfaction in how their systems had reacted to the changes in workload, information density, and typology of data.

Social, economic, and cultural differences also shaped how different information strategies coped with the COVID-19 outbreak (10). While some countries had a more developed informatics framework resulting from previous HIS enhancements, others lacked appropriate health information infrastructures capable of meeting the COVID-19 information needs. The pandemic has also exacerbated existing inequalities across HIS globally and highlighted their weaknesses. Although funding was released to support HIS during the emergency, the systems should be prepared for any health crisis in advance (4). Unfortunately, COVID-19 will not be the last global health emergency; thus, it is paramount that both regular funding and government support are secured to continue the implementation and improvement of health information management (11).

The COVID-19 pandemic accelerated the adoption of new health information technologies, and a wide array of digital tools were developed to address health information needs (12–14). For example, the Internet of Things (IoT) provided new data sources. Big data, such as location-based and contact tracing data, were integrated to model epidemiological trends, providing key information to decision-makers (15). However, some of these digital tools brought concerns related to national standards, access, acceptability, usability, adoption, and data protection (2). The General Data Protection Regulation (GDPR) (16) and the ePrivacy Directive (17) provide the safeguards for personal data protection in the European Union. The GDPR states that apps should not identify the individual, and no geolocation or movement data should be used (18). In Norway, "Smittestopp," the COVID-19 contact-tracing app, was discontinued on 15 June 2020 after receiving a warning from the Norwegian Data Protection Authority (19). Likewise, the UK government was forced to abandon a centralized coronavirus contact-tracing app due to technical (i.e., unsupported by some devices, inaccurate distance measures) and personal privacy concerns (20). In addition, some of the new digital tools that the pandemic has brought have focused on the interests of organizational stakeholders without considering important ethical, social, and cultural values. Despite rapid increases in digital adoption, mobile phone ownership is not equally embraced by all nations. Global mobile users are still under 67 percent of the population (21). Thus, mobile phone location records will not capture these non-mobile phone users (i.e., lower-income, elderly, marginalized groups) (22). These issues need to be reassessed to support information management while meeting the highest ethical standards during health emergencies.

Despite data dashboards being mentioned only by two participants, these have been extensively used to display relevant COVID-19 data (14). However, it is important to note that several facets of a dashboard can be misrepresented without background knowledge of how the data were originally captured, characteristics of the data, and any biases that might affect interpretation (23).

Some survey respondents identified the lack of interoperability as a critical issue, highlighting the importance of the timely exchange of health information across platforms. Integration of multiple data sources remains challenging despite decades of technological advances. Some of the barriers to interoperability include lack of standards, large amounts of unstructured data (8), data breaches, and mistrust (24). There are promising uses for blockchain technology for system integration, specifically in combination with standards for exchanging healthcare information electronically; however, challenges such as immaturity, high cost, data privacy, poor scalability, and low general performance still need to be addressed (24).

Coordination and data sharing have been particularly challenging in countries with a high degree of regional and local decentralization in their health care and social protection and welfare services. Furthermore, coordination and data exchange also need to be improved between organizations within and outside of the health system (i.e., education, internal affairs, etc.).

The COVID-19 pandemic has also stressed the need to tackle infodemics and find efficient ways to communicate and engage with the population to establish trust in public health officials and the information they provide. Coordinated communication efforts to the political ranks, the public, the media, and between agencies and regional and local health authorities are essential, as knowledge translation is the final output from any surveillance system. The HIS-related issues that emerged during the COVID-19 pandemic need to be addressed by responsible information technology research. Developing a holistic view of complex data ecosystems involves the engagement of various data entities in the research process to allow integration and interoperability (22). Also, questions about the usefulness, applicability, and ethical aspects of some digital surveillance technologies still need to be addressed.

CONCLUSION

Health information systems with their multiple stakeholders have been put to the test, and valuable experience has been gained. Critical gaps have been revealed, such as under-resourced public health services, obsolete health information technologies, and a lack of interoperability to enable seamless data exchange among disparate organizations within the healthcare sector and administrative divisions. The COVID-19 pandemic has provided an opportunity to recognize and close those gaps to ensure better preparedness against future health emergencies.

Adequate financing into out-of-the-box data management systems is needed. People-centered, cradle-to-grave digitized health records that are seamless across health services and shared with public health and social services are key elements for better policy-making.

The advancements made in artificial intelligence and machine learning can potentially establish linkages between animal, environmental, and human health perspectives, ensuring quality health data and accurate information while respecting privacy rights.

The foundation of quality health data is one of the signs of mature health systems, along with universal health coverage and well-functioning community health and social services. The WHO European Region continues to support countries in developing the health information systems of the future.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available due to maintaining confidentiality of identifiable country data.

AUTHOR CONTRIBUTIONS

All authors contributed sufficiently and meaningfully to the manuscript's conception, design, drafting, editing, revising, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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Nutritional Characterization of Street Food in Urban Turkmenistan, Central Asia

Gabriela Albuquerque [1,2]*, Sofia Sousa [1,2,3], Inês Lança de Morais [4], Marcello Gelormini [4], Carla Motta [5], Gerard Bryan Gonzales [6], Azat Ovezov [7], Albertino Damasceno [8,9], Pedro Moreira [1,2,3,10], João Breda [11], Nuno Lunet [1,2,8] and Patrícia Padrão [1,2,3]

[1] EPIUnit, Instituto de Saúde Pública, Porto, Portugal, [2] Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal, [3] Faculdade de Ciências da Nutrição e Alimentação, Universidade do Porto, Porto, Portugal, [4] Nutrition, Physical Activity and Obesity Programme, Division of Noncommunicable Diseases and Life-Course, World Health Organization Regional Office for Europe, Copenhagen, Denmark, [5] Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA), Lisboa, Portugal, [6] Division of Human Nutrition and Health, Wageningen University, Wageningen, Netherlands, [7] National Public Health and Nutrition Centre, Ashgabat, Turkmenistan, [8] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Faculdade de Medicina, Universidade do Porto, Porto, Portugal, [9] Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique, [10] Centro de Atividade Física, Saúde e Lazer, Universidade do Porto, Porto, Portugal, [11] WHO Regional Office for Europe, Athens, Greece

Objective: Describing the availability and nutritional composition of the most commonly available street foods in *Ashgabat*, Turkmenistan.

Methods: One hundred sixty-one street food vending sites (six public markets) were assessed, through a collection of data on vending sites' characteristics and food availability, and samples of commonly available foods (21 homemade; 11 industrial), for chemical analysis.

Results: Fruit, beverages, and food other than fruit were available in 6.8, 29.2, and 91.9% of all vending sites, respectively. Regarding the latter, 52.7% of the vending sites sold only homemade products (main dishes, snacks, cakes, biscuits and pastries, bread, ice-cream chocolate and confectionery, savory pastries and sandwiches), 37.2% only industrial (ice-cream, chocolate and confectionery, cakes, biscuits and pastries, snacks, bread and savory pastries) and 10.1% both. Homemade foods presented significantly higher total fat [homemade 11.6 g (range 6.6–19.4 g); industrial 6.2 g (range 4.0–8.6 g), $p = 0.001$], monounsaturated, polyunsaturated and trans-fat, and sodium and potassium content per serving. Industrial wafers presented the highest mean saturated (11.8 g/serving) and trans-fat (2.32 g/serving) content. Homemade hamburgers presented the highest mean sodium content (1889 mg/serving).

Conclusions: Strategies to encourage the production and sales of healthier street foods, especially homemade, are needed to promote healthier urban food environments in urban Turkmenistan.

Keywords: Central Asia, food processing, nutritional value, ready-prepared foods, street food, Turkmenistan

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Erand Llanaj,
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The University of Sydney, Australia

***Correspondence:**
Gabriela Albuquerque
gabriela.albuquerque@ispup.up.pt

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INTRODUCTION

Non-communicable diseases (NCDs) are the leading cause of death and disability-adjusted life-years globally and in the World Health Organization (WHO) European region, where they account for 70% of all deaths (1). A more burdensome scenario is observed in Central Asian countries, such as Turkmenistan, where NCDs account for 76% of all deaths. Of these, cardiovascular diseases and cancer are among the leading causes of mortality (47.0 and 11.0%, respectively). Moreover, the high prevalence of obesity (18% in adults), diabetes, and other NCDs coexist with micronutrient deficiencies (2); high blood pressure, dietary risks, high body mass index, tobacco, use and malnutrition have been identified as important risk factors for disease burden in Turkmenistan (3). These observations seem to be in line with the reported double burden of malnutrition and nutrition transition in Central Asia (4).

The nutrition transition in the region has been characterized by a decreased consumption of cereal, roots, and tubers, and an increased availability of animal products, sugar, sweeteners, and vegetable oils in recent decades (5). It has also been observed a transition from traditional to more globalized eating patterns. Socioeconomic changes in the region, such as urbanization and increased participation of women in the urban working force, are leading to an increased consumption of food away from home (6), such as street food.

Street food is very popular worldwide, especially in low and middle-income countries (LMIC), due to its low-cost, convenience, considerable portion sizes and taste (7, 8). It has been described that it often replaces home meals, while also being a significant contributor to excess intake of energy and nutrients in several urban settings worldwide (8). Street food is part of the Central Asian gastronomy (9), reflecting locally available food products, practices and consumer preferences (10, 11). Nevertheless, the types of items available and their nutritional composition (8), as well as the role of these smaller businesses in the local food environments remain understudied, particularly in the region (8, 12, 13).

Turkmenistan is an upper-middle-income country in Central Asia, which has experienced positive economic development since the early 2000s, with the annual GDP growth being 6.2% in 2016. The population of the country has also been increasing in this period and was about 5.6 million people in 2016, of which 50.7% lived in urban areas (14). The capital city, *Ashgabat*, is the largest in the country, housing approximately 8,10,000 inhabitants (2018 data) (15). Furthermore, this is one of the countries in the WHO European region where a lack of representative surveys on nutritional status, dietary habits and food composition has been identified (16). Taking all this into consideration, the aim of this study was to characterize the street food environment in *Ashgabat*, focusing on food availability and the nutritional composition of the most commonly available foods and beverages.

METHODS

Setting, Study Design and Eligibility Criteria

This cross-sectional study was implemented within the scope of the FEEDcities project, supported by the WHO – Europe, and followed a stepwise standardized methodology (based on primary data collection through observation of vending sites and interviews with the vendors and chemical analysis of food samples) to characterize the urban food environment in countries in Central Asia and Eastern Europe (17). An evaluation, conducted in October 2016, was designed to provide an overall description of the urban food environment in *Ashgabat*, Turkmenistan [namely including fast-food vending sites, supermarkets and street food vending sites (18)]. This study assesses, specifically, the availability and nutritional composition of street food. The street food definition adopted in this study was the one proposed by Food and Agriculture Organization and WHO, as "ready-to-eat foods and beverages prepared and/or sold by vendors or hawkers especially in the streets and other similar places" (19, 20).

Information provided by local authorities and gathered during field visits before study implementation outlined that most street food vending sites were concentrated in traditional outdoor markets and their surroundings. Thus, local authorities selected six markets, from a total of 10 identified in *Ashgabat*, where this study would be conducted. To define the study area, a 500-m buffer was built around the centroid of each of the selected markets, covering the markets and their surroundings.

Eligible vending sites were defined as the business establishments selling ready-to-eat food, including beverages and/or snacks, from any venue other than permanent storefront businesses or establishments with four permanent walls not selling directly to the street, operating in the predefined perimeter. This included mobile vendors, as well as sellers with semi-static or stationary vending units. The exclusion criteria were the following: (1) food establishments with four permanent walls; (2) permanent storefront business; (3) street vendors selling exclusively non-food products or raw foods not ready-to-eat; (4) food stalls and carts that were part of permanent stores or licensed establishments.

Data Collection: Vending Sites, Vendors and Food Availability

The markets were assessed in seven consecutive days. Field researchers, operating in pairs, canvassed systematically each study area to find street food vendors. The vendors from all eligible vending sites were invited to participate.

At each vending site, after registering the Global Positioning System (GPS) coordinates, the interviewers collected the following information, through direct observation: sex of the vendor, mobility of the vending site and type of physical setup. Stationary vending sites were further classified into formal [stand, showcase, kiosk, cafeteria (vending site with no waiter service, where food is displayed in aligned counters/stalls or booths and customers take their desired food as they walk along)] or improvised (bench with table, vending machine, and other improvised sites such as popcorn machines, refrigerators or freezer machine selling soft ice-cream).

The vendor was then approached by the interviewers, who explained the study objectives and procedures and asked for verbal informed consent to participate in the study. When the vendor agreed, the interviewers carried out computer-assisted personal interviewing, enquiring about food availability, including serving sizes (18). All the 161 eligible street food vendors approached agreed to participate.

Foods available were grouped according to their nature, into fruit (product in *natura*, either fresh or dry), beverages (any alcoholic and non-alcoholic drink) or food other than fruit. Food other than fruit was further classified as homemade (foods of domestic manufacture cooked and/or prepared at home or on the street, even if using industrial ingredients) or industrial (food products produced by the food industry and sold as is without further preparation and/or cooking). Homemade food was also grouped according to the preparation method in cooked or uncooked. Both homemade and industrial foods were grouped according to broader food groups, that were created based on the groups of the WHO nutrient profile model (21): (1) bread; (2) cakes, biscuits and pastries; (3) main dishes (4) sandwiches; (5) savory pastries, (6) snacks and (7) ice-cream, chocolate and confectionery. Beverages were further classified into soft drinks, water, fruit juice-based drinks, fresh fruit juice-based drinks, milk, energy drinks, coffee, tea, fruit smoothies (ice and natural fruit extract-based beverages), alcoholic and traditional beverages. The latter included *ayran* (savory yogurt-based beverage, made by mixing yogurt with water and salt), kephyr (fermented milk drink made with a yeast or bacterial fermentation starter of kefir grains), *yogurt and kompot* (made by cooking fruit in a large volume of water, often with sugar or raisins), non-alcoholic.

Food Sample Collection

Following the computation of the frequency of each of the identified foods and beverages across all the vending sites included in the study, samples of the most commonly available foods and beverages were collected for nutritional composition assessment. The most frequent homemade foods ($n = 21$) were bread (namely *chiorek* and *milk chiorek*), sandwiches and main dishes (doner kebab, fried potatoes, hamburger, hot-dog, pizza, cabbage salad and lentil soup), savory pastries (baked or fried; filled with meat, vegetables or potato, such as sausage roll, *samsa*, *pirozhki*, *fitchi, pirog* and *chebureki*), a snack (boiled corn cob) and cakes and pastries (biscuits, bun, muffin (*keksi*),cake and wafers). The most frequent industrial foods ($n = 11$) were bread, snacks (croutons, chips, salty sticks), biscuits, muffin (*keksi*), gingerbread biscuit (*pryaniki*), wafers, halva, chocolate and ice-cream.

The selection of the vending sites where the food samples were collected was carried out randomly, from the list of the GPS coordinates of the eligible vending sites previously assessed. A sample of each food product, corresponding to one serving, was bought whenever possible at these vending sites. If it was not possible to buy the target foods at the selected coordinates, a systematic selection procedure was followed, in which field researchers start moving north from that point and change direction clockwise (first east, then south, then west, then north again) whenever the limits of the study area or a physical barrier (such as a wall or a canal) were met until reaching vending sites where these foods were available (18). In each vending site, only one sample was collected.

For each selected homemade and industrial food, a total of four samples was defined to be collected from different vending sites. Nevertheless, it was not possible to achieve this for most of them ($n = 28$, out of 32). A total of 76 samples (55 homemade and 21 industrial) were collected in four consecutive days.

Nutritional Composition Assessment

After collection, samples were homogenized, weighted and stored in a freezer (−18°C) until the nutritional composition assessment. Total fat determination was performed according to AOAC 948.15, 2000, methodology with an acid hydrolysis method followed by Soxhlet extraction with petroleum ether (40 – 60°C) as the extraction solvent (22).

Fatty acid profile was determined by gas chromatography. Analysis was performed according to the ISO 12966 (2015–2017) and the Commission Regulation (EC) No. 796/2002 (2002), with slight modifications, as described by Albuquerque et al. (23). A gas chromatograph (Hewlett Packard 7890B series GC-Systems, Waldbronn, Germany) equipped with a flame ionization detector (FID) and a 100 m, 0.25 mm ID, 0.2um column (Agilent HP-88, Santa Clara, United States) was used. Helium was used as a carrier gas at a flow rate of 1.0 ml/min. The oven temperature was programmed as follows: 50°C for 1 min, then to 175°C at 10°C/min, held for 15 min, then finally to 240°C at 4°C/min, held for 15 min. The injector and detector temperatures were 280 and 280°C, respectively. The identification of the fatty acid methyl esters was based on comparison of the retention times of sample peaks with those of a commercially available FAME mixture (Supelco 37 Component FAME Mix) from the supplier (Sigma-Aldrich Co. LLC). The results were expressed on a relative fatty acids basis and grouped as saturated (SFA), monounsaturated (MUFA), polyunsaturated (PUFA), n-3 and n-6 fatty and trans fatty acids (TFA).

Sodium and potassium analyses were performed after an acid digestion in a closed-vessel microwave system (ETHOS UP Microwave Digestion System), as described by Nascimento et al. (24), followed by determination of minerals using an inductively coupled plasma optical emission spectrometer (Agilent 5110 ICP-OES). The analytical results were the average of two determinations per food sample. If the coefficient of variation of duplicates was above 5% for fatty acids and micronutrients another two replicates where performed. In this case, the average of two determinations consistent with the acceptance criterion was calculated. All the analytical results were expressed by serving size, in g.

Statistical Analysis

The vending sites and food availability were characterized through absolute and relative frequencies (categorical variables). Pearson's $\chi 2$ test was used to identify statistically significant differences between formal and informal street food vending sites. Markets were defined as the sampling units. The statistical analyses were conducted adjusting for the clustering at the sampling unit level.

Regarding the nutritional composition assessment, mean serving sizes per food, in g, were calculated as the mean weight of the individual samples collected for each of the foods. Likewise, per-serving levels of each nutrient were calculated as the mean content of the individual samples and expressed in g/serving (macronutrients) or mg/serving (micronutrients). Results were presented for each food, as the mean and range of total fat, including SFA, MUFA, PUFA, n-3 fatty acids, n-6 fatty acids, TFA, sodium and potassium per serving and molar sodium-to-potassium (Na/K) ratios. Contents of sodium and potassium of each sample were converted to millimoles using their molar weights, 23.0 g/mol and 39.1 g/mol, respectively, to calculate individual molar Na/K ratios. The nutritional composition of homemade and industrial foods was compared using the nonparametric Mann–Whitney U test.

A *p*-value (p) <0.05 was considered statistically significant. Statistical analysis was performed using the software STATA® version 15.1 for Windows®.

RESULTS

Food Vending Sites and Vendors

Supplementary Figure 1 depicts the distribution of the selected markets throughout *Ashgabat* city. All vending sites were stationary, of which the most frequent physical setups were formal, such as *stand* (45.6%) and showcases (23.9%). Nearly three in every four street food vendors were women (68.9%).

Food Availability

Fruit, beverages and food other than fruit were available, respectively, in 6.8, 29.2 and 91.9% of the vending sites. Over half of the vending sites (52.7%) sold only homemade, 37.2% only industrial and 10.1% both homemade and industrial foods. Among the vending sites selling homemade foods, all had cooked foods available, while 35.5% of them sold prepared foods. Main dishes, snacks and cakes, biscuits and pastries were the most commonly available groups of homemade foods, in at least 20% of these vending sites. Ice-cream, chocolate and confectionery, cakes, cookies and sweet pastries and snacks were the most frequent groups of industrial foods, available in over 50% of the stationary vending sites selling industrial foods. The most commonly available beverages were soft drinks (78.7%), water (76.6%) and traditional beverages (39.7%). Overall, there were no statistically significant differences in street food availability between improvised and formal street food outlets. The only exceptions were prepared homemade foods, which were more frequent in formal street food vending sites (improvised: $n = 3$; 18.8%, formal: $n = 30$; 39.0%, $p = 0.005$), and homemade snacks (improvised: $n = 11$; 68.8%, formal: $n = 15$; 19.5%, $p = 0.007$), industrial cakes, biscuits and pastries (improvised: $n = 5$; 100.0%, formal: $n = 42$; 64.6%, $p = 0.013$), and tea (improvised: $n = 3$; 37.5%, formal: $n = 5$; 12.8%, $p = 0.044$), which were more frequently available in improvised street food vending sites (**Table 1**).

Nutritional Composition

Overall, homemade foods presented significantly higher total fat (median g/serving: 11.6 vs. 6.2, $p = 0.001$), MUFA (median g/serving: 3.4 vs. 1.9, $p < 0.001$), PUFA (median g/serving: 2.7 vs. 1.0, $p < 0.001$), TFA (median g/serving: 0.2 vs. 0.0, $p = 0.020$), sodium (median mg/serving: 573 vs. 99, $p < 0.001$) and potassium (median mg/serving: 219 vs. 104, $p < 0.001$) contents per serving than industrial foods. In contrast, industrial foods presented, per 100g, a significantly higher content of total fat (median g/100 g: 17.1 vs. 8.8, $p < 0.001$), MUFA (median g/100 g: 5.2 vs. 2.3, $p < 0.001$) and potassium (median mg/100 g: 236 vs. 172, $p < 0.001$). These foods also presented higher SFA content per serving (median: 43.1 vs. 34.1, $p = 0.014$), and per 100 g (median: 2.8 vs. 7.1, $p < 0.001$). The nutritional composition of the collected street foods, per 100 g, is presented in **Supplementary Tables 2**, **3**.

Homemade hamburger and fried potatoes presented the highest mean total fat (32.1 and 32.8 g/serving, respectively). Hamburger presented, in addition, the highest mean MUFA content (10.1 g/serving), while fried potatoes presented, in addition, among the highest mean PUFA content (13.0 g/serving), particularly $n-6$ (12.6 g/serving) and n-3 (0.5 g/serving), although the highest PUFA and n-6 contents were found in homemade *pirozhky* (18.5 and 18.4 g/serving, respectively). Homemade cake and soup presented among the highest values of n-3 fatty acids (0.2 g/serving). Homemade hamburger (11.1 g/serving) and industrial wafer (11.8 g/serving) presented the highest SFA contents. The highest mean TFA contents were found in homemade and industrial wafers (respectively, 0.65 and 1.81 g/serving) (**Table 2**).

The mean sodium content ranged between 9 mg/serving in industrial halva and 1,889 mg/serving in homemade hamburger whereas mean potassium content ranged between 33 mg/serving in homemade biscuits and 1,299 mg/serving in homemade fried potatoes. From the 32 foods analyzed, only six presented average sodium/potassium ratio below 1: industrial chocolate and halva (0.2), wafers (0.3), homemade boiled corn and fried potatoes (0.4), industrial ice-cream (0.9), homemade ice-cream (0.5) and chocolate (0.6). The highest sodium/potassium ratio was found in industrial salty sticks (17.3) (**Table 3**).

DISCUSSION

In *Ashgabat*, street food vending sites selling homemade street foods were the most frequent. Main dishes, snacks and cakes, biscuits and sweet pastries were the most commonly available groups of homemade foods, while ice-cream, chocolate and confectionery, cakes, biscuits and pastries and snacks were the most commonly available groups of industrial foods. The homemade foods presented higher fat (including MUFA, PUFA and TFA), sodium and potassium content per serving than industrial foods, while the later were richer in total fat, MUFA, SFA and potassium per 100 g.

The higher availability of homemade cooked foods may corroborate previous evidence that street food usually replaces home-cooked meals (8). Notwithstanding, when analyzing the

TABLE 1 | Food offer by type of vending site in Ashgabat, Turkmenistan.

	Total (*n* = 161)		**Type of vending site**				
			Improvised (*n* = 21)		**Formal (*n* = 140)**		***p***
	n	**%**	***n***	**%**	***n***	**%**	
Fruit	11	6.8	2	9.5	9	6.4	0.508
Food other than fruit	148	91.9	20	95.2	128	91.4	0.668
Industrial	55	37.2	4	20.0	51	39.8	0.208
Homemade and industrial	15	10.1	1	5.0	14	10.9	
Homemade	78	52.7	15	75.0	63	49.2	
Homemade foods: preparation[a]							
Cooked	93	100.0	16	100.0	57	74.0	0.074
Prepared but non-cooked	33	35.5	3	18.8	30	39.0	0.005[e]
Homemade foods: groups[b]							
Main dishes	33	35.5	3	18.8	30	39.0	0.124
Snacks	26	28.0	11	68.8	15	19.5	0.007[e]
Cakes, biscuits and pastries	19	20.4	0	0.0	19	24.7	0.083
Bread	18	19.4	0	0.0	18	23.4	0.122
Ice-cream, chocolate and confectionery	16	17.2	2	12.5	14	18.2	0.549
Savoury pastries	13	14.0	2	12.5	11	14.3	0.694
Sandwiches	12	12.9	3	18.8	9	11.7	0.528
Industrial foods: groups[c]							
Ice-cream, chocolate and confectionery	54	77.1	3	60.0	51	78.5	0.632
Cakes, biscuits and pastries	47	67.1	5	100.0	42	64.6	0.013[e]
Snacks	39	55.7	2	40.0	37	56.9	0.712
Bread	14	20.0	0	0.0	14	21.5	0.209
Savoury pastries	2	2.9	0	0.0	2	3.1	0.426
Beverages	47	29.2	8	38.1	39	27.9	0.202
Soft drinks	37	78.7	8	100.0	29	74.4	0.157
Water	36	76.6	8	100.0	28	71.8	0.110
Traditional beverages[d]	27	39.7	6	37.5	21	40.4	0.431
Fruit juice-based drinks	22	46.8	5	62.5	17	43.6	0.437
Tea	8	17.0	3	37.5	5	12.8	0.044[e]
Coffee	5	10.6	2	25.0	3	7.7	0.110
Fresh Fruit juice-based drinks	5	10.6	0	0.0	5	12.8	0.589
Milk	4	8.5	0	0.0	4	10.3	0.245
Alcoholic beverages	4	8.5	0	0.0	4	10.3	0.263
Energy drinks	3	6.4	2	25.0	1	2.6	0.116
Fruit smoothies	1	2.1	0	0.0	1	2.6	0.725

[a] *The sum of the values for this variable is higher than the total number of homemade foods, as each vendor could offer foods prepared in different ways.*

[b] *The sum of the values for this variable is higher than the total number of homemade foods, as each vendor could offer foods from different groups.*

[c] *The sum of the values for this variable is higher than the total number of industrial foods, as each vendor could offer foods from different groups.*

[d] *Traditional beverages (non-alcoholic): yoghurt (n = 12), ayran (n = 9), kephyr (n = 5), and kompot (n = 1).*

[e] *Statistically significant differences according to Pearson's Chi-square test, for a confidence level of 95% (p-value < 0.05).*

absolute frequency of homemade and industrial food groups in this street food environment, industrial snacks, cakes, biscuits and savory pastries are the ones available in a larger number of vending sites in comparison with, for example, homemade main dishes, the most popular homemade foods group. This, aligned with the observation that homemade snacks, cakes, biscuits and sweet pastries were also common, might indicate a predominance of snacking options among street foods in *Ashgabat,* both industrial and homemade. Data retrieved from the Food Systems Dashboard shows, in line with these findings, a recent trend of increased availability of packaged and ultra-processed foods at the national level (25). In this study, it was also observed a coexistence of both westernized and traditional options among the most commonly available beverages (e.g. soft drinks and traditional drinks) and foods other than fruit (e.g. hamburger, fried potatoes and *doner kebab*, lentil soup). Altogether, these findings might suggest a possible westernization of food habits in urban Turkmenistan, as observed in other Central Asian urban

TABLE 2 | Nutritional composition (Total fat, MUFA, PUFA, SFA and TFA), per serving, of the street food samples collected in Ashgabat.

	N	Mean serving size (min-max) (g/serving)		Mean total fat (min-max) (g/serving)		Mean MUFA (min-max) (g/serving)		Mean PUFA (min-max) (g/serving)		Mean *n*−6 (min-max) (g/serving)		Mean *n*−3 (min-max) (g/serving)		Mean SFA (min-max) (g/serving)		Mean TFA (min-max) (g/serving)	
Industrial																	
Biscuits	3	30	(29–31)	5.6	(4.4–7.3)	1.4	(0.7–2.2)	0.6	(0.3–1.2)	0.6	(0.3–1.2)	0.0	(0.0–0.1)	3.3	(2.7–3.7)	0.07	(0.01–0.20)
Bread	2	50	(50–50)	1.6	(1.1–2.1)	0.4	(0.2–0.5)	0.8	(0.6–1.0)	0.8	(0.6–1.0)	0.0	(0.0–0.0)	0.3	(0.1–0.5)	0.01	(0.01–0.01)
Chips	2	20	(20–20)	6.0	(5.0–7.0)	1.5	(1.4–1.6)	0.4	(0.3–0.4)	0.4	(0.3–0.4)	0.0	(0.0–0.0)	3.8	(3.0–4.5)	0.06	(0.02–0.09)
Chocolate	1	33	(33–33)	7.4	(7.4–7.4)	0.6	(0.6–0.6)	0.3	(0.3–0.3)	0.3	(0.3–0.3)	0.0	(0.0–0.0)	6.1	(6.1–6.1)	0.01	(0.01–0.01)
Croutons	1	38	(38–38)	4.6	(4.6–4.6)	2.0	(2.0–2.0)	0.7	(0.7–0.7)	0.6	(0.6–0.6)	0.0	(0.0–0.0)	1.5	(1.5–1.5)	0.18	(0.18–0.18)
Halva	2	20	(20–20)	8.0	(8.0–8.1)	2.3	(2.2–2.4)	4.0	(4.0–4.0)	4.0	(4.0–4.0)	0.0	(0.0–0.1)	1.4	(1.3–1.4)	0.01	(0.00–0.01)
Ice-cream	1	70	(70–70)	4.6	(4.6–4.6)	1.4	(1.4–1.4)	0.4	(0.4–0.4)	0.4	(0.4–0.4)	0.0	(0.0–0.0)	2.5	(2.5–2.5)	0.01	(0.01–0.01)
Keksi (muffin)	2	49	(49–49)	9.0	(8.5–9.6)	2.9	(2.5–3.3)	0.8	(0.6–0.9)	0.7	(0.6–0.8)	0.0	(0.0–0.1)	4.6	(3.4–5.7)	0.39	(0.26–0.52)
Pryaniki	2	60	(55–64)	3.1	(2.6–3.5)	0.9	(0.8–1.0)	1.4	(1.3–1.4)	1.4	(1.3–1.4)	0.0	(0.0–0.0)	0.6	(0.2–1.1)	0.01	(0.01–0.01)
Salty sticks	2	48	(46–50)	8.7	(7.7–9.7)	2.8	(2.4–3.2)	1.9	(1.1–2.6)	1.8	(0.9–2.6)	0.1	(0.0–0.1)	3.6	(2.2–5.0)	0.09	(0.04–0.14)
Wafers	3	94	(71–108)	26.2	(16.2–35.7)	9.8	(5.6–14.3)	1.6	(0.9–2.9)	1.5	(0.8–2.7)	0.1	(0.0–0.1)	11.8	(8.4–17.2)	1.81	(0.45–4.45)
Homemade																	
Biscuits	2	33	(32–33)	8.5	(7.8–9.2)	3.0	(2.5–3.4)	1.1	(0.9–1.3)	1.0	(0.8–1.2)	0.1	(0.1–0.2)	3.3	(1.9–4.6)	0.76	(0.33–1.19)
Boiled corn	3	152	(132–163)	1.9	(0.0–3.2)	0.5	(0.0–0.8)	0.9	(0.0–1.4)	0.8	(0.0–1.3)	0.1	(0.0–0.1)	0.4	(0.0–0.8)	0.01	(0.00–0.03)
Bread (*chiorek*)	4	120	(120–120)	2.0	(1.3–3.9)	0.3	(0.2–0.5)	1.3	(0.8–2.5)	1.2	(0.8–2.4)	0.1	(0.0–0.2)	0.3	(0.2–0.6)	0.01	(0.00–0.02)
Bread (*milk chorek*)	3	120	(120–120)	1.1	(0.7–1.5)	0.2	(0.1–0.3)	0.6	(0.4–0.8)	0.5	(0.3–0.7)	0.1	(0.0–0.1)	0.2	(0.2–0.3)	0.00	(0.00–0.00)
Bun	3	94	(71–119)	2.4	(1.1–4.1)	0.6	(0.4–1.0)	0.8	(0.4–1.2)	0.7	(0.4–1.2)	0.0	(0.0–0.0)	0.9	(0.2–1.7)	0.02	(0.01–0.03)
Chebureki	4	99	(47–128)	9.3	(3.0–15.2)	2.1	(0.7–3.8)	4.2	(1.6–6.1)	4.0	(1.5–5.6)	0.1	(0.0–0.5)	2.5	(0.5–5.9)	0.13	(0.04–0.20)
Doner kebab	3	260	(249–270)	28.0	(17.1–37.9)	8.0	(5.2–11.9)	8.0	(5.5–13.0)	7.9	(5.4–12.8)	0.1	(0.1–0.2)	10.1	(5.4–17.5)	0.54	(0.21–0.13)
Fitchi	3	192	(164–243)	13.0	(8.4–15.6)	4.4	(2.7–5.4)	2.2	(1.9–2.7)	2.1	(1.7–2.7)	0.1	(0.0–0.2)	5.4	(3.4–6.8)	0.46	(0.07–0.86)
Fried potatoes	3	195	(175–206)	32.8	(11.2–69.1)	7.9	(1.3–12.6)	13.0	(5.1–27.8)	12.6	(3.8–27.8)	0.5	(0.0–1.3)	10.1	(0.8–25.2)	0.31	(0.05–0.48)
Hamburger	1	288	(288–288)	32.1	(32.1–32.1)	10.1	(10.1–10.1)	9.3	(9.3–9.3)	9.1	(9.1–9.1)	0.1	(0.1–0.1)	11.1	(11.1–11.1)	0.17	(0.17–0.17)
Hot-dog	3	217	(143–346)	17.0	(6.8–31.0)	4.5	(1.8–6.8)	7.9	(1.9–17.2	7.8	(1.9–17.2)	0.1	(0.0–0.2)	3.7	(2.8–5.5)	0.14	(0.03–0.25)
Keksi (muffin)	2	101	(86–115)	15.4	(7.6–23.3)	4.6	(3.5–5.6)	5.6	(0.9–10.4)	5.5	(0.8–10.3)	0.1	(0.1–0.1)	4.3	(2.7–5.9)	0.29	(0.20–0.39)
Pirog (savoury pie)	4	158	(108–213)	12.2	(1.4–20.9)	4.0	(0.5–6.7)	2.0	(0.2–4.2)	2.0	(0.2–4.2)	0.0	(0.0–0.1)	5.5	(0.5–9.9)	0.18	(0.02–0.35)
Pirozhky	4	100	(91–121)	30.3	(5.1–95.4)	5.5	(1.1–16.8)	18.5	(2.7–62.7)	18.4	(2.7–62.4)	0.1	(0.0–0.3)	4.7	(1.0–11.0)	0.26	(0.03–0.73)
Pirozhnoe (cake)	2	102	(91–113)	17.7	(15.2–20.1)	5.3	(4.5–6.0)	3.7	(1.3–6.1)	3.6	(1.2–5.9)	0.2	(0.0–0.4)	7.6	(6.5–8.6)	0.38	(0.15–0.60)
Pizza	1	174	(174–174)	13.2	(13.2–13.2)	3.3	(3.3–3.3)	2.6	(2.6–2.6)	2.5	(2.5–2.5)	0.0	(0.0–0.0)	6.5	(6.5–6.5)	0.21	(0.21–0.21)
Salad (cabbage)	2	101	(99–104)	9.1	(8.1–10.0)	1.9	(1.8–2.0)	4.0	(3.9–4.0)	3.9	(3.9–3.9)	0.0	(0.0–0.1)	2.6	(1.7–3.6)	0.14	(0.07–0.22)
Samsa	1	110	(110–110)	7.9	(7.9–7.9)	2.5	(2.5–2.5)	0.6	(0.6–0.6)	0.6	(0.6–0.6)	0.0	(0.0–0.0)	4.2	(4.2–4.2)	0.13	(0.13–0.13)
Sausage roll	3	84	(71–98)	5.9	(4.8–6.5)	1.4	(1.1–1.9)	2.6	(1.8–3.8)	2.6	(1.7–3.8)	0.0	(0.0–0.0)	1.5	(1.1–2.1)	0.07	(0.01–0.19)
Soup (lentil)	1	382	(382–382)	15.7	(15.7–15.7)	6.6	(6.6–6.6)	3.7	(3.7–3.7)	3.6	(3.6–3.6)	0.2	(0.2–0.2)	4.4	(4.4–4.4)	0.39	(0.39–0.39)
Wafers	3	88	(69–102)	19.9	(8.1–30.1)	5.8	(2.5–8.4)	3.4	(1.5–6.7)	3.4	(1.5–6.6)	0.0	(0.0–0.1)	9.2	(3.7–17.3)	0.65	(0.04–1.09)

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TFA, trans fatty acids.

TABLE 3 | Nutritional composition (Na, K and Na/K), per serving, of the street food samples collected in Ashgabat.

	N	Mean serving size (min-max) (g/serving)		Mean Na (min-max) (mg/serving)		Mean K (min-max) (mg/serving)		Mean Na/K (min-max)	
Industrial									
Biscuits	3	30	(29–31)	66	(44–87)	68	(44–100)	1.9	(0.7–2.5)
Bread	2	50	(50–50)	272	(222–323)	114	(103–125)	4.2	(3.0–5.3)
Chips	2	20	(20–20)	129	(74–184)	89	(29–149)	5.7	(0.8–10.7)
Chocolate	1	33	(33–33)	30	(30–30)	246	(246–246)	0.2	(0.2–0.2)
Croutons	1	38	(38–38)	161	(161–161)	81	(81–81)	3.4	(3.4–3.4)
Halva	2	20	(20–20)	9	(9–10)	99	(96–102)	0.2	(0.2–0.2)
Ice–cream	1	70	(70–70)	39	(39–39)	71	(71–71)	0.9	(0.9–0.9)
Keksi (muffin)	2	49	(49–49)	153	(128–178)	115	(101–129)	2.2	(2.2–2.3)
Pryaniki	2	60	(55–64)	63	(57–68)	103	(92–114)	1.0	(1.0–1.1)
Salty sticks	2	48	(46–50)	885	(739–1031)	95	(60–130)	17.3	(13.5–2.1)
Wafers	3	94	(71–108)	93	(83–111)	520	(362–725)	0.3	(0.2–0.4)
Homemade									
Biscuits	2	33	(32–33)	112	(86–137)	33	(32–33)	5.8	(4.4–7.2)
Boiled corn	3	152	(132–163)	80	(21–195)	401	(326–475)	0.4	(0.1–1.0)
Bread (*chiorek*)	4	120	(120–120)	560	(411–713)	180	(149–211)	5.2	(4.7–5.7)
Bread (milk *chorek*)	3	120	(120–120)	667	(582–767)	179	(164–202)	6.3	(6.0–6.5)
Bun	3	94	(71–119)	121	(79–203)	118	(90–163)	1.6	(1.3–2.1)
Chebureki	4	99	(47–128)	487	(267–650)	177	(146–232)	4.6	(3.1–6.0)
Doner kebab	3	260	(249–270)	985	(799–1228)	711	(570–927)	2.4	(1.7–3.3)
Fitchi	3	192	(164–243)	1157	(756–1470)	313	(242–447)	6.5	(5.2–8.7)
Fried potatoes	3	195	(175–206)	342	(135–568)	1299	(1175–1504)	0.4	(0.2–0.6)
Hamburger	1	288	(288–288)	1889	(1889–1889)	620	(620–620)	5.2	(5.2–5.2)
Hot–dog	3	217	(143–346)	1005	(902–1169)	588	(255–1252)	4.6	(1.6–6.2)
Keksi (muffin)	2	101	(86–115)	356	(355–357)	121	(106–136)	5.1	(4.4–5.7)
Pirog (savoury pie)	4	158	(108–213)	983	(541–1454)	263	(169–356)	6.2	(5.4–6.9)
Pirozhky	4	100	(91–121)	355	(100–554)	165	(108–206)	3.6	(1.6–5.8)
Pirozhnoe (cake)	2	102	(91–113)	277	(258–296)	163	(135–190)	3.0	(2.3–3.7)
Pizza	1	174	(174–174)	1061	(1061–1061)	379	(379–379)	4.7	(4.7–4.7)
Salad (cabbage)	2	101	(99–104)	789	(682–896)	227	(214–239)	5.9	(5.4–6.3)
Samsa	1	110	(110–110)	488	(488–488)	144	(144–144)	5.8	(5.8–5.8)
Sausage roll	3	84	(71–98)	377	(209–591)	140	(95–186)	4.7	(3.0–7.2)
Soup (lentil)	1	382	(382–382)	1189	(1189–1189)	695	(695–695)	2.9	(2.9–2.9)
Wafers	3	88	(69–102)	112	(52–168)	114	(40–181)	1.8	(1.6–2.2)

K, potassium; Na, sodium; Na/K sodium-potassium ratio.

centers (26, 27), with traditional foods and beverages becoming replaced by westernized options and, eventually, main meals by snacking meals.

Homemade street foods are usually available in large servings, being one of the reasons for their popularity (7, 8), a fact also observed in this study. Another difference was additionally observed, regarding the nature of the predominant homemade and industrial food groups, with main dishes and sandwiches (served in larger servings) being only available as homemade options. This may contribute to justify the discrepancies found in the comparison of the nutritional composition per serving and per 100 grams of food. The highest mean fat content values per serving found in homemade main dishes, sandwiches and savory pastries (such as hamburger, *doner kebab*, fried potatoes and *pirozhky*) and in industrial wafers are also in line with previous findings among street foods in Central Asia (26, 27) and Eastern Europe (28). The contribution of each fatty acid to total fat varied widely by food group. The SFA content exceeded 40% of total fat in homemade main dishes and savory pastries, in homemade and industrial bakery products, as well as industrial confectionery and snacks. The mean TFA contribution for the total fat was particularly high in homemade cakes and pastries, reaching a maximum of approximately 10% in biscuits, which is concerning given that TFA were proven to be exceptionally harmful even in small intake amounts (2% of total energy intake) (29, 30). Although there is a dearth of data regarding nutritional composition of food in Turkmenistan, similar TFA levels were reported in industrial biscuits, cakes and wafers commercialized in 2015–16 in countries of the former Soviet Union (31). The heterogeneous fatty acid profile found might reflect not only the wide variability between food groups, as also within the same group, including differences in food preparation. For example, the most complex preparations such as main dishes and sandwiches might involve the use of different cooking methods, and varieties and quantities of ingredients, specifically fats and oils (8). A study conducted in urban and rural slums in India reported an association between the high SFA and TFA amounts in savory pastries and snacks and the oils used to cook them (32). In addition, shortenings, also rich in these fatty acids, are still traditionally used in bakery cooking as they provide desirable tenderness, texture and extend a product's shelf life at a low cost (33, 34). Moreover, although the oils and fats used to cook may conform with quality standards, unsafe cooking practices such as continuous reuse of oil for frying may lead to increased TFA concentrations (35) as well as the formation of other toxic compounds.

In this study, traditional homemade foods were the main sources of sodium, with some main dishes, sandwiches and snacks surpassing half the daily recommended intake of 2,000 mg and, for example, hamburger reaching 95% of this recommendation (36). Some homemade street foods, such as bread and lentil soup, deserve particular attention since they might be expected to be examples of healthier street foods, but present considerable amounts of sodium. This might be even more noticeable in the case of bread, which might be consumed several times throughout the day, inclusively during main meals. Similar findings have been described among street foods in Tajikistan and Kyrgyzstan (37) and, altogether, these might suggest alignment with global observations that meat, bread and bakery products are among the main contributors to daily sodium intake (38). Findings from national studies in Turkmenistan, conducted, respectively in 2017 and 2018, highlight a mean daily sodium intake among the adult population of approximately double the recommended [4,400 mg (25) and 3,800 mg (39)].

Most homemade and industrial street foods groups presented mean molar sodium-to-potassium ratios above the optimal ratio of 1, recommended by the WHO to prevent NCDs (36, 40). This underlines the high sodium content of these foods but also highlights their generally low potassium content (only five out of the 32 analyzed street foods complied with this recommendation). Some garnishes and sandwiches, including potato or vegetables, such as fried potatoes and *doner kebab*, had the highest content of this nutrient [representing 23.8–32.5% of the minimum daily intake recommended 3,510 mg (41)], but most foods presented a maximum of 20% of its minimum daily recommended intake. This observation reinforces the need to increase the availability of nutritionally dense foods and ingredients, such as vegetables and fruit, to the urban population of Turkmenistan. Promoting the consumption of potato, a traditional staple, together with vegetables and pulses, could be an interesting and sustainable strategy to increase potassium availability, coupled with an effort to rely on healthier cooking practices than frying, and to decrease the amount of salt and fat added in preparation.

Many characteristics of the street food availability in the urban food environment of *Ashgabat* seem to be in line with the nutrition transition occurring in Central Asia (5, 42, 43), with important health impacts. Regarding its nutritional composition, the high fat (namely SFA and TFA) and sodium content and low potassium content are among the main risk factors for the development of NCDs (42) and may also contribute to justify the high prevalence and mortality by NCDs in the country, particularly cardiovascular disease (2, 3), and the relatively low life expectancy at birth [68.2 years, in 2019 (14)]. From a public health perspective, it seems timely to address these issues in the design and implementation of national and local health policies, following the global recommendation for increasing local-level interventions, in order to tackle health inequities (44). Following the need for increasing awareness of the harmfulness of TFA and sodium, even in small amounts, several international efforts to eliminate industrially-produced TFA (34) and sodium (45) from the global food supply have been recently intensified, especially in the WHO European region. The WHO recommends that total TFA intake should be limited to < 1% of total energy intake, corresponding to < 2.2 g/day in the diet of a regular adult (2,000 kcal) (30). In Turkmenistan, there are currently no regulations limiting the content of SFA or TFA, neither sodium in foods, in opposition to some of its neighboring countries, members of the Eurasian Economic Union, which have adopted a regulatory limit of 2 g TFA/100 g fat in foods, in partnership between national governments and the food industry (46). Nevertheless, the adoption of similar measures in Turkmenistan might contribute to improving the lipid profile of street food. Despite the challenge of monitoring homemade foods, it is expected that the industrial ingredients used in their preparation would have to follow these standards, resulting, thus in similar compliance to that of industrial foods. In sum, the findings of this study highlight a need to study the commonly used ingredients and practices in street food preparation and the street food manufacturers' motivations to do so. The study of customers' motivations for buying street food and their nutritional literacy could additionally contribute to the design of nutritional education strategies specific to the needs and preferences of all the involved stakeholders.

This study might contribute to reinforce previous literature on street food, providing insight into an understudied region (12) and more urbanized settings (28). The stepwise approach aimed to ensure an unbiased and comprehensive characterization of the street foods available in Ashgabat's foodscape, particularly on the nutritional composition of those most frequent, which reflect their popularity. Although the results may not be generalized due to local cultural specificities, the vast potential of the methodology to be adapted to different settings (17) allows comparison of results. The nutritional composition of the analyzed foods was estimated by chemical analysis, which overcomes limitations of previous studies (8, 12, 42). Future assessments could comprise a broader array of nutrients and energy. In this study, the option for the presentation per serving aimed to emphasize the role of the serving size when discussing the nutritional quality of food. Nevertheless, given that in this research area it is common to present the nutritional composition per 100 g of food, this respective information is available in

Supplementary Tables 1, **2**. Above all, the work developed under this study is anticipated to have contributed to narrowing the evidence gap on food, nutrition and NCDs in Turkmenistan and Central Asia. The findings have the potential to support current efforts in national health and food systems in the scope of the Decade of Action on Nutrition (2016–2025) (47) and contribute to the evolution of healthcare, health and food policy, ultimately improving the population's health.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions. The participants of this study did not agree for their data to be shared publicly, so supporting data is not available. Requests to access these datasets should be directed to GA, gabriela.albuquerque@ispup.up.pt.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Institute of Public Health of the University of Porto. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MG, AD, PM, JB, NL, and PP designed the study. IL supervised the study implementation and data collection. CM and GG were responsible for the conception of the methodology, training and supervision of the chemical analysis of the food samples collected, and preliminary analysis of these results. GA and PP performed the analysis and interpretation of the results. GA drafted the manuscript. All authors critically revised the manuscript and gave their final approval of the manuscript submitted for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.877906/full#supplementary-material

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Analysis of the impact of the armed conflict in Ukraine on the population of Romania

Flavius Cristian Mărcău[1]*†, Cătălin Peptan[1]†, Horaţiu Tiberiu Gorun[2], Vlad Dumitru Băleanu[3] and Victor Gheorman[4]†

[1]Faculty of Education, Law and Public Administration, "Constantin Brâncuşi" University of Târgu Jiu, Târgu Jiu, Romania, [2]"Constantin Brâncuşi" University of Târgu Jiu, Târgu Jiu, Romania, [3]Faculty of Medical and Behavioural Sciences, "Constantin Brâncuşi" University of Târgu Jiu, Târgu Jiu, Romania, [4]Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Craiova, Romania

Purpose: The study aims to highlight the behavior of people in a state in the vicinity of a military conflict zone. Specifically, it highlights the psychological behavior of Romanian citizens after the invasion of Ukraine by the Russian Federation. It was considered appropriate to carry out this study, given the novelty of such a situation, since, after the end of the Second World War, Europe has no longer faced major problems of insecurity caused by armed conflicts of this magnitude.

Methods: The study was based on the questionnaire applied to a number of 1,193 people with permanent residence in Romania and a minimum age of 18 years. The data were collected in the beginning phase of the invasion of Ukraine by the troops of the Russian Federation, i.e. between March 1–17, 2022. The aim was to obtain information that would allow the observation of re-spondents' opinions on the conflict in Ukraine and its potential escalation, and on the other hand, to allow the assessment of quality of life, using the WHQOL-BREEF measurement instrument.

Results: Based on the results of the study, the highest average satisfaction among the four domains of WHOQOL-BREF is represented by the "Psychological" domain, of the category of people with the lowest fear about a potential future war between Romania and the Russian Federation (83.62 ± 17.48). On the contrary, the lowest average is represented by the "Environment" domain, for the category of persons who do not feel protected by the fact that Romania is a NATO member state (61.77 ± 20.96).

Conclusions: The results of the study show that the indices of the quality of life of the people in Romania, as a state in the proximity of a military conflict with the potential to escalate, are negatively influenced by the fears of people who believe that the war in Ukraine will escalate into a regional or global conflict, or that the Russian Federation is going to use its nuclear arsenal against Ukraine or another NATO member state.

KEYWORDS

quality of life, war, Ukraine, Russia, fear, Romania

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EDITED BY
Yohan Robinson,
University of Gothenburg, Sweden

REVIEWED BY
Gour Gobinda Goswami,
North South University, Bangladesh
Simon Grima,
University of Malta, Malta
Per Örtenwall,
University of Gothenburg, Sweden

*CORRESPONDENCE
Flavius Cristian Mărcău
flavius@rstjournal.com

†These authors have contributed equally to this work and share first authorship

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Introduction

The Union of Soviet Socialist Republics (USSR) de jure collapsed in 1991, although it had been a state of collapse since 1989, as a result of anti-totalitarian demonstrations in Central and Eastern Europe and the implosion of the communist regime (1). The new independent states that emerged from the collapse of the USSR remained largely within the sphere of influence of the Russian Federation, the de facto successor of the former USSR. Thus, shortly afterwards, various disputes began between the post-communist states: Armenia and Azerbaijan in 1991–1994 and 2020, following the Nagorno-Karabakh region dispute; Tajikistan between 1992 and 1997; Abkhazia and South Ossetia between 1991 and 1993 and 1998; Transnistria between 1990 and 1992. It should be noted that the Russian Federation has been indirectly involved, through proxy states, in most of the conflicts that have arisen near its borders (2).

In 2014, against the background of internal dissensions in Ukraine caused by the expression of attachment to the values of the West, it was possible for an epicenter of insecurity to emerge, which was followed by the illegal annexation of the Crimean Peninsula by the Russian Federation (3). Such an action was condemned by the leaders of Western states, and economic sanctions were also imposed on the Russian Federation (4). However, many Russian intellectuals believe that Ukraine has no right to exist as an independent state, arguing that it is an artificial construction, and that Ukrainians and Russians are the same people and share the same culture (5).

The annexation of the Crimean Peninsula by the Russian Federation was only the beginning of a long period of tension between pro-Russians and pro-Westerners in the Crimean, Donetsk and Luhansk areas.

On February 24, 2022, the Russian Federation invaded Ukraine, justifying its actions by the so-called desire to denazify (6) and protect Russian nationals on the territory of Ukraine. The actions of the Russian Federation have been severely criticized and sanctioned by the international community, bringing down a new Iron Curtain over Europe, stretching from Norway, from the Barents Sea to Turkey, to the Adriatic Sea, behind which, so far, the states of Belarus and the Russian Federation are located (7). For the first time since the end of Second World War, a military conflict has arisen in Europe which, if it escalates, can bring together the constituent elements of a potential regional or global conflict.

The political implications of the so-called "special military operations" initiated by the Russian Federation are particularly important, given the impact it has on the whole world, so that the regional and global geopolitical and security architecture may undergo profound changes.

In the context of the crisis in Ukraine and the aggressive rhetoric of the Russian Federation with expansionist overtones, some neighboring states - which felt that their national security interests or their political or economic interests were affected - such as Sweden and Finland, or Ukraine, Georgia and the Republic of Moldova, have initiated steps to join NATO or the European Union - which may substantially alter the geopolitical architecture of the European continent, with implications also at global level.

On the other hand, the adoption and application of political and economic sanctions against the Russian Federation by some countries in the democratic world has given new meaning to relations between the BRICS countries (Russian Federation, China, India, Brazil and South Africa) - given their demographic potential and their economic and geopolitical importance - and the idea of a 'new world order' is being put forward in international political circles, in which the BRICS countries would counterbalance the influence of the United States and their NATO partners.

A novelty on the international relations scene is that this armed conflict has succeeded in a very short time in uniting many of the states of the world, around a common goal - the desire for world peace - in a way that no one has been able to do so in the last half century.

It must be acknowledged, however, that the resurgence of armed conflict in Europe has led to many changes in the psychological state of the population. The fear of war has seriously affected the behavior of people living in the states in the immediate vicinity of Ukraine, creating a series of potentially apocalyptic scenarios in the collective mind. The emergence of the crisis in Ukraine at a temporary moment characterized by the global COVID-19 pandemic has superimposed a military security threat on top of a medical security threat, the cumulative effects of which can be seen in increased reactive symptoms of depression-anxiety among the affected population. The population was overwhelmed by anxiety, and in some cases the background anxiety reached the intensity of real panic attacks. Anxiety is described by mental health specialists as fear without purpose (8). Anxiety is usually anticipatory in nature. People who suffer from anxiety experience an intense and often prolonged fear of possible future events (9). In other words, the feeling of uncertainty and the inability to anticipate the short and medium-term perspective, generates a major discomfort that visibly alters the quality of life (10). Clearly, it is very difficult to distinguish between the two types of threat - military and pandemic, which have totally different causalities, manifestations and evolutions - on the behavior of the affected population. By the way of questionnaire design, the present study focuses on highlighting the respondents' quality of life assessment indices on the four major domains ("physical," "environmental," "psychological," and "social"), determined only by the influence of the armed conflict in Ukraine, while the cumulative influences of the pandemic crisis could be a future direction of study.

The armed conflict in Ukraine (Figure 1) is a novelty for the adult population in Romania due to its gravity, complexity and the possibility of escalation, so as to directly affect Romania.

TABLE 1 Required data and research questions.

Required data	Questions
The possibility of war between Romania and the Russian Federation in the near future	Have people who believe in a potential war between Romania and the Russian Federation in the near future developed such a fear as a result of Romania's NATO membership and the presence of foreign troops on Romanian territory?
The belief that the Russian Federation has planned to invade Romania or another NATO member state	Do people who believe in the imminent war of between the Russian Federation and Romania have lower indices of the quality of life compared to people who do not believe that?
The belief that the President of the Russian Federation, Vladimir Putin, will start a nuclear war against NATO member states (including Romania)	
The degree of the population's perception of their personal security, as a result of Romania being a NATO member state	Do people who have a high degree of trust in NATO have better indices of the quality of life than people who have a low degree of trust?
The degree of the population's perception of Romania's security, as a result of the presence of NATO's military capabilities on its territory	
The degree of the population's perception of NATO member states' intervention in case of an attack by the Russian Federation on Romania	

TABLE 2 The timing of this survey according with Russia-Ukraine war days.

Days of survey	Days of war	Numbers of responses
1	5	132
2	6	144
3	7	115
4	8	98
5	9	75
6	10	72
7	11	51
8	12	57
9	13	81
10	14	60
11	15	27
12	16	33
13	17	46
14	18	54
15	19	33
16	20	67
17	21	48
		Total = 1,193

From a psychological point of view, the new situation creates a period of uncertainty and fear among the population, so it is necessary to assess their perceptions of the conflict in Ukraine and to measure their quality of life, starting with the first days of the conflict.

The hypothesis of this research is based on the fact that the citizens of Romania, as a state in the immediate vicinity of the war, developed feelings of fear, apprehension and worry about the possible escalation of the conflict in a regional or global one, so that their quality of life indices suffered from the moment the Russian Federation decided to invade Ukraine.

The objectives of the research are to validate/invalidate the research hypothesis, through the answers provided to a set of predetermined questions (see Table 1), based on the processing of data obtained through the questionnaire applied. In this way it will be possible to conclude on the existence of certain correlations between the selected variables in order to complete our study.

Research methods

Participants

The study was conducted between 1 and17 March, 2022, starting on the fifth day of the invasion of the Russian Federation in Ukraine, and consisted of an online questionnaire (social networks and websites) administered to adults in Romania. The receipt of responses is shown in Table 2.

Any person, with a permanent residence in Romania and aged 18 years or older could participate in completing the questionnaire.

Participation in the research was voluntary, anonymous and unpaid. No data were collected on the identifiers of the respondents.

Procedure

A questionnaire developed on the Google Forms platform was applied to the study participants, and was distributed

TABLE 3 Socio-demographic data of the participants.

Age	% of the Romanian population*	Sex				Environment of residence		Educational level				
		Female		Male		Urban	Rural	Secondary education	High school	Faculty	Masters	PhD
		N	%	*N*	%							
18–25	10.6%*	253	21.2%	209	17.5%	243	219	1	280	156	25	-
26–30		80	6.7%	71	5.9%	109	42	–	40	67	42	2
31–35		62	5.2%	71	5.9%	95	38	–	23	56	51	3
36–40	34.5%*	63	5.2%	64	5.3%	100	27	1	31	58	33	4
41–45		45	3.77%	57	4.7%	74	28	–	18	47	27	10
46–50		35	2.93%	38	3.1%	57	16	1	16	35	12	9
51–55		32	2.68%	31	2.6%	50	13	–	22	19	13	9
56–60	19.9%*	12	1.01%	15	1.2%	25	2	–	5	8	10	4
61–65		11	0.92%	21	1.7%	27	5	1	9	13	4	5
66+	19.3%*	8	0.67%	15	1.2%	17	6	2	6	11	2	2

*2021 Romania population by age group according to Eurostat (https://ec.europa.eu/eurostat).

TABLE 4 Participants' opinion on a possible armed attack by the Russian Federation on Romania or another NATO member state.

	Are you afraid of a possible war between Romania and the Russian Federation in the near future? (Q4)		To what extent do you think the Russian Federation is planning to invade Romania or another NATO member state? (Q5)	
(5) To a very large extent	30.2%		14.8%	
(4) To a large extent	16.8%		17%	
(3) Neutral	23.1%		27.3%	
(2) To a small extent	12.1%		17.9%	
(1) To a very small extent	17.6%		22.8%	
Descriptive statistics	Mean	3.30	Mean	2.83
	Standard error	0.042	Standard error	0.039
	Standard deviation	1.455	Standard deviation	1.353
	Variance	2.116	Variance	1.831
	Kurtosis	−1.246	Kurtosis	−1.129
	Skewness	−0.284	Skewness	0.116

via a web link. The questionnaire could only be completed by those who ticked "Yes" to the question concerning the permanent residence in Romania and the minimum age of 18 years.

Measurements

The questionnaire consisted of 46 questions and was structured in two parts: (1) Acquiring socio-demographic and opinion data on the war in Ukraine and the degree of insecurity felt by respondents feel as a result of Romania being located in the immediate vicinity of the conflict and (2) measuring the quality of life of participants.

The questions in the questionnaire were written in Romanian and aimed to determine the participants' opinions on the armed conflict in the vicinity of Romania.

Thus, the information obtained in the first part of the questionnaire allowed the comparison of the quality of life of the participants in order to validate/invalidate the research hypotheses, by providing answers to the questions in Table 1.

In order to determine the quality of life of the participants, the WHOQOL-BREEF measurement instrument, consisting of 26 questions, was applied, given that the WHOQOL-100 may be too broad to be used in large- studies. The quality of life,

TABLE 5 Participants' opinion on a possible nuclear attack launched by the Russian Federation on Romania or another NATO member state.

		To what extent do you think the Russian Federation will launch a nuclear attack on Ukraine? (Q6)		To what extent do you think the President of the Russian Federation, Vladimir Putin, will start a nuclear war against NATO member states? (Q7)
(5) To a very large extent		15.7%		12.5%
(4) To a large extent		14.5%		11.9%
(3) Neutral		26.8%		25.5%
(2) To a small extent		18.3%		20.1%
(1) To a very small extent		24.8%		29.7%
Descriptive statistics	Mean	2.79	Mean	2.58
	Standard error	0.040	Standard error	0.039
	Standard deviation	1.377	Standard deviation	1.355
	Variance	1.895	Variance	1.935
	Kurtosis	−1.143	Kurtosis	−1.005
	Skewness	0.184	Skewness	0.387

TABLE 6 The opinion of the participants regarding the state of Romania as a NATO member state.

		To what extent do you feel protected by the fact that Romania is a NATO member state? (Q8)		To what extent do you consider the presence of NATO military capabilities on the territory of our state to be beneficial for Romania's security? (Q9)
(5) To a very large extent		24.8%		35.2%
(4) To a large extent		23.8%		22.6%
(3) Neutral		27.9%		25.3%
(2) To a small extent		12.3%		7.9%
(1) To a very small extent		11%		8.8%
Descriptive statistics	Mean	3.39	Mean	3.68
	Standard error	0.037	Standard error	0.037
	Standard deviation	1.283	Standard deviation	1.270
	Variance	1.646	Variance	1.613
	Kurtosis	−0.862	Kurtosis	−0.579
	Skewness	−0.366	Skewness	−0.643

according to the WHO, is a subjective, psychological state, which implies that a self-assessment questionnaire is the most appropriate for measuring it (11). Regarding the step of checking and cleaning the data and calculating the scores of the major domains, the WHOQOL User Manual was used (12).

Statistical analysis of data

In order to process the data obtained through the questionnaire, Excel programs, part of the Microsoft Office Professional Plus 2021, and IBM SPSS Statistics 26 were used. These were installed on a computer with the Windows 11 Professional operating system.

The data collected through the questionnaire were centralized in an Excel file and then visualized, extracted and statistically analyzed.

The variables used for the analysis concerned the participants' opinion on: (1) the possible invasion of Romania by the Russian Federation; (2) the possible invasion of a NATO member state by the Russian Federation; (3) the possibility of the outbreak of a nuclear war as a result of the decision of the President of the Russian Federation; (4) the participants' perception of Romania's security in terms of NATO membership.

The data extracted from the questionnaire were statistically analyzed by applying descriptive statistics in order to determine the distribution frequencies, percentages, average scores and standard deviation. In order to determine the degree of correlation, the average scores of the quality of life, among

TABLE 7 The opinion of the participants regarding the NATO response in case of an invasion of Romania by the Russian Federation.

		Do you think that in case of an attack by the Russian Federation on Romania, the NATO member states will come to our aid? (Q10)		To what extent do you think that in the event of an attack by the Russian Federation on Romania, the USA will not intervene in the conflict and leave Romania to fight alone? (Q11)
(5) To a very large extent		37.8%		12%
(4) To a large extent		24.7%		11.1%
(3) Neutral		22%		25.1%
(2) To a small extent		8.8%		21.3%
(1) To a very small extent		7%		30.2%
Descriptive statistics	Mean	3.77	Mean	2.53
	Standard error	0.036	Standard error	0.039
	Standard deviation	1.236	Standard deviation	1.343
	Variance	1.527	Variance	1.903
	Kurtosis	−0.452	Kurtosis	−0.939
	Skewness	−0.728	Skewness	0.440

TABLE 8 Participants' views on the influence of the Ukrainian conflict on their lives.

		Does the current military conflict in Ukraine have any influence on your life? (Q16)
(5) To a very large extent		20.2%
(4) To a large extent		18.1%
(3) Neutral		27.8%
(2) To a small extent		15%
(1) To a very small extent		18.6%
Descriptive statistics	Mean	3.35
	Standard error	0.034
	Standard deviation	1.191
	Variance	1.418
	Kurtosis	−0.684
	Skewness	−0.297

the variables, the Pearson test was applied, and the Kendell and Spearman tests were applied to determine the correlation between the variables extracted from the first part of the questionnaire.

T-tests and one-way ANOVA tests were applied to compare the mean differences. Statistical significance was set as a *P*-value <0.05.

Results

The questionnaire was applied to a number of 1,193 people, their socio-demographic data being presented in Table 3.

Participants' perception of the war in Ukraine

Regarding the Russian Federation's invasion of Ukraine, 95.4% of respondents are aware of it. The sources of information since the beginning of the conflict have been varied, with 63.8% of respondents considering that they had access to reliable sources, which provided credible information about the events in the neighboring state. However, "fake news" information is present in the public space, especially on social media, and is responsible for distorting the truth by presenting false or truncated information in order to manipulate public opinion about the ongoing armed conflict. Thus, 79.6% of respondents believe that false or misleading information can cause panic among the Romanian population.

Fear of a possible war caused by the invasion of the Russian Federation in Romania is present in 47.1% of respondents, while 38.1% of them believe that Romania or another NATO member state will be invaded by the Federation Russian (see Table 4).

Weapons of mass destruction, especially nuclear weapons, create serious fears among the Romanian population, with 30.3% of respondents believing that the Russian Federation will launch a nuclear attack against Ukraine, and 24.5% believing that a nuclear attack on NATO member states is a realistic and possible scenario (see Table 5).

Romania benefits from the presence of NATO troops on its territory in order to strengthen its eastern flank, as a result of the politico-military commitments. However, 23.3% of respondents do not feel protected by Romania's NATO membership, but 57.8% of respondents believe that the presence of the Alliance's military capabilities on Romanian territory is beneficial to state security (see Table 6).

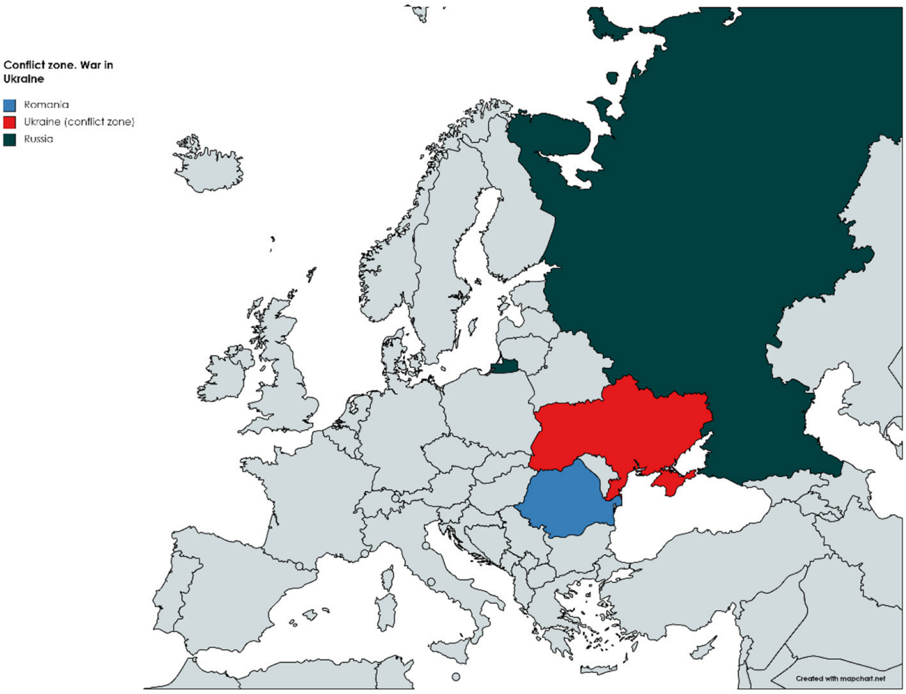


FIGURE 1
Conflict zone. War in Ukraine. Source: This map was created on www.mapchart.net.

TABLE 9 The participants' answer to the question "How do you rate your quality of life during the conflict in Ukraine?"

	N	Minimum	Maximum	Mean		SD	Variance
	Statistic	Statistic	Statistic	Statistic	SE	Statistic	Statistic
Q1	1,193	1	5	3.26	0.029	1.004	1.009

TABLE 10 Descriptive statistical analysis of quality of life, on the whole sample, according to the four major areas.

	N	Minimum	Maximum	Mean	SD
PHYS	1,193	3.57	100.00	70.8718	18.06358
PSYCH	1,193	0.00	100.00	78.7755	19.12893
SOCIAL	1,193	0.00	100.00	74.0360	22.70409
ENVIR	1,193	3.13	100.00	70.5758	18.45976

It should be noted that NATO leaders reiterated at the Brussels Summit on 24 March 2022 their firm commitment to the collective defense of the Allies (13). In the unlikely event that the Russian Federation launches an attack on Romania or any other NATO member state, Article 5 of the NATO Charter obliges the Allies to intervene against the aggressor state (14). However, 15.8% of respondents believe that Romania will not receive help from Allies in the event of military aggression by the Russian Federation, and 23.2% believe that the US will not intervene in a potential military conflict between Romania and the Russian Federation (see Table 7).

The participants believe that 38.3% of the Russian Federation's invasion of Ukraine is an event that has influenced their lives (see Table 8).

Quality of life of participants

Participants' quality of life varies depending on the variables being reported to, so in terms of the answer to the question "How do you rate your quality of life during the conflict in Ukraine?", the median of the answers was around 3.26 ± 0.029 (see Table 9).

The total values, according to the four major domains (Physical, Psychological, Social and Environmental), are between 70.57 ± 18.45 and 78.77 ± 19.12 (see Table 10).

TABLE 11 The association between socio-demographic data, specific questions and WHQOL-BREEF.

		Physical health	Psychological health	Social relationship	Environmental health	Quality of life (QOL)	Health satisfaction
Gender	Male	74.45 (17.47)	83.34 (17.52)	75.84 (21.97)	73.23 (17.67)	3.39 (1.04)	4.02 (0.975)
	Female	69.16 (18.10)	77.07 (19.62)	73.17 (23.00)	69.30 (18.70)	3.20 (0.979)	3.88 (1.00)
		$P = 0.761$	$P = 0.903$	$P = 0.503$	$P = 0.173$	$P = 0.790$	$P = 0.713$
Studies	Middle and high school	71.08 (17.96)	77.92 (19.12)	73.66 (22.62)	70.69 (18.92)	3.23 (1.05)	4.01 (1.00)
	University studies	70.74 (18.13)	79.30 (19.1)	74.26 (22.76)	74.25 (22.76)	3.28 (0.970)	3.88 (0.991)
		$P = 0.914$	$P = 0.730$	$P = 0.635$	$P = 0.456$	$P = 0.235$	$P = 0.274$
Environment of residence	Urban	70.48 (18.11)	77.79 (19.16)	73.73 (22.55)	70.26 (18.07)	3.27 (0.972)	3.89 (0.992)
	Rural	71.64 (17.95)	80.77 (18.93)	74.64 (23.02)	71.20 (19.22)	3.25 (1.068)	4.01 (1.01)
		$P = 0.887$	$P = 0.721$	$P = 0.349$	$P = 0.159$	$P = 0.839$	$P = 0.118$
Age	<30	71.55 (17.99)	76.93 (20.29)	74.22 (22.94)	72.14 (18.30)	3.27 (1.057)	4.09 (0.972)
	>30	70.15 (18.12)	80.71 (17.62)	73.83 (22.47)	68.92 (18.49)	3.26 (0.946)	3.75 (1.001)
		$P = 0.072$	$P = 0.977$	$P = 0.829$	$P = 0.644$	$P = 0.263$	$P = 0.520$
Q4[a]	1–2	76.48 (17.03)	83.62 (17.48)	76.61 (21.95)	74.37 (16.90)	3.47 (1.08)	4.12 (0.940)
	4–5	67.23 (18.33)	75.22 (19.80)	72.15 (23.80)	67.73 (19.35)	3.14 (1.00)	3.82 (1.04)
		$P = 0.114$	$P = 0.463$	$P = 0.409$	$P = 0.665$	$P = 0.394$	$P = 0.674$
Q5[b]	1–2	75.07 (16.69)	82.73 (16.59)	76.59 (20.70)	73.53 (15.81)	3.39 (1)	4.05 (0.936)
	4–5	67.99 (18.83)	75.40 (21.20)	71.82 (25.00)	68.44 (20.07)	3.14 (1.04)	3.87 (1.03)
		$P = 0.609$	$P = 0.788$	$P = 0.973$	$P = 0.851$	$P = 0.483$	$P = 0.699$
Q7[c]	1–2	73.76 (17.34)	81.83 (17.59)	75.28 (21.66)	72.38 (16.78)	3.34 (1.01)	3.98 (0.952)
	4–5	66.01 (18.62)	74.31 (20.18)	71.47 (25.41)	67.43 (21.01)	3.16 (1.03)	3.83 (1.04)
		$P = 0.432$	$P = 0.941$	$P = 0.353$	$P = 0.233$	$P = 0.641$	$P = 0.362$
Q8[d]	1–2	66.67 (20.82)	76.09 (22.47)	69.08 (25.12)	61.77 (20.96)	3.06 (1.03)	3.65 (1.08)
	4–5	73.90 (16.34)	81.09 (17.08)	77.38 (20.78)	75.67 (16.11)	3.38 (1.03)	4.10 (0.936)
		$P = 0.263$	$P = 0.801$	$P = 0.849$	$P = 0.173$	$P = 0.208$	$P = 0.701$
Q16[e]	1–2	74.63 (17.25)	82.51 (18.44)	76.22 (21.84)	73.71 (17.66)	3.41 (1.06)	4.10 (0.951)
	4–5	67.58 (18.32)	75.28 (19.72)	71.65 (23.90)	67.02 (19.47)	3.06 (1.03)	3.78 (1.07)
		$P = 0.772$	$P = 0.985$	$P = 0.292$	$P = 0.934$	$P = 0.688$	$P = 0.299$

Mean (SD).
One Sample T-test for compar means.
One Way ANOVA used for P value.
[a] Are you afraid of a possible war between Romania and the Russian Federation in the near future?
[b] To what extent do you think the Russian Federation planned to invade Romania or another NATO member state?
[c] To what extent do you think Russian President Vladimir Putin will start a nuclear war against NATO member states?
[d] To what extent do you feel protected by the fact that Romania is a NATO member state?
[e] Does the current military conflict in Ukraine have any influence on your life?
1 - To a very small extent; 2 - To a small extent; 4 - To a large extent; 5 - To a very large extent.

Association between socio-demographic data and WHOQOL-BREEF

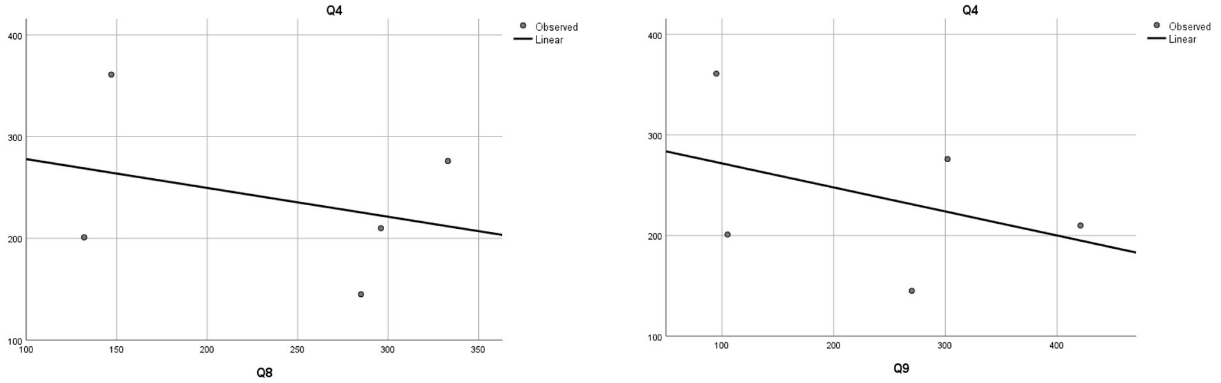
The comparative analysis of the four major domains, depending on the socio-demographic data of the participants and the answers given to the specific questions in the first part of the questionnaire are shown in Table 11.

Discussions

As can be seen in the section presenting the results, respondents have different views on the war between Ukraine and the Russian Federation and its potential escalation into a regional, continental or global conflict.

It should be noted that 47% of respondents fear a possible war between the Russian Federation and Romania, while 31.8%

TABLE 12 Correlation of the question that aims to measure the fear of war (Q4) and the questions measuring the opinion on Romania's NATO membership (Q8) and the presence of the Alliance troops on the Romanian territory (Q9).



Q4 - Are you afraid of a possible war between Romania and the Russian Federation in the near future?

Q8 - To what extent do you feel protected by the fact that Romania is a NATO member state?

Q9 - To what extent do you consider the presence of NATO military capabilities on the territory of our country to be beneficial for Romania's security?

Kendell	Correlation coefficient	0.200	Kendell	Correlation coefficient	−0.200
	Sig. (2-tailed)	0.624**		Sig. (2-tailed)	0.624**
Spearman	Corelation coefficient	0.200	Spearman	Correlation coefficient	−0.200
	Sig. (2-tailed)	0.747**		Sig. (2-tailed)	0.747**

** Correlation is significant at the 0.01 level (2-tailed).

For a correlation to be very strong, the correlation coefficient must be as close as possible to 1, and sig. as close as possible to 0.

believe, to a large and very large extent, that the Russian Federation has planned to invade Romania as well, although there is no information, clues or statements in this regard. Such views are determined by the fact that Romania was under influence of the USSR (15) until 1989, and the Russian Federation wants to regain influence over the former Soviet states (16).

The Russian Federation's nuclear weapons (17), as well as its nuclear policy (18), also create serious anxiety among respondents, with 30.2% believing, to a large and very large extent, that a nuclear attack on Ukraine is possible, while 24.4% considering the scenario of a nuclear attack on NATO member states likely to happen. These fears have also been raised by President Vladimir Putin, who has made a declarative statement about the scenario of a nuclear attack on NATO member states if they were to intervene in support of Ukraine (19). We believe that such a scenario may be possible, but it is unlikely to happen.

The security that NATO provides to Romania (20) is questioned by 23.3% of respondents, who believe that they do not feel protected by the fact that our country is part of this alliance, and 16.7% of respondents consider the presence of NATO troops on the territory of Romania as not beneficial. Such opinions may be based on the fear of a potential war with the Russian Federation as a result of Romania's NATO membership or due to the deployment of some US military capabilities on the Romanian territory. However, such a hypothesis is invalidated, as there are no correlations between variables, by the Kendall and Spearman statistical tests - as shown in Table 12 - performed between the data obtained from the answers to the question aimed at measuring the fear of war (Q4) and the questions measuring the opinion on Romania's NATO membership (Q8) and the presence of NATO troops on the Romanian territory (Q9).

15.8% of participants in the study believe that NATO member states will not intervene in a potential invasion of Romania by the Russian Federation, and 23.1% believe that the US will not intervene in the event of a war against Romania.

In this context, it should be mentioned that Romania's security is at the highest level ever reached, being strengthened by the military capabilities of the allies present on its territory, and with the outbreak of the invasion of Ukraine, NATO leaders decided to set up four battle groups to be deployed in Romania, Hungary, Bulgaria and Slovakia as part of the Alliance's response to Russia's unprovoked invasion of Ukraine (21).

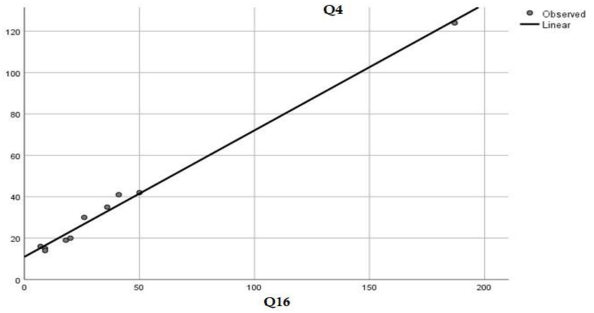
The fear of a potential escalation of the conflict in Ukraine is strongly felt among the participants with 38.3% of them believing, to a large and very large extent, that the war started by the Russian Federation has affected their lives. There is also a strong correlation (Table 13) between those who have a high fear of a war between Romania and the Russian Federation in the near future (Q4) and people who believe that the invasion of the Russian Federation in Ukraine has affected their lives (Q16).

Based on the results of this study, the highest average satisfaction among the four domains of the WHOQOL-BREF is represented by the "Psychological" domain of the category of people who have the least fear about a potential future war between Romania and the Russian Federation (83.62 ± 17.48). On the contrary, the lowest average is represented by the "Environment" domain for the category of people who do not feel protected by the fact that Romania is a NATO member state (61.77 ± 20.96).

Following the comparative analysis of the medians of the major domains, we found that in all major domains, females have a lower score than that recorded in the case of men, with a significant difference in the "Physical" domain (Male: 75.45 ± 17.47, Female: 69.16 ± 18.10). Studies in the literature suggest clear differences in the approach to stress between women and men, and these differences can have multiple biological, psychological or social explanations. Incidence rates for depression and anxiety are higher in women (22). However, the risk of developing an affective or anxiety disorder in men is high, and the lower incidence of these rates among the male population does not reveal the existence of a stress protection factor or an appropriate coping strategy specific to men, but rather emphasizes the low referral rate of men to psychiatric services. This low referral rate of men to psychiatric services prevents diagnosis and implicitly the beginning of a treatment which leads to a negative evolution and a poor prognosis.

The studies of the participants in this research (secondary studies vs. university studies) do not reveal significant differences. However, participants with higher education had a higher average score in three out of four domains, except for the "Physical" domain, where participants with secondary education scored 71.08 ± 17.96 compared to 70.74 ± 18.13, the score obtained by participants with higher education (23). The level of education is generally a protective factor that allows individuals to identify an accurate picture of the situation and the level of risk that exists. In other words, it is assumed that people with a high level of education have sufficient intellectual potential to develop coping strategies superior to those with no education. However, in the present armed conflict, things are different. The element of surprise has struck everyone, given that the vast majority of the population had not considered the existence of a real war. Many people considered this scenario to be impossible in an era of civilization and the rule of law, democracy and dignity. The outbreak of the armed conflict reset the moral values and mechanisms of psychosocial adaptation of the population, and this sudden, violent and surprising "reset" was accompanied by a wide range of individual interpretations. From everyday medical practice it is observed that the behavioral responses of patients are always proportional to their educational level. This is probably how the insignificant differences in this chapter of our research can be explained.

TABLE 13 Correlation of answers with 4 and 5 to the questions concerning the fear of a future war in Romania and the Russian Federation and the opinion of the participants on the influence of the conflict in Ukraine on their lives.



Q4 - Are you afraid of a possible war between Romania and the Russian Federation in the near future?

Q16 - Does the current military conflict in Ukraine have any influence on your life?

Kendell	Correlation coefficient	0.899
	Sig. (2-tailed)	0.000**
Spearman	Correlation coefficient	0.960
	Sig. (2-tailed)	0.000**

** Correlation is significant at the 0.01 level (2-tailed).

For a correlation to be very strong, the correlation coefficient must be as close as possible to 1, and sig. as close as possible to 0.

The rural residence environment shows a higher average score in all four major domains compared to the participants living in urban areas, with the highest score in the "Psychological" domain (80.77 ± 18.93), and the lowest in the "Environment" domain (71.20 ± 19.22). The residence environment is undoubtedly an important socio-demographic indicator in terms of stress management. In Romania, people living in rural areas have limited access to authentic sources of information, and the risk of misinformation is huge. The presentation of false, inaccurate, contradictory news, the so-called "fake-news" has a strong anxiety-provoking effect, significantly altering the quality of life (24).

The evaluation of the data collected shows that there are no significant differences in the indices for assessing the quality of life of respondents across the four major domains, in relation to age groups. However, it should be noted that the group of respondents aged <30 years is characterized by a score of 76.93 (20.29) in the "Psychological" domain, about 4 pp (percentage points) less than the score of 80.71 (17.62) recorded in the category of respondents aged > 30 years. Regarding the "Evironment" domain, the situation is diametrically opposed, the group of respondents aged <30 years is characterized by a score of 72.14 (18.30) being about 4 pp higher than the score of 68.92 (18.49) recorded in the category of respondents aged> 30 years.

The four major domains calculated based on the answers to the specific questions in the first part of the questionnaire (Q4, Q7, Q8 and Q16) reveal, according to Table 11, that the research hypothesis proposed in this study is supported. Thus, participants who show an increased fear of a potential war between Romania and the Russian Federation, a potential nuclear attack on Ukraine or on a NATO member state, or consider that the war in Ukraine has affected their lives, have a significantly lower average, in all four major domains, compared to people who do not show such fears. The maximum average is obtained in the "Psychological" domain (83.62 ± 17.48), for people who have no fears about a future conflict, and the minimum average in the "Physical" domain (67.23 ± 18.33) for people who believe that there will be a conflict between Romania and Russia in the near future. Poikolainen, Kanerva and Lonnqvist consider that no study has examined whether the fear of nuclear war is an expression of intrapsychic factors coming from the deep irrational layers of the unconscious or a response to a real danger (25). Thus, neither can we launch a theory on these issues.

As for Question Q5, it was assigned the role of control for Question Q4, with the aim of having a very clear view of the results of the participants' quality of life. Thus, from a theoretical point of view, we should have obtained similar results for the quality of life of those who answered similarly (1–2 and 4–5) to the two questions. The maximum difference for those who answered 4 and 5 is 0.71 for the "Environment" domain, and for those who answered 1 and 2, the maximum difference is 1.41 for the "Physical" domain.

The largest difference between the average scores for the same major domain is the "Physical" domain in Q4. Participants who have fears about a future conflict between Romania and the Russian Federation (67.23 ± 18.33) have an average of 9.25 times lower than those who do not have such fears (76.48 ± 17.03).

Research limitations

This study has many positive aspects, but also some limitations, as it is among the few existing studies addressing such an issue.

A limitation of the research is the application of the survey in the online environment. Although our research is qualitative, based on the number of responses obtained, in terms of sample, there is a possibility that biased respondents may self-select. Also, only people who had access to the Internet could answer the questionnaire.

Conclusions

The results of the study show that the indices of the quality of life of people in Romania, as a state in the vicinity of a military conflict with the potential for escalating, are negatively affected by the fears of people who believe that the war in Ukraine will escalate into a regional or global conflict.

Although there are no significant differences in the assessment indices of the quality of life of respondents in the four major domains in relation to age groups, it should be noted that the group of respondents aged <30 years is more affected by the impact on the "physical" domain of the military conflict in the vicinity of Romania, while the category of respondents aged> 30 is more affected by the alteration of environmental factors, both domains characterizing the basic needs of the person. According to the data obtained, it can be hypothesized that during an armed conflict, citizens in its vicinity of the conflict are more interested in providing basic needs (the "Physical" and "Environment" domains) than for higher needs (the "Psychological" and "Social" domains).

The comparative analysis of the medians of the major domains shows that in all major domains, females score lower than males with a significant difference in the "Physical" domain.

On the other hand, the rural residence environment has a higher average score in all four major domains compared to the urban residence envrionment, with the highest score in the "Psychological" domain, and the lowest in the "Environment" domain.

In relation to the respondent's educational background, there are no significant differences in the assessment indices of the quality of life of respondents in the four domains, with the greatest differences for higher education graduates in the "Psychological" and "Environment" domains.

Finally, according to the data presented in the results section and their interpretations, we believe that the research hypothesis, stated in the introductory section, is valid, the invasion of Ukraine by the Russian Federation influencing the quality of life of adults in Romania due to fears developed by the participants.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Constantin Brâncuși University of Târgu Jiu. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.964576/full#supplementary-material

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EDITED BY
Melissa A. Valerio-Shewmaker,
University of Texas Health Science
Center at Houston, United States

REVIEWED BY
Natasa Krsto Rancic,
University of Niš, Serbia
Katarzyna Zatonska,
Wroclaw Medical University, Poland
José Pablo Miramontes González,
Hospital Universitario Río
Hortega, Spain

*CORRESPONDENCE
Justyna Grudziąż-Sękowska
jgrudziaz@cmkp.edu.pl

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Public knowledge and awareness of diabetes mellitus, its risk factors, complications, and prevention methods among adults in Poland—A 2022 nationwide cross-sectional survey

Kuba Sękowski, Justyna Grudziąż-Sękowska*,
Jarosław Pinkas and Mateusz Jankowski

School of Public Health, Centre of Postgraduate Medical Education, Warsaw, Poland

Introduction: Regular monitoring of public awareness of diabetes is necessary to provide effective educational and preventive strategies. This study aimed to assess (1) public knowledge and awareness of diabetes among adults in Poland, as well as (2) to identify sociodemographic factors associated with public awareness of diabetes.

Methods: This cross-sectional survey was carried out between 24 and 27 June 2022, on a non-probability random quota sample of 1,051 adults in Poland. The questionnaire included ten questions related to the awareness of risk factors, symptoms, and complications of diabetes.

Results: Among the respondents, 10.5% had diabetes and 43.8% declared that they have a history of diabetes in their family. Only 17.3% of respondents declared a good level of knowledge of diabetes. Out of 10 symptoms of diabetes analyzed in this study, high blood sugar (80.7%) and chronic fatigue (74.6%) were the most recognized. Out of 8 diabetes risk factors analyzed in this study, overweight/obesity (80.4%) and unhealthy diet (74.1%) were the most recognized diabetes risk factors, while only 22.7% of respondents indicated tobacco use. The diabetic foot was the most recognized diabetes complication (79.8%), but approximately half of the respondents indicated vision problems (56.9%), kidney damage (52.1%), or cardiovascular diseases (50.2%) as diabetes complications. Female gender, having higher education and having a family member with diabetes were the most im-portent factors associated ($p < 0.05$) with a higher level of awareness of diabetes.

Conclusions: This study demonstrated insufficient public awareness of diabetes among adults in Poland. Gender and educational level were the most important factors significantly associated with the awareness of the selected aspects of diabetes, while self-reported financial situation and place of residence had none or marginal influence.

The presented data manifest the importance of adopting a comprehensive education strategy regarding diabetes in Poland

KEYWORDS

diabetes mellitus, diabetes risk factors, public knowledge, prevention, preventive medicine, Poland

1. Introduction

Diabetes remains one of the four most prevalent non-communicable diseases (NCDs) in the world (1–3). It results in disability and premature death while creating an increasing burden on health systems, economic development, and the wellbeing of a large proportion of the global population (4). The most common forms of diabetes are type 1 diabetes, in which complete insulin deficiency causes the destruction of the pancreatic beta cells, and type 2 diabetes, in which insulin resistance can lead to hyperglycemia (5–7). Most diabetes cases (up to 95% of diabetic patients) are type 2 diabetes (so-called insulin-independent) (6, 7).

The International Diabetes Federation (IDF) estimates that as of 2021 there were 537 million people with diabetes worldwide, and this was predicted to increase to 783 million by 2045 (8). The incidence of diabetes is more prevalent in highly developed countries, but the highest rate of increase in cases is in developing countries (9). The continuing upward trend is mainly caused by the increase in the number of diabetes patients with type 2 diabetes (10), which is attributed to population growth and aging (39.7%), increased incidence (28.5%), and the interaction of these two factors (31.8%) (11). It is widely believed that the main cause of type 2 diabetes is a high-energy Western-style diet combined with a sedentary lifestyle, which underlines the role of lifestyle as the most important risk factor for type 2 diabetes (12).

Poland is a European Union (EU) member state with a high diabetes burden (13, 14). The prevalence of diabetes in Poland is estimated at 8% of the population (14). The prevalence of diabetes in Poland is significantly higher than in other EU (mean 6.3% of the population), and it is estimated that the prevalence of diabetes in Poland will rise to 11% in 2040 (15).

According to the Polish National Health Fund (a public payer in the universal health insurance system in Poland), most of the patients with diabetes who visited a doctor were females (55.1%), and the average life expectancy of diabetes patients was 15 years lower than the average for the general Polish population (16). Moreover, there are public health concerns about the under diagnosis of diabetes in Poland (14, 17). The COVID-19 pandemic may have a negative impact on the diagnosis of diabetes in Poland, as only 63% of adults in Poland had a blood sugar test during the COVID-19 pandemic (18).

Diabetes prevention, as well as disease management, requires both medications and lifestyle changes (19). Patients diagnosed with diabetes should be actively involved in disease management, as a high level of compliance may significantly increase the quality of life and prevent/delay long-term diabetes complications (20). The level of patients' knowledge of diabetes plays an important role in the self-management of the disease. It is considered that patients with good disease knowledge have a better understanding of the nature and consequences of diabetes and are less prone to various complications and severe exacerbations of diabetes (21, 22). Both Polish and internationally recognized standards for the treatment of diabetes emphasize that all patients should receive diabetes education and self-management training and support (23, 24). In Poland, diabetes screening is carried out as a part of general screening program, without separated program addressed to high-risk populations.

Early detection of diabetes requires both health care practices and patients' engagement (interest) based on their perception of this disease (individual health literacy level) (25). The level of health literacy affects people's decisions and actions, which includes the ability to choose and access the appropriate form of health care (26). Thus, public knowledge and awareness of diabetes reduce the gaps in diabetes under diagnosis as well as prevent long-term complications among patients with a diabetes diagnosis. Regular monitoring of public awareness of diabetes is necessary to provide effective educational and preventive strategies.

Therefore, this study aimed to assess (1) public knowledge and awareness of diabetes among adults in Poland, with a particular emphasis on diabetes risk factors, complications, and prevention methods, as well as (2) to identify sociodemographic factors associated with public awareness of diabetes symptoms and risk factors.

2. Materials and methods

2.1. Study design and population

This cross-sectional survey was carried out between 24 and 27 June 2022, on a non-probability random quota sample of 1,051 adults in Poland. Data were collected using a dedicated IT system (online panel) developed by the specialized poll company in Poland (The Nationwide Research Panel Ariadna) on behalf of the authors that pro-vide the scientific context of the study (27). A computer-assisted web interview (CAWI) method was used. Respondents were randomly selected from the dataset of 110,000 individual users of the Nationwide Research Panel Ariadna (27). Quota sampling was based on the stratification model (gender; age; place of residence) adjusted to the demographic characteristics of the Polish population according to the reports presented by the Central Statistical Office of the Republic of Poland. A similar research methodology was used in previous studies (28, 29).

The study protocol was reviewed and approved by the Ethical Review Board at the Centre of Postgraduate Medical Education, Warsaw, Poland (No. 70/2022; date of approval: 08 June 2022).

2.2. Questionnaire and measures

The research tool was a questionnaire developed for the purpose of this study. In preparation for the questionnaire, the previously published studies on diabetes awareness were analyzed. A particular emphasis was given to studies that used Diabetic Knowledge Questionnaire (DKQ24) (30) and Diabetes Knowledge Test (DKT) questionnaire (31). A particular emphasis was given to studies that used Diabetic Knowledge Questionnaire (DKQ24) (30) and Diabetes Knowledge Test (DKT) questionnaire (31). The questionnaire included ten questions related to the awareness of risk factors, symptoms, and complications of diabetes, as well as questions regarding the diagnosis of diabetes by a doctor and the history of diabetes in the family. Questions also addressed the personal characteristics of the respondents.

2.2.1. Awareness of diabetes symptoms

Respondents were asked about their awareness of the symptoms of diabetes, using the question: "What do you think are the symptoms of diabetes (please select all that apply)?" With ten mutually non-exclusive answers. Respondents were asked to select "yes" or "no" for each answer choice.

2.2.2. Awareness of the risk factors for diabetes

Respondents were asked about their awareness of the risk factors for diabetes, using the question: "What do you think are the risk factors for diabetes (please select all that apply)?" With eight mutually non-exclusive answers. Respondents were asked to select "yes" or "no" for each answer choice.

2.2.3. Awareness of diabetes prevention methods

Respondents were asked about their awareness of the diabetes prevention methods, using the question: "What do you think are diabetes prevention methods (please select all that apply)?" With five mutually non-exclusive answers.

2.2.4. Awareness of diabetes complications

Respondents were asked about their awareness of diabetes complications, using the question: "What do you think are diabetes complications (please select all that apply)?" With six mutually non-exclusive answers.

Moreover, respondents were asked about their health status - "Has a doctor ever told you that you have diabetes?" (yes/no). Respondents who said yes, were asked about the type of diabetes diagnosed by a doctor (type 1 diabetes; type 2 diabetes; gestational diabetes; I do not know). Also, a question on the history of diabetes in the family was addressed.

2.3. Data analysis

The data were analyzed with SPSS software version 28 (IBM Corp, Armonk, NY, USA). The distribution of categorical variables was shown by frequencies and proportions. Cross-tabulations and chi-squared tests were used to compare categorical variables.

Associations between personal characteristics [(1) gender, (2) age group, (3) having higher education, (4) marital status, (5) having children, (6) place of residence, (7) a number of household members, (8) occupational status, (9) self-reported financial situation, (10) having diabetes, (11) history of diabetes in the family] and awareness of (1) diabetes symptoms and (2) risk factors for diabetes were analyzed using multivariable logistic regression models. The strength of association was measured by the odds ratio (OR) and 95% confidence intervals (95% CI). The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Characteristics of the study population

Data were obtained from 1,051 individuals aged 18–85 years, 53.3% were females (Table 1). Most of the respondents were married (49.5%), 42.8% had higher education and one-third (32.3%) lived in rural areas. Among the respondents, 10.5% had diabetes. Out of 110 respondents with diabetes, 56.4% had type 2 diabetes, 15.5% had type 1 diabetes, and 11.8% had gestational diabetes. Among the respondents with diabetes, 16.4% were unaware of the type of diabetes they were diagnosed with. Out of all respondents, 43.8% declared that they have a history of diabetes in their family, wherein most of the respondents were not aware of the type of diabetes in their family (21.6% of all the respondents), 19% had a history of type 2 diabetes in the family, 6.5% type 1 diabetes and 1.5% reported gestational diabetes. Characteristics of the study population are presented in Table 1.

3.2. Respondents' knowledge of diabetes

Most of the respondents declared a moderate (46.3%) level of knowledge of diabetes and only 17.3% of respondents declared rather good or very good knowledge of diabetes (Table 2). Out of 10 symptoms of diabetes analyzed in this study, high blood sugar (80.7%) and chronic fatigue, feeling sleepy during the day (74.6%) were the most recognized symptoms. Most of the respondents (57.4%) were aware that polydipsia is a symptom of diabetes, but only 42% of respondents indicated polyuria as a symptom of diabetes (Table 2). Persistent skin itching (19.7%) and increased risk of infections (22.6%) were the least recognized symptoms of diabetes. Out of 8 diabetes risk factors analyzed in this study, overweight/obesity (80.4%), unhealthy diet (74.1%) and genetic predisposition (69.5%) were the most recognized diabetes risk factors (Table 2). Tobacco use (22.7%) was the least recognized risk factor for diabetes. Approximately three quarters of respondents were aware that limited consumption of carbohydrates (sugars) in the diet (77.1%), weight reduction in overweight or obese people (75.1%) or regular physical activity (73%) are diabetes prevention methods. Diabetic foot was the most recognized diabetes complication (79.8%). More than half of respondents were aware that diabetes may lead to vision problems (56.9%), kidney damage (52.1%) or cardiovascular diseases (50.2%). Details are presented in Table 2.

There were statistically significant differences in the percentage of respondents who correctly indicated diabetes symptoms by gender, age, educational level, marital status, having children, and place of residence. Moreover, respondents who were diagnosed with diabetes or those with history of diabetes in the family more often correctly indicated diabetes symptoms (Table 3). There were significant differences ($p < 0.05$) in the percentage of respondents who correctly indicated diabetes risk factors depending on the gender, age, educational level, having children, number of household members occupational status (Table 4). Those who had diabetes more often indicated overweight/obesity as diabetes risk factors. Moreover, the percentage of respondents who correctly indicated diabetes risk factor was higher among those respondents who had history of diabetes in the family (Table 4).

In general, the percentage of respondents who correctly indicated diabetes complications was higher among females (Table 5). Moreover, public awareness of diabetes complications

TABLE 1 Characteristics of the study population ($n = 1,051$).

Variable	Total sample $n = 1,051$	
Overall	***n***	**%**
Gender		
Female	560	53.3
Male	491	46.7
Age (years)		
18–29	226	21.5
30–39	209	19.9
40–49	190	18.1
50–59	202	19.2
60+	224	21.3
Educational level		
Primary	28	2.7
Vocational	109	10.4
Secondary	464	44.1
Higher	450	42.8
Marital status		
Single	250	23.8
Married	520	49.5
Informal relationship	164	15.6
Divorced/widowed	117	11.1
Having children		
Yes	643	61.2
No	408	38.8
Place of residence		
Rural	339	32.3
City below 20,000 residents	122	11.6
City from 20,000 to 99,999 residents	237	22.5
City from 100,000 to 499,999 residents	200	19.0
City above 500,000 residents	153	14.6
Number of household members		
1	159	15.1
2 or more	892	84.9
Occupational status		
Active	663	63.1
Passive	388	36.9
Self-reported financial situation		
Good	401	38.2
Moderate	406	38.6
Bad	244	23.2
Having diabetes		
Yes	110	10.5
No	941	89.5
History of diabetes in the family		
Yes	460	43.8
No	591	56.2

TABLE 2 Respondents' knowledge of diabetes ($n = 1,051$).

Variable	Overall ($n = 1,051$)	
	n	%
Self-reported level of knowledge on diabetes		
Very bad	80	7.6
Rather bad	302	28.7
Moderate	487	46.3
Rather good	137	13.0
Very good	45	4.3
What do you think are the symptoms of diabetes? (multiple-choice question; positive answers)		
High blood sugar (hyperglycemia)	848	80.7
Polyuria	441	42.0
Increased thirst or a feeling of dry mouth (polydipsia)	603	57.4
Unexpected excessive weight loss	310	29.5
Slow-healing wounds	615	58.5
Deterioration of vision (e.g., blurred vision)	539	51.3
Numbness and/or tingling of hands or feet	271	25.8
Increased risk of infections (e.g., bacterial or fungal skin infections)	238	22.6
Persistent skin itching	207	19.7
Chronic fatigue, feeling sleepy during the day	784	74.6
What do you think are the risk factors for diabetes? (multiple-choice question; positive answers)		
Excessive alcohol consumption	326	31.0
Smoking cigarettes/tobacco	239	22.7
Overweight/obesity	845	80.4
Low physical activity level (e.g., sedentary lifestyle)	649	61.8
Unhealthy diet (e.g., eating highly processed foods, high amounts of fatty foods, low fiber intake)	779	74.1
Arterial hypertension	311	29.6
Age > 40–45 years	301	28.6
Genetic predisposition (history of diabetes in the family)	730	69.5
What do you think are diabetes prevention methods? (multiple-choice question; positive answers)		
Regular physical activity	767	73.0
Limited intake of fats in the diet	569	54.1
Limited consumption of carbohydrates (sugars) in the diet	810	77.1
Limited alcohol consumption	471	44.8
Weight reduction in overweight or obese people	789	75.1
What do you think are diabetes complications? (multiple-choice question; positive answers)		
Cardiovascular diseases such as heart attack or stroke	528	50.2
Kidney damage	548	52.1
Vision problems/loss of vision	598	56.9
Limb amputation (e.g., Leg amputation)	708	67.4
Diabetic foot	839	79.8
Damage to the nervous system leading to sensory disturbances	311	29.6

increased with the age (Table 5). The percentage of respondents who correctly indicated diabetes complications was higher among those respondents who had higher education (Table 5). Respondents who had children more often indicated vision problems, limb amputation, and diabetic foot as a diabetes complication ($p < 0.05$). In general, the percentage of respondents who correctly indicated symptoms of diabetes increased with the size of the place of residence (Table 5). There were no statistically significant differences in the percentage of respondents who correctly indicated

TABLE 3 Awareness of diabetes symptoms by sociodemographic factors ($n = 1{,}051$).

Variable	**Diabetes symptoms - percentage of respondents who answered "yes" by sociodemographic factors**									
	High blood sugar		**Polyuria**		**Increased thirst or a feeling of dry mouth (polydypsia)**		**Unexpected excessive weight loss**		**Slow-healing wounds**	
	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***
Gender										
Female	478 (85.4)	**<0.001**	267 (47.7)	**<0.001**	279 (67.7)	**<0.001**	197 (35.2)	**<0.001**	374 (66.8)	**<0.001**
Male	370 (75.4)		174 (35.4)		224 (45.6)		113 (23.0)		241 (49.1)	
Age (years)										
18–29	162 (71.7)	**<0.001**	75 (33.2)	**0.048**	108 (47.8)	**<0.001**	65 (28.8)	0.1	94 (41.6)	**<0.001**
30–39	152 (72.7)		92 (44.0)		111 (53.1)		55 (26.3)		110 (52.6)	
40–49	157 (82.6)		81 (42.6)		108 (56.8)		46 (24.2)		115 (60.5)	
50–59	176 (87.1)		90 (44.6)		129 (63.9)		66 (32.7)		137 (67.8)	
60+	201 (89.7)		103 (46.0)		147 (65.6)		78 (34.8)		159 (71.0)	
Educational level										
Primary	19 (67.9)	**0.04**	10 (35.7)	**0.02**	13 (46.4)	0.05	3 (10.7)	**0.01**	14 (50.0)	0.3
Vocational	80 (73.4)		37 (33.9)		55 (50.5)		23 (21.1)		57 (52.3)	
Secondary	375 (80.8)		182 (39.2)		257 (55.4)		136 (29.3)		271 (58.4)	
Higher	374 (83.1)		212 (47.1)		278 (61.8)		148 (32.9)		273 (60.7)	
Marital status										
Single	182 (72.8)	**<0.001**	103 (41.2)	0.7	136 (54.4)	0.2	66 (26.4)	0.6	121 (48.4)	**<0.001**
Married	431 (82.9)		223 (42.9)		304 (58.5)		155 (29.8)		322 (61.9)	
Informal relationship	130 (79.3)		63 (38.4)		88 (53.7)		52 (31.7)		94 (57.3)	
Divorced/widowed	105 (89.7)		52 (44.4)		75 (64.1)		37 (31.6)		78 (66.7)	
Having children										
Yes	543 (84.4)	**<0.001**	280 (43.5)	0.2	394 (61.3)	**0.001**	202 (31.4)	0.09	412 (64.1)	**<0.001**
No	305 (74.8)		161 (39.5)		209 (51.2)		108 (26.5)		203 (49.8)	

(Continued)

TABLE 3 (Continued)

Variable	**Diabetes symptoms - percentage of respondents who answered "yes" by sociodemographic factors**									
	High blood sugar		**Polyuria**		**Increased thirst or a feeling of dry mouth (polydypsia)**		**Unexpected excessive weight loss**		**Slow-healing wounds**	
	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***
Place of residence										
Rural	269 (79.4)	0.2	123 (36.3)	0.09	178 (52.5)	0.3	83 (24.5)	0.08	186 (54.9)	0.3
City below 20,000 residents	104 (85.2)		52 (42.6)		75 (61.5)		34 (27.9)		72 (59.0)	
City from 20,000 to 99,999 residents	182 (76.8)		102 (43.0)		139 (58.6)		83 (35.0)		142 (59.9)	
City from 100,000 to 499,999 residents	165 (82.5)		90 (45.0)		119 (59.5)		61 (30.5)		116 (58.0)	
City above 500,000 residents	128 (83.7)		74 (48.4)		92 (60.1)		49 (32.0)		99 (64.7)	
Number of household members										
1	125 (78.6)	0.5	70 (44.0)	0.6	101 (63.5)	0.09	49 (30.8)	0.7	98 (61.6)	0.4
2 or more	723 (81.1)		371 (41.6)		502 (56.3)		261 (29.3)		517 (58.0)	
Occupational status										
Active	529 (79.8)	0.3	280 (42.2)	0.8	371 (56.0)	0.2	197 (29.7)	0.8	382 (57.6)	0.4
Passive	319 (82.2)		161 (41.5)		232 (59.8)		113 (29.1)		233 (60.1)	
Self-reported financial situation										
Good	326 (81.3)	0.8	178 (44.4)	0.5	221 (55.1)	0.5	129 (32.2)	0.3	237 (59.1)	0.5
Moderate	329 (81.0)		165 (40.6)		239 (58.9)		111 (27.3)		243 (59.9)	
Bad	193 (79.1)		98 (40.2)		143 (58.6)		70 (28.7)		135 (55.3)	
Having diabetes										
Yes	98 (89.1)	**0.02**	63 (57.3)	**<0.001**	83 (75.5)	**<0.001**	47 (42.7)	**0.001**	77 (70.0)	**0.01**
No	750 (79.7)		378 (40.2)		520 (55.3)		263 (27.9)		538 (57.2)	
History of diabetes in the family										
Yes	391 (85.0)	**0.002**	221 (48.0)	**<0.001**	299 (65.0)	**<0.001**	161 (35.0)	**<0.001**	312 (67.8)	**<0.001**
No	457 (77.3)		220 (37.2)		304 (51.4)		149 (25.2)		303 (51.3)	

(Continued)

TABLE 3 (Continued)

Variable	Diabetes symptoms - percentage of respondents who answered "yes" by sociodemographic factors									
	Deterioration of vision		Numbness and/or tingling of hands or feet		Increased risk of infections		Persistent skin itching		Chronic fatigue, feeling sleepy during the day	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Gender										
Female	308 (55.0)	**0.01**	149 (26.6)	0.5	156 (27.9)	**<0.001**	142 (25.4)	**<0.001**	458 (81.8)	**<0.001**
Male	231 (47.0)		122 (24.8)		82 (16.7)		65 (13.2)		326 (66.4)	
Age (years)										
18–29	86 (38.1)	**<0.001**	64 (28.3)	0.5	42 (18.6)	0.3	32 (14.2)	**0.003**	153 (67.7)	**0.02**
30–39	103 (49.3)		60 (28.7)		54 (25.8)		33 (15.8)		149 (71.3)	
40–49	102 (53.7)		42 (22.1)		39 (20.5)		34 (17.9)		148 (77.9)	
50–59	120 (59.4)		52 (25.7)		47 (23.3)		55 (27.2)		163 (80.7)	
60+	128 (57.1)		53 (23.7)		56 (25.0)		53 (23.7)		171 (76.3)	
Educational level										
Primary	14 (50.0)	**0.01**	9 (32.1)	**0.006**	7 (25.0)	**<0.001**	2 (7.1)	**0.02**	17 (60.7)	0.1
Vocational	51 (46.8)		18 (16.5)		11 (10.1)		14 (12.8)		74 (67.9)	
Secondary	217 (46.8)		107 (23.1)		80 (17.2)		86 (18.5)		349 (75.2)	
Higher	257 (57.1)		137 (30.4)		140 (31.1)		105 (23.3)		344 (76.4)	
Marital status										
Single	110 (44.0)	**0.046**	72 (28.8)	0.1	53 (21.2)	0.8	45 (18.0)	0.1	177 (70.8)	0.4
Married	283 (54.4)		117 (22.5)		124 (23.8)		109 (21.0)		393 (75.6)	
Informal relationship	82 (50.0)		48 (29.3)		35 (21.3)		24 (14.6)		122 (74.4)	
Divorced/widowed	64 (54.7)		34 (29.1)		26 (22.2)		29 (24.8)		92 (78.6)	
Having children										
Yes	354 (55.1)	**0.002**	156 (24.3)	0.2	151 (23.5)	0.4	141 (21.9)	**0.02**	498 (77.4)	**0.008**
No	185 (45.3)		115 (28.2)		87 (21.3)		66 (16.2)		286 (70.1)	
Place of residence										
Rural	165 (48.7)	0.7	73 (21.5)	**0.01**	57 (16.8)	**0.02**	51 (15.0)	**0.04**	246 (72.6)	0.7
City below 20,000 residents	65 (53.3)		27 (22.1)		27 (22.1)		29 (23.8)		91 (74.6)	
City from 20,000 to 99,999 residents	125 (52.7)		71 (30.0)		58 (24.5)		59 (24.9)		182 (76.8)	
City from 100,000 to 499,999 residents	108 (54.0)		47 (23.5)		56 (28.0)		37 (18.5)		146 (73.0)	
City above 500,000 residents	76 (49.7)		53 (34.6)		40 (26.1)		31 (20.3)		119 (77.8)	

(Continued)

TABLE 3 (Continued)

Variable	Diabetes symptoms - percentage of respondents who answered “yes” by sociodemographic factors									
	Deterioration of vision		Numbness and/or tingling of hands or feet		Increased risk of infections		Persistent skin itching		Chronic fatigue, feeling sleepy during the day	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Number of household members										
1	79 (49.7)	0.7	44 (27.7)	0.6	40 (25.2)	0.4	37 (23.3)	0.2	120 (75.5)	0.8
2 or more	460 (51.6)		227 (25.4)		198 (22.2)		170 (19.1)		664 (74.4)	
Occupational status										
Active	343 (51.7)	0.7	173 (26.1)	0.8	155 (23.4)	0.5	126 (19.0)	0.5	490 (73.9)	0.5
Passive	196 (50.5)		98 (25.3)		83 (21.4)		81 (20.9)		294 (75.8)	
Self-reported financial situation										
Good	206 (51.4)	0.6	102 (25.4)	0.8	92 (22.9)	0.5	71 (17.7)	0.4	299 (74.6)	0.3
Moderate	214 (52.7)		109 (26.8)		97 (23.9)		84 (20.7)		311 (76.6)	
Bad	119 (48.8)		60 (24.6)		49 (20.1)		52 (21.3)		174 (71.3)	
Having diabetes										
Yes	79 (71.8)	**<0.001**	43 (39.1)	**<0.001**	27 (24.5)	0.6	27 (24.5)	0.2	83 (75.5)	0.8
No	460 (48.9)		228 (24.2)		211 (22.4)		180 (19.1)		701 (74.5)	
History of diabetes in the family										
Yes	276 (60.0)	**<0.001**	145 (31.5)	**<0.001**	124 (27.0)	**0.003**	106 (23.0)	**0.02**	374 (81.3)	**<0.001**
No	263 (44.5)		126 (21.3)		114 (19.3)		101 (17.1)		410 (69.4)	

The bold values present results that meet the statistical significance requirement set at $p < 0.05$.

TABLE 4 Awareness of risk factors for diabetes by sociodemographic factors ($n = 1{,}051$).

Variable	Risk factors for diabetes - percentage of respondents who answered "yes" by sociodemographic factors											
	Excessive alcohol consumption		Smoking cigarettes/tobacco		Overweight/obesity		Low physical activity level		Unhealthy diet		Genetic predisposition	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Gender												
Female	170 (30.4)	0.6	139 (24.8)	0.09	471 (84.1)	**0.001**	378 (67.5)	**<0.001**	453 (80.9)	**<0.001**	452 (80.7)	**<0.001**
Male	156 (31.8)		100 (20.4)		374 (76.2)		271 (55.2)		326 (66.4)		278 (56.6)	
Age (years)												
18–29	67 (29.6)	0.1	51 (22.6)	0.2	163 (72.1)	**<0.001**	131 (58.0)	0.2	152 (67.3)	**0.02**	136 (60.2)	**<0.001**
30–39	73 (34.9)		47 (22.5)		159 (76.1)		136 (65.1)		152 (72.7)		139 (66.5)	
40–49	66 (34.7)		49 (25.8)		150 (78.9)		108 (56.8)		141 (74.2)		130 (68.4)	
50–59	64 (31.7)		53 (26.2)		182 (90.1)		133 (65.8)		153 (75.7)		157 (77.7)	
60+	56 (25.0)		39 (17.4)		191 (85.3)		141 (62.9)		181 (80.8)		168 (75.0)	
Educational level												
Primary	3 (10.7)	**0.002**	6 (21.4)	**<0.001**	18 (64.3)	**<0.001**	18 (64.3)	**<0.001**	20 (71.4)	**<0.001**	14 (50.0)	**0.03**
Vocational	21 (19.3)		13 (11.9)		74 (67.9)		49 (45.0)		63 (57.8)		70 (64.2)	
Secondary	147 (31.7)		92 (19.8)		363 (78.2)		262 (56.5)		343 (73.9)		319 (68.8)	
Higher	155 (34.4)		128 (28.4)		390 (86.7)		320 (71.1)		353 (78.4)		327 (72.7)	
Marital status												
Single	72 (28.8)	0.4	49 (19.6)	0.2	194 (77.6)	0.5	144 (57.6)	0.5	174 (69.6)	0.1	159 (63.6)	0.09
Married	162 (31.2)		128 (24.6)		420 (80.8)		327 (62.9)		386 (74.2)		369 (71.0)	
Informal relationship	59 (36.0)		41 (25.0)		132 (80.5)		103 (62.8)		124 (75.6)		114 (69.5)	
Divorced/widowed	33 (28.2)		21 (17.9)		99 (84.6)		75 (64.1)		95 (81.2)		88 (75.2)	
Having children												
Yes	202 (31.4)	0.7	157 (24.4)	0.1	538 (83.7)	**<0.001**	407 (63.3)	0.2	500 (77.8)	**<0.001**	467 (72.6)	**0.005**
No	124 (30.4)		82 (20.1)		307 (75.2)		242 (59.3)		279 (68.4)		263 (64.5)	
Place of residence												
Rural	103 (30.4)	0.5	76 (22.4)	0.4	266 (78.5)	0.4	198 (58.4)	0.5	251 (74.0)	0.7	218 (64.3)	0.06
City below 20,000 residents	46 (37.7)		33 (27.0)		98 (80.3)		76 (62.3)		89 (73.0)		85 (69.7)	
City from 20,000 to 99,999 residents	68 (28.7)		46 (19.4)		186 (78.5)		145 (61.2)		179 (75.5)		173 (73.0)	
City from 100,000 to 499,999 residents	60 (30.0)		44 (22.0)		165 (82.5)		129 (64.5)		142 (71.0)		137 (68.5)	
City above 500,000 residents	49 (32.0)		40 (26.1)		130 (85.0)		101 (66.0)		118 (77.1)		117 (76.5)	

(Continued)

TABLE 4 (Continued)

Variable	Risk factors for diabetes - percentage of respondents who answered "yes" by sociodemographic factors											
	Excessive alcohol consumption		Smoking cigarettes/tobacco		Overweight/obesity		Low physical activity level		Unhealthy diet		Genetic predisposition	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Number of household members												
1	35 (22.0)	**0.008**	27 (17.0)	0.06	125 (78.6)	0.5	90 (56.6)	0.1	111 (69.8)	0.2	111 (69.8)	0.9
2 or more	291 (32.6)		212 (23.8)		720 (80.7)		559 (62.7)		668 (74.9)		619 (69.4)	
Occupational status												
Active	230 (34.7)	**<0.001**	169 (25.5)	**0.005**	525 (79.2)	0.2	410 (61.8)	0.9	478 (72.1)	0.05	450 (67.9)	0.1
Passive	96 (24.7)		70 (18.0)		320 (82.5)		239 (61.6)		301 (77.6)		280 (72.2)	
Self-reported financial situation												
Good	126 (31.4)	0.8	79 (19.7)	0.2	331 (82.5)	0.2	247 (61.6)	0.9	312 (77.8)	0.1	282 (70.3)	0.9
Moderate	121 (29.8)		100 (24.6)		327 (80.5)		249 (61.3)		293 (72.2)		281 (69.2)	
Bad	79 (32.4)		60 (24.6)		187 (76.6)		153 (62.7)		174 (71.3)		167 (68.4)	
Having diabetes												
Yes	34 (30.9)	0.9	19 (17.3)	0.1	97 (88.2)	**0.03**	76 (69.1)	0.09	87 (79.1)	0.2	83 (75.5)	0.1
No	292 (31.0)		220 (23.4)		748 (79.5)		573 (60.9)		692 (73.5)		647 (68.8)	
History of diabetes in the family												
Yes	165 (35.9)	**0.003**	114 (24.8)	0.2	380 (82.6)	0.1	319 (69.3)	**<0.001**	364 (79.1)	**0.001**	359 (78.0)	**<0.001**
No	161 (27.2)		125 (21.2)		465 (78.7)		330 (55.8)		415 (70.2)		371 (62.8)	

The bold values present results that meet the statistical significance requirement set at $p < 0.05$.

diabetes complications by self-reported financial situation or number of household members (Table 5). Individuals diagnosed with diabetes or those with a history of diabetes in the family were more aware of diabetes complications (Table 5).

The percentage of respondents who correctly indicated diabetes prevention methods was higher among females (Table 6). Moreover, public awareness of diabetes prevention methods increased with age and educational level (Table 6). Those who had ever been married as well as those who had children more often correctly indicated diabetes prevention methods. The percentage of respondents who were aware that limited sugar intake and weight reduction in overweight/obese individuals are diabetes prevention methods was higher among those who lived in the largest cities ($p < 0.05$). Respondents who lived with at least one person more often declared that a limited intake of sugar is a diabetes prevention method ($p < 0.05$). Moreover, those with passive occupational status more often declared limited sugar intake as a diabetes prevention method ($p < 0.05$). Individuals diagnosed with diabetes or those with a history of diabetes in the family were more aware of diabetes prevention methods. There were no differences ($p > 0.05$) in public awareness of diabetes prevention methods de-pending on financial status or having a diagnosis of diabetes.

3.3. Factors associated with respondents' awareness of diabetes symptoms

Female gender and having higher education were the most important factors associated ($p < 0.05$) with a higher level of awareness of most of the diabetes symptoms (Table 7). Older respondents were more aware ($p < 0.05$) that high blood sugar, polyuria, polydipsia, slow-healing wounds, deterioration of vision, and chronic fatigue are the symptoms of diabetes (Table 7). Respondents who lived in cities from 20,000 to 99,999 residents were more likely to indicate unexpected excessive weight loss, numbness/tingling of hands or feet, and persistent skin itching as diabetes symptoms. Respondents who were diagnosed with diabetes were more likely ($p < 0.05$) to indicate polyuria, polydipsia, unexpected excessive weight loss, deterioration of vision, and numbness/tingling of hands or feet as diabetes symptoms. In general, respondents with a history of diabetes in the family had a higher level of knowledge of diabetes symptoms (Table 7). In the multivariable logistic regression model, there was no influence ($p > 0.05$) of (1) marital status, (2) having children, (3) number of household members, (4) occupational status, and (5) financial situation on the respondents' awareness of diabetes symptoms.

3.4. Factors associated with respondents' awareness of diabetes risk factors

Females were more likely ($p < 0.05$) to indicate overweight/obesity, low physical activity level, unhealthy diet, and genetic predisposition as diabetes risk factors (Table 8). Respondents over 40 years were more likely to indicate overweight/obesity, unhealthy diet, and genetic predisposition as diabetes risk factors ($p < 0.05$). Respondents with higher education were more aware of diabetes risk factors ($p < 0.05$). Respondents who had children were more likely to indicate overweight/obesity as a diabetes risk factor ($p = 0.04$). Respondents who lived alone were less likely to indicate excessive alcohol consumption as a diabetes risk factor ($p = 0.02$). Occupationally active individuals were more likely to indicate excessive alcohol consumption as a diabetes risk factor ($p = 0.03$). Respondents with a good financial situation were more likely to indicate overweight/obesity and an unhealthy diet as diabetes risk factors. General, respondents with a history of diabetes in the family had a higher level of knowledge of diabetes symptoms (Table 8). In the multivariable logistic regression model, there was no influence ($p > 0.05$) of the place of residence and health status (having diabetes) on the respondents' awareness of diabetes symptoms.

4. Discussion

To the authors' best knowledge, this is the most up-to-date study on the public awareness of diabetes among adults in Poland. This study revealed a limited level of public awareness of diabetes. The percentage of respondents who declared a lack of knowledge or little knowledge about diabetes was more than double the percentage of respondents who reported having good or rather good knowledge about this disease. Out of 10 symptoms of diabetes analyzed in this study, just half of them were correctly indicated by more than 50% of the respondents. Less than a quarter of respondents were able to point out such symptoms as increased risk of infections and persistent skin itching. Most of the respondents were able to correctly point overweight/obesity, unhealthy diet, and genetic predisposition as risk factors for diabetes, while excessive alcohol consumption, arterial hypertension, and being over 40–45 years old were recognized by less than one-third of respondents. Tobacco use was the least recognized diabetes risk factor. Respondents were also able to correctly identify most of the complications caused by diabetes, as well as preventive measures. Public awareness of selected aspects of diabetes varied by sociodemographic factors, of which gender, age, and educational level were the most important.

According to the review conducted by Gautam and Gupta knowledge is considered a key element in the control of diabetes mellitus epidemics (32). However, data on public awareness of

TABLE 5 Awareness of diabetes complications by sociodemographic factors ($n = 1{,}051$).

Variable	Diabetes complications - percentage of respondents who answered “yes” by sociodemographic factors											
	Cardiovascular diseases		Kidney damage		Vision problems/loss of vision		Limb amputation		Diabetic foot		Damage to the nervous system	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*	*n* (%)	*p*
Gender												
Female	298 (53.2)	**0.04**	326 (58.2)	**<0.001**	353 (63.0)	**<0.001**	414 (73.9)	**<0.001**	486 (86.8)	**<0.001**	185 (33.0)	**0.009**
Male	230 (46.8)		222 (45.2)		245 (49.9)		294 (59.9)		353 (71.9)		126 (25.7)	
Age (years)												
18–29	107 (47.3)	0.5	101 (44.7)	**0.01**	81 (35.8)	**<0.001**	115 (50.9)	**<0.001**	156 (69.0)	**<0.001**	63 (27.9)	**<0.001**
30–39	115 (55.0)		98 (46.9)		113 (54.1)		140 (67.0)		155 (74.2)		78 (37.3)	
40–49	96 (50.5)		108 (56.8)		114 (60.0)		124 (65.3)		150 (78.9)		50 (26.3)	
50–59	104 (51.5)		112 (55.4)		141 (69.8)		161 (79.7)		171 (84.7)		73 (36.1)	
60+	106 (47.3)		129 (57.6)		149 (66.5)		168 (75.0)		207 (92.4)		47 (21.0)	
Educational level												
Primary	14 (50.0)	**<0.001**	11 (39.3)	**<0.001**	9 (32.1)	**<0.001**	12 (42.9)	**<0.001**	18 (64.3)	**<0.001**	9 (32.1)	**<0.001**
Vocational	40 (36.7)		47 (43.1)		49 (45.0)		65 (59.6)		75 (68.8)		13 (11.9)	
Secondary	218 (47.0)		223 (48.1)		253 (54.5)		298 (64.2)		362 (78.0)		124 (26.7)	
Higher	256 (56.9)		267 (59.3)		287 (63.8)		333 (74.0)		384 (85.3)		165 (36.7)	
Marital status												
Single	127 (50.8)	0.8	125 (50.0)	0.8	121 (48.4)	**0.004**	141 (56.4)	**<0.001**	182 (72.8)	**0.002**	80 (32.0)	0.8
Married	254 (48.8)		273 (52.5)		311 (59.8)		361 (69.4)		421 (81.0)		150 (28.8)	
Informal relationship	88 (53.7)		85 (51.8)		89 (54.3)		114 (69.5)		131 (79.9)		48 (29.3)	
Divorced/widowed	59 (50.4)		65 (55.6)		77 (65.8)		92 (78.6)		105 (89.7)		33 (28.2)	
Having children												
Yes	325 (50.5)	0.8	342 (53.2)	0.4	403 (62.7)	**<0.001**	467 (72.6)	**<0.001**	542 (84.3)	**<0.001**	184 (28.6)	0.4
No	203 (49.8)		206 (50.5)		195 (47.8)		241 (59.1)		297 (72.8)		127 (31.1)	
Place of residence												
Rural	166 (49.0)	0.3	148 (43.7)	**0.005**	171 (50.4)	**0.03**	206 (60.8)	**0.01**	243 (71.7)	**<0.001**	87 (25.7)	0.3
City below 20,000 residents	67 (54.9)		68 (55.7)		68 (55.7)		81 (66.4)		101 (82.8)		42 (34.4)	
City from 20,000 to 99,999 residents	127 (53.6)		131 (55.3)		141 (59.5)		162 (68.4)		199 (84.0)		76 (32.1)	
City from 100,000 to 499,999 residents	101 (50.5)		111 (55.5)		119 (59.5)		145 (72.5)		163 (81.5)		57 (28.5)	
City above 500,000 residents	67 (43.8)		90 (58.8)		99 (64.7)		114 (74.5)		133 (86.9)		49 (32.0)	

(Continued)

TABLE 5 (Continued)

Variable	Diabetes complications - percentage of respondents who answered “yes” by sociodemographic factors											
	Cardiovascular diseases		Kidney damage		Vision problems/loss of vision		Limb amputation		Diabetic foot		Damage to the nervous system	
	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***	***n* (%)**	***p***
Number of household members												
1	75 (47.2)	0.4	86 (54.1)	0.6	89 (56.0)	0.8	106 (66.7)	0.8	133 (83.6)	0.2	48 (30.2)	0.9
2 or more	453 (50.8)		462 (51.8)		509 (57.1)		602 (67.5)		706 (79.1)		263 (29.5)	
Occupational status												
Active	336 (50.7)	0.7	342 (51.6)	0.6	377 (56.9)	0.9	451 (68.0)	0.6	514 (77.5)	**0.02**	206 (31.1)	0.2
Passive	192 (49.5)		206 (53.1)		221 (57.0)		257 (66.2)		325 (83.8)		105 (27.1)	
Self-reported financial situation												
Good	193 (48.1)	0.4	215 (53.6)	0.5	228 (56.9)	0.9	272 (67.8)	0.6	323 (80.5)	0.8	118 (29.4)	0.9
Moderate	205 (50.5)		203 (50.0)		228 (56.2)		278 (68.5)		324 (79.8)		122 (30.0)	
Bad	130 (53.3)		130 (53.3)		142 (58.2)		158 (64.8)		192 (78.7)		71 (29.1)	
Having diabetes												
Yes	61 (55.5)	0.2	62 (56.4)	0.3	81 (73.6)	**<0.001**	83 (75.5)	0.06	101 (91.8)	**<0.001**	45 (40.9)	**0.006**
No	467 (49.6)		486 (51.6)		517 (54.9)		625 (66.4)		738 (78.4)		266 (28.3)	
History of diabetes in the family												
Yes	270 (58.7)	**<0.001**	261 (56.7)	**0.008**	289 (62.8)	**<0.001**	333 (72.4)	**0.002**	385 (83.7)	**0.006**	157 (34.1)	**0.004**
No	258 (43.7)		287 (48.6)		309 (52.3)		375 (63.5)		454 (76.8)		154 (26.1)	

The bold values present results that meet the statistical significance requirement set at $p < 0.05$.

TABLE 6 Awareness of diabetes prevention methods by sociodemographic factors ($n = 1{,}051$).

Variable	Diabetes prevention methods - percentage of respondents who answered "yes" by sociodemographic factors									
	Regular physical activity		Limited intake of fats in the diet		Limited consumption of carbohydrates (sugars) in the diet		Limited alcohol consumption		Weight reduction in overweight or obese people	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	p	*n* (%)	*p*	*n* (%)	*p*
Gender										
Female	431 (77.0)	**0.002**	330 (58.9)	**<0.001**	459 (82.0)	**<0.001**	267 (47.7)	**0.046**	450 (80.4)	**<0.001**
Male	336 (68.4)		239 (48.7)		351 (71.5)		204 (41.5)		339 (69.0)	
Age (years)										
18–29	146 (64.6)	**0.002**	99 (43.8)	**0.003**	149 (65.9)	**<0.001**	96 (42.5)	0.9	138 (61.1)	**<0.001**
30–39	158 (75.6)		120 (57.4)		162 (77.5)		95 (45.5)		155 (74.2)	
40–49	130 (68.4)		97 (51.1)		142 (74.7)		83 (43.7)		136 (71.6)	
50–59	155 (76.7)		119 (58.9)		160 (79.2)		94 (46.5)		170 (84.2)	
60+	178 (79.5)		134 (59.8)		197 (87.9)		103 (46.0)		190 (84.8)	
Educational level										
Primary	18 (64.3)	**<0.001**	12 (42.9)	**0.003**	18 (64.3)	**0.001**	6 (21.4)	**<0.001**	16 (57.1)	**<0.001**
Vocational	63 (57.8)		50 (45.9)		71 (65.1)		36 (33.0)		69 (63.3)	
Secondary	328 (70.7)		235 (50.6)		355 (76.5)		201 (43.3)		344 (74.1)	
Higher	358 (79.6)		272 (60.4)		366 (81.3)		228 (50.7)		360 (80.0)	
Marital status										
Single	174 (69.6)	0.4	113 (45.2)	**0.01**	170 (68.0)	**<0.001**	101 (40.4)	0.4	171 (68.4)	**0.005**
Married	388 (74.6)		296 (56.9)		418 (80.4)		238 (45.8)		399 (76.7)	
Informal relationship	116 (70.7)		92 (56.1)		125 (76.2)		75 (45.7)		120 (73.2)	
Divorced/widowed	89 (76.1)		68 (58.1)		97 (82.9)		57 (48.7)		99 (84.6)	
Having children										
Yes	485 (75.4)	**0.03**	368 (57.2)	**0.01**	518 (80.6)	**<0.001**	287 (44.6)	0.9	506 (78.7)	**<0.001**
No	282 (69.1)		201 (49.3)		292 (71.6)		184 (45.1)		283 (69.4)	
Place of residence										
Rural	236 (69.6)	0.5	170 (50.1)	0.2	245 (72.3)	**0.002**	149 (44.0)	0.8	238 (70.2)	**0.02**
City below 20,000 residents	91 (74.6)		66 (54.1)		101 (82.8)		59 (48.4)		88 (72.1)	
City from 20,000 to 99,999 residents	175 (73.8)		142 (59.9)		187 (78.9)		101 (42.6)		187 (78.9)	
City from 100,000 to 499,999 residents	149 (74.5)		110 (55.0)		145 (72.5)		93 (46.5)		149 (74.5)	
City above 500,000 residents	116 (75.8)		81 (52.9)		132 (86.3)		69 (45.1)		127 (83.0)	

(Continued)

TABLE 6 (Continued)

Variable	Diabetes prevention methods - percentage of respondents who answered "yes" by sociodemographic factors									
	Regular physical activity		Limited intake of fats in the diet		Limited consumption of carbohydrates (sugars) in the diet		Limited alcohol consumption		Weight reduction in overweight or obese people	
	n (%)	*p*	*n* (%)	*p*	*n* (%)	p	*n* (%)	*p*	*n* (%)	*p*
Number of household members										
1	109 (68.6)	0.2	72 (45.3)	**0.02**	122 (76.7)	0.9	61 (38.4)	0.08	119 (74.8)	0.9
2 or more	658 (73.8)		497 (55.7)		688 (77.1)		410 (46.0)		670 (75.1)	
Occupational status										
Active	472 (71.2)	0.09	359 (54.1)	0.9	493 (74.4)	**0.006**	305 (46.0)	0.3	489 (73.8)	0.2
Passive	295 (76.0)		210 (54.1)		317 (81.7)		166 (42.8)		300 (77.3)	
Self-reported financial situation										
Good	295 (73.6)	0.3	219 (54.6)	0.8	318 (79.3)	0.07	186 (46.4)	0.7	305 (76.1)	0.4
Moderate	303 (74.6)		215 (53.0)		317 (78.1)		176 (43.3)		309 (76.1)	
Bad	169 (69.3)		135 (55.3)		175 (71.7)		109 (44.7)		175 (71.7)	
Having diabetes										
Yes	86 (78.2)	0.2	62 (56.4)	0.6	91 (82.7)	0.1	45 (40.9)	0.4	90 (81.8)	0.08
No	681 (72.4)		507 (53.9)		719 (76.4)		426 (45.3)		699 (74.3)	
History of diabetes in the family										
Yes	358 (77.8)	**0.002**	282 (61.3)	**<0.001**	375 (81.5)	**0.002**	219 (47.6)	0.1	366 (79.6)	**0.003**
No	409 (69.2)		287 (48.6)		435 (73.6)		252 (42.6)		423 (71.6)	

The bold values present results that meet the statistical significance requirement set at $p < 0.05$.

TABLE 7 Factors associated with awareness of diabetes symptoms among adults in Poland ($n = 1{,}051$)—multivariable logistic regression model.

Variable	**Factors associated with awareness of diabetes symptoms among adults in Poland**									
	High blood sugar		**Polyuria**		**Increased thirst or a feeling of dry mouth (polydipsia)**		**Unexpected excessive weight loss**		**Slow–healing wounds**	
	OR (95%CI)	***p***	**OR (95%CI)**	***p***	**OR (95%CI)**	***p***	**OR (95%CI)**	***p***	**OR (95%CI)**	***p***
Gender										
Female	1.76 (1.26–2.47)	**0.001**	1.68 (1.29–2.20)	**<0.001**	2.49 (1.90–3.26)	**<0.001**	1.75 (1.31–2.34)	**<0.001**	2.03 (1.55–2.67)	**<0.001**
Male	Reference		Refe;rence		Reference		Reference		Reference	
Age (years)										
18–29	Reference		Reference		Reference		Reference		Reference	
30–39	1.07 (0.67–1.71)	0.9	1.61 (1.05–2.47)	**0.03**	1.14 (0.75–1.75)	0.5	0.78 (0.49–1.25)	0.3	1.57 (1.03–2.41)	**0.04**
40–49	1.98 (1.14–3.45)	**0.02**	1.70 (1.06–2.73)	**0.03**	1.48 (0.92–2.38)	0.1	0.72 (0.43–1.22)	0.2	2.40 (1.49–3.86)	**<0.001**
50–59	3.06 (1.68–5.57)	**<0.001**	1.86 (1.15–3.00)	**0.01**	1.99 (1.22–3.23)	**0.006**	1.12 (0.67–1.87)	0.7	3.43 (2.10–5.62)	**<0.001**
60+	3.85 (1.91–7.78)	**<0.001**	1.78 (1.03–3.05)	**0.04**	1.86 (1.08–3.22)	**0.03**	1.20 (0.68–2.13)	0.5	3.93 (2.25–6.86)	**<0.001**
Having higher education										
Yes	1.43 (1.02–2.01)	**0.04**	1.45 (1.11–1.89)	**0.007**	1.53 (1.16–2.02)	**0.002**	1.39 (1.04–1.85)	**0.03**	1.23 (0.93–1.62)	0.1
No	Reference		Reference		Reference		Reference		Reference	
Marital status										
Single	Reference		Reference		Reference		Reference		Reference	
Married	0.85 (0.49–1.49)	0.6	0.75 (0.47–1.18)	0.2	0.71 (0.44–1.13)	0.1	0.90 (0.54–1.49)	0.7	0.95 (0.59–1.52)	0.8
Informal relationship	1.06 (0.62–1.81)	0.8	0.74 (0.46–1.17)	0.2	0.80 (0.51–1.27)	0.3	1.08 (0.66–1.77)	0.8	1.21 (0.77–1.93)	0.4
divorced/widowed	1.38 (0.62–3.09)	0.4	0.71 (0.40–1.26)	0.2	0.54 (0.30–1.00)	0.05	0.75 (0.40–1.41)	0.4	0.75 (0.41–1.37)	0.3

(Continued)

TABLE 7 (Continued)

Variable	Factors associated with awareness of diabetes symptoms among adults in Poland									
	High blood sugar		Polyuria		Increased thirst or a feeling of dry mouth (polydipsia)		Unexpected excessive weight loss		Slow–healing wounds	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Having children										
Yes	1.01 (0.63–1.63)	0.9	0.97 (0.66–1.42)	0.9	1.25 (0.85–1.83)	0.3	1.22 (0.80–1.85)	0.4	1.08 (0.73–1.59)	0.7
No	Reference		Reference		Reference		Reference		Reference	
Place of residence										
Rural	Reference		Reference		Reference		Reference		Reference	
City below 20,000 residents	1.18 (0.65–2.12)	0.6	1.12 (0.72–1.73)	0.6	1.18 (0.75–1.85)	0.5	1.02 (0.63–1.65)	0.9	0.89 (0.57–1.40)	0.6
City from 20,000 to 99,999 residents	0.69 (0.45–1.05)	0.08	1.24 (0.87–1.77)	0.2	1.12 (0.78–1.61)	0.5	1.55 (1.06–2.27)	**0.02**	1.00 (0.69–1.43)	0.9
City from 100,000 to 499,999 residents	1.00 (0.61–1.78)	0.9	1.34 (0.92–1.95)	0.1	1.14 (0.78–1.67)	0.5	1.23 (0.82–1.85)	0.3	0.91 (0.62–1.33)	0.6
City above 500,000 residents	1.04 (0.61–1.78)	0.9	1.48 (0.98–2.23)	0.06	1.09 (0.72–1.67)	0.7	1.26 (0.81–1.97)	0.3	1.16 (0.76–1.79)	0.5
Number of household members										
1	0.72 (0.42–1.24)	0.2	0.95 (0.61–1.49)	0.8	1.36 (0.86–2.16)	0.2	1.15 (0.71–1.87)	0.6	1.25 (0.79–1.98)	0.3
2 or more	Reference		Reference		Reference		Reference		Reference	
Occupational status										
Active	1.15 (0.78–1.70)	0.5	1.06 (0.77–1.45)	0.7	0.97 (0.71–1.34)	0.9	1.19 (0.85–1.68)	0.3	1.10 (0.80–1.52)	0.6
Passive	Reference		Reference		Reference		Reference		Reference	

(Continued)

TABLE 7 (Continued)

Variable	Factors associated with awareness of diabetes symptoms among adults in Poland									
	High blood sugar		Polyuria		Increased thirst or a feeling of dry mouth (polydipsia)		Unexpected excessive weight loss		Slow–healing wounds	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Self–reported financial situation										
Good	1.30 (0.85–1.99)	0.2	1.30 (0.93–1.83)	0.1	0.97 (0.68–1.37)	0.8	1.22 (0.85–1.77)	0.3	1.40 (0.99–1.99)	0.05
Moderate	1.10 (0.72–1.67)	0.7	1.01 (0.72–1.41)	0.9	0.99 (0.70–1.40)	0.9	0.91 (0.63–1.32)	0.6	1.20 (0.85–1.70)	0.3
Bad	Reference		Reference		Reference		Reference		Reference	
Having diabetes										
Yes	1.48 (0.77–2.86)	0.2	2.03 (1.33–3.1!)	**0.001**	2.29 (1.41–3.72)	**<0.001**	1.89 (1.22–2.92)	**0.004**	1.31 (0.83–2.08)	0.3
No	Reference		Reference		Reference		Reference		Reference	
History of diabetes in the family										
Yes	1.62 (1.15–2.28)	**0.005**	1.50 (1.16–1.95)	**0.002**	1.66 (1.27–2.17)	**<0.001**	1.56 (1.18–2.06)	**0.002**	2.04 (1.55–2.68)	**<0.001**
No	Reference		Reference		Reference		Reference		Reference	

(Continued)

TABLE 7 (Continued)

Variable	Factors associated with awareness of diabetes symptoms among adults in Poland									
	Deterioration of vision		Numbness and/or tingling of hands or feet		Increased risk of infections		Persistent skin itching		Chronic fatigue, feeling sleepy during the day	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Gender										
Female	1.32 (1.01–1.72)	**0.04**	0.98 (0.73–1.33)	0.9	1.91 (1.39–2.64)	**<0.001**	2.14 (1.52–3.01)	**<0.001**	2.10 (1.55–2.84)	**<0.001**
Male	Reference		Reference		Reference		Reference		Reference	
Age (years)										
18–29	Reference		Reference		Reference		Reference		Reference	
30–39	1.52 (0.99–2.32)	0.05	0.97 (0.61–1.53)	0.9	1.27 (0.77–2.12)	0.4	0.95 (0.53–1.70)	0.9	1.13 (0.71–1.78)	0.6
40–49	1.94 (1.21–3.09)	**0.006**	0.76 (0.44–1.28)	0.3	1.06 (0.74–2.33)	0.9	1.24 (0.67–2.29)	0.5	1.82 (1.08–3.07)	**0.02**
50–59	2.66 (1.65–4.29)	**<0.001**	0.97 (0.57–1.63)	0.9	1.32 (0.74–2.33)	0.3	2.07 (1.14–3.75)	**0.02**	2.11 (1.23–3.62)	**0.007**
60+	2.21 (1.29–3.79)	**0.004**	0.59 (0.32–1.09)	0.09	1.31 (0.69–2.47)	0.4	1.47 (0.75–2.88)	0.3	1.37 (0.75–2.50)	0.3
Having higher education										
Yes	1.63 (1.25–2.13)	**<0.001**	1.69 (1.25–2.28)	**<0.001**	2.31 (1.68–3.16)	**<0.001**	1.69 (1.22–2.35)	**0.002**	1.28 (0.95–1.74)	0.1
No	Reference		Reference		Reference		Reference		Reference	
Marital status										
Single	Reference		Reference		Reference		Reference		Reference	
Married	0.90 (0.60–1.42)	0.7	0.68 (0.41–1.14)	0.1	1.09 (0.62–1.89)	0.8	0.88 (0.49–1.59)	0.7	0.84 (0.50–1.40)	0.5
Informal relationship	1.08 (0.68–1.69)	0.8	0.93 (0.57–1.51)	0.8	0.96 (0.55–1.69)	0.9	0.70 (0.38–1.30)	0.3	1.00 (0.61–1.65)	0.9
divorced/widowed	0.87 (0.49–1.55)	0.6	1.11 (0.59–2.10)	0.7	0.71 (0.36–1.40)	0.3	0.76 (0.38–1.52)	0.4	0.76 (0.39–1.48)	0.4

(Continued)

TABLE 7 (Continued)

Variable	Factors associated with awareness of diabetes symptoms among adults in Poland									
	Deterioration of vision		Numbness and/or tingling of hands or feet		Increased risk of infections		Persistent skin itching		Chronic fatigue, feeling sleepy during the day	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Having children										
Yes	1.01 (0.69–1.47)	0.9	1.01 (0.66–1.55)	0.9	1.28 (0.75–2.17)	0.4	1.12 (0.69–1.81)	0.7	1.26 (0.82–1.92)	0.3
No	Reference		Reference		Reference		Reference		Reference	
Place of residence										
Rural	Reference		Reference		Reference		Reference		Reference	
City below 20,000 residents	0.93 (0.60–1.45)	0.8	0.90 (0.54–1.52)	0.7	1.18 (0.69–2.01)	0.6	1.50 (0.88–2.56)	0.1	0.90 (0.55–1.49)	0.7
City from 20,000 to 99,999 residents	1.04 (0.73–1.49)	0.8	1.63 (1.10–2.42)	**0.02**	1.50 (0.98–2.31)	0.06	1.69 (1.09–2.62)	**0.02**	1.14 (0.76–1.71)	0.5
City from 100,000 to 499,999 residents	1.08 (0.75–1.57)	0.7	1.13 (0.73–1.74)	0.6	1.74 (1.12–2.70)	**0.01**	1.13 (0.69–1.83)	0.6	0.91 (0.60–1.39)	0.7
City above 500,000 residents	0.86 (0.57–1.30)	0.5	1.95 (1.24–3.05)	**0.004**	1.56 (0.96–2.54)	0.08	1.23 (0.73–2.07)	0.4	1.23 (0.76–1.98)	0.4
Number of household members										
1	0.93 (0.60–1.45)	0.7	0.88 (0.54–1.43)	0.6	1.28 (0.75–2.17)	0.4	1.25 (0.72–2.16)	0.4	1.20 (0.72–1.98)	0.5
2 or more	Reference		Reference		Reference		Reference		Reference	
Occupational status										
Active	1.08 (0.79–1.47)	0.6	0.88 (0.62–1.25)	0.5	1.04 (0.71–1.52)	0.8	0.94 (0.63–1.38)	0.7	0.85 (0.59–1.22)	0.4
Passive	Reference		Reference		Reference		Reference		Reference	

(Continued)

TABLE 7 (Continued)

Variable	Factors associated with awareness of diabetes symptoms among adults in Poland									
	Deterioration of vision		Numbness and/or tingling of hands or feet		Increased risk of infections		Persistent skin itching		Chronic fatigue, feeling sleepy during the day	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Self–reported financial situation										
Good	1.25 (0.89–1.76)	0.2	1.09 (0.74–1.61)	0.7	1.12 (0.74–1.70)	0.6	0.83 (0.54–1.27)	0.4	1.33 (0.91–1.94)	0.1
Moderate	1.20 (0.86–1.68)	0.3	1.17 (0.80–1.71)	0.4	1.16 (0.78–1.75)	0.5	0.89 (0.59–1.34)	0.6	1.30 (0.89–1.90)	0.2
Bad	Reference		Reference		Reference		Reference		Reference	
Having diabetes										
Yes	2.52 (1.59–4.00)	**<0.001**	2.43 (1.55–3.81)	**<0.001**	1.18 (0.72–1.94)	0.5	1.26 (0.77–2.08)	0.4	0.92 (0.56–1.51)	0.7
No	Reference		Reference		Reference		Reference		Reference	
History of diabetes in the family										
Yes	1.84 (1.42–2.39)	**<0.001**	1.72 (1.29–2.31)	**<0.001**	1.50 (1.11–2.04)	**0.009**	1.38 (1.00–1.91)	0.5	1.91 (1.40–2.60)	**<0.001**
No	Reference		Reference		Reference		Reference		Reference	

The bold values present results that meet the statistical significance requirement set at $p < 0.05$.

TABLE 8 Factors associated with awareness of risk factors for diabetes among adults in Poland ($n = 1{,}051$)—multivariable logistic regression model.

Variable	Factors associated with awareness of risk factors for diabetes among adults in Poland											
	Excessive alcohol consumption		Smoking cigarettes/tobacco		Overweight/obesity		Low physical activity level		Unhealthy diet		Genetic Predisposition	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Gender												
Female	0.91 (0.69–1.20)	0.5	1.26 (0.93–1.72)	0.1	1.50 (1.07–2.09)	**0.02**	1.57 (1.20–2.06)	**<0.001**	1.94 (1.44–2.62)	**<0.001**	3.11 (2.31–4.18)	**<0.001**
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Age (years)												
18–29	Reference		Reference		Reference		Reference		Reference		Reference	
30–39	1.24 (0.80–1.92)	0.3	0.75 (0.45–1.23)	0.3	1.24 (0.76–2.01)	0.4	1.22 (0.79–1.88)	0.4	1.37 (0.86–2.17)	0.2	1.36 (0.86–2.13)	0.2
40–49	1.18 (0.73–1.92)	0.5	0.85 (0.50–1.45)	0.6	1.80 (1.04–3.12)	**0.04**	0.90 (0.56–1.43)	0.6	1.66 (0.99–2.77)	0.05	1.74 (1.05–2.87)	**0.03**
50–59	1.13 (0.69–1.86)	0.6	0.98 (0.57–1.67)	0.9	5.03 (2.63–9.60)	**<0.001**	1.48 (0.91–2.39)	0.1	1.86 (1.10–3.15)	**0.02**	2.85 (1.67–4.86)	**<0.001**
60+	1.02 (0.57–1.80)	0.9	0.68 (0.36–1.27)	0.2	2.39 (1.22–4.71)	**0.01**	1.09 (0.63–1.88)	0.8	2.12 (1.14–3.92)	**0.02**	1.99 (1.10–3.60)	**0.02**
Having higher education												
Yes	1.24 (0.94–1.64)	0.1	1.78 (1.31–2.43)	**<0.001**	2.58 (1.80–3.70)	**<0.001**	2.19 (1.66–2.88)	**<0.001**	1.66 (1.22–2.26)	**0.001**	1.44 (1.07–1.94)	**0.02**
No	Reference		Reference		Reference		Reference		Reference		Reference	
Marital status												
Single	Reference		Reference		Reference		Reference		Reference		Reference	
Married	0.86 (0.53–1.40)	0.5	1.06 (0.62–1.83)	0.8	0.40 (0.22–0.70)	**0.001**	0.95 (0.59–1.51)	0.8	0.52 (0.31–0.88)	**0.01**	0.92 (0.56–1.53)	0.8
Informal relationship	1.08 (0.68–1.73)	0.7	1.11 (0.65–1.89)	0.7	0.81 (0.47–1.40)	0.4	1.02 (0.64–1.62)	0.9	0.88 (0.53–1.47)	0.6	1.08 (0.66–1.76)	0.8
divorced/widowed	1.21 (0.65–2.26)	0.5	0.81 (0.40–1.64)	0.6	0.53 (0.25–1.13)	0.1	1.08 (0.60–1.94)	0.8	0.83 (0.42–1.64)	0.6	0.78 (0.40–1.49)	0.4
Having children												
Yes	1.03 (0.69–1.54)	0.9	1.36 (0.87–2.14)	0.2	1.61 (1.02–2.55)	**0.04**	1.03 (0.70–1.51)	0.9	1.51 (0.99–2.29)	0.05	0.98 (0.65–1.49)	0.9
No	Reference		Reference		Reference		Reference		Reference		Reference	

(Continued)

TABLE 8 (Continued)

Variable	Factors associated with awareness of risk factors for diabetes among adults in Poland											
	Excessive alcohol consumption		Smoking cigarettes/tobacco		Overweight/obesity		Low physical activity level		Unhealthy diet		Genetic Predisposition	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Place of residence												
Rural	Reference		Reference		Reference		Reference		Reference		Reference	
City below 20,000 residents	1.33 (0.85–2.08)	0.2	1.22 (0.75–2.00)	0.4	0.81 (0.47–1.40)	0.4	0.96 (0.61–1.50)	0.9	0.74 (0.45–1.21)	0.2	0.99 (0.62–1.62)	0.9
City from 20,000 to 99,999 residents	0.95 (0.65–1.38)	0.8	0.84 (0.55–1.29)	0.4	0.81 (0.53–1.25)	0.3	1.06 (0.74–1.52)	0.8	0.96 (0.64–1.43)	0.8	1.34 (0.91–1.98)	0.2
City from 100,000 to 499,999 residents	1.04 (0.70–1.54)	0.9	0.98 (0.63–1.52)	0.9	1.04 (0.64–1.67)	0.9	1.21 (0.83–1.77)	0.3	0.75 (0.49–1.14)	0.2	1.03 (0.69–1.55)	0.9
City above 500,000 residents	1.16 (0.75–1.78)	0.5	1.32 (0.83–2.11)	0.2	1.30 (0.75–2.26)	0.4	1.32 (0.86–2.02)	0.2	1.03 (0.64–1.67)	0.9	1.60 (0.99–2.57)	0.05
Number of household members												
1	0.55 (0.39–0.90)	**0.02**	0.82 (0.47–1.42)	0.5	0.65 (0.37–1.13)	0.1	0.70 (0.45–1.10)	0.1	0.60 (0.37–1.00)	0.05	1.05 (0.64–1.72)	0.8
2 or more	Reference		Reference		Reference		Reference		Reference		Reference	
Occupational status												
Active	1.45 (1.04–2.03)	**0.03**	1.27 (0.87–1.84)	0.2	0.75 (0.50–1.12)	0.2	0.93 (0.67–1.28)	0.6	0.78 (0.55–1.12)	0.2	0.85 (0.60–1.21)	0.4
Passive	Reference		Reference		Reference		Reference		Reference		Reference	
Self–reported financial situation												
Good	0.91 (0.64–1.30)	0.6	0.68 (0.45–0.99)	**0.047**	1.67 (1.09–2.54)	**0.02**	0.91 (0.64–1.29)	0.6	1.57 (1.07–2.31)	**0.02**	1.22 (0.84–1.78)	0.3
Moderate	0.87 (0.61–1.24)	0.5	0.97 (0.67–1.43)	0.9	1.34 (0.89–2.02)	0.2	0.89 (0.63–1.25)	0.5	1.03 (0.71–1.49)	0.9	0.97 (0.67–1.40)	0.9
Bad	Reference		Reference		Reference		Reference		Reference		Reference	
Having diabetes												
Yes	1.07 (0.68–1.69)	0.8	0.70 (0.41–1.20)	0.2	1.83 (0.96–3.47)	0.07	1.45 (0.92–2.29)	0.1	1.19 (0.71–2.00)	0.5	1.18 (0.72–1.94)	0.5
No	Reference		Reference		Reference		Reference		Reference		Reference	
History of diabetes in the family												
Yes	1.44 (1.09–1.89)	**0.01**	1.18 (0.87–1.60)	0.3	1.32 (0.94–1.84)	0.1	1.75 (1.33–2.29)	**<0.001**	1.60 (1.18–2.17)	**0.003**	2.08 (1.54–2.80)	**<0.001**
No	Reference		Reference		Reference		Reference		Reference		Reference	

The bold values present results that meet the statistical significance requirement set at $p < 0.05$.

diabetes are limited (33–36). Most recently published articles refer to studies conducted in developing countries such as India (33), Pakistan (34), Jordan (35), and Kenya (36). In contrary to this study, the abovementioned studies were carried out among respondents already diagnosed with diabetes or healthcare workers – not the general population (33–36). In Poland, the most recent available study on public awareness of diabetes was conducted in 2017 by Sobierajski (37). According to a 2017 study, general knowledge about risk factors, symptoms, and complications of diabetes in Poland was low. In 2017, only two (high blood sugar level, feeling sleepy) out of 16 symptoms of diabetes analyzed in the study, two out of 18 complications (diabetic coma, diabetic foot), and one out of 12 risk factors (overweight/obesity) were correctly identified by more than a half of respondents (37). When compared to 2017, findings from our study suggest that the level of public awareness of diabetes in Poland has increased. Nevertheless, significant gaps in public awareness of diabetes in Poland still exist, especially related to awareness of diabetes risk factors.

Awareness of symptoms of diabetes is crucial to early detection of the disease. However, the current study revealed a low level of awareness of major symptoms of diabetes in the general population in Poland. High blood glucose remained the most recognizable symptom of diabetes, as was pointed out by over 80% of respondents. This is a significant change compared to the 2017 study by Sobierajski (37) in which this symptom was identified by 56.5% of respondents. Other symptoms were indicated by a comparable percentage of respondents in 2017 and the current study. High blood glucose was also the most recognized symptom of diabetes indicated in studies carried out in developing countries (33–36). In this study, older respondents (aged 50 and over) were over three times more likely than younger respondents to indicate high blood glucose as a symptom of diabetes. Better knowledge of disease symptoms among older people is contrary to a study by Sørensen et al., who observed a decreasing health literacy with the age (38).

In this study, females, those with higher education, respondents diagnosed with diabetes as well as those with a history of diabetes in the family were more likely to correctly indicate symptoms of diabetes. This observation is in line with the study by Dos Santos et al. (39) (gender differences), and Kim et al. (40), who reported gender and educational differences in the level of public knowledge of diabetes. In this study, marital status, self-reported financial situation, and occupational status had no significant influence on public awareness of symptoms of diabetes. This is contrary to findings by Duplaga, who identified that health literacy in Poland was related to age, marital and vocational status (41).

A healthy lifestyle pattern is a well-known factor associated with decreased risk for diabetes, especially type 2 diabetes (42). Our study showed that knowledge about risk factors of diabetes in Poland is insufficient and unevenly distributed. Most of the respondents were able to point out overweight/obesity, unhealthy diet, and genetic predisposition as diabetes risk factors. Females and respondents over 40 years were significantly (up to three times) more likely to indicate these risk factors than other respondents. Having a higher education also influenced the public awareness of risk factors of diabetes (except for excessive alcohol consumption). As over 25% of Poles aged 15 and over are daily smokers and alcohol dependency remains one of the key problems in Poland, the public awareness of tobacco and alcohol use as a risk factor for diabetes is very limited (28).

Out of 11 different factors analyzed in this study, the number of household members, occupational status, and history of diabetes in the family were significantly associated with a higher level of awareness of excessive alcohol consumption as a diabetes risk factor. The number of household members and educational level were the only factors significantly associated with a higher level of awareness of tobacco smoking as a diabetes risk factor. In this study, a high level of awareness of overweight/obesity and unhealthy diet as a risk factor for diabetes may result from extensive campaigns on di-et-related diseases that were carried out in Poland in recent years (43). We can hypothesize that a low level of awareness of alcohol and tobacco consumption as a risk factor for diabetes may result from a relatively low number of educational campaigns on diabetes risk factors or its limited effectiveness. Particular attention should be paid to males who are at higher risk of substance use and presented a lower level of aware-ness of diabetes risk factors, especially alcohol and tobacco use.

Findings from this study on awareness of diabetes prevention methods reflect the knowledge of respondents about its risk factors. The most recognized diabetes prevention methods were limited consumption of carbohydrates (sugars) in the diet, weight reduction, and regular physical activity. A higher level of awareness of diabetes prevention methods was associated with higher age and educational level, as well as being married and having children.

It is believed that effective diabetes education can minimize the risk of long-term diabetes complications (44). Findings from this study show that only the most visible complications of this disease (diabetes foot, limb amputation) were widely recognized by adults in Poland. This finding corresponds with a high rate of lower limb amputations performed in Poland (approx. 7–8 thousand each year) of which over a half is performed in diabetic patients (1.7 per 1,000 patients diagnosed with diabetes) (45). This study showed a low level of awareness of diabetes-related nephropathy or neuropathy among adults in Poland. This finding underlines the need to increase the level of public awareness of long-term diabetes-related complications, especially those which do not show any visible symptoms for many years. As in the case of risk factors, symptoms, and prevention methods, awareness of diabetes-related complications was significantly associated with female gender, older age, and higher education level.

Out of 11 sociodemographic factors analyzed in this study, gender and education-al level were the most important factors significantly associated with a higher level of general knowledge on diabetes. In this study older age was associated with better knowledge about the disease which is contrary to the study by Sørensen et al. (38). Findings from this study also showed, that having a person with diabetes in the family leads to a better understanding of this condition. We can hypnotize that this is due to a specific character of diabetes – as a chronic disease, that manifests in older age and the patient often requires family support and engagement in disease management. These may supplement, but should not substitute a proper diabetic education, that should be provided as a part of a public health intervention on diabetes. In this study, diagnosis of diabetes had a limited impact on the level of knowledge on diabetes (two out of six questions on complications and none of the questions on prevention methods), so we can hypothesize that the effectiveness of currently available educational activities targeted to patients with diabetes is limited and requires further improvements.

This study has numerous practical implications for public health interventions in Poland. It reveals an insufficient level of public awareness of diabetes, its risk factors, symptoms, and complications, as well as available preventive methods. This finding underlines a need to conduct a nationwide educational campaign on diabetes. Personalized communication should be targeted to younger individuals as well as males without higher education, as these groups were identified as those with the lowest level of awareness of diabetes. Moreover, this study indicates poor quality of education for patients already diagnosed with diabetes in Poland. General practitioners as well as internal medicine specialists and diabetologists should be actively involved in educational activities targeted to patients at higher risk of diabetes. Findings from this study also underline the positive influence of having a family member with diabetes on the level of awareness of diabetes among other family members. The COVID-19 pandemic has a negative impact on diabetes care in Poland (13, 46), so public health interventions aimed to increase the level of public awareness of diabetes are needed to reduce the diabetes burden in Poland. Further studies should analyze the impact of the health system and diabetes education provided by healthcare workers on public awareness of diabetes.

This study has some limitations. The study was carried out using the CAWI re-search method, which excludes the direct interaction of the interviewer with the respondent (e.g., the ability to assess the competencies of the respondents, and her/his ability to understand the questions asked). The study questionnaire was limited to the most prevalent symptoms, risk factors, and complications. History of diabetes (both diagnosed by a doctor and diabetes in the family) was self-declared, and medical records were not verified due to the study design. Moreover, this research method includes only subjects who have internet access (though more than 92% of households in Poland now have internet access) (47). Nevertheless, this is the most comprehensive and up-to-date study on public knowledge and awareness of diabetes that was carried out among adults in Poland, after the COVID-19 pandemic outbreak.

5. Conclusions

This study demonstrated insufficient public awareness of diabetes among adults in Poland. Gender and educational level were the most important factors significantly associated with the awareness of the selected aspects of diabetes, while self-reported financial situation and place of residence had none or marginal influence. Moreover, the current study indicated significant gaps in the knowledge about risk factors for diabetes and its complications, as well as methods to prevent them. The presented data manifest the importance of adopting a comprehensive education strategy regarding diabetes in Poland.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocol was reviewed and approved by the Ethical Review Board at the Centre of Postgraduate Medical Education, Warsaw, Poland (No. 70/2022; date of approval: 08 June 2022). The patients/participants provided their written informed consent to participate in this study.

Author contributions

KS: conceptualization, data curation, formal analysis, investigation, project administration, visualisation, and writing an original draft. JG-S: conceptualization, investigation, methodology, and manuscript review and editing. JP: conceptualization, supervision, and manuscript review and editing. MJ: conceptualization, formal analysis, and manuscript review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Natalya Glushkova,
Kazakhstan School of Public Health, Kazakhstan

REVIEWED BY
Assiya Kussainova,
Semey State Medical University, Kazakhstan
Hao-yu Lin,
First Affiliated Hospital of Shantou University Medical College, China

*CORRESPONDENCE
Abduzhappar Gaipov
✉ abduzhappar.gaipov@nu.edu.kz
Anna Midlenko
✉ anna.midlenko@nu.edu.kz

[†]These authors have contributed equally to this work and share first authorship

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Prevalence, incidence, and mortality rates of breast cancer in Kazakhstan: data from the Unified National Electronic Health System, 2014–2019

Anna Midlenko[1*†], Kamilla Mussina[2†], Gulnur Zhakhina[2], Yesbolat Sakko[2], Gyunel Rashidova[3], Bolat Saktashev[4], Dauren Adilbay[5], Oxana Shatkovskaya[6] and Abduzhappar Gaipov[2,7*]

[1]Department of Surgery, School of Medicine, Nazarbayev University, Astana, Kazakhstan, [2]Department of Medicine, School of Medicine, Nazarbayev University, Astana, Kazakhstan, [3]School of Sciences and Humanities, Nazarbayev University, Astana, Kazakhstan, [4]Department of Mammology, Oncological Center of Tomotherapy "UMIT", Astana, Kazakhstan, [5]Department of Otolaryngology Head and Neck Surgery, Louisiana State University Health Sciences, Shreveport, LA, United States, [6]Department of Scientific and Strategic Activities, Kazakh Research Institute of Oncology and Radiology, Almaty, Kazakhstan, [7]Clinical Academic Department of Internal Medicine, CF "University Medical Center", Astana, Kazakhstan

Background: Although there are numerous sources of epidemiologic information on breast cancer in Kazakhstan, none of them have specifically examined the burden of this disease. Therefore, this article aims to provide an overview of the breast cancer prevalence, incidence, mortality, and distribution and changes over time in Kazakhstan based on nationwide large-scale healthcare data from the National Registry in order to encourage more research on the impact of various diseases at the regional and national levels.

Methods: The study cohort included all adult women older than 25 years who were diagnosed with breast cancer in any clinical setting of the Republic of Kazakhstan during the period of 2014–2019. The data were extracted from the Unified Nationwide Electronic Health System (UNEHS) to get an overview of descriptive statistics, incidence, prevalence, and mortality rate calculations and the Cox proportional hazards regression model. All survival functions and factors associated with mortality were tested for significance.

Results: The cohort population ($n = 55,465$) comprised subjects with the age at the diagnosis of breast cancer from 25 to 97 years, with a mean of 55.7 ± 12.0 years. The majority of the study population belonged to the age group 45–59 years, which is 44.8% of the cohort. The all-cause mortality rate of the cohort is 16%. The prevalence rate increased from 30.4 per 10,000 population in 2014 to 50.6 in 2019. The incidence rate varied from 4.5 per 10,000 population in 2015 to 7.3 in 2016. Mortality rates were stable and high in the senile age patients (75–89 years old). Breast cancer mortality was positively associated with women who had been diagnosed with diabetes, HR 1.2 (95% CI, 1.1–2.3), whereas it was negatively associated with arterial hypertension, HR 0.4 (95% CI, 0.4–0.5).

Conclusion: Overall, Kazakhstan is experiencing an increase in the incidence of breast cancer cases, but the mortality rate has started to decline. The switch to population mammography screening could reduce the breast cancer mortality rate. These findings should be utilized to help Kazakhstan determine what cancer control priorities should be utilized, including the need to implement efficient and affordable screening and prevention programs.

KEYWORDS

breast cancer, incidence, mortality, prevalence, Kazakhstan breast cancer, Kazakhstan

1. Introduction

Breast cancer is one of the most commonly seen malignant diseases among the female population worldwide, represents the most commonly diagnosed type of cancer, and was the main reason for cancer-related death in 2020 (1, 2).

Overall, the number of cancer incidences and mortality rates are rapidly growing worldwide. There was an estimated rate of 19 million new breast cancer cases and approximately 10 million cancer deaths worldwide in 2020, and there is an estimated rate of breast cancer death of ∼11 million by 2030 (3, 4).

Breast cancer is the foremost and most commonly diagnosed type of cancer, which is closely followed by lung, colorectal, prostate, and stomach cancers (5, 6). Breast cancer ranks first for its incidence in a majority of countries and is the fifth highest cause of cancer-related mortality globally, accounting for one in four cancer diagnoses in female individuals and one in six cancer-related deaths (4).

Breast cancer incidence is significantly higher in developed countries than in developing countries (55.9 and 29.7 per 100,000, respectively), with the highest incidence rates registered in Australia and New Zealand, Western and Northern Europe, and North America and the lowest rates in Central America, Eastern and Middle Africa, and South-Central Asia. The mortality rates among women in developed countries are also 17% higher than those among women in developing countries (15.0 and 12.8 per 100 thousand, respectively) (2, 4, 7). Nevertheless, incidence rates of breast cancer have been rising in the last few years in developing countries, where rates were historically very low (5, 8, 9). Breast cancer incidence in developing countries demonstrates low numbers in comparison with developed countries because there is an insufficiency of data and no effective cancer registry, and the age-standardized incidence rates are estimated based on data from other countries and hospital registries (10).

Breast cancer incidence in the former Soviet Union countries was generally lower in comparison with European countries, with age-standardized rates ranging from 19.5 cases per 100 thousand population in Tajikistan to 57.5 in Georgia in 2020. At the same time, the mortality rate is considered to be similar to and higher than that in European countries (11).

The majority of the former Soviet Union countries have mammography-based health screening programs but are typically provided on an as-needed basis with insufficient quality, according to the WHO Country Capacity Survey 2019 (12). In most countries that offer regular mammography screening, the target age of the screened population is from 50 to 69 years old, but in some countries, such as Georgia, Kazakhstan, and Russian Federation, it also covers women who are 40–49 years old and younger (13).

Kazakhstan is a former Soviet Union republic with a population of 19 million and with almost 11 million urban population. The median age in Kazakhstan is 30.7 years with 78 years of life expectancy at birth in female patients and 69.6 years in male patients. There are nearly 4.6 thousand new cases of breast cancer and 1.3 thousand deaths registered in Kazakhstan annually; however, this report is limited to demographic, regional, and cause-specific associations with prevalence, incidence, and mortality rates (14).

Breast cancer epidemiological studies enable the development of program efficiency indicators and the evaluation of program implementation outcomes. They also enable the planning of screening and diagnostic activities targeted at early disease identification (14, 15).

Epidemiological data on breast cancer in Kazakhstan are available from different resources; however, there is not enough publication examining the prevalence of breast cancer in Kazakhstan. There are only five studies on breast cancer epidemiology in Kazakhstan published on PubMed from 2012 to 2021, and data were retrieved from regional and national cancer centers and cancer registries. Those studies provide information on cancer statistics but do not show any correlation with comorbidities.

This study aims to provide an overview of breast cancer prevalence, incidence, mortality, and distribution and changes over time in Kazakhstan based on the Unified Nationwide Electronic Health System (UNEHS). The registry includes both inpatient and outpatient registries. The main information for epidemiological investigation is patient's demographics, data on morbidity and mortality, comorbidities, complications, and medical procedures. Analysis from this database will assess epidemiological data on breast cancer in Kazakhstan and the impact of various diseases at the regional level on breast cancer outcomes. Additionally, the results of this study will help to identify possible opportunities for improvement of local public health when comorbidities are taken into account in the future. It may lead to optimal patient care with improved breast cancer patient outcomes.

2. Methods

2.1. Study design and settings

The data were retrieved from the "Electronic Registry of Inpatients", which is one of the parts of the Unified Nationwide

Electronic Health System (UNEHS), which was introduced at the end of 2013 to synchronize health data storage across the nation's healthcare system (16).

The registry includes both inpatient and outpatient registries. The main information for epidemiological investigation is patient's demographics, data on morbidity and mortality, comorbidities, complications, and medical procedures. Every patient is assigned a unique life-long population registry number (RpnID). RpnID uniquely identifies each citizen within any registry of UNEHS, and it is used to perform data linkage between different registries and for the creation of the main outcome variable—all-cause mortality. All diagnoses are coded by the International Classification of Diseases, Tenth Revision (ICD-10) (C50.0–C.50.6 for breast cancer). ICD-10 codes corresponding to breast cancer disease are used for studying the epidemiology of disease by the calculation of prevalence and incidence along with being analyzed as explanatory variables for outcomes.

2.2. Study population

The study population consisted of patients with breast cancer in any clinical setting of the Republic of Kazakhstan during the period from 2014 to 2019. The cohort included all adult women older than 25 years. All-cause mortality was taken from patients with breast cancer. The data cleaning and management procedures are represented in the flow chart (Figure 1).

2.3. Statistical analyses

Data analysis was performed using Stata MP2 16.1 version. Descriptive statistics were performed to characterize the socio-demographic and medical characteristics of the study population. Mean and standard deviation were described as continuous variables with normal distribution, and frequencies and proportions were determined as categorical variables. Two-sided *t*-tests for parametric and Mann–Whitney *U*-tests for nonparametric data were performed to determine the difference between groups. The proportions were determined by Pearson's chi-square tests or a Fisher exact test.

The Cox proportional hazards (PH) regression analysis was performed to estimate unadjusted and adjusted socio-demographic hazard functions for the prediction of survival probabilities of breast cancer patients as well as the investigation of associations with other risk factors such as hypertension, diabetes, and stroke. The magnitude of hazard ratios (HR) and the width of their 95% confidence intervals (CI) were considered in order to decide whether associations are statistically and clinically significant.

Cox regression analyses were performed to demonstrate crude and adjusted hazard ratios. A total of three multivariable analysis models were constructed to test the adjusted effect of variables on mortality. The models were adjusted for potential confounders depending on the theoretical background and their availability in the database. In the first model, unadjusted socio-demographic predictors (age, ethnicity, and residence) were included. In the second model, variables were adjusted to demographics. In the third model, comorbidities such as arterial hypertension, diabetes, and stroke were added to Model 2. In all models, the stepwise selection method was used. The fit of the models was evaluated by the Akaike information criterion, Bayesian information criterion, and global goodness-of-fit test. The statistical significance level was set at a *p*-value of 0.05.

3. Results

During the study period, 55,465 cases of breast cancer were registered from 2014 to 2019. The socio-demographic and some medical characteristics of the patients are presented in Table 1. The age at diagnosis of breast cancer cases ranges from 25 to 97 years with a mean age of 55.7 ± 12.0 years. The majority of the study population is the age group 45–59 years, which is 44.8 % of the cohort. The most represented ethnic groups were Kazakh (40.8%), followed by other ethnic groups (39.5%). Almost all cohorts (94.6%) are urban, and 98.5% of patients were hospitalized as planned. All-cause mortality for the cohort is 16%. The median follow-up time was 4.1 years (IQR, 2.0–9.0 years). Crude death rate (per 1,000 people) revealed that older age groups, Russian ethnic groups, rural residents, and urgent hospital admissions are considered risk factors for breast cancer mortality. Non-communicable diseases such as hypertension, diabetes, and stroke were taken as comorbidities. Data analysis showed that the majority of patients had hypertension (33.7%).

Incidence, prevalence, and crude mortality rates were assessed and are shown in Figure 2. Breast cancer incidence varied from 4.7 per 10,000 population in 2014 to 5.4 in 2019. The prevalence rate increased from 30.4 per 10,000 population in 2014 to 50.6 in 2019. At the same time, there was no obvious difference in breast cancer mortality for the observed period with a stable index of 2.0 per 10,000.

The all-cause mortality rate of patients with breast cancer per 1,000 person-years is presented in Figure 3. Mortality rates varied from 61.4 per 1000 in 2014 to 54.4 in 2019.

There were no major changes in age-specific incidence among breast cancer patients for the analyzed period of time with a stable and high incidence in the age group of 60–75 years with the highest rate of 25.3 per 10,000 in 2018 (Figure 4). At the same time, mortality rates did not show the same trend in the aforementioned group of patients. Standardized mortality rates were stable and high in senile age patients (75–89 years old).

Table 2 represents the association between socio-demographic and medical characteristics with all-cause mortality rates of breast cancer from 2014 to 2019. The Unadjusted Cox proportional hazard model shows that the older age group (>90) has the highest hazard of death (14.5) than other age groups. Slightly increasing trends can be observed in models adjusted to demographics and to comorbidities such as hypertension, diabetes, and stroke. Russian ethnic group had a 10% higher risk of death than other ethnic groups in the unadjusted model. However, in models adjusted to demographics and comorbidities, other ethnic groups showed a 10% higher risk of death. Patients with diabetes as a comorbidity had a 10% higher risk of death in the adjusted PH model.

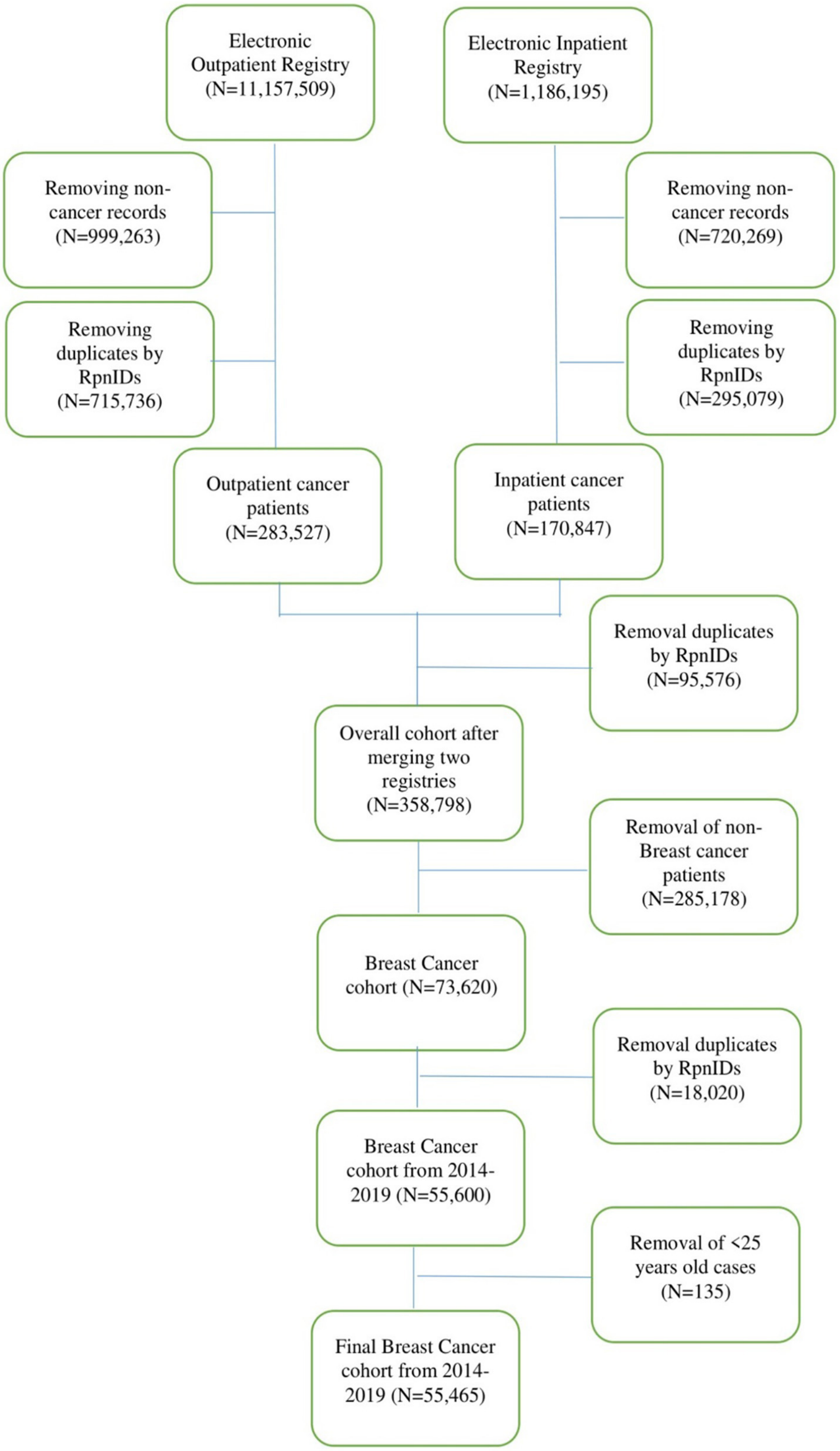

FIGURE 1
Flow chart diagram of cohort set-up.

TABLE 1 Socio-demographic and medical characteristics of patients with breast cancer.

Demographic characteristics	Total $n = 55{,}465$	Alive $n = 46{,}336$ (84%)	Dead $n = 9{,}129$ (16%)	*p*-value	Mortality rate per 1,000 PY [95% CI]
Age, mean ± SD	55.7 ± 12.0	54.8 ± 11.6	59.8 ± 13.2	<0.0001	
Age groups, *n* (%)				<0.0001	
25–44	10,089 (18.2)	8,903 (88.2)	1,186 (11.8)		12.7 [12.0; 13.4]
45–59	24,861 (44.8)	21,521 (86.6)	3,340 (13.4)		19.0 [18.4; 19.6]
60–74	16,684 (30.1)	13,534 (81.1)	3,150 (18.9)		36.8 [35.5; 38.1]
75–89	3,741 (6.7)	2,332 (62.3)	1,409 (37.7)		96.9 [92.0; 102.2]
>90	90 (0.2)	46 (51.1)	44 (48.9)		192.9 [143.5; 259.2]
Ethnicity, *n* (%)				<0.0001	
Other	21,858 (39.5)	18,727 (85.7)	3,131 (14.3)		23.8 [23.0; 24.7]
Kazakh	22,591 (40.8)	18,572 (82.2)	4,019 (17.8)		24.3 [23.6; 25.1]
Russian	10,867 (19.7)	8,908 (82.0)	1,959 (18.0)		27.1 [25.9; 28.3]
Residence, *n* (%)				<0.0001	
Rural	3,017 (5.4)	2,796 (92.7)	221 (7.3)		30.1 [26.4; 34.3]
Urban	52,448 (94.6)	43,540 (83.0)	8,908 (17.0)		24.6 [24.1; 25.1]
Hospital admission, *n* (%)				<0.0001	
Planned	22,215 (98.5)	19,115 (86.0)	3,100 (14.0)		48.5 [46.9; 50.3]
Urgent	327 (1.5)	159 (48.6)	168 (51.4)		156.4 [134.4; 181.9]
Comorbidities, *n* (%)					
Hypertension	18,719 (33.7)	16,452 (87.9)	2,267 (12.1)	<0.0001	15.8 [15.2; 16.5]
Diabetes	6,250 (11.3)	5,022 (80.4)	1,228 (19.6)	<0.0001	25.6 [24.2; 27.1]
Stroke	1,037 (1.9)	615 (59.3)	422 (40.7)	<0.0001	51.1 [46.4; 56.2]
Surgeries	7,175 (12.9)	6,755 (94.1)	420 (5.9)	<0.0001	

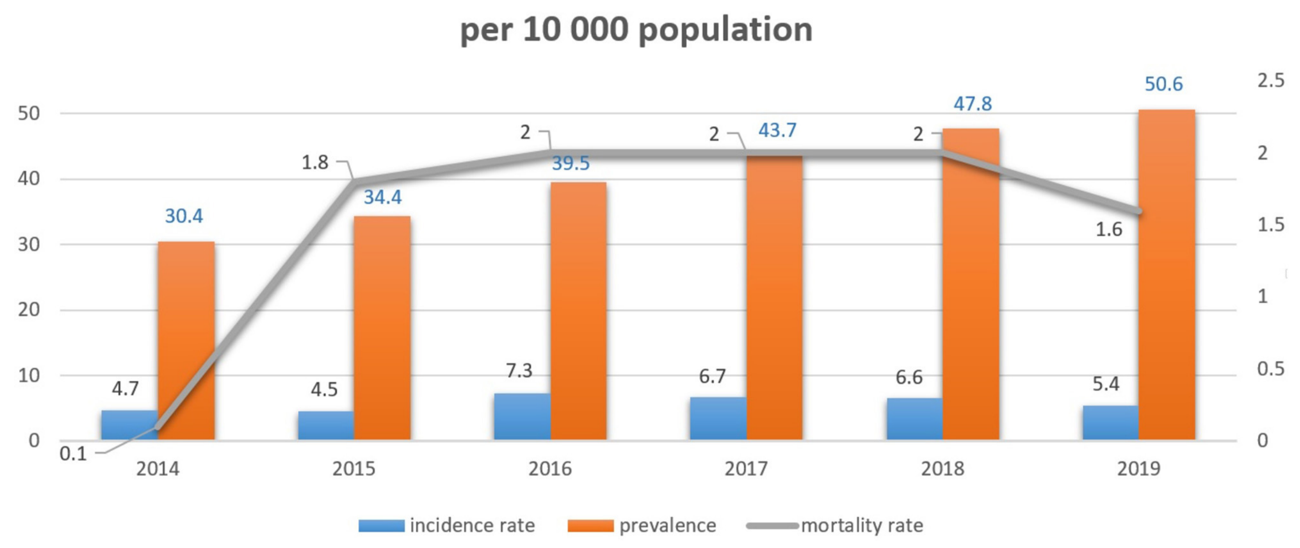

FIGURE 2
Incidence, prevalence and mortality rates of patients with breast cancer.

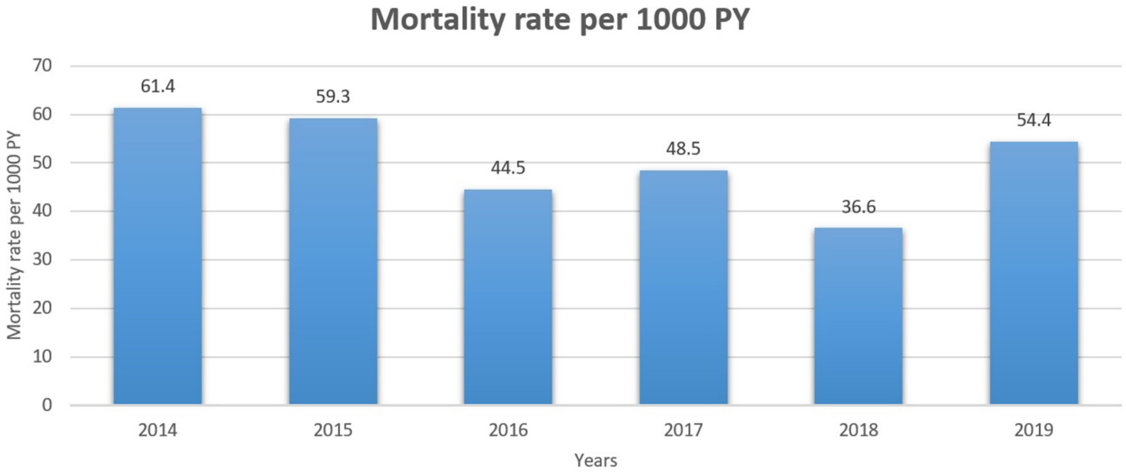

FIGURE 3
All-cause mortality rate of patients with breast cancer per 1000 person-years for 2014–2019 years.

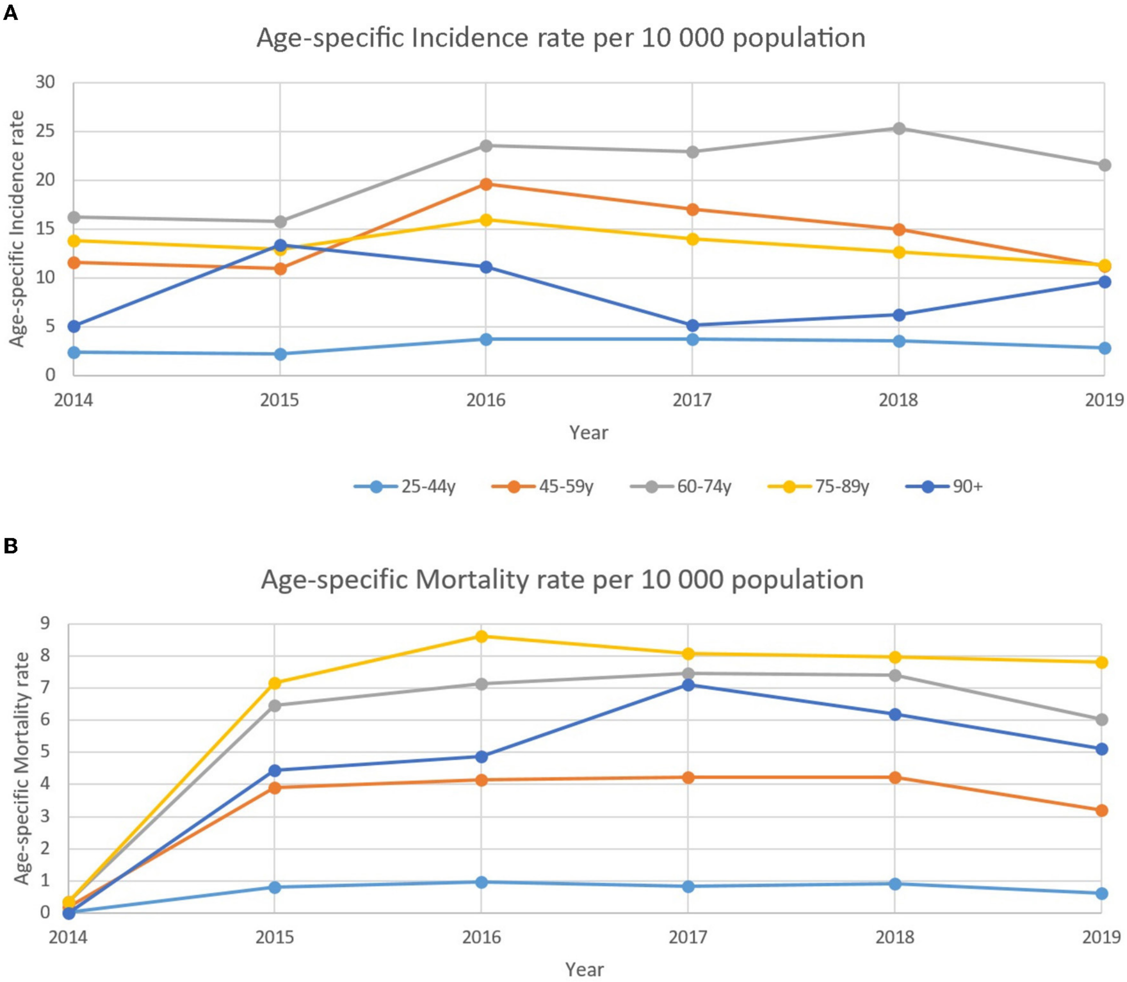

FIGURE 4
(A) Age-specific incidence rate of patients with breast cancer per 10,000 population between 2014–2019. **(B)** Age-specific standardized mortality rate of patients with breast cancer per 10,000 population between 2014–2019.

TABLE 2 Association between socio-demographic and medical parameters and all-cause mortality rates of breast cancer between 2014 and 2019.

Variable	Unadjusted HR (95% CI)	*p*-value	Adjusted to demographics HR (95% CI)	*p*-value	Adjusted to comorbidities HR (95% CI)	*p*-value
Demographics						
Age groups, *n* (%)						
25–44	ref.		ref.		ref.	
45–59	1.5 [1.4; 1.6]	<0.0001	1.6 [1.4; 1.7]	<0.0001	1.7 [1.6; 1.8]	<0.0001
60–74	2.9 [2.7; 3.1]	<0.0001	3.0 [2.8; 3.3]	<0.0001	3.4 [3.2; 3.7]	<0.0001
75–89	7.5 [6.9; 8.1]	<0.0001	7.9 [7.3; 8.6]	<0.0001	8.6 [7.9; 9.3]	<0.0001
>90	14.5 [10.7; 19.6]	<0.0001	15.7 [11.6; 21.3]	<0.0001	16.4 [12.1; 22.1]	<0.0001
Ethnicity, *n* (%)						
Kazakh	ref.		ref.		ref.	
Other	1.1 [1.0; 1.1]	0.014	1.2 [1.1; 1.3]	<0.0001	1.2 [1.1; 1.3]	<0.0001
Russian	1.2 [1.1; 1.2]	<0.0001	1.1 [1.0; 1.2]	<0.0001	1.1 [1.0; 1.2]	<0.0001
Residence, *n* (%)						
Urban	ref.		ref.		ref.	
Rural	1 [0.9; 1.1]	0.996	1.2 [1.1;1.4]	0.005	1.0 [0.9; 1.1]	0.985
Comorbidities						
Hypertension	0.5 [0.5; 0.6]	<0.0001			0.4 [0.4; 0.5]	<0.0001
Diabetes	1.1 [1.0; 1.1]	0.036			1.2 [1.1; 1.3]	<0.0001
Stroke	2.2 [2.0; 2.4]	<0.0001			2.0 [1.8; 2.2]	<0.0001

4. Discussion

This is the first in-depth epidemiological study in Kazakhstan and Central Asia, assessing the prevalence, incidence, and mortality rates of breast cancer using the Unified National Electronic Health System, 2014–2019.

We found that breast cancer incidence in Kazakhstan corresponds with worldwide trends and is increasing over the investigated period, while mortality rates slowly decline. This rise in incidence rate may be partially explained by alterations in lifestyle—such as later marriage, later first pregnancy, and fewer number of deliveries—the use of oral contraceptive pills, inactivity/obesity, and smoking. It is also conceivable that this growth is influenced in part by more accurate breast cancer detection and diagnosis. Breast cancer screening has been offered in Kazakhstan to women between 50 and 60 years old at a 2-year interval since 2008. Since 2014, 80% of mammography equipment was digitalized, and the screening age was raised to 40–70 years old.

The incidence rate of breast cancer for the study period among the female population in Kazakhstan varied from 4.5 to 7.2 cases per 10,000 persons. Age trends of breast cancer diagnosis vary slightly among the Asian and European countries; in Saudi Arabia, it is 55.68 years; in Iran, it is 46.76 ± 1.19 years, while in the USA, it is 63 years, and the global trend is 62 years old (17, 18). The average age of patients with BC in the republic of Kazakhstan during the study period was 55.7 ± 12.0 years and corresponds with the global trends.

Despite the average age of diagnosis in our study falling within 50–60 years, approximately 20% of our study population was younger and would not have been diagnosed with the screening program. It should be mentioned that the age of breast cancer patients is an important risk factor and prognostic factor. During the study period, 18.2% of patients were diagnosed with breast cancer at a young age (25–44 years). This category of patients does not fall under the criteria for mammographic screening in Kazakhstan which starts at the age of 40 (19). Data revealed that breast cancer is the most common cancer type in adolescents and young adults of age 15–39 years, accounting for one-third of all newly diagnosed cancer cases in young women. According to SEER, 5.6% of all invasive breast cancer cases were diagnosed in young women (6, 20). Young patients with breast cancer are more likely than older patients to present with advanced disease or aggressive biological tumor subtypes, such as triple-negative or HER2-positive breast cancer. Moreover, breast cancer in young patients was strongly associated with family history and genetic mutations in the BRCA1 or BRCA2 genes leading to the development of breast and ovarian cancers.

Young patients have a higher mortality rate than older patients, even among those with early-stage breast cancer (21). Young patients are also more susceptible to treatment-related adverse effects and cancer-related psychosocial problems. The medical community must pay particular attention to this reality, addressing these issues by drafting regulations and guidelines and establishing medical systems focused on early identification and prevention of breast cancer in young and adolescent patients (22).

In our study, 44.8% of patients diagnosed with breast cancer were patients belonging to 44–59 years with an average age of 57 ± 12.0 years, and this age is below the mean age of breast cancer diagnosis in other countries. The possible reason explaining this fact might be related to the best adherence to breast cancer screening among this group of patients. The fact that younger patients are more often diagnosed with aggressive tumor phenotypes may lead to their capture by the inpatient registry as they are receiving more aggressive treatment. Our study showed that 94% of all patients were from urban areas, and we explain this fact with better screening coverage of urban citizens in comparison with rural areas. The abovementioned groups of patients are an able-bodied population. Currently in Kazakhstan, like in other countries, jobs are increasingly moving out of agriculture into the urban services sector; at the same time, the urbanization rate will increase in Kazakhstan from 63 to 64% by 2050 (23). Among women aged from 45 to 64 years, breast cancer was commonly associated with higher work and home productivity days lost in the first 2 years since the diagnosis (24). As seen in other studies, productivity losses and potential losses in public finance associated with breast cancer in Europe increased to 20% in 2014 compared to 2010 (25). Islami et al. assessed lost profit as $6.2 billion due to premature mortality because of breast cancer among all age patients in 2015 (26). Further study should be done to assess the lost market earning due to breast cancer diagnosis among the Kazakhstan population. The peak of breast cancer incidence was at the age of 60–75 years, and it might correspond with the aging population in Kazakhstan. Data show that in 2021, nearly 8.17% of Kazakhstan's total population was aged 65 years and older, but in 2014, 6.76% were older than 65 years.

The majority of European countries reported that breast cancer was the leading cause of cancer-related deaths in 2018 with European Union breast cancer mortality rates from 17.9 in 2002 to 15.2 per 1,00,000 population in 2012 (1, 27, 28). Breast cancer shows the most prevalent malignancy and the second-largest cause of cancer-related deaths among Asian women (29). Across the coming 10 years, it is expected that the number of breast cancer-related deaths will rise in Asian nations. According to studies, Asia's mortality rates for breast cancer varied greatly in 2017 from 8.6 in East Asia to 15.0 per 1,00,000 patients in South Asia (30).

The mortality rate in breast cancer patients during the study period among the female population of the country did not show any negative or positive trend and varied from 1.8 to 2.0 per 10,000 patients and was the highest in senile patients, and it corresponds with available data. The study by Freedman R. showed that the risk of death over a 6-year follow-up period increased with age, counting 42% of women aged 75–84 years and 66% of women aged ≥85 years (31). While the relative survival rate of patients with advanced breast cancer has increased in recent years for those aged 65 to 75, there has been no improvement for those who are over 75 years (32).

As expected, patients who died were older on average (75–89 years), and it can be explained by the number of comorbidities. Many studies have reported that several comorbidities are associated with a lower survival rate among all breast cancer patients, and a high proportion of older patients die from non-cancer-related causes (31, 33, 34). All-cause mortality rates in our study varied from 61.4 per 1000 in 2014 to 54.4 in 2019. The most common comorbidity reported among breast cancer survivors in our study was hypertension (33.7%), followed by a history of surgery (12.9%), diabetes mellitus (11.3%), and stroke (1.9%).

Breast cancer mortality was positively associated in women who had been diagnosed with diabetes, 232 HR 1.2 (95% CI, 1.1–2.3), whereas it is negatively associated with arterial hypertension, HR 0.4 (95% CI, 0.4–0.5).

Cardiovascular disease is a known leading cause of non-cancer-related deaths in women who were diagnosed with breast cancer worldwide. The risk of cardiovascular disease is increased by both chemotherapy and radiotherapy. Different chemotherapy medications such as anthracyclines, fluoropirimidines, taxanes, and HER-2 targeted agents are associated with a high risk of cardiomyopathy, heart failure, as well coronary artery disease (35, 36). Vo et al. showed that patients who underwent previous breast cancer treatment in the US had a lower risk of heart disease and associated mortality in comparison with the general population. Those findings might be explained by national heart screening programs, improved healthcare access, and the expanding awareness of cardiovascular risk factors among healthcare providers and breast cancer patients (37). Our study also shows that more attention should be applied to clinical decision-making assistance in cancer survivors in order to manage late cardiovascular complications in this cohort of patients in Kazakhstan (38).

Our data correspond with the number of studies showing that diabetes increases the risk of breast cancer relapse and breast cancer-related deaths (39, 40). Diabetes patients in Sweden were shown to have a 45% higher chance of dying from breast cancer than non-diabetics in a hospital-based cohort study (39). There are different possible explanations for the impact of diabetes mellitus on the survival of patients with breast cancer. First, diabetes mellitus led to an increase in tumor cell proliferation rate which in turn can lead to an increased risk of breast cancer recurrence rate.

Breast cancer patients with diabetes mellitus developed insulin resistance and chronic hyperinsulinemia which might stimulate insulin receptor signaling and induce breast cancer cell proliferation and growth (41, 42). Diabetes mellitus as well as other comorbidities may decrease a patient's treatment options, leading to increased mortality due to a higher risk of treatment side effects (43).

It has to be emphasized that age-specific mortality rates were lower in patients who are older than 90 years compared to those who are 75–89 years old. This fact might be explained by the less aggressive tumor subtypes of that group of patients and the fact that significantly fewer patients who are older than 80 years underwent radiation therapy and chemotherapy as a part of their treatment (44, 45).

Our study had several advantages. In Kazakhstan, it is the first study to give comprehensive epidemiological data on incidence, prevalence, and mortality rates for breast cancer. Additionally, for a 6-year period, the whole female population of Kazakhstan was included in the study's big cohort (2014–2019). Data from medical records were connected to sociodemographic data and patient comorbidities.

However, this report does have several significant shortcomings. These issues stem from the UNEHS flaws, which were introduced in 2014 and are still being worked on. This system does not provide information on the patient's past medical history, past pregnancy and delivery history, education status, marital status, general family history, cancer disease stages, cancer molecular subtypes, and treatment given to patients. In this study, we have not had an opportunity for a detailed analysis of the breast cancer subtypes and stages as these data belong to the National Oncology Registry. It will, therefore, be a task for our subsequent investigations. The presence of these crucial variables could enhance the study's findings.

5. Conclusion

Breast cancer continues to be one of the leading causes of mortality in Kazakh women despite recent declines in incidence. To lower the death rate, it is crucial to continue developing evidence-based early identification policies and to optimize existing treatment approaches.

Breast cancer incidence in Kazakhstan is overall increasing, while mortality rates have begun to decline. The switch to population-based, high-quality mammography screening could reduce breast cancer mortality. These findings should be used to help Kazakhstan establish priorities for cancer control, including the need for the implementation of successful screening and prevention programs that are both cost-effective and efficient as well as the planning of future cancer services based on the allocation of limited resources to ensure their operationalization. Future research should be done to understand the role of effective management of comorbidities among breast cancer patients as an action to improve disease prognosis.

Data availability statement

Dataset is not publicly available. Requests to access these datasets should be directed to Republican Center of Electronic Healthcare.

Ethics statement

The study was approved by the NU Institutional Review Ethics Committee (651/24112022 on 28/11/2022), with an exemption from informed consent.

Author contributions

AM, KM, and AG: conceptualization, methodology, validation, investigation, and writing—original draft preparation. KM and AG: software and formal analysis. KM, GZ, YS, and GR: data curation. AG, BS, DA, and OS: writing—review and editing. AM and KM: visualization. AG: supervision, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Yuliya Semenova,
Nazarbayev University, Kazakhstan

REVIEWED BY
Dariga Smailova,
Kazakh National Medical University, Kazakhstan

*CORRESPONDENCE
Alexander Bongers
✉ alex.bongers@outlook.com

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Understanding COVID-19 vaccine hesitancy in health care professionals in Central and West Asia: lessons for future emergency mass vaccination campaigns

Shalkar Adambekov[1,2], Alexander Bongers[1]*, Jonathan Hare[1], Dragoslav Popovic[1], Harsha Rajashekharaiah[1], Stefan M. Lawson[1], Giovanna Riggall[1], Larissa Kokareva[1] and Brian Chin[3]

[1]Crown Agents, London, United Kingdom, [2]Department of Epidemiology, Biostatistics, and Evidence Based Medicine, Al-Farabi Kazakh National University, Almaty, Kazakhstan, [3]Asian Development Bank, Manila, Philippines

A Quick Assessment of Vaccine Hesitancy approach was developed to collect population insights on vaccination hesitancy for low resource environments. Insights into COVID-19 vaccine hesitancy were collected through online webinars with heads of healthcare departments and anonymized online surveys of healthcare managers (HCM) and primary healthcare workers (HCW) in four countries in Central and West Asia (Armenia, Georgia, Tajikistan, and Kyrgyzstan) between 28 February 2022 and 29 March 2022. From the responses to the survey some key themes identified that underpinned in vaccine hesitancy across the region were perceived understanding of vaccine efficacy, conflict with individual religious beliefs, concerns for side effects, and the relatively rapid development of the vaccine and that improving communications strategies to address these concerns would be critical in combatting vaccine hesitancy through any future public health emergencies.

KEYWORDS

vaccine hesitancy, LMIC, snowball sampling, communications, knowledge attitudes

1. Introduction

Up until March 2023, 13.23 billion doses have been administered globally with 5.52 billion people, equivalent to 69% of global population having received at least one dose of a COVID-19 vaccine (1). Although significant progress has been made in upscaling COVID-19 vaccination globally, coverage in many Low- and Middle-Income countries (LMICs) lags behind developed nations, with 23.3% of people in low-income countries having received their full vaccination regimen (2, 3). Significant barriers to vaccination still exist in low- and middle-income countries and addressing them in detail is essential in reaching country immunization goals as well as WHO vaccination targets of 70% of the total population of every country while achieving 100% coverage among at-risk populations such as those over age 60 and healthcare workers (4–6).

Many barriers to increasing COVID-19 vaccination coverage can be broadly categorized into three main areas: (1) Procurement and supply chain, (2) Distribution, including cold chain management and (3) Socio-economic challenges including vaccine hesitancy. The challenges around procurement and distribution have been well documented (7) whereas capturing the intricacies of the socio-economic challenges is more complex and varies greatly across countries and regions.

Any response to vaccine hesitancy requires strategies that address the immunization policy, population-specific communication strategies, capacity building, behavior change, and collaborations across a wide range of stakeholders including health care workers (HCWs). Some of the considerations that can contribute to different vaccine hesitancy profiles include the accelerated timescale for development of vaccines, the utilization of novel technologies in vaccine development, structural and underlying lack of governmental or institutional trust in public health management, the interdependency with other preventative public health measures, and perceived (8–12).

Health care workers (HCWs) are at the forefront of nay healthcare emergency and yet are frequently expected to implement mass vaccination programs often supported with limited training, supervision, or guidance, as was observed with the COVID-19 vaccination programs (13, 14) coupled to HCWs being a priority group for receiving emergency use vaccines. This combination frequently leads to a situation whereby despite a high vaccination rate of HCWs this does not translate to high coverage among the general population and collecting insights on vaccination issues from HCWs could be important to inform policy on strategies to combat vaccine hesitancy in the general population (15).

In this perspective, the Vaccine Advisory Firm for Central and West Asia, a consortium of Crown Agents and FHI360, under a technical assistance project funded by the Asian Development Bank, describe the implementation of a Quick Assessment of Vaccine Hesitancy (QAVH) approach to facilitate rapid collection of population insights in to vaccination hesitancy and provides a summary of the responses received within across 4 countries in Central and West Asia (Armenia, Georgia, Kyrgyzstan, and Tajikistan) targeting key HCWs. Finally we propose that implementing similar cloud-based data input approaches targeting key populations can be used to provide a contemporaneous, cross-sectional snap-shot of opinions to augment traditional large knowledge, attitude, and practice (KAP) surveys when looking to formulate procedures for acute health emergencies.

2. Quick assessment of vaccine hesitancy

While vaccine hesitancy to routine immunization programs is well researched (16–18) the traditional profile of hesitancy does not necessarily directly transfer to emergency use vaccination campaigns, as witnessed with COVID-19 vaccine and research into this is an ongoing activity as the world transitions to a COVID-19 endemic state (19–21). To facilitate obtaining real-time insights, the deployment of Quick Assessment of Vaccine Hesitancy (QAVH); a rapid procedure for sampling key, healthcare populations on their attitudes to mass vaccination campaigns that can be used to supplement existing data sources. QAVH comprises obtaining data through rapid, multiple choice question surveys combined with reviewing country reports from the Ministries of Health. The QAVH approach uses free, cloud-based online tools and leverages established administrative resources within each countries' Ministry of Health (MoH) to generate data profiles on hesitancy from all levels of the healthcare system including vaccine program managers through to frontline care providers. Data collection is facilitated through a combination of online webinars with heads of healthcare departments, and surveys of healthcare managers and primary HCWs.

2.1. Webinars

Online webinars with key stakeholders from countries' MoH and development partners were used to raise the profile and understanding of vaccine hesitancy as well as data collection on vaccine communication and demand creation challenges. For the survey of HCWs in Central and West Asia, two webinars were provided at least a week apart with attendees from participating countries as well as attendees from non-participating countries including Turkmenistan and Pakistan. The first webinar concentrated on setting the reporting requirements for healthcare managers. The second webinar concentrated on collecting reports from healthcare managers on subnational (regional and district) vaccine hesitancy issues. Healthcare managers provided structured presentations with a focus on collecting insights on the factors that drive hesitancy based on reporting requirement set by MoH. The insights provided were used to inform the development of survey questions for healthcare managers and primary HCWs.

2.2. Cloud-based surveys

Surveys of healthcare managers are used to collect communication and demand issues as perceived by the representatives of the healthcare system. The healthcare managers can include heads of hospitals, district health departments, or other types of local-level health managers. The survey of primary HCWs aims to collect primary level data on hesitancy issues, including misinformation reported to primary healthcare providers during patient visits, vaccination sessions, or through social media or personal communication with other people.

These surveys were made available online and were targeted to primary HCWs and healthcare managers with a policy of active follow-up pursued to foster engagement through established communication channels with primary HCWs and healthcare managers, as well as personal communication tools including online chats, messengers, and social media. Snowball sampling (22) was the preferred method of survey rollout for the QAVH approach since it is cheap, simple, and requires fewer human resources. The links to the surveys were sent through established communication channels, such as WhatsApp groups for healthcare workers or e-mail distribution, with a request to share with other colleagues.

2.3. Survey results summary

As a proof-of implementation for using this QAVH approach within an ongoing public health emergency we collected data from COVID-19 vaccine hesitancy surveys for healthcare managers and primary HCWs submitted between 28 February 2022 and 29 March 2022 from respondents in 4 countries in Central and West Asia (Armenia, Georgia, Tajikistan, and Kyrgyzstan). The survey was provided to 529 potential respondents, 522 (99%) of which agreed to participate and seven (1%) declined participation. Only answers from those who proactively consented to participate included for analysis (65 healthcare managers and 457 primary HCWs).

In summary, of the 522 respondents who agreed to participate, 503 (96.3%) were fully vaccinated, comprising 438 HCWs and all 65 healthcare managers, 13 HCWs (2.5%) had received only one vaccine dose, and 6 HCWs (1.2%) were not vaccinated (Figure 1A). The importance of vaccination communication to reach immunization targets was supported across the surveyed countries. Over half of respondents agreed (46% agreed, 12% strongly agreed) with the statement that the communication campaign had been successful in their country, and most respondents (68% agreed, 20% strongly agreed) supported the statement that the communication campaign in their country could be improved (Figure 1B). The notion that the communication campaign was successful in the respondent's country was disagreed by over 22% of the surveyed healthcare managers, while 18% were undecided on the issue (Figure 1C). While 88% of respondents trust in the safety and efficacy of vaccines was greater than the public trust (Figure 1D) there was concern that there was a degree of vaccine hesitancy among HCWs who are at the frontline of the vaccine effort. However, further survey responses illustrated that trust in the safety and efficacy across all the vaccines available varied significantly, which could indicate that hesitancy may be toward specific vaccine types and not the COVID-19 vaccine in general. While the discussion around mandatory vaccination is multifactorial, with 79% of primary HCWs supporting its implementation (Figure 1E), it does support the consensus that most of the respondents support and advocate for the role of vaccination in a countries' COVID-19 response. This is further supported by further survey responses illustrating that 74% of respondents were not under administrative or other pressure to be vaccinated against COVID-19 (Figure 1F). The full demographics of respondents are summarized in Table 1.

These survey results were predominantly sought to further understand the vaccine hesitancy profile in the region. However, we also used these results alongside feedback obtained during the webinars from countries in the region to inform our collaboration with the countries to subsequently develop and disseminate training videos in several languages to counter vaccine hesitancy, prioritizing knowledge gap areas in vaccine manufacturing, vaccine regulation, benefits of immunization as well as ensuring quality during storage and distribution (these videos are available at https://www.youtube.com/@VaccineAdvisoryFirmAsia/playlists and within the Supplementary data). The end-user multifunctionality of these surveys is another advantage that can be incorporated in to developing real-time policy and training programs for key stakeholders.

3. Summary

While many countries have prioritized access to vulnerable cohorts based on age and risk, global vaccine supply should now facilitate access for most people eligible for COVID-19

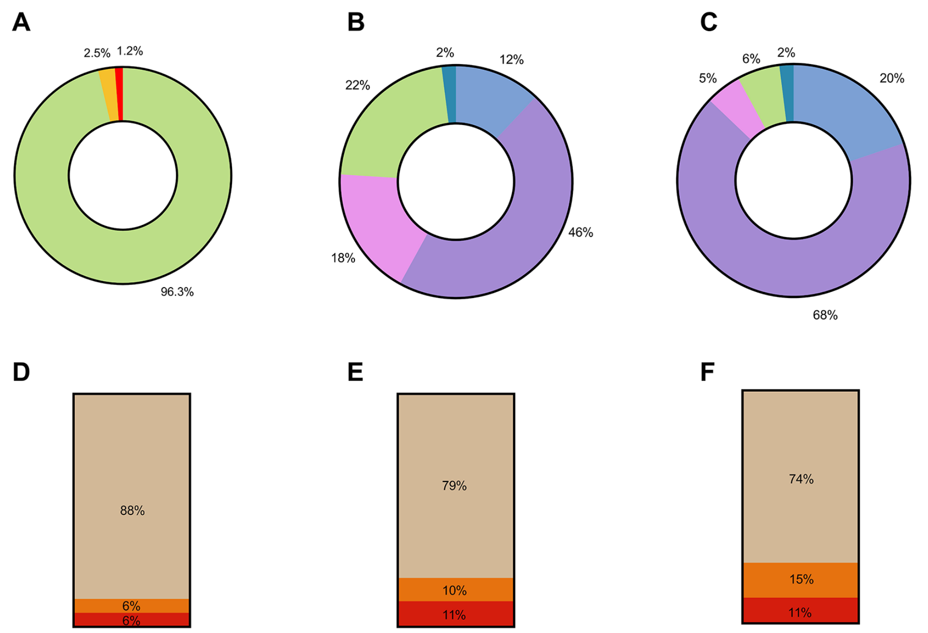

FIGURE 1
Summary of QAVH survey responses. **(A)** Percentage distribution of vaccination status across all 522 survey respondents. Green—% fully vaccinated, Yellow—% partially vaccinated, Red—% unvaccinated. **(B)** Response by 65 Healthcare Managers to the following statement: "The communication campaign is successful in my country/region." Blue—strongly agree, purple—agree, pink—undecided, green—disagree, teal—strongly disagree. **(C)** Responses by 65 Healthcare Managers to the following statement: "The communication campaign needs some improvement in my country/region." Blue—strongly agree, purple—agree, pink—undecided, green—disagree, teal—strongly disagree. **(D)** Responses by 457 Primary Healthcare Workers to the following statement: "Do you trust the efficacy and safety of the COVID-19 vaccines used to vaccinate the public?." **(E)** Responses by 457 Primary Healthcare Workers to the following statement: "Do you think COVID-19 vaccination should be mandatory?." **(F)** Responses by 457 Primary Healthcare Workers to the following statement: "Have you been subjected to administrative or other pressure to get vaccinated against COVID-19?." Beige—yes, orange—no, red—prefer not to respond.

TABLE 1 Demographics of survey respondents.

	Armenia	Georgia	Kyrgyzstan	Tajikistan	No location
Total participants	52 (0)	12 (34)	0 (7)	1 (399)	0 (17)
Male	21 (0)	4 (7)	0 (0)	0 (345)	0 (2)
Female	30 (0)	8 (27)	0 (7)	1 (54)	0 (15)
Age-range					
18–24	1 (0)	0 (1)	0 (0)	0 (40)	0 (0)
25–34	11 (0)	0 (0)	0 (4)	0 (135)	0 (1)
35–44	20 (0)	3 (4)	0 (2)	0 (89)	0 (1)
45–54	9 (0)	4 (10)	0 (1)	1 (85)	0 (8)
55–64	10 (0)	4 (16)	0 (0)	0 (43)	0 (6)
65–74	1 (0)	1 (3)	0 (0)	0 (7)	0 (1)
Degree level					
Gradate	39 (0)	9 (28)	0 (0)	1 (151)	0 (12)
Postgraduate*	13 (0)	3 (6)	0 (7)	0 (214)	0 (5)
No degree	0 (0)	0 (0)	0 (0)	0 (34)	0 (0)

Responses presented from healthcare managers and healthcare workers (in parentheses). *Postgraduate degrees include secondary specialized educations.

vaccination. However, despite sufficient supply, most countries are now experiencing a significant slowdown in COVID-19 vaccination uptake. While there are different barriers to COVID-19 vaccination in different countries and in subnational regions and districts, a significant contributor to the slowing rates of COVID-19 vaccination currently being observed is vaccine hesitancy.

To improve uptake in the short-term of available COVID-19 vaccines as well as preparing for future emergency mass vaccination campaigns it is essential for different countries' vaccination program administrators to understand their individual degree of vaccine hesitancy and key concerns in order to develop strategies and policies to address vaccine hesitancy. We have demonstrated that anonymized online surveys are a useful and cost-effective way to gather information on the country's vaccine hesitancy profile especially when combined with regular webinars to engage with HCWs.

The QAVH approach does not require significant financial or human resources compared with traditional population data collection tools which can make it an easily accessible and readily deployable tool to augment traditional population-based surveys. This QAVH approach may have greater applicability in LMICs which are frequently resource light for developing the larger epidemiological studies necessary to fully appreciate the levels of vaccine hesitancy data in key at-risk populations and could facilitate development of key, evidence-based communication and demand creation activities and strategies in future acute public health emergencies. Most importantly, rapid data collection and analysis facilitated by these tools allowed us in collaboration with countries to identify knowledge gaps and develop training videos to address these gaps. The results from this study support the conclusion from previous studies that combatting vaccine hesitancy within the region of Central and West Asia will require a multipronged approached focusing on enhanced digital engagement to address the concerns of healthcare professionals, improving communication strategies for health service provider and apply solutions based on real-time behavioral insights to reinforce demand (6, 8).

3.1. Limitations

We developed the QAVH approach to quickly assess vaccine hesitancy issues in low resource environments and limited timeframes and can be adopted in the early stages of future acute public health emergencies, especially if countries do not have the results of general population KAP surveys available. There are several limitations of QAVH approach to be aware of, which implies it should not be considered a replacement for general population KAP surveys:

- the survey uses proxy population (HCWs and managers);
- sampled population may not be representative of the target population, though this could be mitigated through careful identification of appropriate sampling;
- response biases could affect data collection due to differences in vaccination rates between sample populations and general population;
- data is collected using the snowball sampling, which could hamper the heterogeneity in the sample; and
- insights collected from healthcare or stakeholder representatives might not be accurate due to administrative pressure for better results or a lack of established information collection network.

3.2. Key recommendations for deploying a QAVH approach

- Engage with a range of stakeholders and key policy makers to raise understanding on the hesitancy profile and the development of communication partnerships to facilitate wide-reaching messaging.
- Use webinars with key stakeholders and key opinion leaders in order to inform development of more precise surveys for data collection, such as selecting target populations or identifying specific vaccine hesitancy issues.

- Every effort should be undertaken to ensure the anonymization of survey responses.
- Use a specific sampling technique when deploying surveys, such as snowball sampling, sometimes referred as chain-referral sampling, in which existing subjects provide referrals to recruit samples required for a research study. This method allows accessing hard to reach populations, can dramatically increase the sample size from few starting points and allow for insights to be collected from participants without bias undue due to perceived administrative pressure or a lack of established information collection network.
- The timeline for deploying a QAVH approach depends on the capacity and experience of the MoH with surveys and data collection, but generally should not take more than 4–6 weeks.
- Share the results of surveys immediately with a range of stakeholders to facilitate the development of strategies to address identified knowledge gaps.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SA conceptualized the study, designed the methodology, analyzed the data, interpreted the results, and drafted the initial manuscript. AB conceptualized the study, visualized the data, and contributed to data analysis and interpretation. AB, DP, HR, JH, SL, GR, and LK reviewed and edited drafts of the manuscript. BC reviewed and edited the manuscript and provided overall supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

SA, AB, JH, DP, HR, SL, GR, and LK were employed by Crown Agents. BC was employed by Asian Development Bank.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1196289/full#supplementary-material

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EDITED BY
Natalya Glushkova,
Al-Farabi Kazakh National University,
Kazakhstan

REVIEWED BY
Narelle Warren,
Monash University, Australia
Oxana Tsigengagel,
Semey State Medical University, Kazakhstan

*CORRESPONDENCE
Islam Salikhanov
✉ islam.salikhanov@unibas.ch

†These authors share first authorship

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Improving palliative care outcomes in remote and rural areas of LMICs through family caregivers: lessons from Kazakhstan

Islam Salikhanov[1*†], Maria C. Katapodi[1†], Gulnara Kunirova[2] and Byron L. Crape[3]

[1]Department of Clinical Research, University of Basel, Basel, Switzerland, [2]President of the Kazakhstan Association of Palliative Care, Almaty, Kazakhstan, [3]Nazarbayev University School of Medicine, Nur-Sultan, Kazakhstan

Approximately 60 million people require palliative care worldwide, and nearly 80% of them live in low- and middle-income countries (LMICs). Providing palliative care in remote and rural areas of LMICs requires special consideration to ensure equitable access to healthcare. This perspective aims to deliver pragmatic, context-oriented policy recommendations designed to improve palliative care outcomes in Kazakhstan by capitalizing on existing resources and considering its unique geopolitical and sociocultural context. With approximately half of the population in Kazakhstan residing in remote and rural regions, the provision of healthcare services – specifically palliative care – mandates particular attention to ensure equal access to high-quality care. To understand challenges of implementing palliative care in remote and rural regions of Kazakhstan and to propose tailored solutions, 29 key stakeholders, including family caregivers, health professionals, and palliative care administrators, were identified in five regions of Kazakhstan. The main challenges encountered by family caregivers include lack of palliative care skills, the need for home-based care from mobile services, and high out-of-pocket expenditures. The challenges highlighted by healthcare providers and administrators were the lack of formal education in palliative care, shortage of opioids, and limited societal awareness and state support. Based on challenges elaborated from stakeholders and existing literature in palliative care and family caregiving, this perspective advocates against replicating the strategies implemented in high-income countries. Family caregivers play a critical role in implementing affordable and efficient palliative care in resource-limited settings. Enhancing their competencies through digital training and increasing access to palliative care services through mobile teams are tailored and localized solutions that address specific challenges in Kazakhstan. It is postulated that these recommendations may find utility in other LMICs, potentially benefiting nearly 48 million individuals who require these services.

KEYWORDS

palliative care, stakeholders, challenges, family caregivers, LMICs

Introduction

WHO defines palliative care as an approach that enhances quality of life of patients and their families facing life-threatening illnesses (1). It aims to alleviate suffering through early identification, comprehensive assessment, and pain management, while also addressing physical, psychosocial, and spiritual problems (1). This care philosophy affirms life, accepting dying as a normal process, providing support for an active life until death, and extending support to the family throughout and after the patient's illness (1). Approximately 60 million people need palliative care worldwide in 2020, and nearly 80% of them live in low- and middle-income countries (LMICs) (2–4). Despite growing demand, access to palliative care in LMICs remains limited. The demand for palliative care in LMICs is projected to double by 2060, yet these countries lack the necessary infrastructure to establish and distribute these services, especially in rural and remote areas (4, 5). According to the United Nations, 3 billion people worldwide who live in rural and remote areas face significant challenges such as poverty and limited access to healthcare and education, creating critical challenges for policymakers and development organizations (6). The Lancet Commission on the Value of Death suggested that strengthening palliative care services in LMICs requires comprehensive approaches that consider the unique challenges faced by communities in these settings and leverage innovative solutions to improve access to care (3).

Investing in palliative care in LMICs has the potential to improve health equity worldwide (2, 3). WHO estimates that only 14% of patients worldwide who need palliative care have access to such services, primarily in countries with more robust economies (7). This leads to an unequal distribution of suffering among patients and their families, especially among those who are economically disadvantaged, socially excluded, or reside in remote and rural regions. Palliative care in LMICs can improve the quality of life of patients and their family caregivers by increasing access to medications essential for pain and symptom management (8, 9). Studies in Kenya, India, and Bangladesh found that introducing palliative care services in rural districts led to long-term cost-savings, as patients received home- and community-based care, reducing the need for costly hospitalizations and other healthcare services (4, 10). Palliative care services can contribute to health equity by addressing the underlying social determinants of health, such as poverty, lack of access to services, and discrimination (6, 11). As the demand for palliative care in LMICs increases, it is important to identify tailored local solutions. Adopting the strategies and approaches of high-income countries is neither feasible nor sustainable due to limited resources and lack of healthcare infrastructure in LMICs.

Knowledge GAP

There has been significant attention dedicated to the challenges faced by palliative care patients in remote regions. These challenges are well-documented in the literature, as evident in 30 systematic reviews published with the last 9 years, which emphasize the need to develop healthcare solutions tailored to LMICs (8, 12–38). However, there is significant lack of recommendations for the development of context-specific and tailored solutions suitable and sustainable for resource-limited nations (2, 3, 39). Despite the fact that the majority of palliative care patients in LMICs reside in remote rural areas, the literature lacks recommendations on how to address the distinct challenges they face within their unique cultural, economic, financial, and national contexts in LMICs (2, 3, 19).

The Lancet Commission on the Value of Death underscores the significant role of community healthcare workers in providing palliative care in remote and rural regions. However, even though this approach has demonstrated its effectiveness in higher income settings, it may not necessarily be feasible in LMICs due to shortages of workforce, funding, and infrastructure (2, 3, 22). Hence, there is a need to generate research-based insights that can foster the development of recommendations uniquely adapted to the conditions of these rural and remote settings, thereby, better serving the majority of palliative care patients in LMICs (2, 3, 22, 40). Therefore, this perspective aims to deliver pragmatic, context-oriented policy recommendations designed to improve palliative care outcomes in Kazakhstan by capitalizing on existing resources and considering its unique geopolitical and sociocultural context. While the Lancet Commission provides a broader framework for the development of healthcare solutions, this perspective provides context-specific, tailored recommendations that are solidly grounded in the challenges reported by stakeholders in resource-limited settings of Kazakhstan (2, 3).

Palliative care in Kazakhstan

Situated in Central Asia, Kazakhstan is a low-middle income country characterized by a unique geography that significantly impacts healthcare delivery. Spread across 2.7 million km^2 with a sparse population of only seven individuals per km^2, Kazakhstan's vast and disperse demographic landscape presents considerable challenges to accessing health services, especially for the nine million inhabitants residing in remote and rural areas (41).[1] This problem is notably acute in palliative care delivery, a burgeoning need fueled by the country's demographic shift towards an increasingly aging population – a trend consistent with other LMICs (42). Despite an estimated 107,000 individuals currently requiring palliative care services, the resources remain scarce (4, 43). With only 45 physicians and 101 nurses serving 1,925 palliative care beds, the Quality of Death Index places Kazakhstan 50th out of 80 countries (44). As reported by the World Hospice Palliative Care Alliance, Kazakhstan's palliative care system is only at a preliminary stage of integration into the healthcare system, indicating a pressing need for development to meet national requirements and international standards (4, 43). Since 2016, Kazakhstan implements 'The Road Map of Palliative Care Development,' a strategy outlining key steps for policy development, educational initiatives, and service implementation, all tailored to enhance palliative care services uniquely suited to the country's context (45).

This perspective examines the challenges of developing palliative care services in Kazakhstan, as an example of developing such services in LMICs that are searching for affordable solutions to transform their

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[1] https://data.worldbank.org/indicator/EN.POP.DNST?end=2020&locations=KZ&start=1961&view=chart

own healthcare system. According to the Lancet Commission Report, lack of data hinders the evaluation of palliative care services in LMICs (3). Addressing this challenge requires research on stakeholder needs, i.e., family caregivers of terminal patients, healthcare providers, and policy makers (46, 47). This Perspective presents a comprehensive synthesis of challenges faced by key stakeholders in palliative care in Kazakhstan, and offers suggestions for improving palliative care outcomes in resource-limited and remote and rural settings. Our suggestions could be relevant to other LMICs in Central Asia beyond Kazakhstan.

Challenges of palliative care stakeholders in Kazakhstan

We identified 29 key stakeholders in palliative care in Kazakhstan between August 2021 and April 2022, and assessed their needs regarding palliative care services, along with the challenges they encountered. Supplementary Table S1 provides a comprehensive overview of the demographic characteristics of our diverse group of stakeholders, which includes family caregivers, physicians, nurses, and administrators. Stakeholders were identified from three hospices and three cancer centers located in five different regions of Kazakhstan, spanning the northern, southern, and eastern parts of the country. Only one cancer center and two hospices were located in the major cities of Astana and Almaty, respectively. We assessed their needs and challenges through semi-structured interviews conducted in Russian (Supplementary Table S2). All participants were fluent in the language. Following data collection, we utilized a descriptive content analysis approach to identify the key challenges faced by palliative care stakeholders. Supplementary Table S3 contains representative quotes from participants across all stakeholder groups, illustrating the key insights that emerged during the interviews. The procedures adhered to the good research practice guidelines of the Medical Research Council (50). The Nazarbayev University Institutional Research Ethics Committee (IREC413/24052021) approved the study.

The key stakeholders comprised 12 adult family caregivers, 12 healthcare providers, and 5 administrators of palliative care services. Family caregivers assisted with palliative procedures (such as massage, hygiene, prevention of bedsores, etc.) for terminally ill cancer patients who had been receiving inpatient palliative care for at least 14 days. The healthcare providers, consisting of five physicians, five nurses, and two psychologists, each had a minimum of 3 years of experience in palliative care. Both family caregivers and healthcare providers were recruited from the same facilities. The administrators, who were employed by Non-Governmental Organizations (NGOs), frequently interacted with the Ministry of Health and participated in policymaking, each having a minimum of 5 years of experience in palliative care services.

Figure 1 summarizes the factors influencing family caregivers' perceptions of palliative care, reflecting their understanding of the patients' experiences and perceptions. This figure presents the challenges reported by family caregivers and further elaborated on by healthcare providers and administrators. The goal is to demonstrate that future policies and interventions should be tailored to address the factors negatively affecting perceptions about palliative care, such as inadequate referrals from healthcare providers. Reflecting on the roadmap for palliative care development in Kazakhstan, we outline specific challenges to providing palliative care in the country and suggest recommendations to address these issues (48).

Lack of caregiving skills, mobile palliative care services for home-based care, and loss of income and high out-of-pocket expenditures

Palliative care services in Kazakhstan, encompassing both inpatient and outpatient settings, are heavily dependent on family caregivers. This is particularly the case in remote and rural areas where half of the population resides. However, most family caregivers lack the knowledge and practical skills related to patient care.

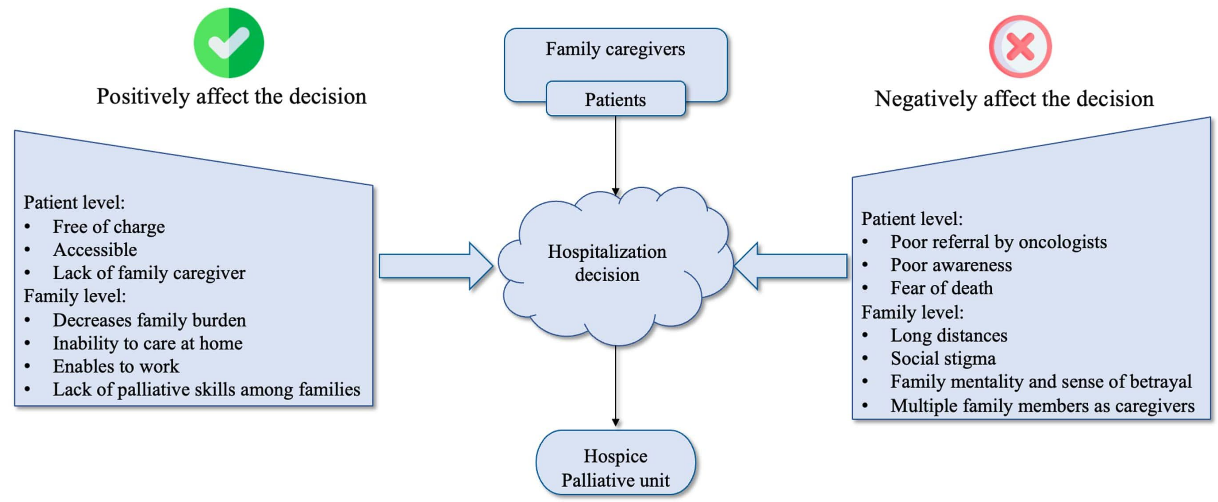

FIGURE 1
Factors associated with the decision to receive inpatient palliative care.

Although nursing staff provide demonstrations of basic procedures in inpatient settings, these are very unsystematic. A terminal cancer diagnosis and the subsequent necessity for family caregiving often result in a significant loss of income for the entire family, either due to the patient's inability to work or the family caregiver leaving their job to provide care. Most family caregivers favor home-based care and support from mobile teams over inpatient palliative care services. Home-based care would enable many of them, especially in remote and rural areas, to minimize long-distance travel to inpatient services, retain jobs, and minimize the loss of income for the entire family. However, mobile teams are largely unavailable, e.g., there is only one mobile team that covers the palliative care needs of Almaty, a city with a population of two million.

The lack of sufficient state funding and universal health coverage results in high out-of-pocket medical expenses, which consume a large portion of family income. This financial burden further exacerbates catastrophic health expenditures for families living in remote and rural areas and increases inequalities, with some families being able to afford more expensive treatment, equipment, and consumables than others.

Poor formal education and shortage of opioids for pain management

The formal education of healthcare providers in palliative care is insufficient due to a shortage of academics and other teaching staff with expertise in this field. Only a small number of physicians and other healthcare providers have received training abroad through state-funded educational programs. The majority of training is acquired 'on the job', which often results in a poor understanding of the nature of palliative care. This issue is particularly impactful on the nursing workforce, where heavy workloads and unmet expectations can lead to burnout and a high turnover rate among new nurses. Remote and rural areas suffer disproportionately from these issues because trained specialists typically prefer to seek employment in larger cities rather than rural areas (2, 49).

The lack of formal education of healthcare providers in palliative care often leads to a fear of prescribing opioids (opiophobia) among physicians and oncologists (50, 51). In Kazakhstan, 95% of terminally ill patients suffer from severe pain at the end of their lives and do not have access to opioids (48). The problem has been exacerbated by increased government control in attempt to combat drug trafficking. Few medications are available for pain control, including only weak opioids and small amounts of oral morphine, making access to pain medication difficult in remote and rural areas. This leads to many avoidable hospitalizations as patients are forced to be admitted to a hospice or palliative unit to receive opioids.

Lack of societal awareness and state support

A general lack of awareness about palliative care within the broader population presents another barrier to the development and delivery of effective services. Misunderstandings about the role of palliative care often create false expectations that patients will receive curative treatment. These unmet expectations can lead to stigmatization of palliative care services and foster anger and hostility towards healthcare providers. This issue is exacerbated in remote and rural areas where healthcare awareness is generally lower. The absence of robust and comprehensive policies and regulations regarding palliative care in Kazakhstan has led to the development of these services without active governmental involvement. As a result, palliative care often remains unincorporated into existing healthcare systems, leading to issues such as a lack of accountability, insufficient quality control, and limited availability and accessibility of palliative services (7). Stakeholders suggest that the key to further developing palliative care involves enhancing cooperation between stakeholders and the government, as well as garnering increased support from governmental organizations.

Recommendations

Palliative care in Kazakhstan is currently delivered in various settings, such as hospices, palliative units of cancer centers, sparse mobile teams, and single palliative beds in general hospitals (48). The understanding of, and approach to, palliative care varies greatly across these settings. To address the establishment and expansion of palliative care in Kazakhstan, both horizontal and vertical integration of the existing diverse services should be implemented (Figure 2).

Horizontal integration aims for the standardization and consistency of palliative care delivery across different settings such as mobile teams, hospices, and palliative care units. This would include a uniform approach to medical procedures, pain and symptom management, medication availability, spiritual patient support, and comprehensive family caregiver assistance, which encompasses skills training, psychosocial support, and grief counseling.

For instance, out of 1,900 palliative beds in the country, 1,100 are single beds scattered across various units (e.g., general therapy, pulmonology) and dispersed over a vast geographical area. Data on these single palliative beds is scarce, making it challenging to understand the differences and effectiveness of these services. Implementing horizontal integration could involve redistributing these single beds into newly established hospices or increasing the number of mobile units, with the aim of achieving a consistent understanding and practice of palliative care across all settings. The focus should be on creating or maintaining a homelike environment with significant family caregiver involvement.

Vertical integration, on the other hand, refers to a hierarchical structure of palliative care stakeholders and parties involved, with the government taking the leading role in policymaking (as shown on p.37 of the Global Atlas of Palliative Care) (4). The government would form a policy umbrella over other parties involved, such as NGOs, charities, and volunteers. Vertical integration could enable smoother policymaking and more clearly defined roles in palliative care management and decision making. In Kazakhstan's current palliative care scenario these roles are not well defined, while NGOs often assume a leading role in palliative care policy and funding. The absence of the Ministry of Health as a major stakeholder is a limitation of this perspective, considering its crucial role as a primary healthcare stakeholder with responsibilities in shaping policies and distributing resources.

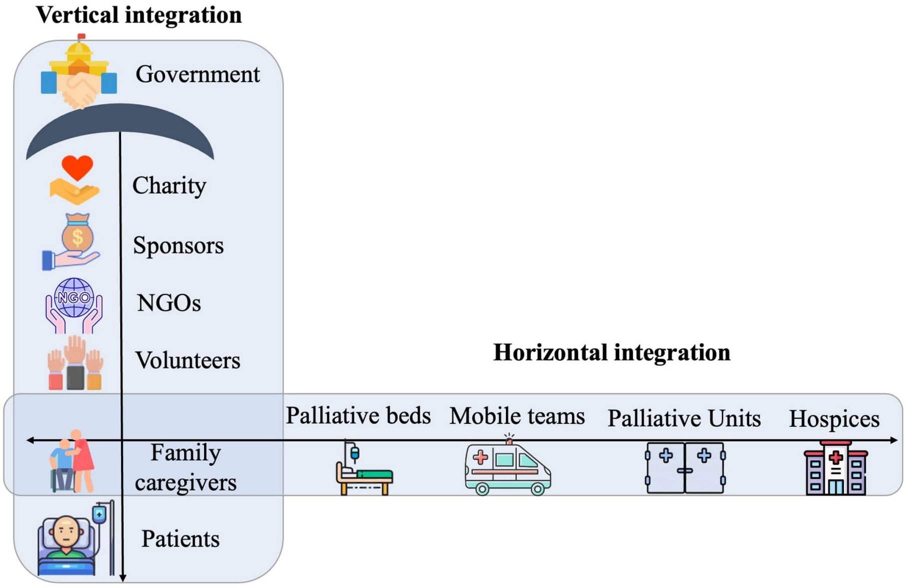

FIGURE 2
Vertical and horizontal integration of palliative care services.

Enhance competencies of family caregivers through training and increase access to palliative care through home-based mobile services

Improving family caregivers' competencies through training and expanding access to palliative care via home-based mobile services can be both financially feasible and cost-effective, especially in remote and rural areas of Kazakhstan and potentially other LMICs. Home-based care not only reduces costs compared to inpatient care but also enhances patient outcomes by increasing access to essential care and reducing hospitalizations (52). Increasing the number of mobile teams would also help address disparities in accessing these services in remote and rural areas, where traditional healthcare facilities may be limited or non-existent (9, 40, 52). Given that the majority of palliative patients in Kazakhstan are cared for by their families, equipping family caregivers with proper training can support them in delivering high-quality home-based care. This approach not only lessens the burden and financial strain associated with terminal disease but also ensures optimal use of scarce resources at both family and societal levels (53). Training programs could focus on enhancing caregivers' knowledge and self-efficacy in basic palliative care procedures, such as hygiene and feeding, while also offering resources to support them psychologically and address caregiver burden (54, 55). Guided by mobile teams, trained caregivers will be more capable of managing pain, preventing bedsores, and addressing other symptoms. Leveraging the surge of digital technologies in the post-Covid-19 era, online and m-Health courses could reach family caregivers even in remote and rural areas of Kazakhstan and other LMICs (56, 57).

The literature extensively emphasizes the importance of family caregiver training and support, particularly in LMICs (3, 53–56, 58–62). Family caregivers are acknowledged as integral to long-term care, and all health professionals are encouraged to incorporate them into care teams and provide enhanced support to families (63).[2] The growing body of evidence underscores the need to address the challenges faced by family caregivers in these contexts, thus reinforcing our recommendations for enhancing competencies and implementing comprehensive programs for family caregivers in Kazakhstan (3). The sense of coherence, rituals, traditions, and long-term mutual support that families and communities provide to the dying or grieving cannot be replaced by healthcare professionals (3). Education platforms for family caregivers have already demonstrated the feasibility of achieving significant enhancement in the well-being of patients and their families (64, 65). In rural and remote areas, family caregivers struggle with inadequate healthcare infrastructure and, even more, with a shortage of qualified healthcare personnel. Therefore, they should be given particular attention in the context of palliative training (66). In 2017, it was estimated that in the US alone, 41 million family caregivers provided 34 billion hours of care, corresponding to an economic value of $470 billion (63). Given these estimates and that palliative care relies heavily on family caregivers in Kazakhstan, our recommendation for supporting and training them becomes imperative for LMICs.

Establish a comprehensive palliative care system and increase awareness of palliative care in remote and rural areas

Increased opportunities to educate healthcare providers and access to pain medication are interconnected key components of the horizontal integration of palliative services, promoting a consistent approach to care delivery in different contexts of remote and rural

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[2] http://resource.nlm.nih.gov/101767885

regions (67). Training in palliative care would help minimize variations in care provision, enabling uniform approach to effective use of medication for pain management, symptom control, and psychosocial support across all settings. By integrating pain management into the horizontal axis of palliative care services, healthcare providers can ensure that patients receive the care they need regardless of their geographic location or socioeconomic status. This entails streamlining bureaucratic procedures related to the import and distribution of pain medications to reduce delays and ensure their availability.

Local production of pain medications could lower costs and lessen the disproportionate economic impact of fluctuating exchange rates on LMICs. The successful implementation of strategies for affordable local morphine production in Uganda in 2003 exemplifies the importance of promoting local production of pain medication. This strategy significantly improves the quality of life of patients and family caregivers and remains affordable for LMICs (68).[3] In Uganda, the cost of 110 days of pain management with oral morphine equals the price of a loaf of bread, thereby providing essential pain relief and ensuring a satisfactory quality of life for all palliative patients until death (68). The Kazakhstan Association of Palliative Care successfully engaged the Ministry of Health and the Police Department to facilitate a five-fold increase in the availability of fentanyl patches. This accomplishment underscores the importance of advocacy and collaboration in addressing the country's palliative care needs. Annual awareness-raising campaigns organized by the Kazakhstan Association of Palliative Care, supported by hospices, hospital units, physician organizations, and NGOs, attract hundreds of volunteers and generate considerable social media attention. These campaigns advocate for an integrated approach to palliative care, emphasizing its long-term societal benefits (69).[4]

Discussion

Our recommendations, based on the unique challenges and needs of LMICs, prioritize the efficient use of available resources. In this perspective, we argue against adopting a universal approach that merely replicates the expensive strategies of high-income countries, as it is neither sustainable nor advisable. Instead, we endorse the adoption of more nuanced, tailored, and context-specific approaches. Some specific practices, interventions, and policies prevalent in high-income countries (HICs) might be adaptable or translatable for palliative care interventions in LMICs. These may include:

Low-cost medications: some HICs use expensive medications for symptom management. In LMICs, affordable, generic, and essential medications should be prioritized, and alternative treatments that are more accessible should be explored.

Nonspecialized workforce: HICs often have a specialized workforce dedicated to palliative care. In LMICs, training non-specialist healthcare providers such as primary care providers and nurses in palliative care principles may be more feasible and sustainable, enabling them to provide care within their communities with the assistance of family caregivers.

Basic infrastructure: HICs may have specialized facilities for end-of-life care. In LMICs, integrating palliative care services into existing hospices or developing home-based services may be a more feasible approach, especially with the assistance of family caregivers.

Integrated care systems: some HICs have multiple uncoordinated palliative care providers. In LMICs, it is vital to develop a coordinated, collaborative approach that engages all stakeholders in optimizing resources and ensuring continuity of care. Creating a centralized system that connects healthcare providers, NGOs, and government agencies can help coordinate and optimize resources and ensure more efficient care provision.

Replicating strategies of HICs could lead to the misallocation of scarce resources and the introduction of policies that do not resonate with local populations' needs, thereby hindering the development of palliative care services in LMICs (70, 71). The insights gained from the current advancements in palliative care in Kazakhstan present invaluable lessons about the challenges and opportunities inherent in developing such services in other LMICs. These insights highlight the importance of crafting local solutions to cater to the unique needs of these populations, with family caregivers as an integral part of these solutions.

Target 3.8 of the United Nations Sustainable Development Goals underlines the objective of attaining universal health coverage by 2030, which includes access to crucial health services and protection from financial risks (72).[5] However, the realization of universal health coverage is unattainable without palliative care. Despite the evidence-based nature of this perspective, we intentionally focused on formulating tailored policy recommendations in response to the well-documented challenges. By highlighting these key challenges and recommendations, this perspective can provide guidance to health authorities and policymakers in LMICs striving to improve palliative care within their communities. A shift towards community-based care can reduce healthcare costs, improve patients' access to care – especially those who might otherwise lack it – and enhance the overall well-being and quality of life of remote and rural communities in LMICs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Nazarbayev University Institutional Research Ethics

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[3] https://www.hospice-africa.org/uganda/

[4] https://www.thewhpca.org/events-2021/item/1750-meters-above-sea-level-whpcday21-in-almaty

[5] https://unstats.un.org/sdgs/metadata/?Text=&Goal=3&Target=3.8

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Author contributions

IS conceived and designed the analysis, collected the data, analyzed the data, and wrote the paper. MK conceived and designed the analysis, contributed data and analysis tools, and wrote the paper. GK collected the data and wrote the paper. BC conceived and designed the analysis and wrote the paper. All authors contributed to the article and approved the submitted version.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1186107/full#supplementary-material

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Yuliya Semenova,
Nazarbayev University, Kazakhstan

REVIEWED BY
Oxana Tsigengagel,
Semey State Medical University, Kazakhstan
Marina Izmailovich,
Karaganda State Medical University, Kazakhstan

*CORRESPONDENCE
Aliya Zhylkybekova
✉ zhylkybekovaa@gmail.com

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Measures to support informal care for the older adults in Kazakhstan: a review of the current status

Aliya Zhylkybekova[1]*, Andrey Turlayev[2], Andrej M. Grjibovski[3,4,5,6] and Gulbakit K. Koshmaganbetova[1]

[1]Department of Evidence-Based Medicine and Scientific Management, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan, [2]Department of Law, Buketov Karaganda University, Karaganda, Kazakhstan, [3]Central Scientific Research Laboratory, Northern State Medical University, Arkhangelsk, Russia, [4]Department of Epidemiology and Modern Vaccination Technologies, I.M. Sechenov First Moscow State Medical University, Moscow, Russia, [5]Department of Biology, Ecology and Biotechnology, Northern (Arctic) Federal University, Arkhangelsk, Russia, [6]Department of Health Policy and Management, Al-Farabi Kazakh National University, Almaty, Kazakhstan

The demand for informal caregivers to support the older adults has grown worldwide in recent decades. However, informal caregivers themselves require support. This article aims to examine existing support measures for caregivers of the older adults in the Republic of Kazakhstan. Relevant articles and grey literature were identified through manual searches on Google and Google Scholar, as well as electronic searches using indexed databases like PubMed, Web of Science, and Scopus. Moreover, the reference lists of identified sources and government ministry websites were meticulously scrutinized. This review highlights the scarcity of research on caregiver support measures in Kazakhstan, supported by the lack of peer-reviewed articles on this subject. A comprehensive analysis of the literature shows that in Kazakhstan's legislative framework, "caregivers" exclusively refers to individuals providing care for a first-degree disability. The responsibility of caring for older adults parents lies with able-bodied children. However, there is a lack of registration and assessment procedures to evaluate the burden and quality of life of caregivers. As a result, the medical and social support provided to caregivers is standardized, failing to adequately address their unique needs and requirements. The analysis of current support measures for informal caregivers highlights the need to develop support mechanisms and recognize individuals providing informal care as key figures in the long-term care system.

KEYWORDS

Kazakhstan, caregiver, older adults, social support, medical support, legislation

1. Introduction

The global population of older individuals is continuously growing in both absolute numbers and relative proportions. As reported by the World Health Organization (WHO), in 2010, there were 524 million people aged 65 and above, and this number is projected to reach 1.5 billion by 2050 (1). Similarly, the age composition of the population in Kazakhstan is also experiencing a transformation in line with these global patterns. By 2050, the population of individuals aged 65 and older is expected to double from the 2019 figures, increasing from 1.4 million to 3.4 million. Consequently, their share of the total population of the country will rise from 7.5% in 2019 to over 14% by 2050 (2). The United Nations (UN) Population Fund (UNFPA) notes that the demographic situation in the northeastern region of the country and certain parts of central Kazakhstan bears resemblance to that of European countries (3).

Recent statistics indicate that approximately one in every five older adults individuals surveyed in Kazakhstan requires some form of assistance. The need for assistance is particularly prevalent among those aged 60–69 years (22%) and those above 70 years (31%). When faced with the need for physical support, 69% of individuals over the age of 65 seek assistance from their children, while a mere 0.8% seek help from social services (4). This trend may be attributed to socio-cultural factors and the underdeveloped nature of the formal care system (5, 6). The growing number of older individuals with specific needs subsequently amplifies the demand for both formal and informal caregivers.

Informal care emerges as a viable substitute for formal long-term care in the context of older adults individuals. By relying on informal caregivers, older adults can maintain their residence in familiar surroundings, thereby mitigating the strain on healthcare and social welfare systems, while concurrently alleviating the burden on the state budget (1). However, it is important to acknowledge that assuming caregiving responsibilities can yield both advantageous and detrimental effects on the mental and physical well-being of informal caregivers (2). Table 1 presents a comprehensive list of these effects.

Various nations have different approaches to providing assistance and services to caregivers responsible for the well-being of older adults individuals in need of care. These approaches are primarily influenced by factors such as the country's income level, legislative and sociocultural characteristics, and the type of funding allocated to the long-term care system.

Primary healthcare plays a pivotal role in this system, encompassing comprehensive aspects of individuals' physical, mental, and social well-being. Adopting such an approach enables the delivery of integrated care across individuals' lifespans, including health promotion, disease prevention, treatment, and rehabilitation, all tailored to align with their everyday lives. Such considerations hold particular significance for informal caregivers who undertake the responsibility of caring for the older adults (3).

State support for informal care in Kazakhstan is in the developmental stage and requires substantial improvements. The strategic documents of the Republic of Kazakhstan related to health and social support lack adequate provisions for identifying and assessing caregivers' burden and needs, as well as providing financial support and ensuring occupational health conditions for these individuals.

Previous studies conducted in Kazakhstan have primarily focused on the needs of older individuals (4–6) or assessing the competencies of caregivers in caring for critically ill patients (23). Significantly, there is a lack of official data on the current number of formal and informal caregivers operating in the Republic of Kazakhstan.

Presumably, the majority (95%) of caregivers are informal and do not receive sufficient medical and social support tailored to their specific needs. This analysis is significant in facilitating the effective development of support mechanisms for familial care of the older adults and individuals with disabilities in Kazakhstan.

TABLE 1 Positive and negative effects of care on informal caregivers.

Positive effect	Ref	Negative effect	Ref
Family solidarity	(7, 8)	Risk of cardio-vascular diseases	(9, 10)
Learning knowledge and skills	(8)	Disruption of regular sleep	(11–13)
Affection, compassion	(8)	Risk of Diabetes mellitus 2 type	(14)
Self-confidence	(8)	Anxiety symptoms	(13, 15)
Personal growth	(8)	Social isolation	(16–18)
		Financial difficulties	(19, 20)
		Decrease work performance	(21, 22)

2. Methods

2.1. Search strategy

In our scoping review, relevant articles and grey literature were identified through manual searches on Google and Google Scholar, as well as electronic searches using indexed databases like PubMed, Web of Science, and Scopus. Additionally, the reference lists of all identified sources and the websites of government ministries were thoroughly reviewed. Figure 1 presents the details of the screening process, indicating that a total of 14 records out of 166 were included in our final synthesis. The websites address of government ministries is presented in Supplementary Table S1. The search was conducted using Medical Subject Headings (MeSH) and keywords, both separately and in combination, with the use of Boolean operators (AND/OR). The search strategies are presented in Supplementary Table S2. All records had to be in full text and written in English, providing comprehensive information regarding the policies supporting informal caregivers of the older adults in the Republic of Kazakhstan. The review period spanned from January 28, 2023, to June 1, 2023. We used the reference manager software program EndNote to download relevant citations and subsequently eliminated any duplicate articles. Following this, we exported the obtained data to Excel for further examination and analysis in the review process.

2.2. Study selection and data extraction

Two authors (AZ and AT) conducted a rigorous analysis of the titles and abstracts of all identified articles and legal acts to ascertain their eligibility according to the inclusion criteria. Subsequently, the full-text articles and relevant legal acts were meticulously reviewed by three authors (AZ, AT, and AG) for potential inclusion. In cases where differences of opinion arose, they were resolved through deliberative discussions led by a fourth author (GK).

Data synthesis in this study was conducted following the Arksey and O'Malley framework, utilizing a descriptive approach to concisely summarize the primary findings and identify common themes and patterns among the selected studies (24). The evaluation of the included studies and legal acts was based on their relevance to the research question and their legal significance, thereby assessing their quality.

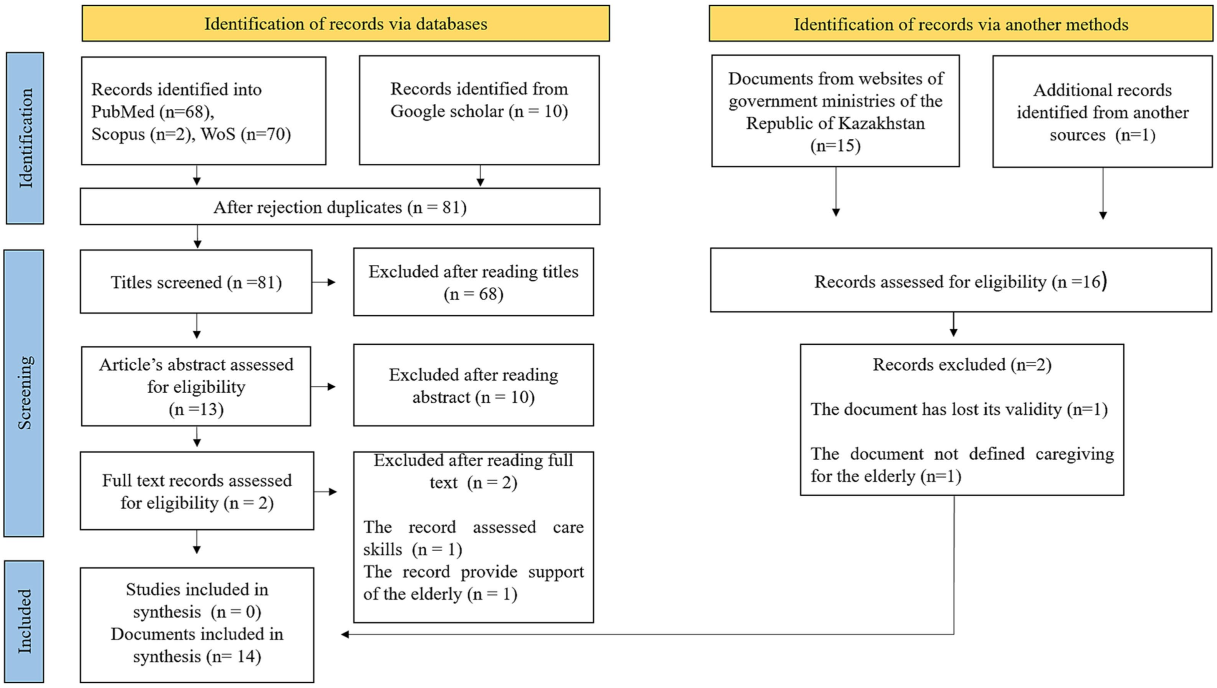

FIGURE 1
PRISMA flow diagram.

3. Assessment of policy

This review highlights the limited research conducted on support measures for caregivers in Kazakhstan, as evidenced by the scarcity of peer-reviewed articles on this topic. To bridge this research gap, we have explored the "grey literature" to gather relevant information. Our analysis entails summarizing the key laws, standards, and regulations pertaining to the medical and social challenges associated with informal caregiving for the older adults. Furthermore, we have examined the availability of support for informal caregivers of the older adults within the legal framework of the Republic of Kazakhstan. Additionally, we have scrutinized the legal aspects concerning the support provided to employees who care for their family members, including provisions for reduced working hours, paid or unpaid leave, and financial compensation. Through our search process, we have identified the primary legal acts addressing the medical and social issues concerning caregivers in Kazakhstan. The key provisions are presented in Supplementary Table S3. Moreover, we have analyzed and ranked the state policies regarding caregiver support in our country, making comparisons with international experiences.

3.1. Introduction of the term caregiver

Older adults individuals who face functional impairment, disability, or chronic illness rely on assistance to compensate for their reduced ability to carry out daily activities. This support can be obtained through both formal and informal care. Formal care is administered by governmental organizations, local, national, or international non-governmental organizations (NGOs), or commercial entities. It often involves professional caregivers such as nurses, doctors, social workers, and hired nurses. On the contrary, informal care entails the support provided by family members, neighbors, friends, and volunteers.

Until recently, the term "caregiver" was absent from the legislative documents of the Republic of Kazakhstan. However, with the recent addition of the Law of the Republic of Kazakhstan "On Special State Benefits" in 2022, the concept of a "caregiver" was introduced for the first time. According to this law, a caregiver is defined as an individual who directly provides care to a person with a first-degree disability, irrespective of their familial relationship. The status of a caregiver is granted to only one individual upon the request of a person with a first-degree disability, and it is based on a disability certificate (25).

According to the legislation of the Republic of Kazakhstan, individuals are classified as having a first-degree disability if they exhibit persistent, significant, or pronounced impairments of bodily functions resulting from diseases, consequences of injuries, or defects. These impairments lead to a pronounced limitation in their ability to perform one or more categories of life activities (26).

In the classification system, limitations in life activities are categorized into three degrees based on their severity. The first degree signifies a partial limitation in performing life activities. The second degree indicates that an individual is capable of carrying out life activities partially or with the assistance of unauthorized individuals. The third degree pertains to individuals who are completely dependent on others to carry out life activities.

To determine a first-degree disability, the criteria for life activities should be assessed at the third degree for one or several the following indicators: self-service, mobility, work capacity (labor activity), ability to learn, orientation (or inability to orientate, or disorientation), communication, and self-control.

3.2. Legislative norms in older adults care provision

Article 27 of the Constitution of the Republic of Kazakhstan emphasizes the significance of family values and social welfare, explicitly stipulating the duty of able-bodied children to assume the responsibility of caring for their disabled older adults parents and grandparents (27). Additionally, Article 145 of the Code of Marriage and Family elaborates on the legal obligations imposed on children to fulfill their caregiving duties. Failure to meet these obligations can result in various repercussions, as outlined in in Article 146 of the Code on Marriage and Family. These consequences may include the requirement for children to contribute to alimony payments and cover additional expenses arising from parental illness or the need for external caregiving services (28).

3.3. Social welfare

Social support in the Republic of Kazakhstan operates within the legal framework established by the Social Code. As per this Code, special social services are defined as a comprehensive range of services designed to address objective barriers that impede individuals or families from leading fulfilling lives. The primary objective of these services is to promote equal opportunities for community integration, fostering social cohesion among citizens (29). The legislation governs the provision of specialized social services, specifically targeting individuals or families facing challenging life circumstances. These circumstances may arise from factors such as illness, injury, age, or disability, resulting in a complete or partial loss of self-care ability, mobility, or access to necessities. The Code encompasses a range of services, including social and household support, socio-medical assistance, socio-psychological counseling, socio-pedagogical interventions, social and occupational guidance, socio-cultural activities, socio-economic aid, and socio-legal assistance (29).

However, delivering the full range of services necessitates a multidisciplinary team comprising not only healthcare and social welfare professionals but also legal experts, economists, and psychologists. This is due to the complex nature of the required assistance, which extends beyond the scope of a social worker's capabilities alone. Persistent challenges exist, including low qualifications of social workers, substandard quality of care and support services provided to those in need, inadequate development of home assistance programs, and a shortage of trained social workers Currently, a mere 1.3% of the older adults population in the Republic of Kazakhstan receives social services and home care, underscoring the limited reach of these services. The home-based services primarily encompass household cleaning, grocery shopping, and medication procurement, with the associated expenses borne by the clients themselves (30). Notably, that older adults individual facing difficult life circumstances, who have able-bodied adult children or a spouse, are ineligible for special social services at home (31).

In addition to the provision of home care services, the Republic of Kazakhstan offers specialized social services in the realm of social welfare for the population in hospitals and semi-hospital settings. These services are designed for individuals who require long-term or temporary (up to 6 months) daytime stay and, and their funding is provided by the government (31, 32). However, it is noteworthy that Kazakhstan has a limited number of institutions, amounting to only 13, that provide palliative and medical care, encompassing hospices, nursing centers, and departments for symptomatic treatment and palliative care. The collective bed capacity of these facilities does not exceed 500, potentially indicating inadequate resources to accommodate all patients in need. Furthermore, individuals residing in remote areas often face challenges in accessing palliative and nursing care, thereby exacerbating the barriers to care for those who require it (6, 33). The development of alternative palliative care options such as mobile teams, home hospices, and day care centers, remains relatively insufficient (6). This situation can be attributed, in part to the relatively lower allocation of state budget expenditures in the Republic, which range from 3.5 to 4.5 times lower in the social sphere compared to more socially and economically developed countries. In situations where additional private care services are necessary, the recipients of social services bear the responsibility of covering the associated costs (31).

In accordance with the key documents concerning social support, caregiver support involves providing essential training to family members regarding the fundamental aspects of home healthcare. Furthermore, health and social service professionals have the responsibility of delivering social and psychological assistance to family members who reside with individuals benefiting from these services. The ultimate objective is to create a nurturing psychological environment while effectively addressing and resolving conflicts (29, 34).

3.4. Work-care balance

3.4.1. Part-time work

Balancing work responsibilities with caregiving duties for older adults individuals frequently presents challenges. Caregivers may encounter difficulties in maintaining their financial income, which can sometimes result in a complete loss of income. Addressing this issue, Article 70 of the Labor Code of the Republic of Kazakhstan include provisions for part-time employment for employees caring for sick family members. Notably, reduction in working hours does not impede the employee's entitlement to paid annual leave, calculation of work experience, or other labor rights (35).

3.4.2. Older adults care leave

The Labor Code of the Republic of Kazakhstan includes provisions for paid parental leave (35). However, it does not extend the same support to individuals taking leave to care for older adults relatives. In contrast, France has implemented a family leave policy that considers regular caregiving for older adults relatives on par which childcare (36). In Kazakhstan, similar to Russia, employees have the option to take unpaid leave for family and other valid reasons, with the duration determined through agreement between the employee and employer (35, 37, 38).

It is crucial to highlight that caregivers for the older adults in Kazakhstan are ineligible to obtain sick leave on behalf of their older adults relatives (39). This particular circumstance can present supplementary difficulties for individuals who are obliged to fulfill caregiving responsibilities for their older adults relatives.

3.5. Caregiver allowance

In the Republic of Kazakhstan, caregiver allowances are exclusively provided to individuals who care to those classified as having a first-degree disability (40). The enactment of the Social Code (41) has resulted in an increase in the amount of the caregiving allowance, now set at 1.61 times the subsistence minimum, compared to 1.4 times the subsistence minimum in 2021 (40). The subsistence minimum refers to the minimum cash income per person, reflecting the cost of a basic food basket.

According to the Law on Minimum Social Standards and their Guarantees, the subsistence minimum denotes the minimal monetary income per individual, equivalent in value to the expenses associated with the basic food basket. The basic food basket represents a basic assortment of essential food items, commodities, and services required to sustain human life, both in tangible and monetary terms. It comprises of: (a) the food basket; and (b) a fixed portion of non-food items and services. The determined value for the minimum subsistence amount, used for calculating the extent of social payments for the year 2023, stands at 40,567 tenge (42).

3.6. Healthcare support

In Kazakhstan, the provision of medical services operates through a dual system consisting of both public and private sectors. The public healthcare system functions under the framework of compulsory health insurance, where in both employers and employees contribute to the health insurance system to a certain extent. As per the legislation of the Republic of Kazakhstan, individuals who are not employed but are responsible for caring for a person classified as having first-degree disability have their medical service contributions paid by the state (43). However, individuals caring for the older adults who do not meet the criteria for disability classification do not have access to planned public health services. In such instances, caregivers are required to make private health insurance payments, which can pose challenges if they encounter unemployment and subsequent loss of income.

4. Actionable recommendation

Policy changes

- A crucial step towards recognizing and supporting caregivers who are not affiliated with formal medical or social organizations is to develop and incorporate the concept of "informal (family) care" into legislation. By introducing this concept into the legislation, Kazakhstan can acknowledge the valuable role played by informal caregivers and establish a legal framework that safeguards their rights and provides the necessary support.
- It is essential to develop and introduce the term "caregiver" into the legislation, which should extend beyond individuals caring for first-degree disabled individuals. This development will help determine the specific individuals who qualify as caregivers.
- It is necessary to develop comprehensive criteria for assessing the caregiving needs of individuals aged 65 and older. Based on these assessments, various levels of medical and social support should be formulated. This approach ensures that older adults individuals and their caregivers receive the appropriate range of medical and social services according to the severity of their condition.
- It is crucial to establish clear criteria for transitioning to part-time work and caregiving leave. Additionally, it is necessary to include caregivers who provide temporary supervision for older adults individuals when they fall ill in the list of individuals eligible for sick leave. This inclusion will grant caregivers the required flexibility in their employment while fulfilling their caregiving responsibilities. Prioritizing the establishment of these criteria is imperative for effectively supporting caregivers.

Raising public awareness and changing societal attitudes toward caregiving

- Raise awareness about the indispensable role of caregivers and the challenges they encounter to foster understanding, empathy, and recognition within society.
- Increase the involvement of volunteers in the provision of social services, enhance accountability, and engage capable family members in supporting and caring for older adults individuals.
- Collaborate with media outlets to promote positive depictions of caregivers and share their stories, highlighting their contributions and inspiring others to support and appreciate caregivers.

Strengthening collaboration between healthcare and social service providers

- Establish interdepartmental collaboration between medical and social services, including the consolidation of client databases and the creation of a legal framework to facilitate this cooperation.
- Develop joint training programs that bring together healthcare professionals and social service providers, enhancing their understanding of caregivers' needs and promoting effective teamwork.
- Implement integrated care plans involving both healthcare and social service providers, facilitating joint assessment, planning, and the delivery of comprehensive care for older adults individuals.

Development and implementation of a comprehensive caregiver support program

- Provide specialized training programs for caregivers, focusing on topics such as caregiving techniques, self-care, and managing the needs of older adults individuals. This training will equip caregivers with the necessary knowledge and skills to effectively care for both themselves and the older adults, ultimately reducing stress and anxiety.
- Establish support groups and counseling services to offer emotional support and guidance to caregivers, allowing them to share their experiences and seek advice from professionals. Introduce respite care services that temporarily relieve caregivers from their responsibilities, enabling them to take breaks and attend to their own needs.
- Providing financial assistance is essential to alleviate the financial burden experienced by caregivers. This support can be facilitated through the utilization of legal and economic mechanisms such

as care allowances, tax deductions, health insurance, and pension contributions. Financial support becomes particularly crucial when caregivers are compelled to forego employment in order to fulfill their caregiving responsibilities.

- It is imperative to develop a comprehensive process for the identification, screening, assessment of the caregiving burden and quality of life, and provision of specialized medical and psychological assistance to caregivers, while simultaneously guaranteeing their access to essential support and resources.

5. Discussion

We conducted a scoping review and synthesis of policies and practices related to informal care in the Republic of Kazakhstan. Throughout our review, we identified six main themes, which include the introduction of the term "caregiver," legislative norms in older adults care provision, social welfare, work-care balance, caregiver allowance, and healthcare support.

Revision of legislation to incorporate the concept of "informal (family) care" is of utmost importance, along with the development and implementation of legal norms that regulate informal (family) care in the Republic of Kazakhstan, drawing upon the best global practices. The most commonly used definition of an informal caregiver in the literature is as follows: "An informal caregiver refers to a non-professional individual who voluntarily provides care or assistance, at any given time, to a family member, friend, neighbor, or any other person with a long-term mental or physical illness, disability, or age-related condition" (44). As per the German Social Code, informal caregivers are defined as "individuals who provide non-professional care to individuals who are unable to care for themselves due to health issues." Additionally, the requirement for care must be continuous for a minimum duration of 6 months and reach a certain level of severity (45).

In Portugal, Decree 2022 outlines the criteria for recognizing informal caregivers and establishes support measures for them. The status of an informal caregiver can only be granted to one applicant per household, provided that they reside with the care recipient and offer full-time care. Moreover, the caregiver must not be engaged in any paid professional or other activities that would conflict with their responsibility of providing continuous care to the individual in need (46, 47).

The legal obligation of providing care for older adults family members being the responsibility of their children is a widely acknowledged norm in numerous countries, such as China, Bangladesh, India, Singapore, Brazil, Mexico, Russia, Turkey, Algeria, Argentina, Chile, Singapore (48, 49). This norm is also observed in the Republic of Kazakhstan. In Japan, under the previous civil code, the eldest son was entitled to inherit the family's property, and his wife, as the daughter-in-law, bore a legal and moral responsibility to care for her husband's parents. However, with the introduction of the New Civil Code in 1947, the responsibility for parental care was extended equally to all children. This legal provision remained the societal norm until recently, when the National Long-term Care Insurance Act was enacted. This act establishes a comprehensive set of measures for older adults care, funded through insurance premiums (50).

However, in Scandinavian countries such as Sweden, Denmark, Netherlands, and Norway, long-term care has been recognized as a social risk factor since 1980. As a result, the primary legal responsibility for older adults care has been assigned to the state. In these countries, the contribution of the family to informal care provision is relatively lower compared to countries where family care is the predominant approach. On the other hand, countries like Austria, Belgium, Canada, Germany, France, Switzerland, the United Kingdom, and the United States share the responsibility for care between the state and the family. Their systems combine government-provided universal benefits and means-tested caregiver's allowance (51).

In addition to legislation, the cultural and social characteristics of each country play a significant role in shaping the perception of older adults care. In Asian culture traditional values and cultural norms continue to emphasize the sons' responsibility for older adults care alongside state policies (52–56). Similarly, in Kazakhstan, national family traditions still serve as an important source of support for the older adults (5). However, there has been a recent shift towards a change in family composition, with a transition from extended families to nuclear families and the older adults living separately from their children. This change may lead to an increased demand for formal care services.

In Kazakhstan, to be eligible for special social services, certain criteria must be met, including reaching retirement age and living alone within a community or being disabled (29). However, in countries such as the United States, Germany, and Japan, publicly funded long-term care services are established based on a comprehensive care needs assessment, which plays a crucial role in determining the provision of social services (57, 58). The competency framework considers functional disability, which is assessed based on the individual's ability to perform activities of daily living (ADL), instrumental activities of daily living (IADL), and cognitive tasks. In Germany, for instance, there are five levels of care needs depending on the degree of functional disability, each corresponding to a different package of medical and social assistance (59).

It is important to highlight that the right to part-time employment for informal caregivers in Kazakhstan applies exclusively to family members and relatives. Consequently, if the caregiver is assisting a distant relative, friend, or neighbor, transitioning to part-time work may present certain difficulties. Similar situations are observed in countries such as Germany (60), Japan (61), Great Britain (62), and France (36), where the scope of informal care recognized by employers is limited to family members and relatives. Nonetheless, unlike the legislation in the aforementioned countries, the Labor Code of Kazakhstan does not specify the conditions for part-time employment. It does not provide information regarding the length of employment required at a specific enterprise or company before exercising this right, the duration of the permitted part-time arrangement, or the types of enterprises and job positions eligible for this right. Furthermore, the Labor Code does not mention the possibility of transitioning to remote work if deemed necessary.

In Kazakhstan, unlike many countries where implemented leave systems specifically designed to cater to the long-term care of close relatives, such provisions are not currently in place. Generally, the policies regarding payment for sick leave differ from those for caregiving leave, with sick leave typically providing a limited number of days with full wage restoration. For instance, several states in the United States, including California, Connecticut, Massachusetts, Oregon, and Vermont, have implemented paid sick leave laws that allow workers to use sick leave when caring for sick family members (63).

While some states offer unpaid leave, others provide compensation to address caregiving needs. For instance, Austria, the Czech Republic, Luxembourg, and Germany have established paid leave for older adults care (46). In Germany, workers can avail themselves of a short-term leave program for up to 10 days when nursing care is required, with 90% of their wages covered through a caregiver allowance (64). In Canada, individuals caring for terminally ill close relatives are entitled to up to 28 weeks of unpaid family leave per year (65). The US Family and Medical Leave Act (FMLA) allows for up to 12 weeks of unpaid leave within a 12-month period to address short- or long-term caregiving needs (66). Some states, like California and New York, have introduced paid family leave at the state level (67), wherein workers receive 67% of their wages during care leave (68). In Japan, a system exists where two-thirds of the salary is compensated for a certain period through unemployment insurance for individuals on care leave (61). In France, workers have the right to up to three months of unpaid care leave, which can be renewed within one year (36).

Paid leave is considered one of the most effective and practical ways to support long-term care workers. Having access to paid care leave offered by employers significantly facilitates the ability to provide regular or temporary informal care to older adults parents and relatives (69). Unfortunately, in countries where such policies are lacking, caregivers may face challenges in balancing their caregiving responsibilities with their work obligations.

In Kazakhstan, benefits are primarily designated for the support and assistance of individuals classified as belonging to the first-degree disability. However, it is noteworthy that over two-thirds of the member countries in the Organization for Economic Co-operation and Development (OECD) have implemented schemes to provide financial compensation to informal caregivers. These care allowances are distributed either directly to caregivers in the form of a caregiver allowance or as compensation to care recipients. Several nations, such as Netherlands, Sweden, the United Kingdom, and Germany, have adopted a dual approach, offering both types of care allowances to aid their citizens in the provision of care for their loved ones (46).

In Germany, caregivers are eligible to receive a caregiver allowance if they provide regular care for a minimum of 10 hours per week to one or more individuals requiring assistance (45). In Canada, caregivers are provided with a caregiver allowance amounting to 55% of the average weekly wage for the duration of their leave. It should be noted that individuals receiving this benefit are not permitted to engage in full-time employment during this period (65).

In Russia, the allowance for older adults care is provided to individuals who care for those over the age of 80, regardless of their family relationship or cohabitation. The allowance, amounting to 1,200 rubles, is credited monthly to the recipient's pension account. The caregiver must be unemployed but capable of working according to pension legislation and should not be receiving unemployment benefits from the employment service (70).

In the United States, Medicaid offers care allowances to adult children, relatives, or grandchildren who provide care. The caregiver is expected to receive compensation ranging from 1,550 to 2,550 dollars per month, depending on the level of care required by their aging parent and their state of residence (71).

The current healthcare system in the Republic of Kazakhstan lacks consideration for the challenges and requirements of individuals providing home care for the older adults. There is a lack of established legal framework addressing the identification, assessment, and provision of specialized medical and psychological assistance for these caregivers.

Within the strategic documents of the Ministry of Health of the Republic of Kazakhstan, which govern the provision of medical and psychological assistance, the term "guardian" is solely acknowledged in relation to individuals responsible for caring for individuals classified under the first-degree disability. Consequently, caregivers receive healthcare services as regular patients, without consideration for their specific needs. Family members who are providing care for an older adults individual are perceived merely as individuals offering assistance to their older adults relative (72).

In Germany, if a caregiver decides to cease employment in order to provide care, their health insurance benefits will continue throughout the duration of their caregiving responsibilities, as long as they were enrolled in the insurance system prior to assuming their caregiving duties (73).

In the United States, the CARE Act (74) mandates that healthcare providers recognize and register family caregivers, inform them about procedures performed on the older adults, and provide instructions on the tasks expected of caregivers. In Portugal, the assessment of the quality of life and the burden experienced by informal caregivers is legally mandated. Health and social development services also aim to provide psychosocial support to informal caregivers. The importance of rest for informal caregivers is also emphasized. Health services have established self-help groups facilitated by healthcare professionals to foster mutual support and the sharing of experiences among individuals who have lived or are currently experiencing similar situations and challenges, thus minimizing potential feelings of isolation (47).

6. Conclusion

Ensuring high-quality medical and social care should be the primary focus in the development of legal regulations and state policies in the medical and social sectors in the Republic of Kazakhstan. The current system of medical and social support for informal caregivers of the older adults in Kazakhstan requires significant reforms. It is crucial to revise the legislation to incorporate the concept of "informal (family) care" and to develop and implement legal norms that regulate informal (family) caregiving. Additionally, establishing a robust legal framework that governs informal (family) caregiving relationships is essential for both caregivers and employers to establish employment relationships that consider the needs of long-term caregivers. Moreover, implementing a caregiver registration system and conducting screenings to assess care-related burden, as well as the physical and mental health and care-related needs are important for effective monitoring.

Author contributions

AZ, GK, and AG contributed to conception and design of the study. AZ wrote the first draft of the manuscript. AZ, GK, and AT wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1247684/full#supplementary-material

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Factors associated with COVID-19 vaccine confidence among primary care providers in Kazakhstan, March–April 2021

Dilyara Nabirova[1,2,3]*, Roberta Horth[1,2], Lena Kassabekova[2,4], Alden Henderson[5], Aizhan Yesmagambetova[6], Sevak Alaverdyan[7], J. Pekka Nuorti[3,8] and Manar Smagul[2,4]

[1]Division of Global Health Protection in Central Asia, United States Centers for Disease Control and Prevention, Almaty, Kazakhstan, [2]Central Asia Field Epidemiology Training Program, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, [3]Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland, [4]Scientific and Practical Center of Sanitary-Epidemiological Examination and Monitoring, Branch of the National Center for Public Health, Almaty, Kazakhstan, [5]Division of Global Health Protection, United States Centers for Disease Control and Prevention, Atlanta, GA, United States, [6]Ministry of Healthcare, Astana, Kazakhstan, [7]Manoogian Simone College of Business and Economics, American University of Armenia, Yerevan, Armenia, [8]Infectious Diseases and Vaccinations Unit, Department of Health Security, Finnish Institute for Health and Welfare (THL), Helsinki, Finland

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EDITED BY
Natalya Glushkova,
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Haimei Jia,
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Marina Izmailovich,
Karaganda State Medical University, Kazakhstan

*CORRESPONDENCE
Dilyara Nabirova
✉ hny5@cdc.gov

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Introduction: Vaccination is a critical public health intervention, and vaccine hesitancy is a major threat. Globally, confidence in COVID-19 vaccines has been low, and rates of routine immunizations decreased during the COVID-19 pandemic. Because healthcare providers are a trusted source of information on vaccination in Kazakhstan, it was vital to understand their knowledge, attitudes and practices (KAP) related to both routine and COVID-19 vaccines.

Methods: From March to April 2021, we conducted a cross-sectional study among the healthcare providers responsible for vaccination in 54 primary care facilities in three cities in Kazakhstan. All consenting providers anonymously completed structured online questionnaires at their place of work. A provider was classified as having COVID-19 vaccine confidence if they planned to get a COVID-19 vaccine, believed that COVID-19 vaccines are important to protect their community and either believed the vaccine was important to protect themselves or believed that getting a vaccine was safer than getting COVID-19. Statistical analysis included chi-square, Spearman's rank correlation coefficient, and Poisson regression.

Results: Of 1,461 providers, 30% had COVID-19 vaccine confidence, 40% did not, and 30% would refuse vaccination. Participants were mostly female (92%) and ≤ 35 years old (57%). Additionally, 65% were nurses, 25% were family physicians, and 10% were pediatricians. Adequate KAP for routine vaccines was low (22, 17, and 32%, respectively). Adequate knowledge was highest among pediatricians (42%) and family physicians (28%) and lowest among nurses (17%). Misconceptions about vaccines were high; 54% believed that influenza vaccines cause flu, and 57% believed that there is a scientifically proven association between vaccination and autism and multiple sclerosis. About half (45%) of the practitioners felt confident answering patient vaccine-related concerns. In adjusted models, COVID-19 vaccine confidence was positively associated with adequate knowledge of vaccines (prevalence ratio: 1.2, 95% confidence interval: 1.0–1.4) and adequate attitudes related to routine vaccines (3.1, 2.7–3.6).

Conclusion: Our study uncovers critical areas for interventions to improve KAP related to routine immunizations and COVID-19 vaccine confidence among providers in Kazakhstan. The complex relationship between KAP of routine vaccines and COVID-19 vaccine confidence underscores the importance of addressing vaccine hesitancy more broadly and not focusing solely on COVID-19.

KEYWORDS

COVID-19, vaccine confidence, primary care providers, attitude toward vaccination, childhood vaccines, Kazakhstan

Introduction

Vaccines are one of the most successful public health interventions. They contributed to eradication of smallpox, near-elimination of poliomyelitis, reduction of incidence of several vaccine-preventable diseases, increased population lifespan, and saved millions of lives annually (1–4). Vaccines are most effective when global coverage is high. Recent drops in global immunization rates threaten to reverse progress.

The World Health Organization (WHO) declared vaccine hesitancy one of the top 10 global health threats in 2019, before the COVID-19 pandemic began. Factors influencing vaccine hesitancy are complex, but the mass quantities of false and misleading information play an important role. Misinformation amplifies vaccine hesitancy and contributes to the loss of life and reduced quality of life for millions of people, both vaccinated and unvaccinated (5–7).

Primary healthcare providers play a key role in informing people about vaccines, encouraging them to vaccinate, and keeping vaccine coverage high in their populations (8–11). Primary healthcare providers' knowledge, attitude, and beliefs toward vaccination influence their own immunization and can impact patients' vaccine acceptance and increase vaccine uptake. Studies show wide variation in vaccine confidence among providers. Many providers had insufficient knowledge about the safety and effectiveness of vaccines or lacked time and interpersonal skills to persuade patients to vaccinate (12–14).

In Kazakhstan, coverage for childhood immunizations has decreased in recent years, and annually, approximately 5,000 of 360,000 infants are not vaccinated because of parental/caregiver refusal (15). As in many other countries, primary healthcare providers in Kazakhstan are a trusted source of vaccine information for the population (11). However, little is known about primary care providers' views toward vaccines, including their knowledge, attitude, beliefs, and practices, and their ability to advocate for childhood vaccination.

Primary care providers in Kazakhstan have a large patient load. Each physician has 1,500–5,000 patients in their catchment area. Physicians are responsible for disease management programs, including tuberculosis diagnosis and management and administration of vaccination, patient education and other tasks (16). They play a critical role in promoting vaccination by providing accurate information about vaccines, addressing concerns and misconceptions, and administering vaccines to patients.

Over the last decade, national guidelines for routine immunization have been updated four times due to the introduction of new vaccines and changes in the immunization schedule (17–20). Nine childhood and eight adult vaccines against 20 infectious diseases are included in the national vaccine schedule. These vaccines are administered free of charge to patients at public and private primary care facilities. Flu vaccines are also free of charge to high-risk populations, including healthcare providers and children.

COVID-19 vaccines first became available in Kazakhstan in February 2021. They are free of charge. These vaccines had been developed in Kazakhstan and Russia, and there were no publicly available data from clinical trials on the efficacy of these vaccines at the time. Misinformation quickly ensued. Healthcare providers need to be well informed about these vaccines to counter increasing vaccine refusals. Understanding primary healthcare provider confidence in and knowledge about COVID-19 vaccines is crucial.

Therefore, we aimed to (1) determine levels of vaccine confidence among providers toward COVID-19 vaccination; (2) describe knowledge, attitude, and practice toward vaccination, including routine childhood, influenza, and COVID-19 vaccines; (3) assess factors associated with COVID-19 vaccine confidence; and (4) determine the correlation between COVID-19 vaccine confidence and knowledge, attitude, and practice toward childhood and influenza vaccination.

Materials and methods

Study design

We conducted a cross-sectional study among primary healthcare providers in 23 public and 31 private primary care facilities in three geographically dispersed cities: Shymkent (population: 1.1 M), Turkestan (population: 186 K), and Aktobe (population 518 K). These cities were selected because they were considered cities at greatest risk of vaccine preventable disease outbreak and had the highest reported incidence of measles in the country in 2019–2020 despite measles vaccination coverage >95% (15).

Study participants

Participants included all family physicians, pediatricians, and nurses responsible for administrating vaccines who were at their workplace during the study. In each primary care facility, a physician usually works with at least two nurses. Only providers who provided written informed consent were interviewed in three cities between March and April 2021.

No personally identifiable information on providers or the title of the primary care facility was collected during the interviews.

Survey tool

We used an anonymous self-administered structured questionnaire in Kazakh and Russian languages. Seven residents of the Central Asia Frontline and Advanced Field Epidemiology Training Program (FETP) piloted the questionnaire on a small group of providers, revised the questionnaire based on observations and comments of the interviewed piloted group, and then interviewed study participants. Data from the pilot were not included in the final dataset.

We estimated the internal consistency of each question of the questionnaire using Cronbach's alpha coefficient (21). The internal consistency for the 107 questions was 0.899. The average survey length was 20 min.

The survey tool included sociodemographic questions and questions related to vaccine knowledge, attitudes, and practices (Supplementary Tables 1A–D):

- Knowledge (K) was accessed using 26 questions. Each knowledge question was scored as "1-correct," "0-incorrect," or "0-difficult to answer."
- Attitudes (A) were assessed using 55 questions on a five-point Likert scale, where "absolutely disagree," "disagree," "indifferent," "agree," and "absolutely agree," were scored as 1, 2, 3, 4, and 5, respectively.
- Practices (P) were assessed using 14 questions on a three-point Likert scale, where "2 = always," "1 = sometimes," and "0 = never" were rated as 2, 1, and 0, respectively.

Outcomes of interest

The survey tool includes four questions to assess confidence in COVID-19 (22, 23):

1. Do you plan to get the COVID-19 vaccine?
2. Do you believe that the COVID-19 vaccine is important to protect your community?
3. Do you believe that the COVID-19 vaccine is important to protect yourself?
4. Do you believe that the COVID-19 vaccine is safer than getting COVID-19?

Answers to these questions were categorized as follows:

- Vaccine refusal: no to all questions were classified as having vaccine refusal (24).
- Vaccine confidence: affirmative responses to questions 1 and 2 and at least 3 or 4 (24–26).
- Vaccine hesitant: not being in any of the two above categories.

Individual respondents' correct scores for knowledge, attitudes, or practices were summed in each domain. Individual KAP scores for each respondent were then dichotomized as adequate and not adequate KAP for each domain with scores 70% or above as the cut-off (27, 28).

Ethical information

The study was approved by the Ministry of Healthcare of Kazakhstan and the institutional review boards of the Kazakhstan Graduate School of Public Health. This activity was reviewed by the CDC and was conducted consistently with applicable U.S. federal law and CDC policy.[1]

Statistical analysis

Data cleaning and analysis were conducted in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). We accessed the power of our study to detect statistically significant differences (29–31) (Supplementary Figure 1). To assess associations with adequate KAP and vaccine confidence, we used the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. We used Poisson regression to calculate prevalence ratios (PRs) and 95% confidence intervals (CIs) for variables independently associated with COVID-19 vaccine confidence and adequate KAP.

We used Spearman's rank correlation coefficient to measure the correlation between KAP variables and COVID-19 vaccine confidence (32). We also assessed the adjusted relationship between these variables using multivariable Poisson models and present adjusted prevalence ratios (aPR). Variables with a value of $p < 0.05$ in the bivariable analysis and possible confounders were selected for inclusion in multivariable Poisson regression models (33, 34) (Supplementary Table 2). We checked for multicollinearity using the generalized variance inflation factor (35, 36).

Results

Sociodemographic data and vaccine confidence

Of the 3,500 providers employed at the studied primary care facilities, 42% were on-site and available at the time of the study and responded to the survey (69% in Aktobe, 33% in Shymkent, and 28% in Turkestan). Of the 1,461 participants, 951 were nurses (65%), 360 (25%) were family physicians, and 150 (10%) were pediatricians. Among the participants, 1,351 (92%) were female, 832 (57%) were 35 years old or younger, 692 (47%) were from Aktobe, 489 (34%) were from Shymkent, and 280 (19%) were from Turkistan (Table 1).

We found that 435 (30%) had COVID-19 vaccine confidence, and 439 (30%) providers would refuse to receive the vaccine. The proportion with vaccine confidence differed significantly by age, city,

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[1] §See, e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42U.S.C. §241(d); 5U.S.C. §552a; 44U.S.C. §3,501 et seq.

TABLE 1 Perceptions toward COVID-19 vaccination among primary care providers, Aktobe, Shymkent, and Turkestan cities, Kazakhstan, 2021 ($N = 1{,}461$).

Characteristics	Vaccine confidence $n = 435$ (30%[a])	Vaccine hesitancy $n = 587$ (40%[a])	Vaccine refusal $n = 439$ (30%[a])	Total $N = 1{,}461$ (100%[b])	*p* value
Occupation					
Nurse	276 (29)	382 (40)	293 (31)	951 (65)	0.202
Family physician	115 (32)	134 (37)	111 (31)	360 (25)	
Pediatrician	44 (29)	71 (47)	35 (23)	150 (10)	
Gender					
Male	24 (22)	44 (40)	42 (38)	110 (8)	0.076
Female	411 (30)	543 (40)	397 (29)	1,351 (92)	
Age, years					
18–26	84 (19)	150 (26)	108 (25)	342 (23)	0.005
27–35	140 (32)	186 (32)	164 (37)	490 (34)	
36–66	204 (47)	231 (39)	154 (35)	212 (15)	
Missing	7 (2)	20 (3)	13 (3)	40 (3)	
City of residence					
Shymkent	151 (31)	190 (39)	148 (30)	489 (34)	<0.001
Aktobe	232 (34)	266 (38)	194 (28)	692 (47)	
Turkestan	52 (19)	131 (47)	97 (35)	280 (19)	
Professional experience, years					
Median [Min, Max]	10 [1, 44]	7 [1, 46]	6 [1, 41]	8 [1, 46]	<0.001
0–10	236 (26)	376 (41)	295 (33)	907 (62)	
11–20	97 (36)	88 (33)	82 (31)	267 (18)	
21 or more	102 (36)	123 (43)	62 (22)	287 (20)	
Child in the family					
Yes	324 (32)	397 (39)	300 (29)	1,021 (70)	0.043
No	111 (25)	190 (43)	139 (32)	440 (30)	
Number of children in the family					
Median [Min, Max]	2 [1, 6]	2 [1, 7]	2 [1, 6]	2 [1, 7]	0.938
1–2	168 (31)	219 (40)	157 (29)	544 (37)	
3 or more	156 (33)	178 (37)	143 (30)	477 (33)	
Missing	111 (25)	190 (43)	139 (32)	440 (30)	
Older adult in the household					
Yes	104 (32)	122 (38)	99 (30)	325 (22)	0.486
No	331 (29)	465 (41)	340 (30)	1,136 (78)	

[a]Row percent; [b]Column percent.

work experience, and having children in the family. Confidence was 47% among providers 36 years old and above and 19% among those 18–26 years old.

Knowledge about vaccination

Adequate knowledge about vaccination was 22%. It was higher among family physicians (28%) and pediatricians (42%) than among nurses (17%; $p < 0.001$; Table 2). Knowledge related specifically to vaccine contraindications was lowest among nurses, less than half could correctly identify vaccine contraindications, and highest among pediatricians. However, 44% of pediatricians, 54% of family physicians, and 55% of nurses incorrectly believed that influenza vaccine causes flu. Additionally, 50% of providers incorrectly believed that the pertussis vaccine causes sudden infant death syndrome. Just over half (57%) of providers incorrectly believed that there is a scientifically proven association between vaccination and autism and multiple sclerosis. A lower proportion of nurses (44%) than family physicians (56%) believed that COVID-19 vaccination was a justified prevention measure ($p < 0.001$).

TABLE 2 Correct answers to the question on knowledge toward vaccination among primary care providers, Aktobe, Shymkent, and Turkestan cities of Kazakhstan, 2021 (*N* = 1,461).

Characteristics	Total (*N* = 1,461)	Nurse (*n* = 951)	Family physician (*n* = 360)	Pediatrician (*n* = 150)	*p* value[a]
Had adequate vaccine knowledge (scored ≥ 70%)	327 (22)	163 (17)	101 (28)	63 (42)	<0.001
Temporary contraindications to immunization for all vaccines					
Fever, Yes (T)[b]	864 (59)	481 (51)	265 (74)	118 (79)	<0.001
Uncontrolled seizures or progressive encephalopathy, Yes (T)	847 (58)	475 (50)	253 (70)	119 (79)	<0.001
Acute diseases, regardless of temperature, Yes (T)	823 (56)	460 (48)	253 (70)	110 (73)	<0.001
Prematurity, Yes (T)	766 (52)	438 (46)	224 (62)	104 (69)	<0.001
Birth weight < 2,500 g, No (T)	717 (49)	451 (47)	171 (48)	95 (63)	0.001
Steroid use, Yes (T)	659 (45)	371 (39)	195 (54)	93 (62)	<0.001
Antibiotics use, No (T)	452 (31)	319 (34)	99 (28)	34 (23)	0.007
Permanent contraindications to immunization for all vaccines					
Severe allergic reaction to the previous dose, Yes (T)	866 (59)	496 (52)	256 (71)	114 (76)	<0.001
Malignant neoplasms with active chemotherapy, Yes (T)	817 (56)	458 (48)	240 (67)	119 (79)	<0.001
Immunodeficiency diseases, Yes (T)	808 (55)	453 (48)	241 (67)	114 (76)	<0.001
General knowledge about vaccination					
Pertussis vaccine causes sudden infant death syndrome, No (T)	726 (50)	474 (49)	174 (48)	78 (52)	0.743
The flu vaccine causes the flu, No (T)	672 (46)	423 (45)	165 (46)	84 (56)	0.031
It is necessary to restart the Hepatitis B vaccine series if a dose was missed or delayed, No (T)	665 (46)	445 (47)	154 (43)	66 (44)	0.396
Simultaneous administration of multiple vaccines causes chronic health problems (overload the immune system), No (T)	655 (45)	424 (45)	141 (39)	90 (60)	<0.001
There is a scientifically proven association between vaccination and autism, multiple sclerosis, No (T)	630 (43)	411 (43)	151 (42)	68 (45)	0.776
Children who had pertussis may be vaccinated later with a vaccine containing the pertussis component, Yes (T)	429 (29)	261 (27)	110 (31)	58 (39)	0.017
COVID-19 vaccination is an effective preventive measure, Yes (T)	806 (55)	490 (52)	221 (61)	95 (63)	<0.001
COVID-19 vaccination is a justified prevention measure, Yes (T)	699 (48)	417 (44)	201 (56)	81 (54)	<0.001
Efficacy of Sputnik V is >90%, Yes (T)	660 (45)	402 (42)	177 (49)	81 (54)	0.006
Sputnik V is a vector vaccine for COVID-19, Yes (T)	599 (41)	362 (38)	170 (47)	67 (45)	0.007

[a]Chi-square *p* value; [b]T, true answer.

Practices related to vaccination

The proportion with adequate practices related to vaccination differed by profession and was 29% among nurses, 33% among family physicians, and 42% among pediatricians ($p = 0.010$; Table 3). Additionally, 43% of nurses, 44% of family physicians, and 55% of pediatricians felt confident about answering their patients' vaccine-related questions.

Attitudes toward vaccination

Among providers, 246 (17%) had adequate attitudes toward vaccination (scored above 70%), and 41% would get vaccinated against COVID-19 when it became available to them (Figure 1). Among those who refused vaccination (29%), the main reasons for refusing COVID-19 vaccination were side effects and safety concerns (43%), contraindications (43%), and belief that vaccines are not effective in preventing COVID-19 (37%). Half (46%) of providers believed that COVID-19 vaccination was important to slow transmission, and 19% believed that COVID-19 vaccination was more dangerous than getting COVID-19.

For other vaccines, 60% thought it was important for healthcare providers to be vaccinated against influenza, 55% would convince their patients to get vaccinated against childhood diseases or COVID-19, and 24% would rather get sick than get vaccinated themselves. Over half (55%) of providers believed that the 2019–2020 measles outbreak could largely be attributed to patient refusal to vaccinate (55%) and medical contraindications to vaccination (37%). Additionally, 27% believed that fines imposed on healthcare providers for not vaccinating their catchment population led to distorted vaccine coverage rates nationally.

Over 70% of providers believed in the safety and effectiveness of the majority of common childhood vaccinations (Figure 2). However, belief in the effectiveness and safety of COVID-19 vaccines was low.

TABLE 3 Practices toward vaccination among primary care providers, Aktobe, Shymkent, and Turkestan cities of Kazakhstan, 2021 (*N* = 1,461).

Characteristics	Total (*N* = 1,461)	Nurse (*n* = 951)	Family physician (*n* = 360)	Pediatrician (*n* = 150)	*p* value[a]
Had adequate vaccine practice (scored ≥ 70%)	465 (32)	283 (29)	119 (33)	63 (42)	0.010
Relies on own judgment, not manufacturer's recommendations when administering vaccines, Always[b]	514 (35)	338 (36)	131 (36)	45 (30)	0.173
Relies on colleagues' opinions when administering vaccinations and working with those who refuse, Always	350 (24)	234 (25)	87 (24)	29 (19)	0.725
Recommends immunization according to friends and family members, Always	742 (51)	462 (49)	179 (50)	101 (67)	<0.001
Feels it is difficult to talk with parent/individuals about vaccinations, Never	531 (36)	336 (35)	134 (37)	61 (41)	0.344
Feels confident when answering patient questions about vaccines, Always	653 (45)	413 (43)	158 (44)	82 (55)	0.019
Feels comfortable addressing patient's vaccine side effects concerns, Always	634 (43)	403 (42)	159 (44)	72 (48)	0.599
Always receives continuing education in the field of vaccination:	659 (45)	424 (45)	153 (43)	82 (55)	0.031
Independently studying scientific literature on vaccination	492 (34)	287 (30)	154 (43)	51 (34)	<0.001
Attends seminars and trainings held in medical organizations	652 (45)	426 (45)	147 (41)	79 (53)	0.047
Taking online trainings	526 (36)	335 (35)	129 (36)	62 (41)	0.143

[a]Chi-square *p* value; [b]Always is one of the comparison categories of practice variables.

Belief in the effectiveness of Sputnik V was higher than that of the Pfizer-BioNTech COVID-19 vaccine (49 and 29%, respectively). Similarly, belief in safety was 47% for Sputnik V and 32% for the "Pfizer-BioNTech" COVID-19 vaccine.

KAP and sociodemographic variables

Adequate KAP was significantly higher ($p < 0.05$) among females compared to males, among those who worked in Aktobe and Shymkent compared to Turkestan, and among those who had over 20 years of professional experience compared to those who had less (Figure 3). A higher proportion of providers with children had adequate attitudes compared to those without children (19 vs. 12%, respectively; $p = 0.002$). Adequate practice was higher among those who did not have older adult in the household (34%) compared to 25% among whose household had older adult ($p = 0.001$).

Relationship between knowledge, attitudes, and practices

Adequate knowledge about vaccination in general was higher among providers with adequate attitudes (44%; $p < 0.001$; Figure 3). Similarly, adequate attitudes were significantly higher among those with adequate knowledge (33%; $p < 0.001$) and adequate practice (32%; $p < 0.001$). Just as adequate practice was higher among providers with adequate knowledge (46%) and adequate attitude (60%; $p < 0.001$). There was a moderate correlation (Spearman correlation coefficient of 0.42) between adequate attitudes and COVID-19 vaccine confidence (Figure 4). Additionally, the relationships between each domain of KAP are bidirectional, and each individual factor is positively associated with the other three (Table 4).

Bivariable analysis of factors associated with COVID-19 vaccine confidence

COVID-19 vaccine confidence was positively associated with adequate overall vaccine knowledge, knowledge of contraindications, adequate attitudes related to routine vaccination, belief in the effectiveness and safety of vaccines, and years of experience (Table 5). Providers who did not believe that COVID-19 vaccines were safer than getting COVID-19, those who did not think it was important to slow the spread of SARS-CoV-2 and those who did not think vaccines should be compulsory had lower COVID-19 vaccine confidence.

Multivariable analysis of factors associated with COVID-19 vaccine confidence

In the reduced model (Model 1), COVID-19 vaccine confidence was associated with adequate attitude [adjusted prevalence ratio (aPR) = 3.1; 95% CI: 2.7–3.6] and adequate knowledge about routine immunization (aPR = 1.2; 95% CI: 1.0–1.4; Table 5; Supplementary Figure 2). In the fuller model (Model 2), factors associated with COVID-19 vaccination confidence were knowledge of COVID-19 vaccination (aPR = 1.2; 95% CI: 1.0–1.3), positive attitude toward the effectiveness and safety of vaccines (aPR = 2.8; 95% CI: 2.0–3.9), belief that it is important for primary care providers to vaccinate against flu (aPR = 1.5; 95% CI: 1.2–1.8), belief that the role of provider is to encourage timely vaccination (aPR = 1.9; 95% CI: 1.6–2.4), trust in the QazVac vaccine (aPR = 1.4; 95% CI: 1.1–1.8), and trust in the Sputnik V vaccine (aPR = 1.3; 95% CI: 1.0–1.6). Knowledge of contraindications (aPR = 0.9; 95% CI: 0.7–1.0), disagreement that vaccination is important to slow the spread of COVID-19 (aPR = 0.6; 95% CI: 0.4–0.8), that COVID-19 vaccination should be mandatory (aPR = 0.4; 95% CI: 0.3–0.5), and belief that providers have no time to

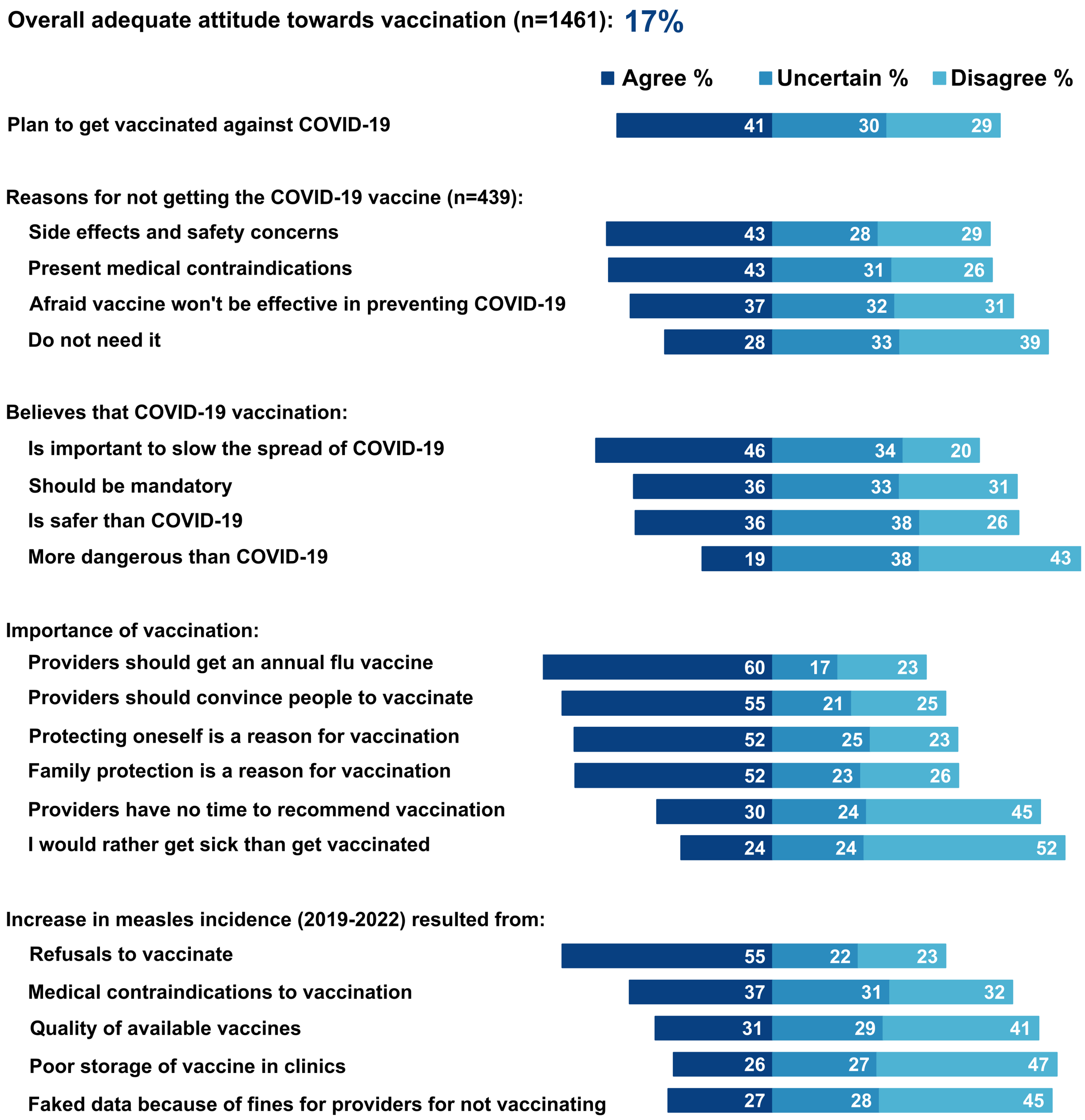


FIGURE 1
Attitudes toward vaccination among primary care providers, Aktobe, Shymkent, and Turkestan, Kazakhstan, 2021 (*N* = 1,461).

convince people to vaccinate (aPR = 0.8; 95% CI: 0.7–0.9) were negatively associated with vaccine confidence.

Discussion

Key findings

Our study found that primary care providers in the cities of Shymkent, Turkestan, and Aktobe in Kazakhstan had low COVID-19 vaccine confidence during the time COVID-19 vaccines were first introduced in the country. Specifically, only 30% of providers had COVID-19 vaccine confidence. This proportion is within the range but low compared to the global average of 77% (range: 28–96%) across 35 studies of COVID-19 vaccine confidence among healthcare providers (37, 38). Additionally, one in three providers would refuse the vaccine, a proportion on the lower end of the range of those that would refuse a vaccine reported in the literature. By comparison, the pooled refusal rate from 51 studies among nurses worldwide was 21% (confidence interval: 17–27%) (39).

Knowledge about vaccines and confidence

Because providers are at elevated risk for COVID-19, the high proportion of providers that would refuse the COVID-19 vaccine was

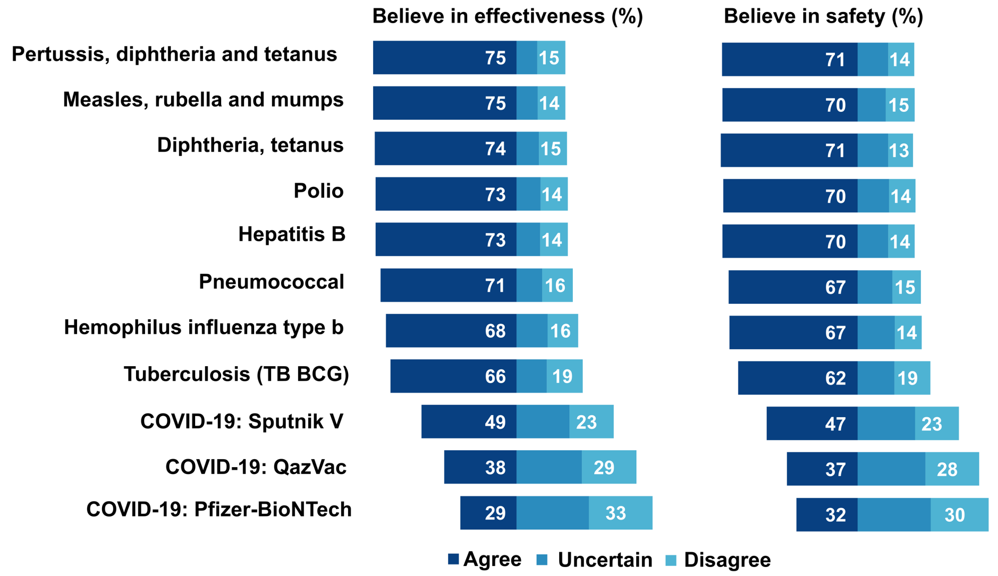


FIGURE 2
Attitudes toward safety and effectiveness of vaccines among primary care providers, Aktobe, Shymkent, and Turkestan, Kazakhstan, 2021 (*N* = 1,461).

concerning but not surprising (40). Low perceived trust in vaccine safety was the most important barrier to vaccination in our study, as it is in the literature (41, 42). We found that less than half of providers believed in safety and effectiveness of the most common COVID-19 vaccines available in Kazakhstan at that time. Low trust in COVID-19 vaccine safety and effectiveness could have been influenced by the lack of published data on the predominant COVID-19 vaccines available in Kazakhstan, Sputnik V, and QazVac (43–45). Most literature on COVID-19 vaccines was predominantly in English, as are most scientific publications, and therefore likely not easily accessible to the majority of healthcare providers in Kazakhstan (46), where 97% of the population speaks Russian and 80% speaks Kazakh (47).

Language is a critical barrier to accessing timely evidence-based medical and scientific literature (41). Proficiency in English is often required to access up-to-date vaccine research, guidelines, and training materials, which can influence medical practitioners' understanding of and confidence in vaccines. Medical education and science in Kazakhstan have relied heavily on Russian-language Soviet textbooks without much if any, training on searching and using indexed peer-reviewed literature (48). Consistent with this is our finding that only approximately one in three providers access scientific literature on vaccines on a regular basis.

Similarly, language likely played an important role in our finding that almost twice as many participants trusted the Sputnik V vaccine safety and efficacy than trusted the Pfizer-BioNTech COVID-19 vaccines, even though the body of published evidence on safety and effectiveness was much larger for the latter. On the one hand, publications about Pfizer-BioNTech and other COVID-19 vaccines were almost exclusively in English. On the other hand, Russian-language misinformation was widely available in news and social media (49).

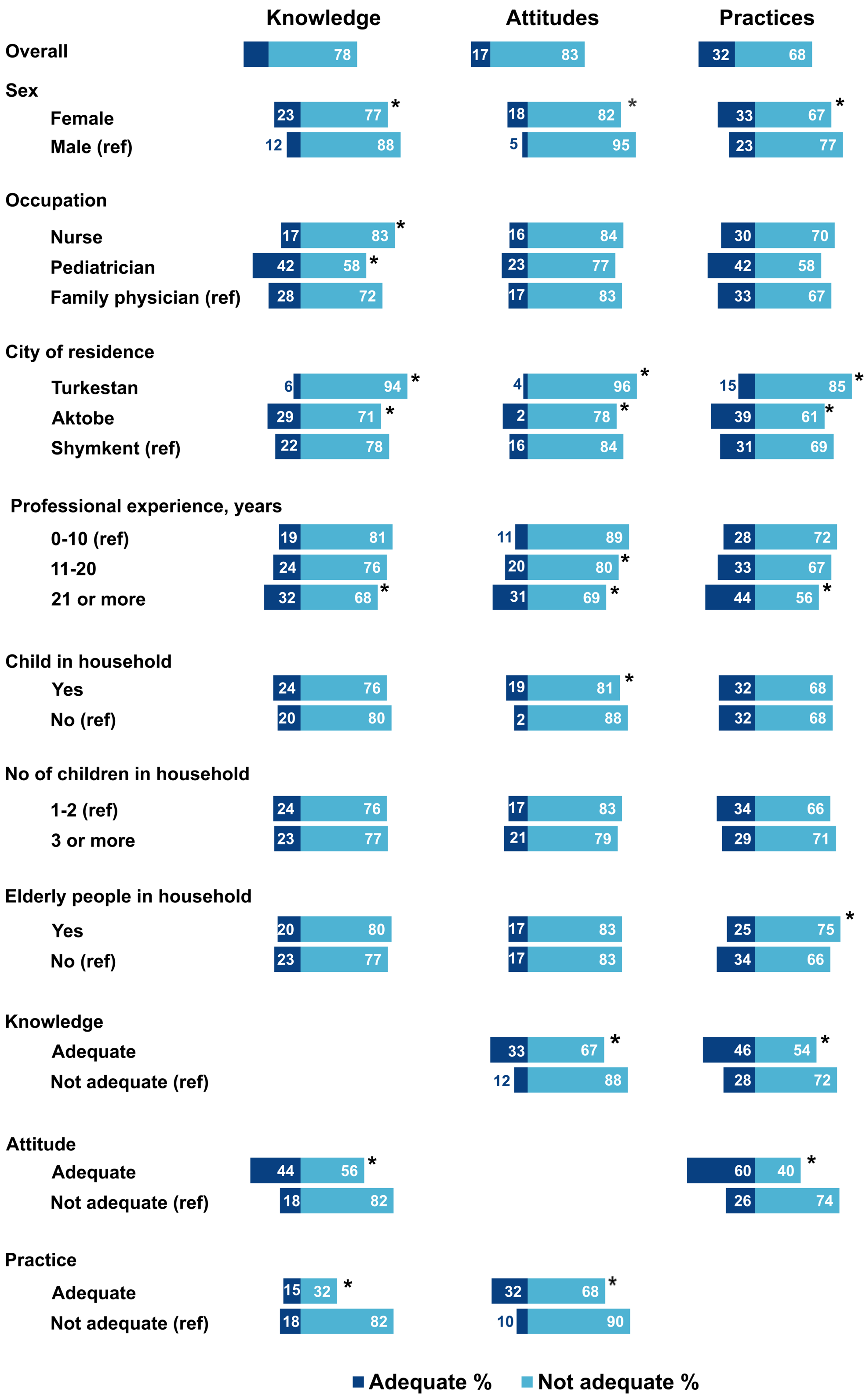
Our data also showed that one in two providers believed common myths about routine vaccinations; this gives further evidence that widespread Internet and social media vaccine misinformation is influencing healthcare provider knowledge about routine vaccines in Kazakhstan. For example, one in two providers still believed, incorrectly, that there is an association between vaccines and diseases such as autism and multiple sclerosis, even though hundreds of studies have been published (mostly in English) demonstrating otherwise. This is particularly worrisome because primary care providers in Kazakhstan are a trusted source on vaccination. Providers' misconceptions may influence knowledge and attitude toward vaccination of the general population and there is rising vaccine hesitancy among the general population as well as high levels of common misperceptions such as belief that measles vaccination leads to autism or multiple sclerosis (50).

Attitudes toward vaccines and confidence

Although providers with adequate knowledge about routine vaccines were 20% more likely to have COVID-19 vaccine confidence, knowledge had a weak positive correlation with attitudes, practice, and confidence. This finding suggests that knowledge alone is not sufficient to influence vaccine attitudes, confidence, and practice. As commonly reported in studies, attitudes related to vaccines play a larger role in influencing confidence and practice (51).

We found that adequate attitudes toward routine vaccines had a strong positive correlation with COVID-19 vaccine confidence. Additionally, providers with adequate attitudes toward routine vaccines were 210% more likely to have COVID-19 vaccine confidence. This finding is consistent with studies showing that healthcare providers with adequate attitudes toward childhood vaccination and acceptance of flu vaccination are more likely to have good attitudes related to COVID-19 vaccines and to get vaccinated (39, 52). This relationship is bidirectional, and people who are hesitant to childhood or flu immunization also tend to have poor attitudes toward COVID-19 vaccines (52–54).

Interestingly, in our multivariable model when controlling for measures of attitudes, we found that vaccine confidence was



	Knowledge Adequate %	Knowledge Not adequate %	Attitudes Adequate %	Attitudes Not adequate %	Practices Adequate %	Practices Not adequate %
Overall		78	17	83	32	68
Sex						
Female	23	77 *	18	82 *	33	67 *
Male (ref)	12	88	5	95	23	77
Occupation						
Nurse	17	83 *	16	84	30	70
Pediatrician	42	58 *	23	77	42	58
Family physician (ref)	28	72	17	83	33	67
City of residence						
Turkestan	6	94 *	4	96 *	15	85 *
Aktobe	29	71 *	2	78 *	39	61 *
Shymkent (ref)	22	78	16	84	31	69
Professional experience, years						
0-10 (ref)	19	81	11	89	28	72
11-20	24	76	20	80 *	33	67
21 or more	32	68 *	31	69 *	44	56 *
Child in household						
Yes	24	76	19	81 *	32	68
No (ref)	20	80	2	88	32	68
No of children in household						
1-2 (ref)	24	76	17	83	34	66
3 or more	23	77	21	79	29	71
Elderly people in household						
Yes	20	80	17	83	25	75 *
No (ref)	23	77	17	83	34	66
Knowledge						
Adequate			33	67 *	46	54 *
Not adequate (ref)			12	88	28	72
Attitude						
Adequate	44	56 *			60	40 *
Not adequate (ref)	18	82			26	74
Practice						
Adequate	15	32 *	32	68 *		
Not adequate (ref)	18	82	10	90		

FIGURE 3
Adequate knowledge, attitudes, and practices toward vaccination among primary care providers, Kazakhstan, 2021 (*N* = 1,461). *Significant difference, Chi-square value of $p < 0.05$; ref.: a reference group.

significantly lower for those with adequate knowledge of contraindications. This finding is in contrast to results from previous studies that demonstrate that high self-reported knowledge of contraindications is associated with higher rates of influenza vaccines (55). This finding demonstrates the importance of attitudes on confidence. We believe this finding could be explained by high

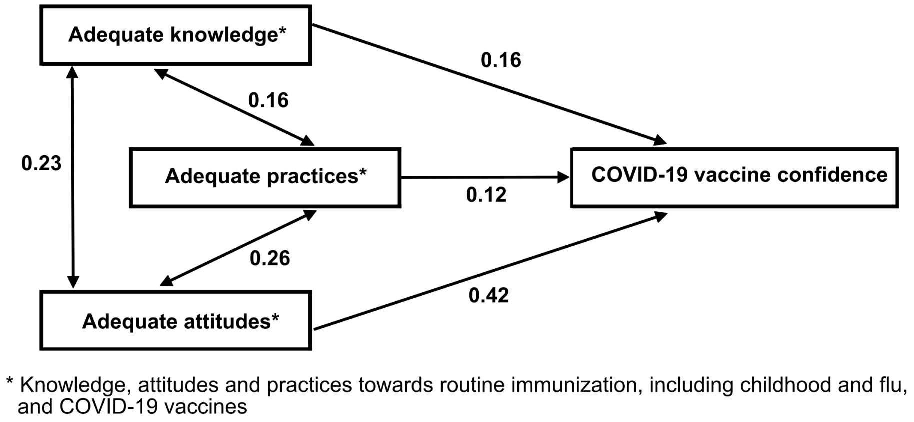


FIGURE 4
Correlation between adequate knowledge, attitude, and practice toward routine vaccination, including childhood, flu, and COVID-19 vaccine confidence, Kazakhstan 2021. Arrows indicate significant associations according to the multivariable regression analysis. Numbers over the arrows are Spearman correlation coefficients.

TABLE 4 The associations between adequate knowledge, attitude, and practice toward routine vaccination and COVID-19 vaccine confidence, Kazakhstan, 2021.

Outcome	Predictor	Correlation		Adjusted prevalence ratio[c]
		coefficient[a]	95%CI[b]	
Vaccine confidence	Overall knowledge	0.16	(0.11–0.21)	**1.2 (1.0–1.4)**
Vaccine confidence	Overall attitude	0.42	(0.37–0.46)	**3.1 (2.7–3.6)**
Vaccine confidence	Overall practice	0.12	(0.07–0.17)	1.0 (0.9–1.1)
Overall knowledge	Overall attitude	0.23	(0.18–0.27)	**1.8 (1.5–2.2)**
Overall attitude	Overall knowledge	0.23	(0.18–0.27)	**1.9 (1.6–2.4)**
Overall knowledge	Overall practice	0.16	(0.11–0.21)	**1.3 (1.1–1.6)**
Overall practice	Overall knowledge	0.16	(0.11–0.21)	**1.3 (1.1–1.5)**
Overall attitude	Overall practice	0.26	(0.21–0.30)	**2.4 (1.9–2.9)**
Overall practice	Overall attitude	0.26	(0.21–0.30)	**1.9 (1.6–2.2)**

[a]Spearman correlation: no correlation 0.00–0.10, weak positive correlation 0.10–0.39, and 0.40–0.69 moderate positive correlation and > 0.70 strong positive correlation.
[b]CI, confidence interval.
[c]Values of $p < 0.05$ highlighted in bold.

knowledge of contraindications among hesitant providers who rely on their knowledge of contraindications to justify avoidance of vaccines that are mandated for healthcare providers, such as influenza, and subsequently COVID-19.

Vaccine practice and confidence

Adequate practices related to vaccines had a weak positive association with adequate attitudes but no correlation with COVID-19 vaccine confidence. Although providers with adequate vaccine practices toward routine vaccines were more likely to have COVID-19 vaccine confidence in bivariable analysis, this relationship was not significant in multivariable models that adjusted for attitudes and knowledge.

Because prior studies have found that providers are a trusted source of vaccine information in Kazakhstan (11), the finding that two-thirds of providers felt it was difficult to speak to patients about vaccines was unexpected. Furthermore, over half of providers reported that they do not always feel confident answering patient questions about vaccines or patient concerns about vaccine side effects. These findings demonstrate a critical need for more comprehensive training programs focusing not only on the technical aspects of vaccination but also on strategies for communicating this information effectively (56). Health systems may need to allocate more resources to aid in vaccine-related discussions, including support staff, patient education materials, or even additional time for appointments.

While we did not ask about reasons for this difficulty in communicating about vaccines with patients, systemic barriers such as workload with 1,500–5,000 individuals in providers' catchment areas, lack of time for detailed patient counseling, fines imposed for not vaccinating the population, or low reimbursement rates for vaccination services can hinder communication and vaccine advocacy.

Difficulty in communicating with patient populations about vaccines could also be related to providers not being up to date on recommendations. Our study found that a low proportion of primary care providers receive continuing education related to vaccination or independently study vaccine-related scientific literature. Policies and

TABLE 5 Factors associated with COVID-19 vaccine confidence among primary health care providers in Kazakhstan, 2021: two multivariable Poisson regression models.

Characteristics		Model 1	Model 2 c
	cPR[a] [95% CI]	aPR[b] [95% CI]	aPR[b] [95% CI]
Adequate knowledge (ref: not adequate)[c]	**1.7 [1.4–1.9]**	**1.2 [1.0–1.4]***	
Knowledge about childhood and flu vaccination	**1.4 [1.2–1.7]**		1.1 [0.9–1.3]
Knowledge on contraindications for vaccination	**1.2 [1.0–1.4]**		**0.9 [0.7–1.0]***
Knowledge about COVID-19 vaccination	**2.3 [2.0–2.7]**		1.2 [1.0–1.3]
Adequate attitude (*ref: not adequate*)	**3.4 [3.0–3.9]**	**3.1 [2.7–3.6]***	
Effectiveness and safety of vaccines	**5.7 [4.2–7.9]**		**2.8 [2.0–3.9]***
Immunization against measles	**1.2 [1.1–1.6]**		1.1 [0.9–1.2]
Disagree with the statement *(ref: agree/uncertain)*:			
Vaccination is important to slow the spread of COVID-19	**0.3 [0.2–0.4]**		**0.6 [0.4–0.8]***
Vaccination should be mandatory	**0.2 [0.2–0.3]**		**0.4 [0.3–0.5]***
I prefer to get sick rather than vaccinated?			1.2 [1.0–1.4]
Agree with the statement *(ref: disagree/uncertain)*:			
Providers should vaccinate against flu	**3.2 [2.6–4.1]**		**1.5 [1.2–1.8]***
The role of a physician is to encourage timely vaccination			**1.9 [1.6–2.4]***
I do not have time to convince people to vaccinate			**0.8 [0.7–0.9]***
I trust QazVac vaccine			**1.4 [1.1–1.8]***
I trust Sputnik V vaccine			**1.3 [1.0–1.6]***
I trust BNT162b2 (Pfizer-BioNTech) vaccine			0.9 [0.8–1.1]
Adequate practice *(ref: not adequate)*	**1.4 [1.2–1.7]**	1.0 [0.9–1.1]	
Continuing education in vaccination *(ref: never)*	**1.3 [1.0–1.6]**		1.1 [0.9–1.4]
Professional experience *(ref: ≤10 years)*			
11–20	**1.4 [1.2–1.7]**	1.1 [0.9–1.4]	1.0 [0.8–1.2]
21 or more	**1.4 [1.1–1.7]**	0.9 [0.7–1.2]	0.8 [0.6–1.0]

[a]cPR, crude prevalence ratio. [b]aPR, adjusted prevalence ratio [CI: confidence interval] (adjusted for age, city of residence, and child in a family). [c]ref: reference group. *Multivariable Poisson regression, significant difference, value of $p < 0.05$.

programs can help encourage proactive engagement with new knowledge (57). Systemic changes can help create a supportive environment for continuous learning, such as dedicated time for studying, promoting the value of continuous learning, and building a culture that encourages curiosity and staying up to date (58).

However, provision of continuous learning opportunities alone is not enough to change attitudes and behaviors. Learning opportunities can be reinforced using evidence-based approaches for behavior and attitude change such as nonjudgmental empathetic listening, personalized storytelling approach, and involvement of provider teams in communication with vaccine hesitant population (59). Also, providers can help change patient behavior and attitudes using evidence-based tools such as the American Medical Association STEPS Forward toolkit (60).

Vaccine confidence and professional category

Similar to other studies, we did not find a significant association of vaccine confidence with age, years of professional experience, residence, presence of child or older adult people in the family, or continuing education in vaccination (61). However, we did find that KAP varied by medical profession, with pediatricians having a higher proportion of adequate KAP, followed by family physicians and nurses. Other studies have similarly found that nurses have lower knowledge and acceptance of COVID-19 vaccines than physicians (62, 63). These differences may be due to the level of training received in these specialties. In Kazakhstan, pediatricians may have higher KAP scores because they have more experience and training in routine immunization compared to other health professions. Family physicians in Kazakhstan have only recently become administrators of routine childhood vaccines (64).

Study limitations

Our study is subject to at least three important limitations. First, our response rate was 42%. We have no information about nonresponders and cannot assess the level and direction of bias that this may have introduced in our results. Vaccine confidence in our study of 30% would range from 12 to 71% if all providers who refused would have participated and were either confident or not. Second, our study only included providers in three cities and may not represent the attitudes of healthcare providers across the entire country. Therefore, these results should not be extrapolated to all providers in Kazakhstan. Third, because participants were interviewed at their place of work, the results may have been subject to social desirability bias. The direction of this bias would likely have inflated our estimate of vaccine confidence. We attempted to mitigate this bias by making surveys anonymous and self-administered rather than using interviewer-assisted surveys. Fourth, we conducted this study during the initial stages of COVID-19 vaccine rollout, and COVID-19 vaccine confidence has grown since that time. However, our findings related to knowledge, attitudes, and practices toward routine childhood and influenza vaccines likely have not. These are likely entrenched KAP that would influence confidence of future vaccines.

Study implications

We conducted this study during the early stages of COVID-19 vaccine rollout in Kazakhstan. COVID-19 vaccines have since become compulsory for healthcare providers and have resulted in high uptake of COVID-19 vaccines in providers. Whether the mandates resulted in increased COVID-19 vaccine knowledge and confidence is not known. However, it is unlikely that these mandates have had any impact on our findings of low levels of knowledge, attitude and practice toward routine vaccines. Changing the knowledge, attitude, practice and COVID-19 vaccine confidence of vaccine hesitant and refusing primary care providers often requires a multifaceted approach, including evidence-based education, dialog that addresses personal beliefs and attitudes, peer and community engagement, and systemic changes that make providing vaccines easier and more rewarding for healthcare providers. Given the vital role of healthcare providers in promoting vaccine uptake among the population, increasing KAP is vitally important to raise vaccine confidence in the general population.

Conclusion

Our study uncovers critical areas for interventions to improve knowledge, attitudes, and practices related to routine immunizations and COVID-19 vaccine confidence among primary care providers in Kazakhstan. Low COVID-19 vaccine confidence was associated with inadequate overall knowledge about routine vaccines, negative overall attitudes, and misconceptions about the safety and effectiveness of both routine vaccines and COVID-19 vaccines. The strong correlation between attitudes toward routine vaccines and COVID-19 vaccine confidence underscores the importance of addressing vaccine hesitancy more broadly and not solely focusing on COVID-19. Our findings also highlight the need to ensure that relevant and reliable vaccine information is accessible in local languages. Policymakers can consider the findings of this study when designing and implementing vaccine strategies to healthcare providers in the vital role they have in fostering public trust in vaccination and achieving high coverage of COVID-19 vaccines and routine immunizations.

Main message

Our study provides evidence of the need to improve knowledge, attitudes and practices related to routine immunizations and COVID-19 vaccination among primary care providers in Kazakhstan. Primary healthcare providers are ambassadors for vaccination and a trusted source of information on vaccination. Providers who are correctly informed and have positive views about vaccines, including COVID-19 vaccines, are able to navigate patient concerns. Kazakhstan has struggled with vaccine hesitancy with decreasing coverage of childhood immunizations and low uptake of COVID-19 vaccines. To our knowledge, this is the first study among healthcare providers in Central Asia that assesses levels of vaccine confidence and links it to knowledge, attitudes, and practices of routine immunizations. We interviewed 1,461 providers in 54 facilities. Participants included nurses, family physicians and pediatricians (65, 25, and 10%, respectively) whose duties include immunizations in 3 cities. We found that just one in three providers had confidence in COVID-19 vaccines. Additionally, less than one in three providers had adequate knowledge, attitudes or practices (22, 17, and 32%, respectively). Adequate knowledge and attitudes were positively correlated with COVID-19 vaccine confidence. Findings highlight the complex relationship between KAP of routine vaccines and COVID-19 vaccine confidence and the need to address hesitancy more broadly.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

DN, RH, LK, MS, AY, and AH: conceptualization. DN, RH, LK, MS, AH, SA, JN, and AY: methodology and writing—review and editing. DN, RH, SA, and LK: software, validation, and formal analysis. DN, LK, MS, and AH: investigation. DN, RH, MS, LK, AY, and JN: resources. DN, RH, AH, MS, and LK: writing—original draft preparation. DN, SA, and RH: visualization. AY, JN, and MS: supervision. MS and LK: project administration. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1245750/full#supplementary-material

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COVID-19 pandemic and other factors associated with unfavorable tuberculosis treatment outcomes—Almaty, Kazakhstan, 2018–2021

Malika Gabdullina[1,2,3]*, Edmond F. Maes[4], Roberta Z. Horth[1,2,5], Panagul Dzhazybekova[6], Gulzhan N. Amanova[1,2,6], Sanam Zikriyarova[2] and Dilyara A. Nabirova[1,2,5]

[1]Central Asia Field Epidemiology Training Program, Almaty, Kazakhstan, [2]Department of Epidemiology, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, [3]National Scientific Center of Phthisiopulmonology, Ministry of Health of the Republic of Kazakhstan, Almaty, Kazakhstan, [4]Rollins School of Public Health, Emory University, Atlanta, GA, United States, [5]United States Centers for Disease Control and Prevention, Central Asia Office, Almaty, Kazakhstan, [6]Scientific and Practical Center for Sanitary and Epidemiological Expertise and Monitoring, Almaty, Kazakhstan

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EDITED BY
Natalya Glushkova,
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REVIEWED BY
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Kyrgyzstan
Patrick Kaonga,
University of Zambia, Zambia

*CORRESPONDENCE
Malika Gabdullina
✉ gabdullina.malika@gmail.com

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Introduction: The COVID-19 pandemic negatively influenced the availability of tuberculosis (TB) services, such as detection, diagnosis and treatment, around the world, including Kazakhstan. We set out to estimate the COVID-19 pandemic influence on TB treatment outcomes by comparing outcomes among people starting treatment before the pandemic (2018–2019) and during the pandemic (2020–2021) and to determine risk factors associated with unfavorable outcomes.

Methods: We conducted a retrospective cohort study among all people newly diagnosed with drug-sensitive pulmonary or extrapulmonary TB at least 18 years old who initiated treatment from 2018 to 2021 in Almaty. We abstracted data from the national electronic TB register. Unfavorable treatment outcomes were ineffective treatment, death, loss to follow-up, results not evaluated, and transferred. We used multivariable Poisson regression to calculate adjusted relative risk (aRR) and 95% confidence intervals (95%CI).

Results: Among 1548 people newly diagnosed with TB during the study period, average age was 43 years (range 18–93) and 52% were male. The number of people initiating treatment was higher before than the pandemic (935 vs. 613, respectively). There was significantly different proportions before compared to during the pandemic for people diagnosed through routine screening (39% vs. 31%, $p < 0.001$), 60 years and older (16% vs. 22%, $p = 0.005$), and with diabetes (5% vs. 8%, $p = 0.017$). There was no difference in the proportion of HIV (8% in both periods). Unfavorable outcomes increased from 11 to 20% during the pandemic (aRR = 1.83; 95% CI: 1.44–2.31). Case fatality rose from 6 to 9% ($p = 0.038$). Risk factors for unfavorable TB treatment outcomes among all participants were being male (aRR = 1.44, 95%CI = 1.12–1.85), having HIV (aRR = 2.72, 95%CI = 1.99–3.72), having alcohol use disorder (aRR = 2.58, 95%CI = 1.83–3.62) and experiencing homelessness (aRR = 2.94, 95%CI = 1.80–4.80). Protective factors were being 18–39 years old (aRR = 0.33, 95%CI = 0.24–0.44) and 40–59 years old (aRR = 0.56, 95%CI = 0.41–0.75) compared to 60 years old and up.

Conclusion: COVID-19 pandemic was associated with unfavorable treatment outcomes for people newly diagnosed with drug-sensitive TB in Almaty, Kazakhstan. People with fewer comorbidities were at increased risk. Results point to the need to maintain continuity of care for persons on TB treatment, especially those at higher risk for poor outcomes during periods of healthcare service disruption.

KEYWORDS

COVID-19, drug-sensitive TB, tuberculosis treatment, unfavorable treatment, Kazakhstan

Introduction

On March 11, 2020, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) to be a pandemic. In the immediate absence of an effective vaccine, "non-pharmaceutical interventions" (NPIs) such as social distancing, restrictions on travel, and remaining at home, were recommended as some of the main strategies to reduce the likelihood of disease transmission. With the exponential growth in the number of seriously ill people, these NPIs served as some of the main tools to reduce the immediate burden on the healthcare system personnel and resources (1). These restrictions and the demands placed on health care personnel (including personnel shortages) led to the postponement of elective health care procedures as well as decreased access to routine care, including the management of people with active tuberculosis (TB). Among countries with a large burden of TB, the reduction in core TB services led to reductions in the detection, diagnosis and treatment of patients with TB (2).

WHO estimates that in many countries with a heavy burden of TB, the number of TB notifications decreased by 18% in 2020 compared to 2019, as COVID-19 pandemic control measures were taken (2). The number of people under active treatment for TB globally also decreased in 2020, totaling 2.8 million people, 1.4 million fewer than in 2019.

After the introduction of the direct observed therapy strategy (DOTS) in 1999, the TB incidence per 100,000 people in Kazakhstan dropped from 162.5 in 2002 to 49.2 in 2020–an overall average decline of about 8–10% per year (3). Also, national TB mortality per 100,000 population decreased from 39.7 in 1999 to 1.9 in 2020. In Almaty, incidence decreased from 70.1 to 23.1 per 100,000 from 2010 to 2021 (Figure 1). From 2010 to 2019, the proportion of TB patients identified during occupational screening fluctuated between 38.8 to 36.6%; during 2020 and 2021, occupational screening only identified 34.2 and 34.0%, respectively (Figure 2).

The progress made in fighting TB in Kazakhstan, as well as worldwide, has been threatened by the COVID-19 pandemic. In particular, the pandemic has led to a decrease in the timely detection of TB in 2020 due to complex factors that resulted in reduced access to services (4). Specific impacts in Kazakhstan include: (1) reduced coverage of the population by preventive TB examinations (44.5% in 2020 compared to 41.9% in 2019), and (2) reduced detection of TB during routine medical check-ups (49.8 to 44.9 per 100,000 population in 2019 to 2020 respectively) (5).

A review of studies on the impact of the COVID-19 pandemic on TB services in various countries revealed that the COVID-19 pandemic negatively affected many aspects of TB control. In India, during the 8-week isolation due to the COVID-19 pandemic, the detection of TB decreased by 59% (6). In China, the diagnosis of multiple-drug-resistant (MDR) TB in the first quarter of 2020 decreased by 17% compared to the same period in 2019 (7). A study in Iran also showed a 55.6% decrease in new TB case detection during the March to June 2020 lockdown compared to previous years (8). A recent study in Italy showed that, despite efforts to maintain TB services, there was a sudden increase in service disruption during the

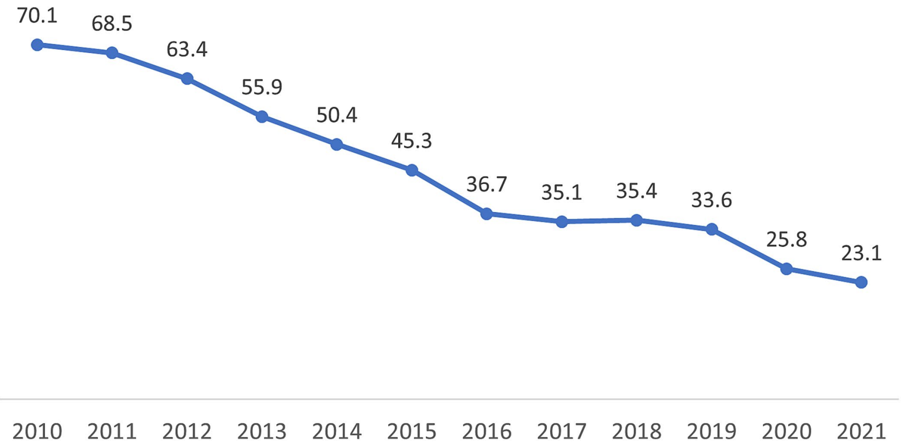

FIGURE 1
Annual incidence of tuberculosis per 100,000 population in Almaty, Kazakhstan, 2010–2021.

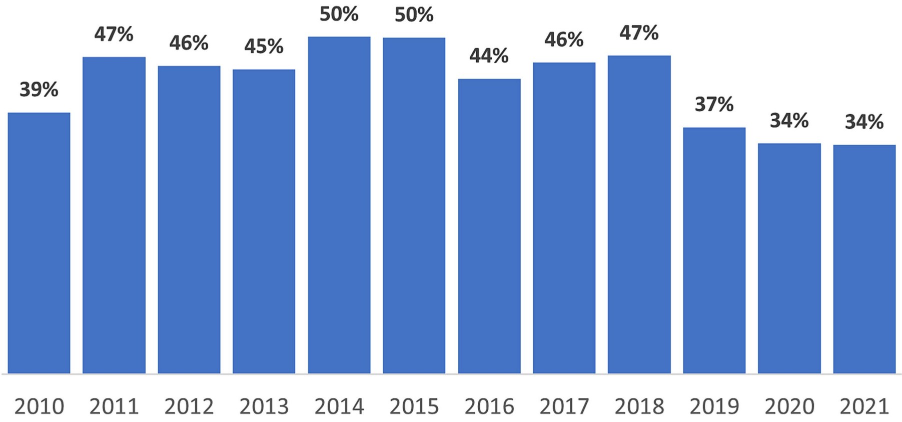

FIGURE 2
Annual proportion of new tuberculosis diagnosis from routine occupational screening in Almaty, Kazakhstan, 2010–2021.

COVID-19 outbreak (9). These service interruptions will likely have long-term consequences on TB burden, and a modeling study predicts a 4% increase in TB deaths worldwide and 5.7% excess deaths in India over the period from 2020 to 2025 due to the COVID-19 lockdown (10–12).

Studies using national data to assess the impact of the COVID-19 pandemic on TB services have not previously been conducted in any Central Asian country. This study examined the potential impact of COVID-19 on TB detection and treatment in Kazakhstan and will help guide recommendations for further planning and policy development of TB control programs in Kazakhstan, as well as other countries with similar economies and health care systems.

The specific aim of the study was to assess the association of the COVID-19 pandemic period and related risk factors with adverse TB treatment outcomes among people newly diagnosed with TB in Almaty, Kazakhstan, 2018–2021.

Materials and methods

Study design

We conducted a retrospective cohort study among people with newly diagnosed TB in Almaty; data were abstracted from patient registries between 08/20/2022 and 12/15/2022. Eligibility for this study was restricted to patients at least 18 years old, living in Almaty, with a first-time TB diagnosis who initiated TB treatment between 2018 and 2021.

Data collection

Patient data was abstracted from Kazakhstan's national electronic database - "Information System National Electronic Register of Tuberculosis Patients." The database is a longitudinal registry where all people diagnosed with TB are mandatorily registered and tracked. The system contains demographic and clinical data on all people ever diagnosed with TB in Kazakhstan.

Study participants

From 2018 to 2021 a total of 2,246 patients with TB were registered in Almaty, Kazakhstan. Analysis was restricted to 1,548 adults 18 years old and above, who were diagnosed for the first-time with drug-sensitive TB. People meeting these criteria without an individual identification number ($n = 24$) were excluded from the study.

To assess the effect of the COVID-19 pandemic on unfavorable TB treatment outcomes, we included only people who initiated treatment and would have already completed treatment before the study began. We excluded people with drug-resistant TB because currently in Kazakhstan the duration of treatment for this group requires several years.

The study population was divided into two groups: people initiating treatment during the COVID-19 pandemic from March 1, 2020, to December 31, 2021 (the "during COVID-19 period" group), and people initiating treatment before the COVID-19 pandemic from January 1, 2018, to February 29, 2020 (the "before COVID-19 period" group) in Almaty.

Key definitions

We used WHO categories and reporting framework for TB, 2013 revision (updated Dec 2014; Jan 2020) to classify treatment outcomes as favorable or unfavorable (13). People were classified as having favorable treatment outcomes if they were considered to be cured or completed treatment. The definition of cured was someone who became smear or culture negative in the last month of treatment and on at least one previous occasion. People were classified as having unfavorable treatment outcomes if they had any of the following outcomes: treatment failure or switched 2nd line treatment, death from any cause, and loss to follow-up or not evaluated. Treatment failure was defined as having completed treatment but remaining smear or culture positive after treatment completion.

Drug-sensitive TB is TB caused by mycobacteria whose strains are sensitive to first-line anti-TB drugs (rifampicin, isoniazid). MDR TB is TB caused by mycobacteria whose strains are resistant to at least rifampicin and isoniazid.

Statistical analysis

We assessed the accuracy and completeness of the data by constructing a line-by-line list of patients in a separate database and sorting them according to the variables under study. Statistically significant value of p was set to ($p < 0.05$). We analyzed the data and performed statistical calculations using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

We calculate crude risk ratios (cRRs) and used the chi-square test to measure the relationship between each individual risk factor, including time of treatment initiation, patient characteristics, with treatment outcome (successful versus unsuccessful). Power to detect difference in proportion from $p1 = 0.11$ to $p2 = 0.20$ from unequal samples ($n1 = 935$ and $n2 = 613$) was 0.99. We ran bivariable and multivariable Poisson regression to assess the contribution of treatment period and risk factors to unfavorable treatment outcomes. We checked for multicollinearity and interactions between explanatory variables. None were found. Results are presented as adjusted risk ratios (aRRs) and 95% confidence intervals.

Ethical considerations

Ethical approval of the study was received from the local ethical commission of the NAO Kazakh National Medical University named after S.D. Asfendiyarov, Kazakhstan. This activity was reviewed by the CDC and was conducted consistently with applicable United States federal law and CDC policy.[1]

Permission to conduct the study was granted by the Local Internal Review Board of the Kazakh School of Public Health and the Internal Review Board at the US Centers for Disease Control and Prevention. Patients' informed consent was deemed not necessary, because this is a retrospective analysis of program data.

Results

We identified 1,548 people who had been newly diagnosed and initiated treatment with drug-sensitive TB from 2018 to 2021. Of these, 60% did so before the COVID-19 pandemic and 40% during the pandemic. Mean age was 43 years old and 50% were 18–39 years old (Table 1). Distribution across age groups differed significantly by period, and a greater proportion of people were 18–39 years old before the pandemic than during the pandemic (52% vs. 46%, respectively). Half (52%) were male and sex did not differ by period of detection. While 58% of all patients in the study were unemployed, the proportion of patients unemployed was similar in the pre-pandemic and pandemic time periods (58% versus 60%, respectively). More people were detected during routine screening before the pandemic (39%) than during the pandemic (31%). Also, more people were detected due to the presentation of symptoms during the pandemic (68%) compared to the pre-pandemic period (60%). People newly diagnosed with drug-sensitive TB were more likely to have diabetes during the pandemic than before (8% vs. 5%).

The proportion of people completing treatment was lower during than before the pandemic (58% vs. 51%, respectively; Table 2). Also, more people were transferred to second-line treatment during the pandemic than before (7% vs. 2%, respectively). The proportion who died from TB or other causes was also significantly higher during (9%) than before the pandemic (6%). There was no significant difference by period of treatment initiation for other outcomes.

People who were newly diagnosed with drug-sensitive TB and initiated on treatment during the pandemic period were 1.85 times more likely [95% confidence interval (CI) = 1.46 to 2.36] to experience an unfavorable outcome compared to people who started treatment prior to the pandemic period (Table 3). People who were 18 to 39 years of age or 40 to 59 years of age were less likely to have an unfavorable outcome (cRR = 0.36 and 0.74, respectively) compared to people who were 60 years or older at time of treatment initiation. Males were more likely to have an unfavorable outcome compared to females (cRR = 1.66). People who were living with HIV or who had alcohol use disorder were more likely to have unfavorable treatment outcome, cRR = 2.49 and 2.99, respectively compared to people without those conditions.

Employment status had five categories that were significantly related to treatment outcome. People who were manual laborers compared to all other categories were less likely to have unfavorable outcome (cRR = 0.58). People who were office workers compared to all other categories were less likely to have unfavorable outcome (cRR = 0.22). People who were students compared to all other categories were less likely to have unfavorable outcome (cRR = 0.08). People who were experiencing homelessness compared to all other categories were more likely to have unfavorable outcome (cRR = 2.94). People who were retired compared to all other categories were more likely to have unfavorable outcome (cRR = 1.46).

After simultaneously adjusting for all significant risk factors from the bivariate analysis, the association between treatment period and unfavorable outcome was aRR = 1.78 (95%CI = 1.41–2.26). The adjusted risk of adverse treatment outcome remained higher in males compared to females (aRR = 1.46, 95%CI = 1.12–1.9, $p = 0.012$; Table 3). Risk of unfavorable outcome remained increased for people living with HIV (aRR = 2.40, 95%CI = 1.74–3.30, $p < 0.001$), having alcohol use disorder (aRR = 2.40, 95%CI = 1.70–3.40, $p < 0.001$), people experiencing homelessness (aRR = 2.70, 95%CI = 1.65–4.43, $p = 0.007$).

Protective factors for adverse treatment outcomes of drug-sensitive TB were younger age 18–39 years (aRR = 0.35, 95%CI = 0.23–0.51, $p < 0.001$) and age 40–59 years (aRR = 0.57, 95%CI = 0.40–0.83, $p = 0.003$) versus 60 or more years of age.

Discussion

Our study found that the COVID-19 pandemic period was associated with unfavorable treatment outcomes among adults newly diagnosed with drug-sensitive TB treatment in Almaty, Kazakhstan. This impact remained even after adjusting for several other risk factors including age, sex, HIV status, alcohol use disorder and employment status.

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[1] See e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

TABLE 1 Socio-demographic and epidemiological characteristics of adults newly diagnosed with drug-sensitive TB, grouped by years at first registration before and during COVID-19 pandemic, 2018–2021, Almaty, Kazakhstan (*n* = 1548).

Characteristics	Total *n* (%)	Before the pandemic[1] *n* (%)	During the pandemic[1] *n* (%)	*P*-value[2]
Overall	1548 (100)	935 (60)	613 (40)	
Age, years				
18–39	768 (50)	488 (52)	280 (46)	**0.005**
40–59	498 (32)	299 (32)	199 (33)	
60+	282 (18)	148 (16)	134 (22)	
Sex				
Men	810 (52)	502 (54)	308 (50)	0.202
Women	738 (48)	433 (46)	305 (50)	
Means of TB diagnosis				
Routine screening	554 (36)	366 (39)	188 (31)	**<0.001**
Test following symptoms	977 (63)	560 (60)	417 (68)	**0.001**
Post-mortem testing	17 (1)	9 (1)	8 (1)	0.702
Employment				
Unemployed	905 (58)	539 (58)	366 (60)	0.452
Manual laborer	215 (14)	135 (14)	80 (13)	0.486
Retired	231 (15)	126 (14)	105 (17)	0.057
Student	87 (6)	61 (7)	26 (4)	0.073
Office worker[3]	61 (4)	46 (5)	15 (2)	**0.021**
Healthcare worker	18 (1)	8 (1)	10 (2)	0.250
Experiencing homelessness	18 (1)	13 (1)	5 (1)	0.430
Risk factors for TB				
Contact with TB patient	18 (1)	10 (1)	8 (1)	0.857
Living with HIV	123 (8)	77 (8)	46 (8)	0.671
Alcohol use disorder	41 (3)	27 (3)	14 (2)	0.574
Drug use disorder	8 (0.5)	2 (0.2)	6 (1)	0.091
Incarceration <2 years	3 (0.2)	2 (0.2)	1 (0.2)	0.999
Diabetes	97 (6)	47 (5)	50 (8)	**0.017**
Pregnant at diagnosis	20 (1)	14 (2)	6 (1)	0.513
Postpartum <1 year	48 (3)	32 (3)	16 (3)	0.452

[1] Before the COVID-19 pandemic = January 1, 2018 to February 29, 2020. During the COVID-19 pandemic = March 1, 2020 to December 31, 2021. [2] From Pearson's Chi-square test with Yates correction. [3] Office worker category captures management, business or financial operations, computer and math, architecture and engineering, sciences, education, sales and related, office and administrative support. Unknown or missing responses are excluded from analysis. Bolded numbers represent *p*-values < 0.05.

TB detection during the COVID-19 pandemic

The overall number of people diagnosed with TB was substantially lower in the first two-years of the pandemic compared to the 2 years before the pandemic. This is consistent with the annual trends in Almaty where there has been a decreasing trend in TB incidence over the last decade, from 70.1 per 100,000 in 2010 to 35.1 in 2017 (the year before our study began). While community control measures, like use hand and respiratory hygiene practices, and social distancing, taken at the onset of the pandemic may have contributed to the reduced transmission of tuberculosis (14), it should be noted that health service delivery disruptions and reduced access to care may have led to fewer screening opportunities and fewer TB incident cases during the pandemic (15, 16). Nevertheless, reduced screening and healthcare service disruptions may also have contributed to the decrease.

The proportion of people newly detected with drug-sensitive TB during routine screening was significantly less during the pandemic than before (2). Systematic screening for TB is a central component of the global strategy to end TB (17). Screening helps detect TB disease early and reduces the risk of unfavorable treatment outcomes. Restrictive lockdowns introduced nationally in Kazakhstan at the onset of the pandemic made it harder for people to leave their houses to go receive preventive healthcare services, including TB screening for people at increased risk of developing TB disease. Also, even if people could leave, preventive services were often not available, because of disruptions in provision of primary care services throughout the country, including Almaty, during this time. People

TABLE 2 Treatment outcomes among adults newly diagnosed with drug-sensitive TB in Almaty before and during the COVID-19 pandemic, Kazakhstan 2018–2021.

Treatment outcomes	Overall	Before the pandemic[1]	During the pandemic[1]	*P*-value[2]
	n = 1548	*n* = 935	*n* = 613	
	n (%)	*n* (%)	*n* (%)	
Favorable[3]	1322 (85)	833 (89)	489 (80)	**<0.001**
Cured	464 (30)	287 (31)	177 (29)	0.479
Treatment completed	858 (55)	546 (58)	312 (51)	**0.004**
Unfavorable[3]	226 (15)	102 (11)	124 (20)	**<0.001**
Treatment failure	92 (6)	32 (11)	60 (10)	**<0.001**
2nd line treatment	57 (4)	15 (2)	42 (7)	**<0.001**
Ineffective treatment	35 (2)	17 (2)	18 (3)	0.203
Died	115 (7)	59 (6)	56 (9)	**0.038**
Died from TB	35 (2)	18 (2)	17 (3)	0.356
Died other causes	80 (5)	41 (4)	39 (6)	0.109
Lost to follow-up	16 (1)	10 (1)	6 (1)	0.933
Result not evaluated	3 (0.2)	1 (0.1)	2 (0.3)	0.712

[1]Before the COVID-19 pandemic = January 1, 2018 to February 29, 2020. During the COVID-19 pandemic = March 1, 2020 to December 31, 2021. [2]From Pearson's Chi-square test with Yates correction. [3]From WHO categories and reporting framework for TB, 2013 revision (updated Dec 2014; Jan 2020). Bolded values are *p*-value < 0.05.

may also have been reluctant to obtain preventive services due to the risk of getting COVID-19 in healthcare facilities because rates of COVID-19 were high among healthcare providers (18).

Not surprisingly, the proportion of people detected with TB who tested because of TB symptoms was higher during the pandemic. Respiratory symptoms of COVID-19 can be similar to those of TB. During the initial phase of the pandemic and before testing was widely available, all people with respiratory symptoms consistent with COVID-19 in Kazakhstan were hospitalized. TB diagnostic tests would have been performed as a differential diagnosis of COVID-19. This is also consistent with our finding that the proportion of people diagnosed with TB increased in groups at higher risk for COVID-19, specifically older populations and people with diabetes. These are two commonly known risk factors for severe COVID-19 (19, 20).

TB treatment outcomes during the COVID-19 pandemic

As expected, our study showed a decrease in the proportion of people completing TB treatment successfully during the pandemic. In Kazakhstan, as in other countries, some TB hospitals and care facilities were reappropriated to provide inpatient care for COVID-19 patients. Similarly, healthcare providers who usually treat people with TB were often reassigned to care for people with COVID-19 (4). Further amplifying this shortage of services, was the increased morbidity of COVID-19 among providers themselves (21). The reassignment of providers away from TB services could have resulted in reduced oversight and continuity of care for directly observed therapy (DOT) services (22).

Our results are consistent with other studies that show the negative impact the COVID-19 pandemic has had on TB treatment outcomes (7, 9, 23). Disruptions in treatment during the pandemic, may also have contributed to the increased proportion of people who failed to complete treatment or who were referred to second line treatment.

Disruptions in treatment may have also contributed to increased mortality, which was 50% higher during the pandemic (9% during vs. 6% before the pandemic). Notably, the proportion whose death was not attributed to TB was increased. There is no information on the cause of death in the database, but COVID-19 may have played a role because patients with active pulmonary TB who acquire COVID-19 have a two times greater risk of COVID-19 mortality (24).

Treatment outcomes

Treatment success rate in our study of 85% was below the 90% target set by WHO, but it is consistent with the global treatment success rate of 86% for new and relapse cases (2). However, the success rate is higher than the success rate for the European region of 72%. Also, the case fatality ratio of 7% in our study is within the WHO target of 10% set for 2020, and in line with the 2025 target of 6.5%. Although case fatality ratios are below targets, there was a significant increase in all-cause mortality among TB patients during the pandemic. The majority of deaths were not attributable to TB. From the data we cannot determine if COVID-19 was a risk factor for the increased fatality rate; however, studies elsewhere have demonstrated that people with TB are at greater risk of dying from COVID-19 (25, 26).

Consistent with literature, men were more likely than women to have an unfavorable treatment outcome, as were people 60 years and older compared to young and middle-aged adults (27). Delayed-care seeking behavior and smoking status, which we did not measure in our study, are known to contribute to sex differences in TB outcomes. Also consistent with literature was the finding that people with health comorbidities and less social stability, such as alcohol use disorder, HIV, and experiencing homelessness, are more likely to have

TABLE 3 Risk factors associated with unfavorable treatment outcome among adults newly diagnosed with drug-sensitive TB, Almaty, 2018–2021.

Characteristics	Total *n* = 1548	Favorable outcome[2] *n* = 1322	Unfavorable outcome[2] *n* = 226	cRR [95% CI]	aRR [95% CI]
Period of diagnosis[1]					
Before the pandemic	935 (60)	833 (89)	102 (11)	Ref.	Ref.
During the pandemic	613 (40)	489 (80)	124 (20)	**1.85 [1.46, 2.36]**	**1.83 [1.44, 2.31]**
Age, years					
18–39	768 (50)	701 (91)	67 (9)	**0.36 [0.26, 0.49]**	**0.33 [0.24, 0.44]**
40–59	498 (32)	408 (82)	90 (18)	**0.74 [0.56, 0.98]**	**0.56 [0.41, 0.75]**
60+	282 (18)	213 (75.5)	69 (24.5)	Ref.	Ref.
Sex					
Male	810 (52)	664 (82)	146 (18)	**1.66 [1.29, 2.14]**	**1.44 [1.12, 1.85]**
Female	738 (48)	658 (89)	80 (11)	Ref.	Ref.
Employment (ref. not in category)					
Unemployed	905 (57)	768 (84)	137 (16)	1.09 [0.85, 1.40]	
Healthcare worker	18 (1)	15 (83)	3 (17)	1.14 [0.40, 3.40]	
Manual laborer	215 (14)	196 (91)	19 (9)	**0.57 [0.36, 0.89]**	
Office worker	61 (4)	59 (97)	2 (3)	**0.22 [0.05, 0.85]**	
Retired	231 (15)	180 (78)	51 (22)	**1.66 [1.26, 1.20]**	
Student	87 (6)	86 (99)	1 (1)	**0.08 [0.01, 0.53]**	
Experiencing homelessness					
Yes	18 (1)	10 (56)	8 (44)	**3.12 [1.83, 5.30]**	**2.94 [1.80, 4.80]**
No	1530 (99)	1312 (86)	218 (14)	Ref	Ref
Contact with TB patient					
Yes	18 (1)	15 (83)	3 (17)	1.14 [0.40, 3.24]	
No	1530 (99)	1307 (85)	223 (15)	Ref.	
HIV positive					
Yes	123 (8)	83 (68)	40 (33)	**2.49 [1.87, 3.33]**	**2.72 [1.99, 3.72]**
No	1425 (92)	1239 (87)	186 (13)	Ref.	Ref.
Alcohol dependency					
Yes	41 (3)	24 (59)	17 (41)	**2.99 [2.04, 4.39]**	**2.58 [1.83, 3.62]**
No	1507 (97)	1298 (86)	209 (14)	Ref.	Ref.
Drug dependency					
Yes	8 (0.5)	6 (75)	2 (25)	1.72 [0.51, 5.74]	
No	1540 (99.5)	1316 (85)	224 (15)	Ref.	
Incarceration ≤2 years					
Yes	3 (0.2)	2 (67)	1 (33)	2.29 [0.46, 11.39]	
No	1545 (99.8)	1320 (85)	225 (15)	Ref.	
Diabetes					
Yes	97 (6)	78 (80)	19 (20)	1.37 [0.90, 2.09]	
No	1451 (94)	1244 (86)	207 (14)	Ref.	
Pregnant at diagnosis					
Yes	20 (1)	17 (85)	3 (15)	1.03 [0.36, 2.94]	
No	1528 (99)	1305 (85)	223 (15)	Ref.	
Postpartum <1 year					
Yes	48 (3)	46 (2)	2 (4)	0.28 [0.07, 1.09]	
No	1500 (97)	1276 (85)	224 (15)	Ref.	

cRR, crude relative risk; aRR, adjusted relative risk. Statistically significant values from Z-test of coefficients from Poisson regression are bolded. [1]Before the COVID-19 pandemic = January 1, 2018 to February 29, 2020. During the COVID-19 pandemic = March 1, 2020 to December 31, 2021. [2]From WHO categories and reporting framework for TB, 2013 revision (updated Dec 2014; Jan 2020). Unknown or missing responses are excluded from analysis. Bolded values are those with *p*-values <0.05.

unfavorable treatment outcomes compared to people without these disadvantages (28).

Study limitations

Due to the retrospective study design based on available data, we are limited to the information that is entered into the electronic database. There may also be errors in the entry of information into the database by employees of medical organizations, such as incorrect clinical and demographic data, and incomplete completion of medical records. Also, because data is collected by medical providers, our results are subject to self-report bias for certain variables with high stigma, such as drug and alcohol use. This bias likely results in underestimation of alcohol and drug use disorder in our study. Also, some variables had few responses and should therefore be interpreted with caution. Our study also did not assess any direct interactions between TB and COVID-19 because there was no information or inconsistently captured information about COVID-19 in the database. This information was incorporated into the database after the study period. Lastly, as an observational study limited to variables that could be found in medical records, we cannot control for all factors that could have contributed to differences in TB outcomes pre and during the COVID-19 pandemic.

Study results in context

Decrease in proportion of people being newly diagnosed with TB from routine screening including occupational health screening, point to the need for maintenance of these essential services during periods of public health emergencies. Service continuity plans that support health care facilities to minimize disruption and ultimately increase the resilience of health services during public health emergencies are needed in preparation for future healthcare crisis (29).

Although there was a decrease in successful TB treatment outcomes during the pandemic, several strategies were adopted during this time that may have mitigated further negative impacts. One strategy included improved triage of patients at primary care and hospital entry. All patients presenting with cough, chest complaints or fever were immediately separated, given respirators, or surgical masks if respirators were not available, and were tested for COVID-19, TB, pneumonia, and acute respiratory viral infections.

Another strategy included the adoption of polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) for rapid testing for differential diagnosis of different respiratory illnesses. During the beginning of the pandemic, Kazakhstan adopted a modified algorithm for rapid laboratory diagnosis of COVID-19 and TB. Rapid diagnosis using PCR-based methods made it possible to almost immediately diagnosis TB and initiate appropriate treatment.

Lastly, the country scaled up video observation therapy for TB. In video observed therapy, healthcare providers observe patients taking their anti-TB medications daily using live or recorded video. Studies elsewhere have found that adherence to treatment is higher among patients on video observed therapy than compared to in-person direct observed therapy (30). In 2018, Kazakhstan began to provide TB patients with smartphones to keep communication with their healthcare providers. Then in 2020, Kazakhstan launched a program to provide smartphones to all TB patients throughout the country (31). The use of video of the observed treatment (VOT) therapy in Kazakhstan allowed clinical staff to continue TB treatment in outpatient settings without interruption during the COVID-19 pandemic. The use of digital technologies during the COVID-19 pandemic also made it possible for providers to maintain communication with patients: conduct online consultation, speak with patients by phone, via telemedicine and mobile messaging.

Conclusion

The COVID-19 pandemic was associated with unfavorable treatment outcomes for people newly diagnosed with drug-sensitive TB in Almaty, Kazakhstan. People with comorbidities (HIV or alcohol use disorder) and those experiencing homelessness were at increased risk of unfavorable outcomes. Detection through routine screening was reduced and the case fatality rate among people on TB treatment was increased during the pandemic. Results point to the need for maintaining routine TB screening and continuity of care for people on TB treatment, especially people at the highest risk of unfavorable outcomes, during times of healthcare service disruptions due to public health emergencies like COVID-19.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The dataset for the study is owned by the government of Kazakhstan. Official requests for the data can be made on request to the government of Kazakhstan. Requests to access these datasets should be directed to gabdullina.malika@gmail.com.

Ethics statement

Ethical approval of the study was received from the local ethical commission of the NAO Kazakh National Medical University named after N.N. S.D. Asfendiyarov, Kazakhstan. This activity was reviewed by the CDC and was conducted consistently with applicable United States federal law and CDC policy. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because information was pulled retrospectively from medical records for programmatic purposes.

Author contributions

MG, RH, and DN contributed to the study design and data analysis. MG, GA, and DN contributed to the design of the study methods. MG and PD organized the data collection. MG, RH, EM, and DN contributed to the interpretation of the data and results of the study and supported with drafting the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention.

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EDITED BY
Antonio Sarría-Santamera,
Nazarbayev University, Kazakhstan

REVIEWED BY
Arnur Gusmanov,
Nazarbayev University, Kazakhstan
Sevil Alkan,
Çanakkale Onsekiz Mart University, Türkiye

*CORRESPONDENCE
Dilyara Nabirova
✉ hny5@cdc.gov

†These authors have contributed equally to this work

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Therapies for people hospitalized with COVID-19 and alignment with national clinical guidelines in a large hospital, Almaty, Kazakhstan, 2020–2021

Saya Gazezova[1,2†], Dilyara Nabirova[1,3,4*†], Ariana Detmar[5], Manar Smagul[1,2], Lena Kasabekova[1,2], Sanam Zikriyarova[1] and Roberta Horth[1,3]

[1]Central Asia Field Epidemiology Training Program, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan, [2]Scientific and Practical Center for Sanitary and Epidemiological Expertise and Monitoring, Almaty, Kazakhstan, [3]Division of Global Health Protection in Central Asia, United States Centers for Disease Control and Prevention, Almaty, Kazakhstan, [4]Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland, [5]Division of Global Health Protection, United States Centers for Disease Control and Prevention, Atlanta, GA, United States

Background: Clinical practice guidelines were continually changing during the COVID-19 pandemic to reflect the best available evidence for a novel virus. In Kazakhstan, the national clinical guidelines for COVID-19 patient care were regularly modified and it was not known if and to what extent these guidelines were being followed in practice.

Methods: We conducted a sub-analysis of data collected from an observational study among people hospitalized with COVID-19 in a large infectious disease hospital in Almaty in four cross-sections of increased COVID-19 incidence: T1 (1 June–30 August 2020); T2 (1 October–31 December 2020); T3 (1 April–31 May 2021); and T4 (1 July–26 October 2021). Modifications to the national COVID-19 treatment guidelines were identified and clinical data were abstracted from electronic medical records. We assessed frequency of antibiotic, glucocorticoid, anticoagulant, and antiviral administered in each period and determined if these aligned with national clinical guidelines. We used multivariable logistic regression to compare practices across periods.

Results: Six modifications were made to national COVID-19 treatment guidelines during this study. Of 1,146 people hospitalized with COVID-19, 14% were in T1, 14% in T2, 22% in T3, and 50% in T4. Anticoagulant treatment was administered to 87% (range: 56%–95%), antibiotic treatment to 60% (range: 58%–64%), glucocorticoid to 55% (range: 43%–64%) and antiviral therapy 15% (range: 7%–22%). Majority of treatments were not aligned with national guidelines, including 98% of anticoagulant use, 95% of antibiotic use, 56% of glucocorticoid use, and 56% of antiviral use. There were no significant changes in practice following changes in guidelines for antibiotic use (64% in T1 to 58% in T2, $p = 0.30$). There was significant increase in use of anticoagulant (84% in T2 vs. 95% in T3, $p < 0.01$), glucocorticoid (43% in T2 vs. 64% in T3, $p < 0.01$), and antiviral treatment (7% in T3 vs. 15% in T4, $p < 0.01$) after guidelines updates.

Conclusion: The majority of treatments administered to people hospitalized with COVID-19 in four periods of high incidence in Almaty were not aligned with updated clinical guidelines. Antibiotic misuse was markedly high throughout. Increased awareness and training on clinical practice guidelines as updates are released may help improve adoption of evidence-based practices.

KEYWORDS

COVID-19, coronavirus infection, clinical guidance, Kazakhstan, antibiotic use

Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic had a large impact on human health which strained healthcare systems around the world. As of 27 July 2023, over 768 million confirmed COVID-19 case-patients and 6.9 million deaths were reported globally (1). In response to an ever-changing evidence base and understanding of COVID-19 epidemiology, countries and health organizations across the world have had to create and frequently adapt hundreds clinical practice guidelines for prompt and effective COVID-19 care (2–8). The World Health Organization regularly updated their guidance for COVID-19 clinical practice to reflect the most recent science (9). However, national guidelines often do not change rapidly enough to reflect the latest scientific evidence (10). Also, practitioners may be slow to learn about changes in clinical guidelines and adopt these in practice. A study in the Netherlands found that healthcare providers follow clinical practice guidelines in only about 67% of time (11).

In Kazakhstan, 1.5 million COVID-19 cases and 19,072 deaths were reported as of 27 July 2023 (12). The country was adapting to changing pandemic with over 2,000 public health decisions and 83 resolutions of the Chief State Sanitary Doctor on sanitary, preventive, and anti-epidemic measures developed. Sixteen modular hospitals dedicated solely to COVID-19 were built in 12 out of 17 oblasts and 3 cities with highest COVID-19 incidence. Additionally, three infectious diseases hospitals were renovated for hospitalization of confirmed and probable COVID-19 cases, and over 63 outpatient healthcare facilities were put into operation to provide ambulatory care for COVID-19 patients (13). Over 3,054 mobile teams provided medical care at home for COVID-19 patients. COVID-19 treatment in the country is provided to patients free of charge both in hospitals and in outpatient facilities. The national clinical management guidance for diagnosis and treatment of COVID-19 was updated 15 times after first release in February 2020 until July 2023 (14). Adoption of these recommendations by clinicians has never been investigated in Kazakhstan.

Timely adoption clinical guideline updates during a pandemic response including of the most up-to-date clinical recommendations published in guidelines are essential to reduce morbidity and mortality in patients with COVID-19. Understanding if and to what extent best practices for patient care were adopted by clinicians is essential as we enter the recovery phase of the pandemic response and prepare lessons learned for future disease threats. The purpose of this study is to describe clinical management practices of clinicians treating hospitalized COVID-19 patients in Almaty, Kazakhstan and to assess these treatments with respect to the changing national clinical guidance during the pandemic.

Methods

Study design

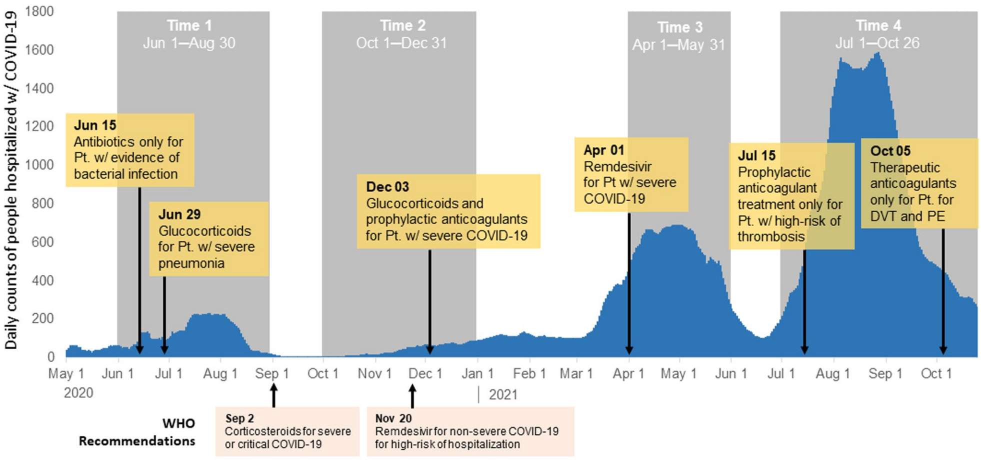
Our study is a secondary analysis of data from an observational study of people 18 years or older hospitalized with COVID-19 in an adult infectious disease hospital in Almaty in four time periods of increased COVID-19 incidence: T1 (1 June–30 August 2020); T2 (1 October–31 December 2020); T3 (1 April–31 May 2021); and T4 (1 July–26 October 2021; Figure 1). The periods were selected during four waves where daily COVID-19 cases were high at a national level.

Study setting

Almaty is the largest city in Kazakhstan with 1.3 million adults. COVID-19 treatment in the country is provided to patients free of charge both in hospitals and in outpatient facilities. The infectious disease hospital where we conducted the study is a specialized Almaty City facility for treating various infectious diseases, including COVID-19 in adults 18 years or older. During the COVID-19 pandemic this was the primary tertiary referral public hospital for caring for COVID-19 patients. It had 3 campuses dispersed geographically in different districts of the city to accommodate high volume of care for people with COVID-19.

Participant selection

Study participants were selected using systematic sampling where every 14th person admitted was selected from the 17,400 people hospitalized with COVID-19 in infectious disease hospital in the four periods of the study. This population was divided into 4 waves reported in Kazakhstan during the study period. The number of adults hospitalized with COVID-19 in the each of the four waves was 2517, 2360, 3779, and 8744, respectively. We used sampling proportional to size for each wave. Assuming 17400 population size and 95% confidence level, sample size of 1146 would be sufficient to have a margin of error of 0.028 or 2.8% with an expected mortality rate was 0.5 (conservative estimate) (1).



Pt. = patients; DVT = Deep vein thrombosis; PE = Pulmonary embolism

FIGURE 1
Modifications to the national clinical protocol for diagnosis and treatment of COVID-19 and histogram of COVID-19 cases in Almaty, Kazakhstan, 2020–2021.

Key definitions

A COVID-19 case was defined using national case definition from this period.

- Confirmed COVID-19 case was defined as people with laboratory confirmation of COVID-19 by PCR, regardless of clinical signs and symptoms.
- Probable cases were defined as patients lacking confirmatory laboratory evidence for SARS-CoV-2, with typical chest imaging examination findings indicative of COVID-19 that met any of the following: (1) received treatment at a medical facility within the past 14 days where a case of COVID-19 was reported, (2) worked in health care settings, including inpatient and outpatient settings within the 14 days prior to the onset of symptoms, (3) had any acute respiratory illness (ARI) with a history of exposure to a confirmed or probable case of COVID-19 within 14 days prior to onset of symptoms, (4) had any acute respiratory infection (ARI) and pneumonia of unspecified etiology, in addition to three or more of the following symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, runny nose, shortness of breath, anorexia/nausea/vomiting, diarrhea, change in mental status.

Severe COVID-19 was defined in medical records using the Ministry of Health (14, 15) as follows:

1) Signs of pneumonia (fever, cough, shortness of breath), plus

- Pulmonary infiltrates on chest x-ray or computer tomography imaging.
- Respiratory rate ≥ 30 breaths per minute,
- Acute respiratory distress syndrome or SpO2 < 90% on room air requiring:
    - o Admission to intensive care unit and
    - o Oxygen supplementation and mechanical ventilation (16).
- Other signs of severe COVID-19 included thromboembolism, sepsis and septic shock and/or
- Multi-organ failure including acute kidney injury, cardiac injury and encephalopathy (17).

Data sources

Clinical data that is stored in unstructured format as notes in patient medical charts such as dates of admission, demographic variables, comorbidities, ICD codes (for COVID-19 diagnosis), symptoms and symptom onset, laboratory testing, and therapies and medications administered were abstracted from hospital records by trained Field Epidemiology Training Program residents and epidemiologists. Data was abstracted in July-August 2022, and data validation and cross-checking was performed. Missing data was searched for in patient medical charts.

Treatment compliance with clinical guidelines was determined for each treatment type for each hospital record. Modifications to national clinical practice guidelines, referred to as guidelines hereafter, for the diagnosis and treatment of COVID-19 during the four time periods were recorded and categorized by the following treatments anticoagulants, antivirals, glucocorticoids, and antibiotics, referred to as treatment hereafter (Supplementary Table 1). For each patient who received any of these four treatments in the time periods after guidelines had been added for that treatment, we determined whether or not patients had met the criteria for receiving the specific treatment. Alignment with guidance was defined by treatment type as:

* Antibiotic treatment only for patients with evidence of bacterial infection.
* Glucocorticoids treatment only for patients with severe COVID-19.
* Antiviral treatment only for patients with severe COVID-19 or risk factors for severe COVID-19 based on age and comorbid conditions.

* Anticoagulant treatment prophylactically only for patients with severe COVID-19 or therapeutically for patients with thrombosis or pulmonary embolism in T2 and T3. In T4, therapeutic treatment only for patients that had signs of thrombosis or pulmonary embolism.

Comorbidity was defined as having any of the following conditions: obesity, hypertension, diabetes mellitus, cardiovascular disease, chronic heart failure, chronic obstructive pulmonary disease, ischemic heart disease without coronary intervention, kidney disease, hypotension, acute heart failure, acute coronary syndrome, ischemic cardiomyopathy at the time of treatment with COVID-19, encephalopathy, acute kidney injury or acute renal failure.

Ethical considerations

Ethical approval of the study was received from the local Ethical Commission of the NAO Kazakh National Medical University named after S.D. Asfendiyarov, Kazakhstan [No. 6 (129), 05/25/2022]. This activity was reviewed by the CDC and was conducted consistently with applicable U.S. federal law and CDC policy.

Statistical analysis

Data cleaning and analysis were performed in R v.4.2.1. Standard summary statistics were used to describe characteristics of patients (sex, age, and comorbidities) and treatments during each of the four periods. To assess trends in proportion of treatment types administered across all periods, with time as a continuous variable, we used quasi-binomial logistic regression controlling for sex, age, comorbidity, severe COVID-19, and vaccination status. We also separately used Cochran-Armitage trend test to assess changes in proportion of treatments administered that were in alignment with national guidelines across T2 to T4 periods. Missing data was treated as a missing category rather than excluded from analysis. *P*-values of <0.05 are considered significant.

Results

There were six updates made to the national clinical management protocol for the diagnosis and treatment of COVID-19 were made during the study period (Figure 1; Supplementary Table 1). The first update occurred during T1 on 15 June 2020 and recommended use of antibiotics only for patients with secondary infection. During T1 a second update was made to recommend use of glucocorticoids for patients with severe pneumonia. The next update occurred in T2 (December 3, 2020) when glucocorticoids were recommended for all patients with severe COVID-19. This update also include recommendation for prophylactic dose anticoagulants (heparin-based) for all patients with severe COVID-19. In T3 on 1 April 2021, an update was made to recommend antiviral medications (Remdesivir) for patients with severe COVID-19 or those with risk factors for severe disease though there was limited availability of Remdesivir in Kazakhstan during this time. There were two changes that occurred in T4. On 15 July 2021, guidelines recommended prophylactic anticoagulant therapy only for hospitalized patients with COVID-19 with signs of thrombosis. Lastly, on 5 October 2021, therapeutic anticoagulant use was recommended for patients with COVID-19 with deep vein thrombosis or pulmonary embolism.

Our study included 1,146 people hospitalized during the four periods. Of these 59% (676) were female and mean age was 57 years old (range 18–96 years; Table 1). Half (51%) of patients were <60 years old, 26% were obese, 64% had a comorbidity, 34% had severe COVID-19, and 10% died. The distribution of patients across the four periods, T1 to T4 respectively, was 14% (165), 12% (141), 22% (256), and 51% (584), respectively. Across the periods, there was a significant ($p < 0.01$) increase in proportion of patients that were ≥60 years old, that had obesity, comorbidity, severe disease, and that died.

Frequency and trends in treatments

Of the four treatment types assessed, anticoagulant treatment was the most administered medication across the four waves with 87% (995) of patients receiving them (Table 2). There was an increasing trend ($p < 0.01$) in the proportion of participants that received anticoagulant treatment across the periods. Also, there was significant change in use of anticoagulant from T2 [when they were first recommended in guidelines to the next period T3 (84% vs. 95%, respectively, $p < 0.01$)].

Antibiotics were administered to 60% (686) (range: 58%–64% across the periods). Adjusted trend analysis shows increasing proportion of participants received antibiotics over time. There was no change in antibiotic use after the guideline update in T1 recommending their use only for secondary infections (64% in T1 to 58% in T2). Cephalosporin antibiotics were the most commonly administered antimicrobials across the 4 periods (78%, 64%, 71%, and 67%, respectively) followed by fluoroquinolones (36%, 32%, 32%, and 35%, respectively, $p < 0.01$).

Glucocorticoid were administered to 55% (626) of participants (range: 43%–56%). Glucocorticoid use increased to 64% in T3 from 43% in T2 when guidelines were updated recommending their use for persons hospitalized with severe COVID-19. The use of glucocorticoid significantly dropped to 56% ($p<0.01$) in T4 though there were no additional changes to guidance related to their use during this time. Lastly, 15% (174) of participants (range 7%–22%) were given antivirals (only during T3 did Remdesivir become available in country before T3 the primary antiviral used was lopinavir-ritonavir). Use of antivirals decreased ($p<0.01$) from 22% in T1 to 7% in T3, but significantly increased ($p<0.01$) to 15% in T4 following recommendations that had been made for their use during T3.

Treatment alignment with national guidance

Of the treatments administered, a large proportion were not aligned with national guidelines. Of the 784 patients who received anticoagulant treatment in T3 and T4 (after guidance had included information on anticoagulant use), it was not in alignment with guidance for the 98% of patients that received it (Table 3). Among the 582 patients who received antibiotic treatment in T2 to T4 (after guidance for antibiotic use had been published), 95% of patients who received it had no signs or diagnosis of bacterial infection. Of the 550 patients that received glucocorticoid in T2 to T4, 53% did not meet

TABLE 1 Characteristics of people hospitalized with COVID-19, Kazakhstan, 2020–2021.

Characteristics	Overall	T1	T2	T3	T4	*P***
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
Total *N* (%)	1,146 (100)	165 (14)	141 (12)	256 (22)	584 (51)	
Sex						
Male	676 (59)	89 (54)	81 (57)	152 (59)	354 (61)	0.12
Female	470 (41)	76 (46)	60 (43)	104 (41)	230 (39)	
Age category						
<60	585 (51)	104 (63)	89 (63)	120 (47)	272 (47)	<0.01
≥60	561 (49)	61 (37)	52 (37)	136 (53)	312 (53)	
Obese						
No	737 (64)	140 (85)	84 (60)	154 (60)	359 (62)	<0.01
Yes	303 (26)	19 (12)	13 (9)	73 (29)	198 (34)	
(Missing)	106 (9)	6 (4)	44 (31)	29 (11)	27 (5)	
Have comorbidities*						
No	411 (36)	82 (50)	71 (50)	99 (39)	159 (27)	<0.01
Yes	735 (64)	83 (50)	70 (50)	157 (61)	425 (73)	
Have severe COVID-19						
No	762 (67)	145 (88)	111 (79)	159 (62)	347 (59)	<0.01
Yes	384 (34)	20 (12)	30 (21)	97 (38)	237 (41)	
Vaccinated against COVID-19						
No	1,033 (90)	161 (98)	134 (95)	246 (96)	492 (84)	<0.01
Yes	109 (9)	0 (0)	0 (0)	7 (3)	92 (16)	
(Missing)	4 (0.3)	0 (0)	1 (0.7)	3 (1)	0 (0)	
Died						
No	1,033 (90)	156 (95)	135 (96)	232 (91)	510 (87)	<0.01
Yes	113 (10)	9 (5)	6 (4)	24 (9)	74 (13)	

T1 (1 June–30 August 2020); T2 (1 October–31 December 2020); T3 (1 April–31 May 2021); and T4 (1 July–26 October 2021). *Including immunocompromised, hypertension, diabetes, cardiovascular disease, congestive heart failure, kidney disease, asthma, obesity. **Wald-test from quasi-binomial logistic regression.

clinical guidelines criteria. Lastly, of the 104 patients who received antiviral treatment, 56%did not meet criteria. The exception of glucocorticoid, there was no increasing trend in alignment with national guidelines over time.

When stratifying treatment types by severe COVID-19 status (Figure 2), we found that proportion of patients receiving glucocorticoid and antibiotics was consistently higher among those with severe COVID-19 across the four time periods.

Discussion

This study aimed to evaluate the clinical management practices of people hospitalized with COVID-19 in Almaty, Kazakhstan, with respect to the changing national clinical guidance. The results revealed multiple modifications to the national clinical management protocol during the study period involving administration of antibiotic, glucocorticoid, anticoagulant, and antiviral treatments.

Updates to national guidance were published online and distributed to hospitals, some webinars were held on the updates. Although there was some evidence of change in treatment in the time immediately after a guidance update, clinical practice alignment with national guidelines was low across all treatment types. This finding is in contrast with other studies that have found that clinicians followed guidelines and treatment of hospitalized patients was generally responsive to changes in medical evidence and public policy over the course of the early phases of the pandemic (8, 11, 18).

Anticoagulants were the most frequently used treatment in our study. High use of anticoagulants observed in this study reflected the growing recognition of thrombotic complications associated with COVID-19 (19). Notably, half of participants were receiving anticoagulants in T1, even before they were added to national guidelines as a recommended practice for people who were hospitalized with severe COVID-19 in guidelines. Although WHO has never included anticoagulant use in COVID-19 treatment guidelines, several clinical trials had evidence for its use during the early stages of the pandemic. Once added to guidelines proportion of patients receiving anticoagulant treatments increased, but many of these patients did not have a diagnosis of severe COVID-19. nor did they have pulmonary embolism (PE) or deep vein thrombosis (DVT). The high rates of anticoagulant use outside of

TABLE 2 Treatments administered to people hospitalized with COVID-19, Kazakhstan, 2020–2021.

Treatments administered	Overall	T1	T2		T3		T4		Crude	Adjusted
	N (%)	*n* (%)	*n* (%)	*P**	*n* (%)	*P**	*n* (%)	*P**	*P***	*P****
Anticoagulant treatment				**<0.01**		**<0.01**		0.11	**<0.01**	**<0.01**
Yes	995 (87)	93 (56)	118 (84)		243 (95)		541 (92)			
No	152 (13)	72 (44)	23 (16)		13 (5)		43 (7)			
Antibiotic treatment				0.30		0.834		0.07	0.28	**<0.01**
Yes	686 (60)	104 (64)	82 (58)		162 (63)		338 (58)			
No	461 (40)	61 (37)	59 (42)		94 (37)		246 (42)			
Glucocorticoid treatment				0.54		**<0.01**		**<0.01**	**<0.01**	0.66
Yes	626 (55)	76 (46)	61 (43)		165 (64)		324 (56)			
No	521 (45)	89 (54)	80 (57)		91 (36)		260 (45)			
Antiviral treatment				**<0.01**		**0.05**		**<0.01**	**<0.01**	**<0.01**
Yes	174 (15)	53 (22)	17 (12)		17 (7)		87 (15)			
No	973 (85)	112 (68)	124 (88)		239 (93)		497 (85)			

T1 (1 June–30 August 2020); T2 (1 October–31 December 2020); T3 (1 April–31 May 2021); and T4 (1 July–26 October 2021). Grayed boxes represent changes made to national clinical practice guidelines in that period; bolded represent *p*-values < 0.05. *Wald-test from generalized linear model adjusting for sex, age, comorbidity, severe COVID-19 and vaccination status comparing current to previous time period. **Wald-test from quasi-binomial logistic regression with no covariables to assess trend across all periods. ***Wald-test from quasi-binomial logistic regression adjusting for sex, age, comorbidity, severe COVID-19 and vaccination status to assess trend across all periods.

TABLE 3 Alignment of treatments administered with national clinical guidelines among people hospitalized with COVID-19, Almaty, Kazakhstan, 2020–2021.

Treatments administered in alignment * with national guidelines	Overall**	T2	T3	T4	*P* ***
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Anticoagulant (*n* = 784)					0.68
Aligned	17 (2)	NA	4 (2)	13 (2)	
Not	767 (98)	NA	239 (98)	528 (98)	
Antibiotic (*n* = 582)					0.25
Aligned	28 (5)	6 (7)	8 (5)	14 (4)	
Not	554 (95)	76 (93)	154 (95)	324 (96)	
Glucocorticoid (*n* = 550)					<0.01
Aligned	260 (47)	17 (28)	80 (49)	163 (50)	
Not	290 (53)	44 (72)	85 (52)	161 (50)	
Antiviral (*n* = 104)					
Aligned	46 (44)	NA	8 (47)	38 (44)	0.80
Not	58 (56)	NA	9 (53)	49 (56)	

T1 (1 June–30 August 2020); T2 (1 October–31 December 2020); T3 (1 April–31 May 2021); and T4 (1 July–26 October 2021). NA, treatment not specified in national guidelines. *Cochran-Armitage trend test. *Alignment refers to having received the treatment and meeting criteria as per guidelines and not aligned means having received the treatment but not meeting criteria as per guidelines. **The denominators are patients who received treatment after guidelines were developed. ***Cochran-Armitage trend test.

recommendations are concerning, as thromboprophylaxis are not without risk, and can result in life-threatening bleeding for patients who do not need it (20).

Over half of hospitalized patients in our study were given antibiotics with cephalosporin antibiotics being the most frequently prescribed. These rates are high but below the global estimate of 75% of COVID-19 patients having received antibiotic prescriptions (21). We found that of the antibiotics administered, 95% were used without evidence of secondary infection. High rates of antibiotic misuse raise concerns about the appropriateness of antibiotic use in COVID-19 management. This finding is consistent with other studies highlighting challenges in antimicrobial stewardship during the pandemic (22). Overuse of antibiotics can contribute to antimicrobial resistance, a global public health concern (23, 24). Efforts should be made to ensure judicious use of antibiotics and adherence to evidence-based guidelines.

Glucocorticoids were first added to the national guidelines in end of June 2020. Our study showed an increase in use of glucocorticoids

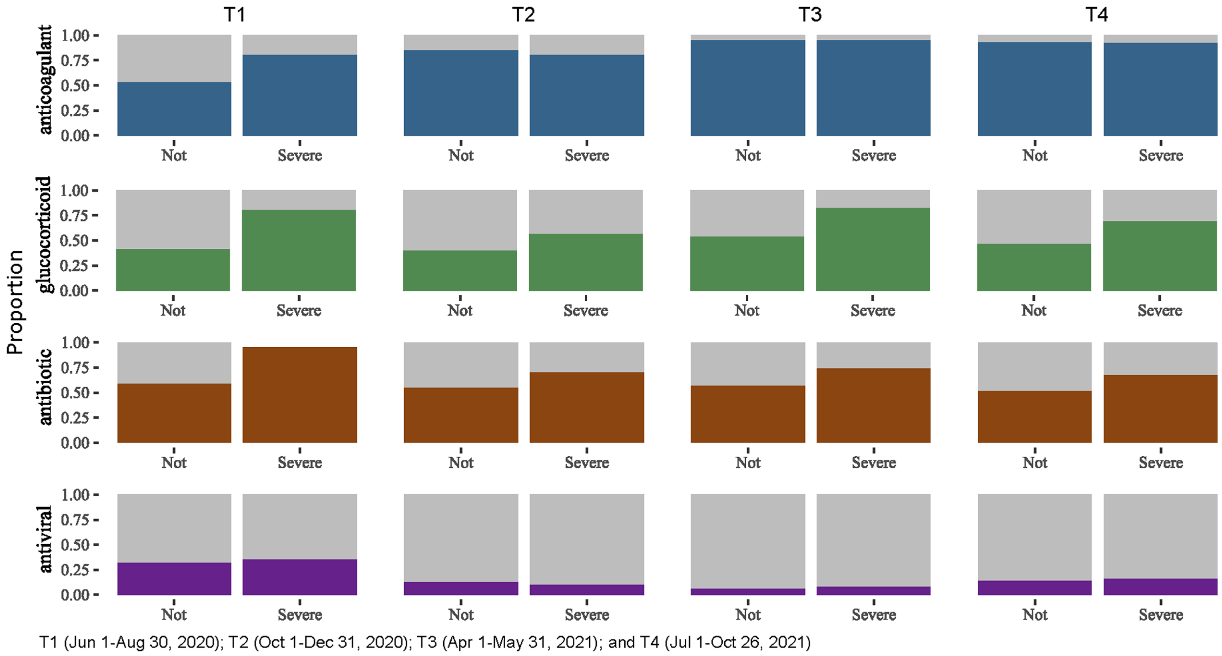


FIGURE 2
Treatments administered for people hospitalized with severe and non-severe COVID-19, Almaty, Kazakhstan, 2020–2021.

and improvement in alignment with guideline updates over period. This finding is noteworthy, as it indicates a potential learning curve and increasing confidence among clinicians in the use of glucocorticoids as a treatment option for COVID-19. This was ahead of WHO guidance which first added it in September 2020; however, clinical trials had demonstrated utility of corticosteroids before WHO guidance (25). Findings from studies at the time demonstrated the efficacy of dexamethasone in reducing mortality among severely ill COVID-19 patients (25, 26). It underscores the importance of updated evidence-based guidelines to guide clinical practice and improve adherence to guidance.

The low frequencies of antiviral treatment observed in this study align with findings from the Solidarity Trial, which failed to demonstrate significant benefits of specific antiviral therapies in COVID-19 treatment. Studies showed limited effectiveness of drugs like remdesivir and lopinavir/ritonavir in reducing mortality or improving clinical outcomes. Moreover, during T1 to T3 of the study there were no COVID-19 specific antivirals available in country, and in T4 Remdesivir was approved experimentally for COVID-19 with very limited availability in country. The findings from this study reflect clinician cautious use of antivirals in COVID-19 treatment and the limited availability of the drug for treatment.

Interpretation of results are subject to some important limitations. Firstly, the study was conducted in a specific hospital system in Almaty, Kazakhstan, which may limit the generalizability of the findings to other regions or healthcare settings. It is also not reflective of all hospitals in Almaty, where 7 multifunctional city hospitals provided treatment for patients with suspected COVID-19, but these were not included in the study. Secondly the study relies on secondary data routinely input by providers in patient electronic medical records. Data entry errors could have occurred especially in moments of high patient load in healthcare facilities. Omission of information would be the most common error in these scenarios. This would have resulted in an underestimate of treatments. It could also result in overestimation of non-adoption of treatment if patients were not classified correctly as having severe COVID-19. Also, the four time periods of our study do not directly align with dates when changes to guidelines were made, and this can attenuate differences between one period and the next. Lastly, we did not interview providers to assess their level of knowledge of guidelines and their own perceived uptake of COVID-19 treatments.

In conclusion, this study highlights the need for improved adoption of evolving clinical practice guidance for people hospitalized with COVID-19 in Almaty, Kazakhstan. Efforts are needed to enhance communication, education, and support for clinicians to ensure real-time and consistent use of evidence-based treatments, promoting appropriate use of medications, and optimizing patient outcomes as part of any pandemic response.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: data are from electronic medical records and restricted due to patient confidentiality regulations. A limited deidentified dataset can be obtained from corresponding author. Requests to access these datasets should be directed to SG, sayagazezova@gmail.com.

Ethics statement

Ethical approval of the study was received from the local Ethical Commission of the NAO Kazakh National Medical University named after N.N. S.D. Asfendiyarov, Kazakhstan [No. 6 (129), 05/25/2022]. This activity was reviewed by the CDC and was conducted consistently with applicable U.S. federal law and CDC policy. See 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3,501 et seq.

Author contributions

DN, RH, and MS contributed to conception of the study. DN, RH, and SG organized the data collection and analysis. SG, DN, SZ, and LK contributed design, methods of the study, and interpretation of the data. RH and MS contributed to interpretation of the study findings. SG wrote the first draft of the manuscript. RH, DN, LK, and SZ wrote sections of the manuscript. RH, AD, and DN reviewed the manuscript at all stages. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the U. S. Centers for Disease Control and Prevention.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1248959/full#supplementary-material

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EDITED BY
Yuliya Semenova,
Nazarbayev University, Kazakhstan

REVIEWED BY
Laura Kassym,
Astana Medical University, Kazakhstan
Assiya Kussainova,
Semey State Medical University, Kazakhstan

*CORRESPONDENCE
Anastasia Peshkovskaya
✉ peshkovskaya@gmail.com

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Health behavior in Russia during the COVID-19 pandemic

Anastasia Peshkovskaya[1,2]* and Stanislav Galkin[1,2]

[1]Tomsk State University, Tomsk, Russia, [2]Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia

In this article, we report results from a nationwide survey on pandemic-related health behavior in Russia. A total of 2,771 respondents aged 18 to 82 were interviewed between January 21 and March 3, 2021. The survey included questions on perceived vulnerability to coronavirus, prevention-related health behavior, readiness for vaccination, and general awareness about COVID-19. Descriptive data showed that 21.2% of respondents reported high vulnerability to the coronavirus, and 25% expressed fear. Moreover, 38.7% of the surveyed individuals reported low trust in vaccination efficacy, and 57.5% were unwilling to take a vaccine, which was much higher than the official data. Based on the evidence obtained, four types of health behavior during the pandemic were constructed. Rational (29.3%) and denying (28.6%) behaviors prevailed in men, while women were found to more likely behave with a vaccine-hesitant demeanor (35.7%). Educational background affected the proportion of respondents with the denying type of health behavior, who were also of younger age. The rational behavioral type was found to be more common among respondents aged above 50 years and prevailed as well among individuals with university degrees. The middle-aged population of Russia was highly compliant with prevention-related health practices; however, vaccine hesitancy was also high among them. Furthermore, health behaviors varied significantly across the Federal Districts of Russia. We are convinced that our results contribute to existing public health practices and may help improve communication campaigns to cause positive health behaviors.

KEYWORDS

pandemic, health behavior, COVID-19, prevention, perceived vulnerability, vaccine hesitancy, conspiracy, public health policy

1. Introduction

The spread of COVID-19 varied significantly over time. The current coronavirus variant of EG.5 was evaluated by the World Health Organization as having low public health risk at the global level (1); however, it has shown increased prevalence, growth advantage, and immune escape properties. As herd immunity rates vary across world regions, epidemiological risks still exist.

Since the first outbreak of COVID-19, individual demographic and socioeconomic characteristics, perceptions of illness, and preventive health behaviors were found to be critical for disease transmission (2–6). Trust in vaccination and, particularly, vaccine hesitancy are also considered highly important (7, 8). Knowledge of relationships between these parameters is fundamental to providing a critical understanding of how experts should best respond to public health challenges. Due to the vaccine skepticism and slower COVID-19 vaccination campaign in Russia reported in the last couple of years compared to most other European countries (9), public policy should consider the dimensions of health behavior to increase disease prevention and vaccination trust.

The aim of this study was to gain an understanding of pandemic-related health behavior in the population of Russia. A range of factors, including basic demographics, educational background, preventive practices, vaccine trust, and conspiracy beliefs, was investigated to plot health behavior determinants during the pandemic.

2. Methods

The survey was conducted from 21 January to 3 March 2021 during a period of the second peak incidence of the coronavirus in Russia that had started in late December 2020 when 29,350 infections were registered per day (10). Due to anti-covid restrictions, the study was implemented online by sharing a direct link to an electronic form on social networks. The survey included questions on perceived vulnerability to coronavirus infection, prevention-related behavioral practices (washing hands, wearing a face mask, physical distancing in public places, etc.), COVID-19 vaccination attitude, and coronavirus awareness (general knowledge and conspiracy beliefs) (see Supplementary Table 1).

The survey sample included the full response data of 2,771 participants (66.9% female) aged 16 to 82 (mean age 25.6 ± 10.8 years), who were residents of the Central Federal District of Russia (40%), Northwestern Federal District (10.4%), Volga Federal District (27.3%), Southern Federal District (10.6%), and Siberian Federal District (6.6%). In all, 5.1% of the respondents preferred not to disclose their place of residence, and 729 respondents (26.3%) reported a history of COVID-19 disease. Most of them reported a mild form of the disease (87.8%), while 12.2% indicated a history of severe COVID-19. Detailed participants' characteristics are presented in Supplementary Table 2.

Participants' degree of compliance with prevention-related behavioral practices was assessed via Question 8. The answer options consisted of a five-point Likert scale, ranging from "Never" to "Always." "Never" and "Rarely" responses to any of the Q8 subquestions were encoded as low compliance with preventive practices. Attitudes toward vaccination were investigated via Question 9 and Question 10 based on a three-point Likert scale with answer options ranging from "Disagree" to "Agree." The response "Disagree" to Q9 or Q10 was weighed as low trust in the COVID-19 vaccine. To allocate complex behavioral types during the pandemic, the data of low vs. high compliance with preventive practices and low vs. high trust to vaccination were aggregated and analyzed.

R software was used to process the data. Measures of frequency and chi-square (χ^2) statistic were applied.

The study was approved by the Ethics Council of Tomsk State University (Approval 101–2020 on 15 December, 2020). All the respondents signed an electronic informed consent form.

3. Results

3.1. Perceived vulnerability to COVID-19, prevention behavior, and vaccination hesitancy

To investigate perceived vulnerability to coronavirus infection, preventive behavior, COVID-19 vaccination attitude, and coronavirus awareness during the second wave of the pandemic in Russia, data on the survey participants' responses were analyzed. At first, we found that 25% of all the respondents were afraid of catching COVID-19, having answered "A lot" (5.7%) and "Quite afraid" (19.3%) to the question "Are you afraid of catching COVID-19?." A total of 21.2% of the respondents perceived themselves as vulnerable to the infection by agreeing with the answers "Extremely" (4.2%) and "Rather highly" (17%) to the question "How vulnerable are you to COVID-19?." In addition, 29.8% of the survey participants reported a relatively high probability of future infection, having answered "Very high" (11.1%) and "Quite high" (18.7%) to the question "What are your chances of catching COVID-19?" Detailed response data are presented in Figure 1A.

Regarding preventive practices, particularly COVID-19 prevention, the majority of the respondents always or at least often followed existing recommendations. They reported washing hands with soap after visiting public places (90.1% in total), wearing a face mask in public places (89.8%), avoiding touching their eyes, nose, and mouth with unwashed hands (62.3%), using hand sanitizers (58.6%), and physical distancing in public places (55.6%) (Figure 1B).

Attitudes toward the COVID-19 vaccine and readiness to vaccinate were of particular interest in this January–March 2021 survey. The survey statement "I will agree to take the COVID-19 vaccine" received 57.7% negative, 19.8% positive, and 22.5% "Do not know" responses. In addition, 38.7% of the respondents disagreed that "a vaccine can help control the spread of COVID-19," 31.6% said they did not know, and 29.7% of the respondents agreed. The statement "COVID-19 vaccination should be mandatory for some groups" was supported by 26.1% of the respondents, while 49.9% disagreed. Detailed response data are presented in Figure 2A.

Data on coronavirus awareness showed that only 24.6% of the respondents believed coronavirus was of a natural origin. Meanwhile, 9.5% believed that "COVID-19 was invented in a laboratory with a purpose," and 49.1% of the survey participants considered a laboratory origin of COVID-19 to be possible or found it difficult to answer (Figure 2B).

Based on the data obtained and considering the dimensions of (1) compliance with prevention-related behavioral practices, low vs. high, (2) trust in a COVID-19 vaccine, including readiness to vaccinate, low vs. high, four behavioral types were constructed for further analysis.

Type 1 "Rational": A total of 753 respondents (27.2%), who reported high compliance with prevention-related behavioral practices and high trust in a COVID-19 vaccine;

Type 2 "Vaccine hesitant": A total of 892 respondents (32.2%), who reported high compliance with prevention-related behavioral practices but low trust in a COVID-19 vaccine;

Type 3 "Denying": A total of 762 respondents (27.5%), who reported low compliance with preventive practices and low trust in a COVID-19 vaccine;

Type 4 "Inconsistent": A total of 364 respondents (13.1%), who reported low compliance with preventive practices but high trust in a COVID-19 vaccine.

On the whole, almost one-third (27.2%) of the surveyed individuals behaved in accordance with recommendations on COVID-19 prevention and were ready to take a vaccine, and another third (27.5%) did not comply with recommendations and showed no trust in preventive practices and vaccination. Another third of the respondents (32.2%) expressed vaccine hesitancy, but they maintained preventive behavior, while 13.1% of the surveyed individuals reported

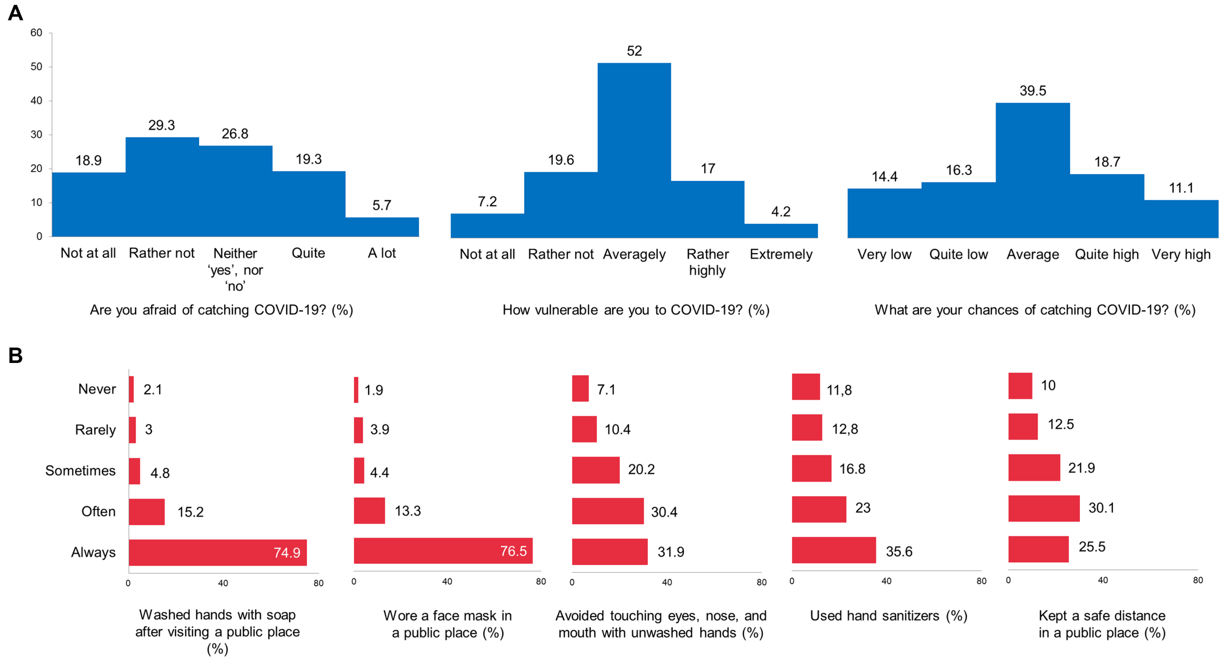

FIGURE 1
Perceived vulnerability to COVID-19 **(A)** and Compliance with prevention measures **(B)**, the data of the nationwide survey in Russia.

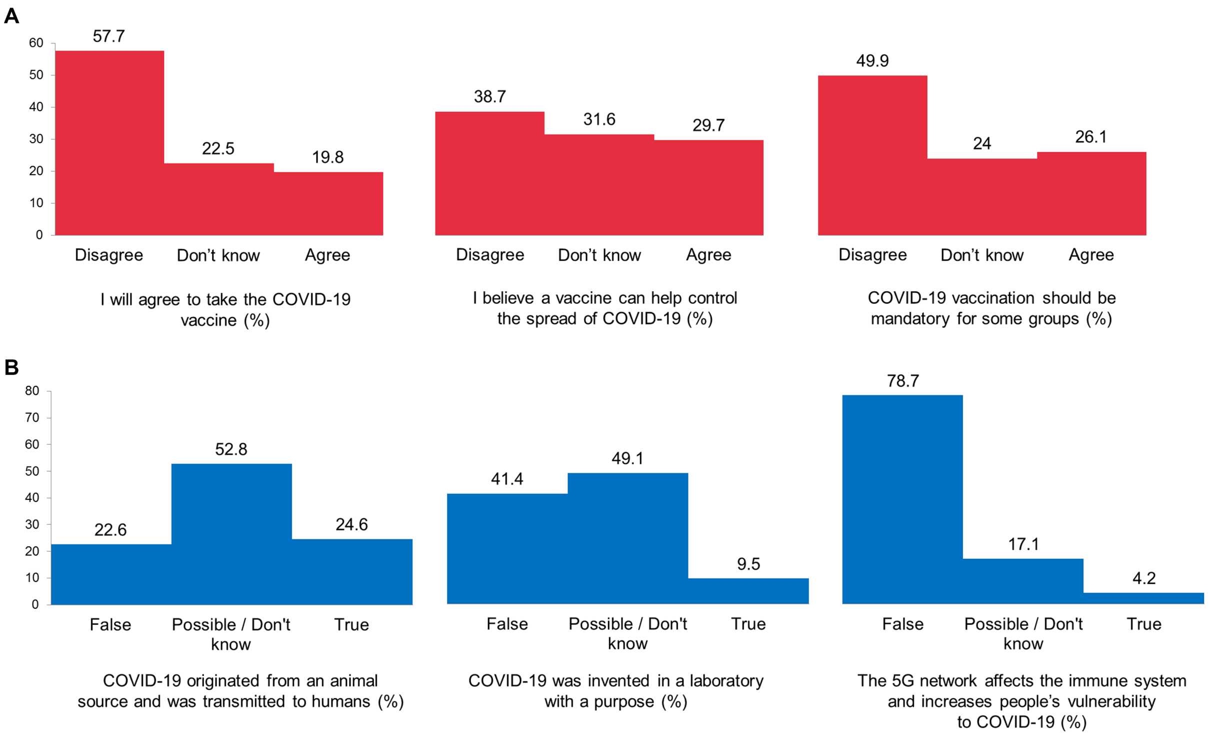

FIGURE 2
Attitudes towards COVID-19 vaccination **(A)** and COVID-19 conspiracy beliefs **(B)**, the data of the nationwide survey in Russia.

trust in a COVID-19 vaccine but not in COVID-19 preventive practices. Next, we analyzed the demographic differentiations of the behavioral types.

3.2. Behavioral types in depth: role of sex, age, education, and COVID-19 conspiracy beliefs

The respondents' behavioral-type distribution by sex showed that the major part of male respondents comprised "Rational" and "Denying" behavioral types (29.3 and 28.6%, respectively), while the female respondents were found to keep mostly "Vaccine-hesitant" behavior (35.7%), χ^2 (3, $N = 2{,}771) = 41.466$, $p < 0.001$. The data on distribution are provided in Table 1.

To investigate the age-specific distribution of the behavioral types, we grouped the respondents by their age. We considered age groups of under 20 years ($n = 921$), 20–29 ($n = 1{,}214$), 30–39 ($n = 278$), 40–49 ($n = 221$), 50–59 ($n = 86$), and 60 years and above ($n = 51$). The results showed that age proportions significantly differed by type, χ^2 (15, $N = 2{,}771) = 96.008$, $p < 0.001$. A weighty percentage of respondents under the age of 30 showed "Denying" and "Vaccine-hesitant" behavior (60.3 and 65.9% of individuals aged less than 30 years, respectively). They all reported low trust in a COVID-19 vaccine, and the younger they were, the lower compliance was with prevention-related behavioral practices. The age groups of 30–39 and 40–49 showed congruent results in prevention – the vast majority of these middle-aged individuals were highly compliant with preventive recommendations. However, they either reported trust in vaccines (rational type in 32.7 and 36.6% of middle-aged participants, respectively) or had low confidence in vaccination efficacy (vaccine-hesitant behavior in 31 and 28.5% of cases, respectively). At the same time, a significant part of the respondents of older ages (50–59 and 60 years and above) were found to have the "Rational" behavioral type. Most of them (60.5 and 43.1%, respectively) reported compliance with preventive practices and trust in vaccination. Table 1 summarizes the age-related data.

Since education is widely considered as a factor that influences perceptions of ongoing events and corresponding behavior, including social and health behavior (11–14), we analyzed the education-based distribution of the surveyed individuals among the behavioral types. The differences were significant by type, χ^2 (12, $N = 2{,}771) = 45.917$, $p < 0.001$, and showed that most of the respondents with incomplete secondary education (40%) comprised the "Denying" behavioral type. At the same time, individuals with secondary and vocational secondary education had "Denying" (30.6 and 33.3%) and "Vaccine-hesitant" (29.4 and 33.9%) health behaviors. The hesitant type was also registered in most of the respondents with incomplete higher education (33.9%), while "Rational" health behavior was found to prevail among individuals with higher education (33%). Detailed distribution data are available in Table 1.

Most respondents who believed in COVID-19 conspiracy theories showed "Denying" behavior (41.5%), whereas individuals with no reported conspiracy beliefs were inclined to "Vaccine-hesitant" (32%)

TABLE 1 Distributions of health behaviors by socio-demographic characteristics and conspiracy beliefs (% by line).

Variable	Rational	Vaccine Hesitant	Denying	Inconsistent
Sex, χ^2 (3, $N = 2{,}771) = 41.466$, $p < 0.001$				
Male	268 (29.3%)	229 (25%)	262 (28.6%)	157 (17.1%)
Female	485 (26.1%)	663 (35.7%)	500 (27%)	207 (11.2%)
Age, χ^2 (15, $N = 2{,}771) = 96.008$, $p < 0.001$				
under 20	225 (24.4%)	287 (31.2%)	292 (31.7%)	117 (12.7%)
20–29	282 (23.2%)	421 (34.7%)	347 (28.6%)	164 (13.5%)
30–39	91 (32.7%)	86 (31%)	59 (21.2%)	42 (15.1%)
40–49	81 (36.6%)	63 (28.5%)	49 (22.2%)	28 (12.7%)
50–59	52 (60.5%)	21 (24.4%)	6 (7%)	7 (8.1%)
60 and above	22 (43.1%)	14 (27.5%)	9 (17.6%)	6 (11.8%)
Education, χ^2 (12, $N = 2{,}771) = 45.917$, $p < 0.001$				
Higher education	309 (33%)	290 (31%)	206 (22%)	132 (14%)
Incomplete higher education	286 (23.9%)	406 (33.9%)	351 (29.4%)	153 (12.8%)
Vocational secondary education	35 (18.8%)	63 (33.9%)	62 (33.3%)	26 (14%)
Secondary education	116 (28.1%)	121 (29.4%)	126 (30.6%)	49 (11.9%)
Incomplete secondary education	7 (17.5%)	12 (30%)	16 (40%)	5 (12.5%)
Conspiracy beliefs, χ^2 (3, $N = 2{,}771) = 47.635$, $p < 0.001$				
Yes	44 (14.5%)	104 (34.2%)	126 (41.5%)	30 (9.8%)
No	709 (28.7%)	788 (32%)	636 (25.8%)	334 (13.5%)

and "Rational" (28.7%) behavioral types, χ^2 (3, $N = 2{,}771) = 47.635$, $p < 0.001$ (see Table 1).

3.3. Regions and health behavior: mapping general trends

Regional data on health behavior prevalence during the second wave of the pandemic in Russia showed that significant differences existed across Federal Districts, χ^2 (15, $N = 2{,}771) = 69.26$, $p < 0.001$ (Table 2). The vast majority of respondents who resided in the Central Federal District showed "Vaccine-hesitant" (36.6%) and "Rational" (30%) health behavior. Most participants from the Volga Federal District belonged to the "Denying" (34.2%) and "Vaccine-hesitant" (30.4%) behavioral types, while residents of the Siberian Federal District showed "Rational" health behavior more often (29.3%). Two of the largest respondents' groups from the Northwestern Federal District were found to behave according to the "Rational" (29%) and "Vaccine-hesitant" (28.7%) types. Finally, the surveyed individuals from the Southern Federal District were more differentiated and showed "Vaccine-hesitant" (29.6%), "Rational" (27.7%), and "Denying" behaviors (27.7%) during the reported period of the pandemic.

4. Discussion

Obviously, a key challenge for health authorities across the world is to encourage people to accept vaccines. The rates of vaccination skepticism we found in Russia were rather high. The majority of respondents (57.7%) in our study disagreed to take a COVID-19 vaccine, and 38.7% also disagreed that a vaccine can help control the spread of the coronavirus. Interestingly, nine months later, the available data from November 2021 reported by the Russian Public Opinion Research Center via a telephone-based survey methodology ($n = 1{,}600$) showed that only 32% of the surveyed participants expressed a negative attitude toward vaccination, only 4% did not want to take a vaccine, and 37% of respondents declared that they have already been vaccinated or found it difficult to answer the question (15). Such a gap in figures may be explained both by the difference in methodology, with possible communication-related self-report bias during the telephone interview, and by a positive dynamic in public opinions and vaccine acceptance by the later time period of November 2021. However, even a 32% share of those who perceived vaccination negatively is a risk factor for public health. Existing strategies should be improved to allow vaccination to be understood and accepted as a social practice.

Conspiracy theories about coronavirus and the pandemic are widespread around the world. For example, a survey conducted in the United States ($n = 2{,}023$) showed that more than 31% agreed that coronavirus was intentionally created and spread (16). The data obtained in our study showed that 49.1% of the respondents considered a laboratory origin of the coronavirus possible or found it difficult to answer, while 9.5% were convinced that laboratory invention of the coronavirus was true. As beliefs in specific conspiracy theories related to the coronavirus are considered among factors negatively affecting the public acceptance of COVID-19 vaccines (17), a high rate of vaccine skepticism registered in Russia may be at least partially explained by the misinformation effect of conspiracy speculations.

Based on the survey evidence on preventive practices and vaccine trust, we allocated four types of health behavior prevalent in Russia during the COVID-19 pandemic and followed their sex-, age-, and education-related specific distributions. The "Rational" and "Denying" behavioral types prevailed in 29.3 and 28.6% of the male subsample, while the female respondents were found to more likely behave in accordance with a vaccine-hesitant demeanor (35.7% of the subsample). This corresponds to the well-described gender differences in behavior (18–20) and the known demographic determinants of health (21, 22), which indicate the greater vulnerability of women to behavioral hesitancy, anxiety, and fear.

The highest rate of COVID-19 conspiracy beliefs (41.5%) was registered among the respondents with "Denying" health behavior, which corresponds, to a certain extent, to the opinions and behaviors interrelation model (23, 24).

Along with that, educational background was found to affect the proportions of respondents with "Rational" and "Denying" behavioral types by doubling the rate of the former from 17.5% among respondents with incomplete secondary education to 33% among individuals with university degrees and by decreasing the rate of the latter from 40 to 22%. "Denying" individuals were also younger (less than 30 years), while "Rational" were older (50 years and above), as older age was and still is a pandemic-related risk factor for heath. The middle-aged population of Russia (30–39 and 40–49 years of age) was highly compliant with prevention-related health practices; however, there were also high rates of vaccine-hesitant behavior among them. As the middle-aged population is most economically active, they should be considered for special targeting when planning a prevention campaign and vaccination promotion.

TABLE 2 Distributions of health behaviors by region (% by line), χ^2 (15, $N = 2{,}771) = 69.26$, $p < 0.001$.

Residence	Rational	Vaccine Hesitant	Denying	Inconsistent
Central Federal District	333 (30%)	406 (36.6%)	260 (23.4%)	110 (10%)
Northwestern Federal District	84 (29%)	83 (28.7%)	75 (26%)	47 (16.3%)
Volga Federal District	161 (21.3%)	230 (30.4%)	259 (34.2%)	107 (14.1%)
Southern Federal District	81 (27.7%)	87 (29.6%)	81 (27.7%)	44 (15%)
Siberian Federal District	53 (29.3%)	42 (23.2%)	47 (26%)	39 (21.5%)
Undisclosed	41 (28.9%)	44 (31%)	40 (28.1%)	17 (12%)

Despite the significant differences in health behaviors that we found across the Federal Districts of Russia, this study was not aimed to comprehensively address regional and cross-regional tendencies. Given the great variability of environmental factors, social capital, cultural health beliefs, and pandemic-related public health policies among the regional units within the Federal Districts, further research is needed to understand the dimensions of health behavior at a regional level.

As the national healthcare agenda is focused on pandemic-related somatic burden (25), existing comorbidities (26), and mental health risks (27), the evidence reported in our study will invigorate knowledge consolidation for a prompt response to potential infection outbreaks and future public health challenges.

5. Conclusion

Our findings contribute to the existing knowledge of health behavior and its determinants. Due to vaccine distrust among the Russian population and the country's slower vaccination campaign compared to most other European countries during the pandemic, the results we have reported may improve disease prevention and advance communication campaigns to cause positive health behaviors.

Data availability statement

The datasets presented in this article are not readily available because of ethical restrictions. Requests to access the datasets should be directed to AP, peshkovskaya@gmail.com.

Ethics statement

The studies involving humans were approved by the Ethics Council of Tomsk State University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AP: Conceptualization, Funding acquisition, Methodology, Validation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. SG: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1276291/full#supplementary-material

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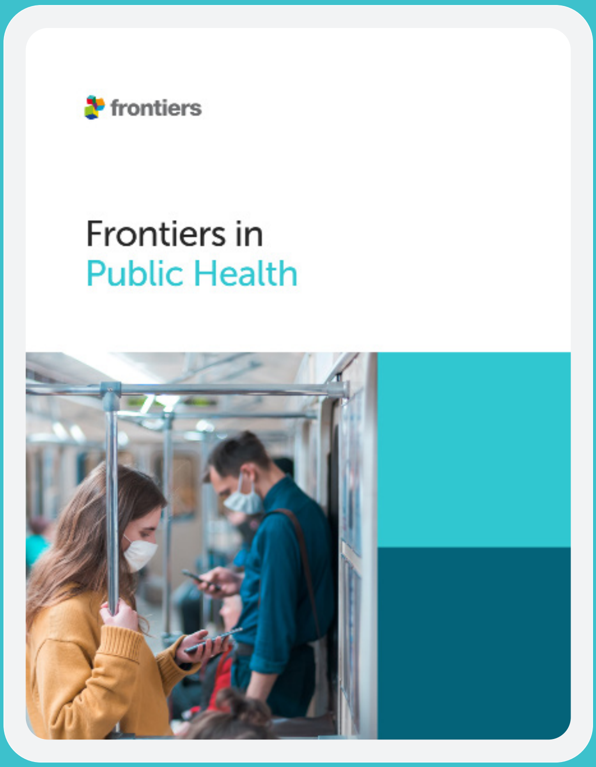

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