

Epidemiological Research Plan for the Years 2023–2033



Table of contents

Abbreviations	3
1. Introduction	5
2. Epidemiological research.....	6
2.1. Definition of epidemiological research	6
2.2. Epidemiological research standards	6
2.3. Epidemiological research in Poland.....	9
2.4. Principal obstacles to the progress of epidemiological research	12
2.4.1. Organisation and staffing	12
2.4.2. Financial aspect	13
2.4.3. Legal environment – access to data	14
2.5. SWOT analysis	15
3. Directions of development of Polish epidemiology	17
3.1. Principal health concerns of the Polish population	17
3.2. Health concerns caused by civilisational progress	18
3.2.1. Multimorbidity	18
3.2.2. Common nature of lifestyle disease risk factors	23
3.2.3. Respiratory diseases	23
3.2.4. Respiratory diseases – allergies in children	24
3.2.5. Addictions and mental health.....	25
3.2.6. Dementia.....	26
3.3. Epidemiological concerns: infectious diseases.....	27
3.3.1 The SARS-CoV-2 pandemic.....	27
3.3.2 Other emerging infectious diseases	29
3.4. The impact of environmental contaminants on human health	29
3.5. New risks to human health.....	31
4. Selected tools, technologies and practices in epidemiological research.....	32
4.1.1. Using innovative omic techniques in epidemiological research.....	32
4.1.2. The development and effective use of medical registries and BIG DATA.....	37
4.1.3. Internationalisation of epidemiological research	38
5. Strategic objectives of the epidemiological research support plan.....	40
5.1. Specific objectives of the Plan	40
6. Plan implementation and monitoring	46
7. References.....	48

Abbreviations

AIDS – Acquired Immunodeficiency Syndrome

AOP – Adverse Outcome Pathway

BPA – Bisphenol A

CMKP – Centre for Postgraduate Medical Education (Pol. *Centrum Medyczne Kształcenia Podyplomowego*)

COVID-19 – Coronavirus Disease 2019

ECAP – Study on the Epidemiology of Allergies in Poland (Pol. *Epidemiologia Chorób Alergicznych w Polsce*)

ECRHS – European Community Respiratory Health Survey

EID – Emerging Infectious Diseases

EZOP – Study on the Epidemiology of Mental Disorders and the Availability of Psychiatric Care (Pol. *Epidemiologia Zaburzeń Psychiatrycznych i Dostępność Psychiatrycznej Opieki Zdrowotnej*)

FeNO – Fraction of Exhaled Nitric Oxide

GBD – Global Burden of Disease

GIS – Chief Sanitary Inspectorate (Pol. *Główny Inspektorat Sanitarny*)

GUS-EHIS – Statistics Poland, European Health Interview Survey

GWAS – Genome-Wide Association Studies

HBSC – Health Behaviour in School-aged Children

IARC – International Agency for Research on Cancer

ICT – Information and Communication Technologies

IHME – The Institute for Health Metrics and Evaluation

IPCZD – Instytut „Pomnik – Centrum Zdrowia Dziecka”

ISAAC – International Study of Asthma and Allergies in Childhood

KBC – Kingston Allergy Birth Cohort

MIHE – Military Institute of Hygiene and Epidemiology (Pol. *Wojskowy Instytut Higieny i Epidemiologii*)

MZ – Polish Ministry of Health

NAMs – New Approach Methodologies

NatPol – Polish National Study on the Incidence of Risk Factors of Cardiovascular Diseases (Pol. *Ogólnopolskie Badanie Rozpowszechnienia Czynn timer Rzyka Chorób Układu Krążenia*)

NFZ – National Health Fund (Pol. *Narodowy Fundusz Zdrowia*)

NIPH NIH - NRI – National Institute of Public Health NIH - National Research Institute (Pol. *Narodowy Instytut Zdrowia Publicznego PZH – Państwowy Instytut Badawczy*)

NPZ – National Health Programme (Pol. *Narodowy Program Zdrowia*)

PFRON – The State Fund for Rehabilitation of Disabled People (Pol. *Państwowy Fundusz Rehabilitacji Osób Niepełnosprawnych*)

PIMS – Pediatric Inflammatory Multisystem Syndrome

COPD – chronic obstructive pulmonary disease

POZ – primary health care (Pol. *podstawowa opieka zdrowotna*)

PRS – Polygenic Risk Scores

PYLL – Potential Years of Life Lost

GDPR – General Data Protection Regulation

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

SNP – single-nucleotide polymorphism

SWOT – Strengths, Weaknesses, Opportunities, Threats

EU – European Union

UNICEF – United Nations Children’s Fund

USA – United States of America

WHO – World Health Organization

WOBASZ – Polish National Multicenter Study of Population Health (Pol. *Wieloośrodkowe Ogólnopolskie Badanie Stanu Zdrowia Ludności*)

WSSE – Voivodeship Sanitary and Epidemiology Station (Pol. *Wojewódzka Stacja Sanitarno-Epidemiologiczna*)

ZUS – Social Insurance Institution (Pol. *Zakład Ubezpieczeń Społecznych*)

1. Introduction

The Medical Research Agency (Pol. *Agencja Badań Medycznych*, ABM) is a state legal entity established by the Act of 21 February 2019 on the Medical Research Agency. ABM's statutory activities involve the following:

- Co-funding research and development in the fields of medicine and health sciences, including interdisciplinary projects selected through calls for proposals, with particular emphasis on clinical, observational and epidemiological research;
- Issuing opinions and appraisals in the fields of medicine and health sciences for public administration bodies or other entities under relevant contracts;
- Initiating and developing international cooperation in the fields of medicine and health sciences as part of project funding programmes, also to cover interdisciplinary projects;
- Initiating and performing own research and development activities.

The Agency's responsibilities regarding the activities set out above include:

- Creating and managing project funding programmes, also to cover interdisciplinary projects;
- Publishing information about any planned or announced calls for proposals;
- Evaluating applications and concluding agreements with beneficiaries;
- Supervising and governing the implementation of projects, including interdisciplinary ones;
- Providing grants for non-commercial clinical trial projects;
- Organising and funding *ad-hoc* research or development activities in medicine and health sciences, with particular emphasis on clinical trials, observational and epidemiological studies, including interdisciplinary projects;
- Communicating the relevant results;
- Supporting businesses in undertaking and developing innovation in medicine and health sciences, also as part of interdisciplinary projects.

ABM's key objective is to support innovation in health care, with particular emphasis on the development of non-commercial clinical trials and research projects. The Agency's main focus is co-funding research and development in the fields of medicine and health sciences, including interdisciplinary projects selected through calls for proposals, with particular emphasis on clinical trials, observational and epidemiological studies, and research projects. The statutory powers vested in the Agency have made it possible to develop a strategic plan that defines the objectives and measures to be undertaken in epidemiological research over the next decade in order to prioritise operations in this area and optimise allocation of funds into individual tranches.

2. Epidemiological research

2.1. Definition of epidemiological research

For the purposes of this Epidemiological Research Plan for the Years 2023–2033, the Agency defines epidemiological research as the activities undertaken in order to develop our understanding of the factors that contribute to the emergence of significant risks to the health of the Polish population. Correct design of an epidemiological study requires a selection of an optimal subject cohort. The cohorts should be large – at least 10,000 subjects. A well-designed epidemiological study can cover a smaller sample size, provided that the sample is representative. The sample size (or the size of study subgroups) must be estimated depending on its statistical power with regard to the primary hypotheses, taking into account the expected recruitment rates. The study population must be selected in a way that makes the results as extrapolatable as possible to the target population, and any difference between the study and the target populations should be evaluable. The study population must be clearly defined, with predetermined inclusion and exclusion criteria.

2.2. Epidemiological research standards

Under the Epidemiological Research Plan for the Years 2023–2033, ABM is going to fund studies whose standards and principal assumptions are discussed in this section.

Undoubtedly, the highest-powered studies are cohort studies. This is the type of research conducted in many countries all over the globe. The greatest numbers of these trials are performed in North America, the UK, the Netherlands, Germany and Nordic countries. Cohort studies make it possible to test meaningful and pioneering research hypotheses. Designing them, however, must be justified by the existing knowledge gaps and clear benefits to be derived from incurring the organisational and financial costs of conducting the study – and, if necessary, pilot studies as well.

Cohort studies can be divided into two subtypes: prospective and retrospective. They both postulate evaluating subjects on the basis of exposure or non-exposure to a given factor or intervention. In a retrospective study, both the exposure and health condition pre-exist the research activities. In a prospective study, the exposure alone may precede the research project, but the health event occurs during the study. Selecting the right type of trial depends on its substantive merits and on logistics. In most cases, retrospective research is easier and quicker, and consequently not as expensive. This type of research is most practicable when the phenomena of interest have long latency periods and require many years of observation before the outcomes are achieved. One limitation of retrospective studies is that the records usually need to have been kept for many years before the study starts, which means their accuracy and completeness, and hence usability, can be suboptimal. A prospective study offers the possibility of using more current records. In many cases it also allows records to be co-generated and supervised in terms of both substance and data collection strategies. Therefore, the benefit of lower costs of retrospective studies

ought to be weighed against the quality of information it can yield. A well-designed prospective cohort study is believed to constitute a particularly valuable source of epidemiological information.⁷⁸

Another type of study used in epidemiology is a retrospective case-control study. It uses existing data to compare two groups.

Its aim is to define the risk factors or causes of diseases and it constitutes a fundamental tool for the evaluation of public health programmes. This type of study cannot be easily replaced with other measures to identify the causes of chronic diseases such as cancer, metabolic conditions or heart disease. It should, however, be borne in mind that such a study is more susceptible to selection bias and errors of assignment to exposure groups.⁷⁹

The table below presents methodological criteria for retrospective case-control studies and cohort studies.

Table 1. Methodological criteria to be met by epidemiological studies co-funded by ABM

<p>Methodological criteria: cohort study</p>	<ul style="list-style-type: none"> • A clearly defined study objective with rationale for selecting the appropriate methodology, in particular with respect to the approach to be used (retrospective vs. prospective). • Identified study population and inclusion criteria along with the enrolment strategy. • Defined type of exposure to be evaluated, as well as methods to detect the exposure and record its outcomes. • List of defined covariates and confounding variables that will be recorded in the study along with a rationale for choosing them. • Description of control points in the study plan along with a rationale for the time interval. • Rationale for the duration of follow-up and evaluation of the need for periodic studies. • Description of study data management and project management procedures. • Missing data handling strategies. • Description of the planned statistical analyses along with the assumed statistical power. • Defined strategies for retrospective data quality evaluations. • Defined procedures for handling losses to follow-up along with the anticipated methods of analysis to be used for a smaller cohort size. • Description of the planned statistical analyses and fixed and random effects models.
	<ul style="list-style-type: none"> • Suggested guidelines for peer review: • The study question must specify: <ul style="list-style-type: none"> ➢ the study population, ➢ the study risk factor(s), ➢ whether the study is meant to detect a beneficial or an adverse impact of a given factor. • Selection effect which can lead to false generalisation of the outcomes: <ul style="list-style-type: none"> ➢ Are cohort representatives recruited from the population? ➢ Does the cohort share any distinctive features? ➢ Does the cohort include all eligible subjects? • Potential sources of measurement errors or class assignment errors: <ul style="list-style-type: none"> ➢ Are the measurement/evaluation methods used subjective or objective?

	<ul style="list-style-type: none"> ➤ Are measurements accurate (is accuracy confirmed?) ➤ Will all subjects be assigned to exposure groups using the same evaluation/measurement procedure? ➤ Is there a system in place to detect all cases with a given status/outcome? ➤ Are the planned methods for evaluating findings the same for the entire cohort? ➤ Will subjects or evaluators be masked (reasons why masking is or is not relevant for the study design)? • Have the authors identified all key confounding factors? • Have the authors identified confounding factors in the project and/or analysis? • Have limitations of the design and techniques been addressed, e.g. regarding modelling, stratification, regression or sensitivity analysis in order to correct, control or adjust for the confounding factors? • Is the duration of follow-up sufficient? <ul style="list-style-type: none"> ➤ Whether beneficial or detrimental, outcomes need time to become evident. • Subjects lost to follow-up may have different outcomes than the ones available for evaluation.
<p>Methodological criteria: retrospective case-control study</p>	<ul style="list-style-type: none"> • Clearly defined study objective with rationale for selecting the appropriate methodology. • Exhaustive description of case selection criteria. • Description of methods for selecting the control group, with account taken of mechanisms to control the balance between control and case groups. • 1:2 selection. • Description of retrospective data sources along with an evaluation of measures to control data quality and robustness. • Has masking been considered and to what degree? Have other mechanisms been suggested to improve objectivity and reduce bias in collecting and evaluating the data? • Description of study data management procedures. • Description of the planned statistical analyses along with the assumed statistical power. • What potential confounding factors can affect the analysis results and conclusions? • Suggested guidelines for peer review: • The study question must specify: <ul style="list-style-type: none"> ➤ the study population, ➤ the study risk factor, ➤ whether the study is meant to detect a beneficial or an adverse impact of a given factor. • Have the authors selected the correct method to answer the study question? • Potential sources of case group selection bias that can affect the reliability of results: <ul style="list-style-type: none"> ➤ Are case groups accurately defined? ➤ Are case groups representative for a given population (in a geographic and/or temporal sense)? ➤ Is a reliable system in place for the selection of all case groups in a given population?

	<ul style="list-style-type: none"> ➤ Are case groups incidental or common in the population (with defined criteria and estimates)? ➤ Are the envisaged study time frames relevant to the disease/exposure (with defined criteria and estimates)? ➤ Is the case group size sufficient (with defined criteria and estimates)? ➤ Has statistical power been calculated? <ul style="list-style-type: none"> • Potential sources of control group selection bias that can affect the reliability of results: <ul style="list-style-type: none"> ➤ Is the control group representative for a given population (in a geographic and/or temporal sense)? ➤ Is there a matching mechanism in place between the case and control groups? Or is it random selection from the population (is the assumed selection method acceptable)? ➤ Is there a method in place for handling missing data (and is the method acceptable)? ➤ Is the assumed control group size acceptable and backed by relevant estimates? • Is exposure assessment described in detail and is it confirmed to be reliable and accurate enough to minimise measurement bias? <ul style="list-style-type: none"> ➤ Are the measurement methods used subjective or objective? ➤ Are the proposed measurements accurate (have they been verified; validation sources)? ➤ Is the proposed method of measurement and evaluation similar in case and control groups? ➤ Is masking used, and if not – are the reasons explained? ➤ Is there a temporal relation in line with Hill's criteria (does exposure precede the exposure effect)? • Save for the exposure of interest, have all groups been treated the same way? Potential confounding factors: genetic, environmental, socioeconomic (have they been addressed in the study design?) • Have the authors considered potential confounding factors in data analysis?
--	--

Apart from the types of high-quality studies mentioned above, there are also other designs available. New or underexplored research problems should be tested in simple observational trials which do not require considerable organisational or financial effort. Simpler research projects (e.g. cross-sectional studies, environmental studies) can be financed in cases where the research objectives and study hypotheses are found to be highly innovative. Financing will not be available, however, for studies whose hypotheses have already been tested in well-designed and properly conducted cohort or experimental trials.

2.3. Epidemiological research in Poland

In Poland, collecting and processing epidemiological data is a statutory responsibility of institutions created specifically for that purpose. The largest institution that collects public statistical data is Statistics Poland (Pol. *Główny Urząd Statystyczny*, GUS). The range of data to be collected by GUS is defined annually by

regulation of the Council of Ministers on the public statistical research programme for a given year (currently Regulation of 19 November 2021 for the year 2022), as set forth in the Act of 29 June 1995 on Public Statistics. Current legislation in Poland also provides for keeping records of important aspects of population health status that are relevant to public health. This applies to selected infectious diseases specified in the Appendix to the Act of 5 December 2021 on the Prevention and Control of Infections and Human Infectious Diseases. The list contains 59 items, and the relevant data collection is a responsibility of the Chief Sanitary Inspectorate (GIS) or specialist health care facilities designated by GIS, dedicated to the diseases included in the list. An example of a GIS-designated database is the National Tuberculosis Registry kept by the Warsaw-based tuberculosis institute Instytut Gruźlicy i Chorób Płuc w Warszawie. Other equally important registries maintained in Poland are:

- Central Registry of Occupational Diseases kept by Instytut Medycyny Pracy im. Jerzego Nofera w Łodzi pursuant to the Regulation of the Council of Ministers of 30 June 2009 on Occupational Diseases,
- National Cancer Registry kept by Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy pursuant to the Regulation of the Minister of Health of 14 June 2018 on the National Cancer Registry,
- Registry of Human Immunodeficiency Virus (HIV) Infections and Acquired Immunodeficiency Syndrome (AIDS) Cases kept by the Department of Infectious Disease Epidemiology and Control of National Institute of Public Health NIH - National Research Institute (NIPH NIH - NRI) pursuant to the Act of 5 December 2021 on the Prevention and Control of Infections and Human Infectious Diseases,
- Polish Registry of Congenital Malformations kept by the Poznań University of Medical Sciences pursuant to the Regulation of the Minister of Health of 12 June 2018 on the Polish Registry of Congenital Malformations,
- National Registry of Cardiac Surgeries kept by Instytut “Pomnik – Centrum Zdrowia Dziecka” (IPCZD) pursuant to the Regulation of the Minister of Health of 30 May 2018 on the National Registry of Cardiac Surgeries,
- Polish Registry of Acute Coronary Syndrome kept by Śląskie Centrum Chorób Serca w Zabrzu pursuant to the Regulation of the Minister of Health of 24 May 2018 on the Polish Registry of Acute Coronary Syndrome,
- National COVID-19 Registry kept by Narodowy Instytut Kardiologii im. Stefana kardynała Wyszyńskiego – Państwowy Instytut Badawczy pursuant to the Regulation of the Minister of Health of 7 April 2020 on the National COVID-19 Registry,
- Familial Hypercholesterolemia Registry kept by Uniwersyteckie Centrum Kliniczne w Gdańsku pursuant to the Regulation of the Minister of Health of 8 January 2020 on the Familial Hypercholesterolemia Registry,

- Registry of Vascular Surgeries kept by Klinika Chirurgii Naczyniowej, Ogólnej i Angiologii w Szczecinie pursuant to the Regulation of the Minister of Health of 8 January 2020 on the Registry of Vascular Surgeries,
- Registry of Non-Malignant Tumours of Major Salivary Glands kept by Klinika Otolaryngologii i Onkologii Laryngologicznej Uniwersytetu Medycznego w Poznaniu pursuant to the Regulation of the Minister of Health of 12 June 2018 on the Registry of Non-Malignant Tumours of Major Salivary Glands.

The main reporting areas applicable in Poland focus on the most prevalent conditions in the population, namely cardiovascular and neoplastic diseases. Other important institutions involved in collecting population health data include the Ministry of Health, the National Health Fund and dedicated research facilities, for example NIPH NIH - NRI, Instytut Medycyny Pracy im. prof. J. Nofera. The information collected by these institutions is largely inaccessible to the public, and in some cases access to it is restricted by law.

One example of public government bodies and state institutions collecting data for the Ministry of Health is the reporting on SARS-CoV-2 incidence and mortality rates in Poland. Case definitions and mortality coding were pre-defined, but the problem was that not all data collection facilities followed them in the same way. Another issue was a circumstance referred to in epidemiology as the iceberg phenomenon, which means underreporting a problem. NFZ is an entity with the widest access to population health data as regards the health services provided. The range of data collected by NFZ is vast and access to them is not made public. NFZ can make data available upon request from other institutions. In making such disclosures, priority is given to educational purposes. NFZ also discloses data on uniform patient groups. The Fund's database allows for detailed analysis of specialised health care services financed under NFZ contracts. Access to the database can be granted remotely⁸³ and as part of the "Healthy Data" programme.

Regular record keeping is supported by projects undertaken as a part of individual research. A study that employs analytical epidemiology methods will not only make it possible to revise routine reporting modalities, but also provide a more extensive outlook on the health situation, taking into account the risk factors contributing to disease prevalence in the population. Observational epidemiological studies require high levels of financial commitment. An analysis of the SYNABA database revealed that of the 570 projects that received funding in the years 2001–2010, 12.9% (n=76) were epidemiological studies, 12.5% (n=74) concerned public health, and a mere 2.8% (n=17) were focused on prevention. In that period, the funds dedicated to project financing totalled PLN 44,086,709. Of that amount, epidemiological projects consumed PLN 7,188,491, i.e. 16.3%, while public health and prevention research used PLN 3,654,683 (8.3%) and PLN 1,157,515 (2.6%), respectively.⁸⁴

The reporting discussed above belongs to the field of descriptive epidemiology, which addresses both traditional and synthetic measures of population health. These measures define a population's health status and needs and are used for planning the scope of medical procedures in Poland.

2.4. Principal obstacles to the progress of epidemiological research

The potential for possible growth in the number of epidemiological studies must be assessed from a number of different perspectives. The factors that directly determine the numbers and types of research projects can be grouped into the following primary areas:

- ➔ organisational aspects and staffing,
- ➔ financial aspects,
- ➔ legal environment.

2.4.1. Organisation and staffing

The key prerequisite for building the personnel resources necessary to carry out population research is the stable and secure funding of subsequent projects. While ensuring its competitiveness and independence in issuing calls for proposals and selecting winners, the public paying agent (regardless of who ultimately distributes the funds) should provide opportunities for long-term funding of epidemiological research. This would make it possible to form epidemiological research groups at the already experienced research institutions.

Currently, there appears to be many potential research contributors among the public health and medical institutions or facilities who have experience in conducting large scale population studies. Of particular importance to epidemiology are research institutes, of which there are 16 in Poland. They are the most numerous in the Mazovian voivodeship.

As regards scientific institutions and research institutes with a potential for epidemiological research, there are a total of 45 such facilities. A considerable number of them are clustered in the Mazovian voivodeship (12) and more than half (24) are medical universities.

Activation and building personnel competence, both in terms of professional merit and project management skills, are key to ensuring reliable performance of large population studies. No data are available regarding the economic viability and organisational efficiency of public funded research projects conducted so far. They have never been evaluated, audited or supervised by epidemiological research experts. It is therefore impossible at this point to assess the organisational and financial efficiency of previously conducted research financed by MZ (NPZ) or from other central public funds.

Most research institutions in Poland operating in the areas of public health, epidemiology or population research are already experienced in conducting nationwide representative studies in their fields of interest.

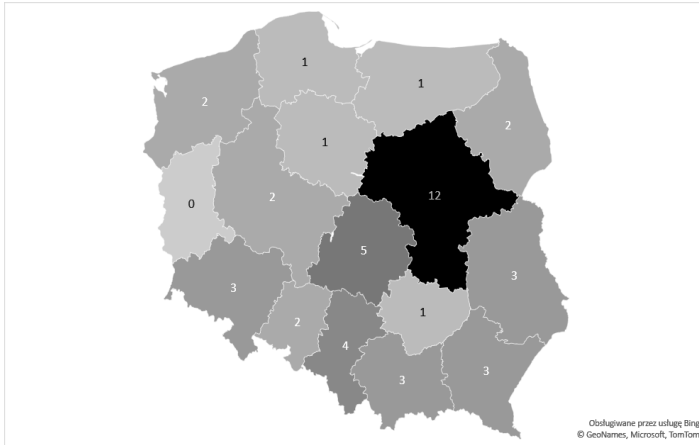


Figure 1. Numbers of research facilities conducting epidemiological studies in Poland by administrative regions.

Of the above-mentioned areas, the most stable one seems to be staffing. The numbers, availability and shared experience of the existing teams offer considerable opportunities for carrying out large-scale epidemiological research. As evidenced by the latest large studies of this type – both in adult (NatPol, WOBASZ, POLSENIOR, EZOP) and paediatric (OLAF, HBSC, EZOP II) populations – there are sufficient resources available to organise and perform a trial and analyse its findings. What is more, besides prominent research institutions, also academic centres tend to exhibit a capacity for effective research performance. This is evidenced by the epidemiological projects NatPol, WOBASZ, and POLSENIOR, where universities took over the role of project leaders.

One of the key elements of a good science base is self-education of personnel. Before the pandemic, doctors and other professionals exhibited very limited interest in epidemiology as a specialisation. At present, a post-pandemic rise of interest can be observed. Specialisation courses in Poland are offered to doctors by NIPH NIH - NRI, Centrum Medyczne Kształcenia Podyplomowego (CMKP), and the Medical University of Lublin, and to non-doctors by NIPH NIH - NRI, Military Institute of Hygiene and Epidemiology (MIHE), CMKP, and Wojewódzka Stacja Sanitarno-Epidemiologiczna (WSSE) in Poznań.

2.4.2. Financial aspect

The absence of a reliable, long-term funding plan for epidemiological research in Poland (save for a few exceptions, mainly in infectious diseases) hinders any effort to establish resources, educate staff and improve their analytical skills using large databases or results. In consequence, research is further impeded even when financial resources do suddenly become available.

This imposes severe restrictions on our potential to implement population research projects. In the long run, any developments in this respect must start from introducing a long-term epidemiological research plan. Eliminating the issue of the absence of reliable funding will create opportunities for introducing nationwide, representative population research in epidemiology. It will also make it possible to develop teams and organisational capabilities of potential contractors. At present, such teams exist mostly owing to the involvement of individuals in research work at their parent institutions.

2.4.3. Legal environment – access to data

One of the organisational impediments to the effective process of epidemiological research is caused by personal data protection regulations, whose impact on research can be twofold. First, they prevent sharing information between study partners and external communities. Second, they can limit the use of data after the study is completed. Epidemiological research focused on specific conditions or disease groups, as well as general population research, requires collecting personal data of the relevant subjects. Currently, due to legal limitations, researchers cannot freely use databases containing special categories of health data owned by public institutions (NFZ, ZUS, PFRON). This makes it very difficult to gain access to potential study subjects other than “healthy general population.” As a result, study costs grow considerably, and it becomes challenging to ensure potential representativeness.

It is therefore advisable to consider allowing a new basis for data processing. An exhaustive catalogue of possible legal bases for processing special categories of personal data is defined in Article 9 of the Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR). In the case discussed here, a potential legal basis could be the one set forth in Article 9(2)(j) of the GDPR: if the processing is necessary for scientific research purposes in accordance with Article 89(1) based on Union or Member State law, or [in Article 9(2)(i) of the GDPR:] if the processing is necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health. “Cross-border threats to health” refer to any threats mentioned in Article 168 of the Treaty on the Functioning of the European Union, i.e. in particular epidemic outbreaks.

“Scientific research purposes” are to be interpreted broadly under the Regulation. This is elaborated on in Recital 159 of the GDPR.

The criteria of necessity for scientific research purposes and relevant state health policies as the legal basis of processing referred to in Article 9(2)(j) of the GDPR must be met together. Two criteria are dependent on the personal data controller; the normative one is objective: there either is a relevant legal basis or there is not, in which case the legal basis as referred to in Article 9(2)(j) of the GDPR cannot be applied. Such a substantive basis for processing, which is required for Article 89(1) of the GDPR to apply, is provided for by Article 7 of the Law on Higher Education and Science Act of 20 July 2018. However, from the point of view of entities involved in commercial research, there is a significant limitation there, as this applies only to entities listed in Article 7. As a result, the present legal environment makes it impossible for commercial research facilities to use the necessity for scientific research purposes (Article 9(2)(j) GDPR) as their legal basis for processing special categories of personal data as part of the project. One solution would be to expand the list of entities to include those that carry out scientific research but whose core activity is commercial business, provided that they ensure an adequate level of data security when processing data for scientific research purposes.

Creating a legal environment allowing, on the one hand, to have special categories of personal data or physical and mental health data (including information on the use of health care services) made available by public institutions, and on the other hand to ensure data security (security level at the research facility) would make it possible to perform scientific research based on considerably larger data sets.

Consideration should also be given to the legal aspects of “further processing”. The principles of further processing are laid down by Article 6(4) of the GDPR, which provides that the controller must ascertain whether such processing is compatible with the purpose of the original processing (i.e. the purpose for which the personal data are initially collected). Further processing can only occur if it is permitted under the data subject’s consent, a legal provision or a positive result of the compatibility test between the original processing purposes and further processing purposes. The European Data Protection Board has argued that a separate legal basis (e.g. Article 9 GDPR) should be provided for further processing if the original legal basis for processing does not cover scientific research purposes. The processing can be based on express consent (e.g. Article 9(2)(a) GDPR) or on the necessity for scientific research purposes (e.g. Article 9(2)(j) GDPR). Every consent must meet the criteria specified e.g. in Articles 4 and 7 of the GDPR, in that it must be freely given, specific, informed and unambiguous. However, in the case of health data, in view of the circumstances of data collection, some of these criteria might not be met, for example the freedom of consent. Therefore, the position of the European Data Protection Board is that consent to scientific research should allow for consenting only to selected areas or aspects of research. The most important risk associated with using consent as the legal basis is the possibility for the subject to revoke it.

Another issue is access to health records to be used for research purposes. The Act of 6 November 2008 on Patient Rights and the Commissioner for Patient Rights sets forth a limited catalogue of entities that can be given access to medical records. A possible solution would be to expand the said catalogue in Article 26 of the Act to include other entities involved in scientific research.

It must also be emphasised that any commissioned epidemiological research must be unequivocally associated with a need to obtain practical and implementable results and at the same time there must be mechanisms in place to have the commissioning or financing entity incorporate these results into strategic documents and executive plans. Otherwise, though contributing to science, the research will effectively have no impact on state policies.

2.5. SWOT analysis

The purpose of this section is to evaluate the potential for introducing a new model of epidemiological research funding and performance using SWOT analysis (Strengths, Weaknesses, Opportunities, Threats). SWOT is one of the fundamental methods used in strategic analysis to assess the advantages, disadvantages, opportunities and risks associated with a given undertaking (plan, project or process), organisation or individual.⁷⁷

Table 2. SWOT analysis

Strengths	Weaknesses
<ul style="list-style-type: none"> • A potentially large network of research sites. • Availability of institutions dedicated to public health research (such as NIPH NIH - NRI) and well-staffed research facilities associated with medical universities, which can be beneficiaries of funding offered under calls for proposals in accordance with the Act on the Medical Research Agency. • Availability of institutions experienced in conducting nationwide surveys and interventional studies. • Research groups experienced in conducting multicentre epidemiological trials. • Experience in working with the tools and procedures used in international projects. • Opportunities to explore epidemiological science. • Opportunity to identify and analyse groups previously unstudied in population-scale research models funded from other than public funds. • Market presence of dedicated and effective businesses involved in field studies or opinion polls. 	<ul style="list-style-type: none"> • No national epidemiological research development programme ensuring stable financing over a 5-year and long-term perspective. • Limited interest in epidemiology on the part of other financing institutions. • Access to the paying agent's public databases – analysis of data on services provided. • Limited interest in epidemiological research shown by the scientific community due to the long-term nature of such research and the challenging process of publishing the results in prominent journals. • Limited access to personal data other than “general” population – a random selection from the PESEL database. • Unfeasibility of targeted research on specified risk groups or patient groups. • Unfavourable legal environment in terms of epidemiological research facilities' limited access to special categories of personal data, which makes it difficult to monitor patients over the long term. • Growing public resistance to trial participation.
Opportunities	Threats
<ul style="list-style-type: none"> • Excellent opportunities for scientific exploration and building a presence in epidemiology. • The developing pandemic as a field of inquiry. • Fast development of new technologies promoting digital lifestyles. • Growing international collaborations, possible shared projects. • Availability of funding for international internships or study visits. • Implementation of the European project “1+Million Genomes” will make it possible to use the data collected by Polish sites and incorporate them into the study of genetic epidemiology. • Availability of advanced epigenetic research methods – an extensive network of centres offering high-throughput sequencing (mapped by ABM). 	<ul style="list-style-type: none"> • Further legal limitations on the access to special categories of personal data. • The pandemic as a factor limiting contact with patients and their mobility. • A profound transformation of Polish health policies and related priorities. • Considerably increasing body of market research that contributes to the growing reluctance of the public to participate in essential but time-consuming epidemiological research.

3. Directions of development of Polish epidemiology

3.1. Principal health concerns of the Polish population

Over the last five decades, the socioeconomic development coupled with rapid technological progress have had a far-reaching impact on the factors that determine human health, contributing to a gradual growth of life expectancy and the aging of societies. The longer life expectancy in both men and women over the last 20 years has significantly altered morbidity rates and the prevailing causes of mortality.

New health needs have also appeared, both individual and community wide.^{1,2,9} ABM offers support primarily in the following areas:

- 1) lifestyle diseases (e.g. diabetes mellitus, cardiovascular diseases, cancer, allergies),
- 2) infectious diseases, including emerging ones (e.g. COVID-19),
- 3) environmental risks (e.g. smog, noise),
- 4) new health concerns (e.g. technostress).

Notably, a 2022 report by GUS reveals that in the years 2000–2015, the Potential Years of Life Lost (PYLL) index kept gradually and distinctly falling both for men and women in Poland. This favourable trend has unfortunately reversed over the last years, and we are now observing a slow increase in the PYLL index for both sexes. Over the entire period in question, PYLL was markedly higher for men than women, as evidenced by the graph below.⁸⁰

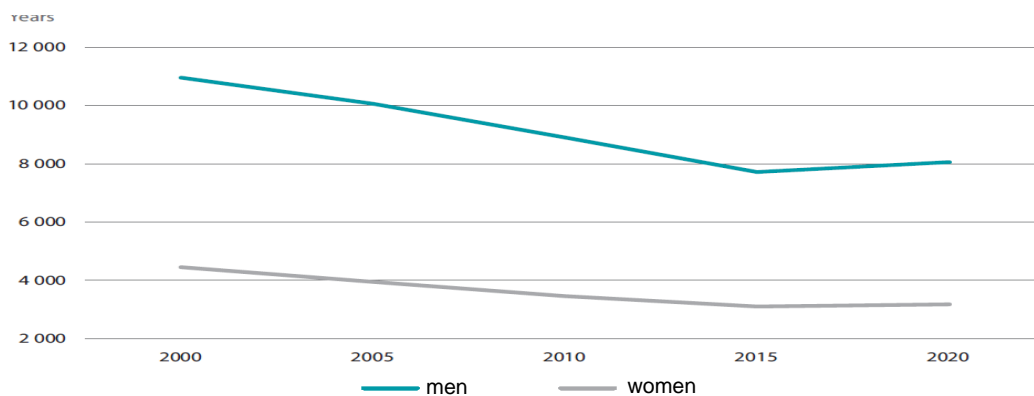


Figure 2. Years of life lost by sexes in selected years in Poland.

Source: *Demographic situation in Poland up to 2020. Death and mortality*; GUS 2022

This situation, brought about by the emerging changes in lifestyle diseases and environmental risk factors, is a clear indication that efforts must be made to reverse this unfavourable trend. The cited report by GUS directly points to the support areas defined by ABM experts as key for an epidemiological research plan.

Evidently, demographics is an important factor shaping the health situation. Even though health is a value defined as physical, mental and social wellbeing and not just absence of disease or other complaints,

epidemiological assessments must be primarily concerned with so-called “negative health indicators”, of which the most important and available one is mortality rate.^{3,4}

At present, the main focus of epidemiological research in Poland is the field of cardiovascular diseases and associated risk factors. Studies conducted in the past decade or completed over the past couple of years, with only a few exceptions (such as EZOP, POLSENIOR 2), investigated mainly the prevalence of risk factors and lifestyle disease complications. This is understandable from the epidemiological point of view, given the necessity to anticipate health needs and the necessary preparations within the health care system. Still, it creates an important knowledge gap as regards other diseases and risk factors. Currently, it seems that future large-scale epidemiological research should also take into consideration less common and not as prevalent morbidities (e.g. neurological, hormonal, autoimmune) as additional components in large population studies. These areas can also be in the focus of larger research. This kind of approach provides an opportunity to carry out additional, satellite projects and examine previously underexplored areas of study, all the while minimising organisational costs. A prerequisite for the performance of such extensive research is that it should be carried out in selected groups (e.g. age groups, demographic groups) within the general “healthy” population that is not based on specific classes of diseases. Specialist studies, for obvious reasons, should be conducted separately, on specific populations of patients or subjects exposed to factors of interest.

Organising separate investigations for each area or study question, while constituting a scientifically and statistically sound approach, can, however, lead to the fragmentation of research potential and higher costs of study performance. It is also important to plan the fields of support so that the measures undertaken are aligned with the key needs for relevant information on the society’s health status.

3.2. Health concerns caused by the civilisational advancement

One of the negative consequences of the civilisational advancement is the emergence of so called lifestyle diseases. These are non-infectious diseases associated with the progress of civilisation that interfere with everyday activities, lead to disabilities and account for over 80% of premature deaths. Lifestyle diseases include e.g. ischaemic heart disease, myocardial infarction, hypertension, asthma, chronic obstructive pulmonary disease, allergies, lung cancer, prostate cancer, breast cancer, ovarian cancer, colorectal cancer, diabetes mellitus, obesity, viral hepatitis, and coronavirus diseases.

3.2.1. Multimorbidity

Multimorbidity is a state of concurrent and chronic presence of multiple diseases whose individual significance from the perspective of potential recovery cannot be hierarchically ranked. According to Wiesner and Bittner, multimorbidity starts with the coexistence of two chronic diseases in one patient.⁵ Multimorbidity is a problem that has lately been claiming more and more clinical and public health resources and efforts. Clinically, it is associated with diagnostic and therapeutic challenges for health care providers and low quality of life for patients,³ resulting not only in reduced treatment effects, but also excessive

mortality rates among the affected patients.^{6,7} On a population scale, multimorbidity is a challenge for the health care system (organisational, financial) which clearly defines health care needs, but also generates expectations from prevention and health promotion programmes.⁸ There is a well-defined connection between multimorbidity and the use of primary health care, ambulatory visits, hospitalisations and hospital re-admissions, and ultimately long-term institutionalisations. The current demographic trends also have a significant impact on the health care system. The proportion of the post-working-age population is growing in societies worldwide. The ageing society affected by multimorbidity exhibits a higher demand for health care services, long-term care, and particularly prevention and treatment of chronic conditions.⁹

Multimorbidity has recently acquired a global dimension.^{10,11} The 2016 report by WHO indicated that, besides constituting a challenge to health care, multimorbidity also requires a comprehensive investigational approach.¹ The WHO report also emphasised that most health care systems practically had not and did not take multimorbidity into account as a priority at the stage of organisation and planning for their many tasks and functions. That is why it is necessary to revisit the health care service catalogue, and, most importantly, investigate the extent and effect of the phenomenon using epidemiological research tools.^{4,12}

In Poland, multimorbidity can affect up to 25% of all adults, mostly sufferers of cardiovascular disease (CVD).^{13,14}

According to the data published by GUS in 2022, CVD is unequivocally the most life-threatening condition in Poland. It is the greatest cause of mortality, accounting for nearly 50% of all deaths in the country. In 2020, Poland recorded a surge in cardiovascular deaths compared to previous years, though it remains to be seen whether it marked a beginning of a changing trend or was just a one-off peak for reasons attributable to the pandemic. That year, CVD claimed over 174,500 lives, accounting for 42.6% of all deaths.⁸⁰

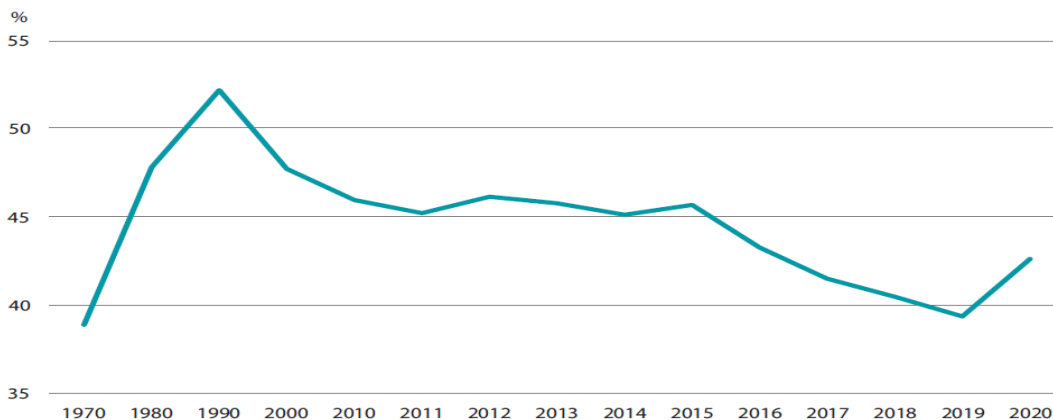


Figure 3. CVD death rates as a percentage of overall mortality per year.

Source: *Demographic situation in Poland up to 2020. Death and mortality*; GUS 2022

In addition to CVD, the Polish society also struggles with another major health concern: cancer. The 2019 publication by the National Cancer Registry (KRN) indicates that malignant cancers constitute the second leading cause of mortality in Poland, accounting for 25.7% deaths in men and 23.2% in women. The problem affects particularly young and middle-aged patients (25–64 years of age). Interestingly, cancer is the top

cause of death in women under 65 years of age, accounting for 31.7% and 46.8% deaths in young and middle-age groups, respectively.⁸¹

The charts below present the structure of mortality due to malignant carcinomas by sex in Poland in 2019.

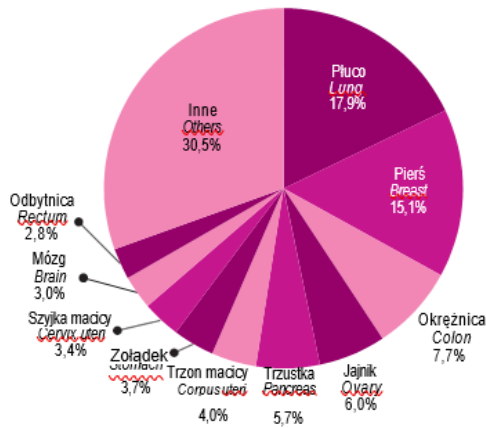


Figure 4. Cancer mortality in women in Poland in 2019.

Source: Cancer in Poland in 2019
KRN 2021

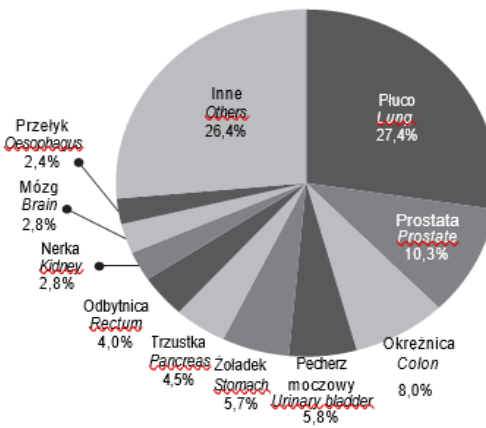


Figure 5. Cancer mortality in men in Poland in 2019.

Source: Cancer in Poland in 2019
KRN 2021

Another major and common health problem in the Polish population are metabolic diseases, most notably diabetes mellitus. According to NFZ, nearly 3 million people in Poland are currently treated for diabetes. This is almost 8% of the entire population. In 2019, over 380,000 new cases were diagnosed and confirmed.⁸² The charts below represent the prevalence rates by different age groups and sexes.

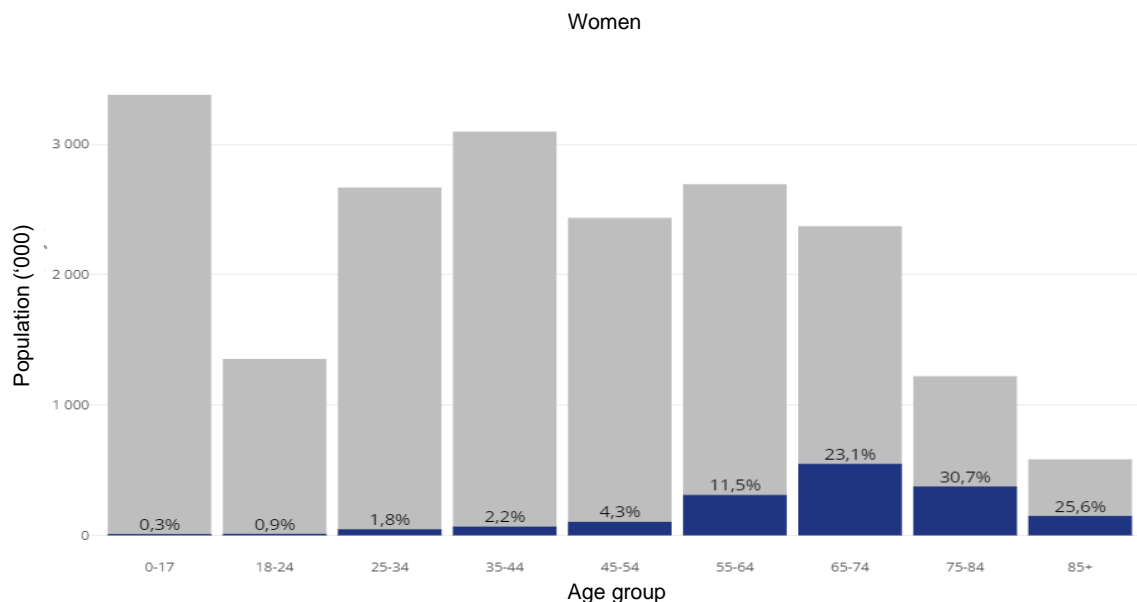


Figure 6. Diabetes prevalence rates in 2019 by age groups in women.

Source: NFZ, epidemiology records – diabetes mellitus: <https://shiny.nfz.gov.pl/cukrzyca/>

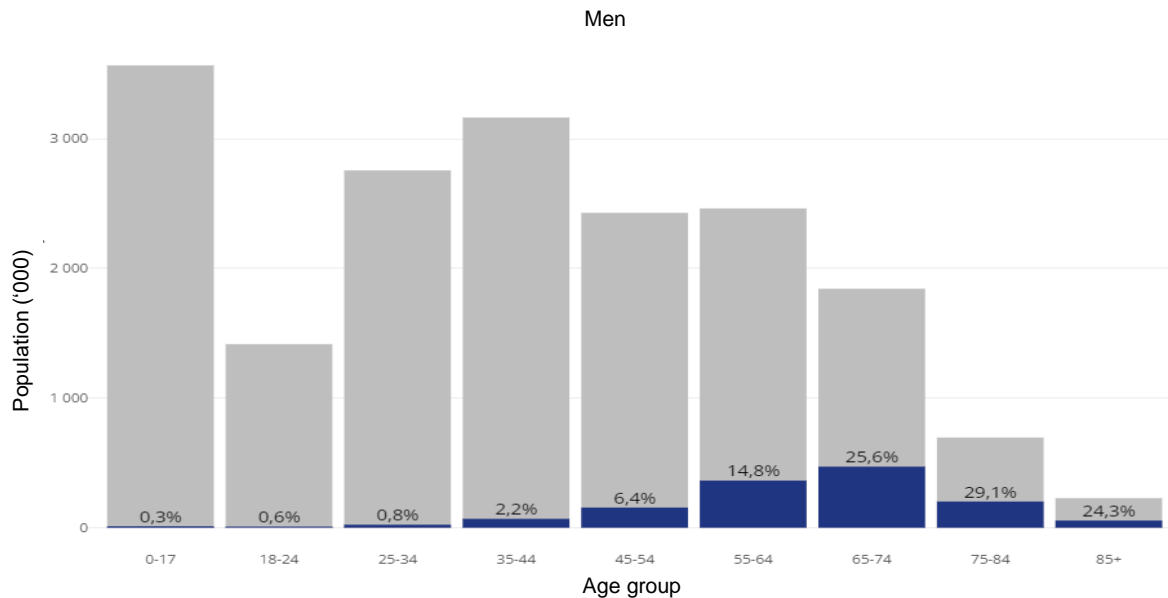


Figure 7. Diabetes prevalence rates in 2019 by age groups in men.

Source: NFZ, epidemiology records – diabetes mellitus: <https://shiny.nfz.gov.pl/cukrzyca/>

The above-mentioned examples of lifestyle diseases have a direct and considerable impact on the potential for multimorbidity in the Polish population.

Most conditions associated with multimorbidity are inextricably linked to chronic inflammation and/or immune ageing. The contribution of the immune system to the progression of many diseases often remains overlooked. It might therefore be worthwhile, while discussing multimorbidity, to pay some attention to the issue of immunodeficiencies. Immunodeficiencies are a class of diseases associated with quantitative and/or functional defects in the innate and adaptive immune response. They can be divided into primary, if they are caused by genetic factors, or secondary, if they are acquired. Whatever the aetiology, immunodeficiencies increase susceptibility to recurrent infections, autoimmune or autoinflammatory conditions, and proliferative and/or neoplastic diseases that typically accompany immune irregularities.⁸⁸ The rate of congenital immunodeficiencies worldwide has been estimated at 1/10,000,⁸⁹ but in view of the ongoing discovery of novel inborn errors of immunity and improved definition of clinical phenotypes,⁹⁰ the collective prevalence is more likely to be approximately 1/1,000–1/5,000.⁹¹ Along with the advancement of diagnostic tools, a total of over 300 types of immunodeficiencies have already been identified, and yet much is still unknown about these disorders⁸⁸ and their impact on the human body. As a consequence, for many patients the right diagnosis comes too late.

The implementation of new-born screening, now a standard e.g. in the US, has brought about significant developments in the epidemiological profile of primary immunodeficiencies. The numbers have been rising

for both paediatric patients achieving adulthood and newly diagnosed adults. More than half of all cases of primary immunodeficiencies are adult patients.

Early diagnosis and suitable treatment are of utmost importance for reducing multiple organ complications and prolonging survival in immunodeficient patients.⁹² Over the last 40 years, recording cases of immunodeficiencies (mainly primary ones) has played a major role in shaping health policies guided by epidemiological measures, monitoring quality of life and care, increasing the availability of genetic tests and clinical trials, and improving our understanding of the aetiopathogenesis of these diseases and the function of the immune system. Still, due to the limited nature of the resources supporting these registries, the inconsistent diagnostic criteria and the challenges associated with record keeping and designing any type of universal platform, the global perspective of this class of diseases remains unclear. On the other hand, secondary immunodeficiencies are largely overlooked and ignored in the efforts to treat the primary condition. All this translates into a need to improve the situation of multimorbid patients with immune disfunctions.

Multimorbidity has a detrimental effect on quality of life, survival and prognosis, and generates significant diagnostic and therapeutic dilemmas that call for an integrated medical approach. The issue of multimorbidity in Poland has not been suitably investigated or addressed from an epidemiological point of view. Compared to other countries, Poland is evidently suffering from a considerable knowledge gap in this respect. This can be justified to some degree by the fact that on a global scale, multimorbidity has only been subject to analysis for some 10-15 years, primarily in Western Europe and North America. Considering our insufficient understanding of the problem of multimorbidity in Poland, a cross-sectional evaluation on the subject becomes a priority. The importance of the issue and the inadequate body of available publications (not just in Poland) makes this topic a prime concern in medical research.² It is essential to explore the incidence and structure of multimorbidity across different population groups, identify the best practices for outpatient and inpatient care, and estimate economic impacts and organisational needs (in the framework of the health care system). Aside from these, another important task is to develop a standard definition of multimorbidity and a method to measure its prevalence.¹⁵

The IT systems currently in use in Poland make it increasingly possible to implement epidemiological evaluation. Such evaluation can be based on data sets known as secondary epidemiological data (drawing from data collected by NFZ's IT system) and primary epidemiological data. In the latter case, multicentre cohort or cross-sectional epidemiological studies can be designed to measure the incidence rate, structure and consequences of multimorbidity, and identify its relevant fundamental risk factors and prevalence, taking into account e.g. age, sex, territorial considerations, and the burden to primary, specialist and inpatient health care.

A compelling argument in favour of implementing epidemiological research in Poland is also its practical dimension, which corresponds with the extremely high social and financial costs of the problem, placing multimorbidity among the fundamental research and application concerns.^{16,17} In light of our country's current needs and the international initiatives in this respect, implementing epidemiological research of

multimorbidity in Poland is an urgent necessity, and besides its cognitive and utilitarian value it would also be a step towards the “life-course epidemiology” model – an approach already being undertaken in the rest of Europe, which transcends the traditional single disease-oriented mindset focused on investigating direct risk factors.¹⁸ The results can be used e.g. to educate doctors and nurses, design effective prevention measures, improve access to essential services (mostly in primary care) and adapt the rehabilitation programmes to the existing needs.

3.2.2. Common nature of lifestyle disease risk factors

An essential element of a rational health policy is having an accurate and reliable understanding of the current health situation in the community and of the factors that contribute to that situation. To evaluate the health status of a population, one needs to determine the prevalence of the most important health problems and risk factors shaping public health and define the directions and the impact of changes to the public health situation. To this end, research is necessary to detect such risk factors and monitor the changing dynamics of population health and health risks in the Polish society. These risk factors are not currently systematically evaluated or monitored in Poland, which leaves a significant unmet health need in this respect. It is necessary to implement a system of nationwide epidemiological research which would help to assess the health status of adults and children, to estimate the prevalence of the key risk factors e.g. of lifestyle diseases, as well as to monitor the dynamics of the health situation and the associated risks. Data from investigations of this kind could also be used in other epidemiological and medical research projects in order to guide health policies, develop prevention strategies, define health education programmes and identify the needs of the population in terms of health care. An important and unique feature of this type of research is enabling the conduction of prevention studies on large groups of people. The results can also be pooled with those of other studies in population health.

Since monitoring and elimination of risk factors is vital to prevent many lifestyle diseases, this type of studies seems to be of key importance for diagnosing long-term or seasonal changes in health behaviours and for monitoring factors that contribute to these changes. They also offer an opportunity for a better and faster response to seasonal health concerns in the population, e.g. epidemic outbreaks or temporary exacerbations of environmental factors such as smog etc. Moreover, such a research focus would be of great value to explore disease aetiologies, to monitor the epidemic outbreak dynamics, or to investigate compliance and health care system accessibility.

3.2.3. Respiratory diseases

Diseases of the respiratory system are very prevalent nowadays and constitute a growing threat to human life and health.

The issue of respiratory diseases is a considerable therapeutic challenge, as there are many contributing factors such as civilisational progress, intensified air pollution and active or passive smoking. Respiratory diseases can be divided into upper and lower respiratory tract conditions of either acute or chronic nature.

Among chronic respiratory diseases, chronic obstructive pulmonary disease (COPD) is now attracting more attention due to its detrimental effect on quality of life, high prevalence, cost of treatment and early mortality rates. This problem increases as the population ages. Unlike asthma, COPD's aetiopathogenesis, prevalence and management are under-investigated, especially in Eastern Europe.¹⁹ For this reason, comprehensive epidemiological research must be initiated in Poland.²⁰ The best option would be cross-sectional studies. They should be based on good epidemiological practice and apply modern methodologies to explore COPD phenotypes using biomarkers, molecular techniques, genetic methods and new imaging tools.²¹ An important aspect of this type of study is estimating the incidence rate of COPD as well as individual and environmental risk factors in the adult populations of rural and urban areas. The test methods could comprise: standard questionnaires, spirometry with bronchodilators, FeNO test, sputum culture tests, exhaled breath condensate, exercise tolerance test and collection of blood for genetic tests. Depending on the techniques used, the research could be performed at selected family doctor surgeries or pulmonology wards.

The proposed field of study aligns well with the current U4Health Programme of the European Union.²² One of the arguments in favour of initiating this type of research is COPD's heterogeneous nature and the insufficiency of the available evidence as compared, for example, to asthma.²³ The results could be used e.g. to educate doctors, plan the availability of modern services also in primary care (diagnostics, targeted therapy), and estimate the cost of medical care in outpatient and inpatient settings.

3.2.4. Respiratory diseases – allergies in children

Allergic diseases constitute one of the most common health issues in children and include asthma, atopic dermatitis, allergic rhinitis and food allergies. In addition to adversely affecting the child's development and future health, they place a heavy burden on the healthcare (in terms of diagnostics, therapy, rehabilitation) and therefore generate high direct and indirect costs.²⁴ Our knowledge of allergies still requires collecting scientific evidence aimed at defining prevalence and incidence rates in the paediatric population, documenting the risk factors (including the importance of environmental and genetic risks), improving prevention, diagnostics and treatment methods, and understanding the organisational and financial aspects of these procedures.¹⁹

Epidemiological research on child allergies conducted in Poland to date (e.g. ISAAC and ECAP) mostly used basic research tools (questionnaires, in most cases). Due to the magnitude of the problem, the unambiguous substantive recommendations and the scarcity of domestic data, it must be concluded that there is a need to implement a comprehensive epidemiological research project concerning child allergies in Poland. The relevant methodology should envisage implementing state-of-the-art cognitive tools for the study of phenotypes, endotypes, genotypes and theratypes.^{20,21}

In addition, among the current research needs in children's respiratory diseases one must not ignore the need to develop an epidemiological definition of asthma.²⁶ Comprehensive and valid arguments can be made for improving research on exposure to risk factors by using larger patient cohorts and modern

methods of monitoring risks and biological responses.²⁷ One major argument in favour of asthma research is the actual absence – since 2003 – of systematic epidemiological data from countries where large, international epidemiological projects used to be conducted (ISAAC, ECRHS; with the exception of the EISL programme, which had its second run in 2012).²⁸ Another subject which has not yet been fully investigated is the influence of environmental factors and the way environmental risks interact with genetic factors.²⁹ Given research needs in the field of child allergies, including asthma, were addressed in the position and recommendations of the European Strategic Forum on Allergic Diseases in 2018.³⁰

The optimal solution would therefore be to perform multicentre epidemiological studies focusing on allergic diseases in the paediatric population in Poland. Depending on the organisational capabilities, these could be cohort, cross-sectional or even case-control studies. They would be to a large extent complementary to the large projects already being implemented, such as ALLIANCE, NZA2CS, KBC, EuroPrevall.^{21,23,31,32} The results could be used e.g. to educate doctors and nurses, plan the availability of modern services in primary care (diagnostics, targeted therapy), and estimate the cost of medical care in outpatient and inpatient settings. Besides, performing such investigations would considerably contribute to the development of modern research tools and resources for Polish epidemiology. Even more added value would come from stimulating countrywide cooperation between research sites, sharing the experience gained in international programmes and promoting good epidemiological practice. It would be an excellent opportunity for young researchers to network and form partnerships that last beyond the research project.

3.2.5. Addictions and mental health

A country's economy relies on a great number of factors. One such factor is essential workforce. Professions of particular social importance include uniformed services, teaching staff and healthcare professionals. The nature of these professions and the circumstances shaping the current labour market put these groups under high stress, often markedly in excess of the accepted standards. This commonly results in burnout. Stress exposure can trigger a number of physiological processes in the human body, potentially leading to many illnesses. The nature of stress-induced conditions can be indirect, such as developing unhealthy habits in response to stress (smoking, alcohol or drug abuse), or direct, activated by stressors. They can be associated e.g. with mental strain. In addition, persisting high stress levels cause increased secretion of corticosteroid hormones (cortisol), inhibiting the activity of the immune system and increasing the risk of tumours.³³

Published studies on physicians have also identified a number of other factors, apart from stress, which can contribute to lost satisfaction from professional practice. These include: long work experience (10–20 years), multiple workplaces, work overload, lack of rewards, workload of over 60 hours a week, or poor relationships with colleagues.³⁴ A study in Polish anaesthesiologists revealed that the risk of severe burnout in this group was up to 70%, and the overall prevalence of burnout syndrome was estimated at 18%.³⁵ The situation is similar in other professions, for example uniformed services. Very little research is carried out in Poland

investigating burnout and mental disorders among police officers, firefighters, border patrol or the military. Few studies have managed to explore this problem to some extent.^{36,37}

Alarming trends with regard to mental disorders can also be observed in paediatric populations. A report by UNICEF showed that the percentage of adolescents reporting two or more psychological symptoms (feeling low, feeling irritable, having sleeping difficulties) more than once a week was approximately 28.3% in 2014.³⁸ According to a report by the Supreme Audit Office, the rate of mental disorders in Polish minors in the years 2017-2019 was at least 9%, which means that approximately 630.000 of children and adolescents below 18 years of age required psychiatric and psychological treatment.³⁹ It must be noted that precise estimates of the incidence rates of mental disorders in the paediatric population are not available due to the absence of population research, especially in Poland.

Nearly any occupation carries a risk of burnout and mental disorders. This problem is the product of a number of determinants. The rates of burnout syndrome and mental disorders have not been thoroughly investigated in Poland and the issue demands extensive exploration, especially among representatives of essential workforce. At the same time it must be borne in mind that an adequate support system for people affected with mental issues should be based on reliable research that makes it possible to monitor mental health indicators, the associated risks, and the efficacy of measures implemented to resolve the problem in local communities. Such research is still lacking. There is therefore an unmet need for long-term cohort studies to verify the estimated magnitude of the issue and the factors that contribute to mental disorders.

3.2.6. Dementia

Dementia is defined as a syndrome of acquired and progressive mental disorders which commonly accompany irreversible brain diseases of diverse aetiologies. The clinical picture includes emotional and personality changes, reduced cognitive functions, and psychopathological disorders.⁴⁰ This broad definition of dementia as a syndrome stems from the fact that it can have many possible causes. They can include progressive diseases, but also chronic conditions following brain damage. The rapid progress of civilisation and the abundance of stimuli can also have a detrimental effect on human psyche. It stands to reason, therefore, that Polish society might soon face a considerable surge in dementia rates, especially in the working-age population. Because of their diverse aetiology, dementias are not well understood and many of them can be considered new concerns that may be expected to gain importance over the coming decades.

Dementia is a major social issue. It primarily affects the elderly, whose numbers are consistently growing. Incidence rates increase with age, which is the best documented risk factor for many types of dementia. Demographic predictions clearly indicate that population structures in Poland and worldwide are going to undergo continued transformation due to the increasing life expectancy, and the proportion of the 65+ age group will have doubled by 2050. Given the projected growth of older age groups in the population and the fact that dementia is inextricably linked primarily with age, the incidence rates of this disorder are bound to rise rapidly, generating higher social costs in every sense of the word. This epidemiological prediction can

provide valuable guidance as regards assessing the prevalence of specific diseases in the near future and planning for future measures aimed at improving health care for those affected.

Currently, Poland has no accurate statistical data regarding the rates of dementia. This is because there is no system in place for efficient monitoring of these numbers, nor are there any databases available that would collect relevant medical histories and details on the situation of the patients and their caretakers. In fact, the Polish health care system in its present form is not geared towards the collection of this data. No screening is conducted to identify individuals at higher risk of developing dementia. Worse still, there are no mechanisms that would facilitate faster differential diagnosis of the type of dementia to guide suitable specialist management and rehabilitation.⁴¹

All this bearing in mind that as it progresses, this progressive and incurable disease will cause patients to increasingly depend on their family members' assistance, time, effort and devoted care. The longer the disease lasts, the more commitment it requires from the patient's caretakers. Since there is no information available on how many patients require institutionalised care, there are consequently no estimates on the numbers of people who take on the role of caretakers, inescapably incurring high mental, physical and social costs.⁴²

The challenges associated with the ageing society and growing numbers of people affected with dementia call for introducing systemic solutions which have already been successfully implemented in other European Union Member States. To this end, the epidemiological landscape of dementia in Poland must be analysed (based on previous studies and findings, extrapolations of international study results) and population epidemiological research must be designed and initiated in order to obtain reliable data on the prevalence of cognitive disorders and dementia that can guide further strategic planning regarding treatment and patient care in our country.

3.3. Epidemiological concerns: infectious diseases

Infectious diseases are one of the major concerns for the Polish population. The COVID-19 pandemic, which broke out in late 2019, put a spotlight on the need for better control and understanding of the different risks closely related to the nature of the infectious agent. In recognition of the current circumstances, the discussion below focuses on the SARS-CoV-2 pandemic and other infectious diseases that may pose a risk to the safety of the Polish population.

3.3.1 The SARS-CoV-2 pandemic

The SARS-CoV-2 pandemic is still a very pertinent topic and virtually every aspect of it has already been explored since its outbreak. According to PubMed, 28 papers on the subject were published in 2019, a number that skyrocketed to a whopping 61,212 in the following year and 76,929 the year after. Subsequent mutations of the virus, the sequelae of infection and excess mortality due to the disease still provide enough motivation to continue large-scale research projects on COVID-19.

At the beginning of the epidemic, the focus was primarily on studying the clinical picture of the acute phase of hospitalisation. Over time, it became evident that after the acute phase, a number of post-COVID-19 symptoms appear. The average time to recovery after COVID-19 was 2–3 week, depending on the severity of the infection. However, in 1 in 5 cases, symptoms persisted for ≥ 5 weeks, even up to ≥ 12 weeks in 1 in 10 patients, regardless of how severe the initial course of infection was. The symptoms reported by patients after SARS-CoV-2 infection became known as “long COVID-19.” If the symptoms of SARS-CoV-2 infection persisted for more than 12 weeks, this became referred to as “post-COVID-19 syndrome.”⁴³

Long COVID-19 symptoms can be very diverse in terms of both nature and severity. COVID-19 sequelae are fairly well documented with regard to the respiratory, cardiovascular, nervous (central and peripheral) and urinary systems. Effects of COVID-19 can also be observed on the psychological level.⁴⁴

One of the complications of COVID-19 is Multisystem Inflammatory Syndrome (MIS-C, also referred to as PIMS in children and MIS-A in adults), which usually follows 4–12 weeks after acute infection. There are reports of other conditions, such as autoimmune diseases, including type 1 diabetes mellitus, alopecia areata, Hashimoto’s disease or psoriasis, whose onset might possibly be related to COVID-19. A study in 143 subjects discharged after COVID-19 from the largest hospital in Rome showed that 87% of the subjects still suffered from at least one persisting symptom up to two months after recovery, and over half still reported fatigue.⁴⁵ In a study by Mandal *et al.* in a group of 384 subjects, full recovery did not occur until approximately 90 days from onset. Notably, 54 days after discharge from hospital, more than half of the subjects still reported dyspnoea, 34% suffered from cough, 69% from fatigue and 14.6% struggled with depression. A control X-ray in 244 subjects revealed that only 62% of them had a completely normal radiological picture.⁴⁶

Research also suggests that persistent symptoms following a SARS-CoV-2 infection can also affect patients whose disease is mild and who have no additional comorbidities. A US telephone survey among adults with laboratory-confirmed COVID-19 treated in an outpatient setting revealed that approximately 35% of these patients had still not recovered 2–3 weeks after the COVID-19 test. This also applied to young adults without additional comorbidities. Among hitherto healthy subjects aged 18–34 years, one in five had not returned to their usual state of health within that time.⁴⁷

There are currently no established causative treatment options for patients with long COVID-19. Their management is symptom-oriented and focuses on symptom alleviation and rehabilitation. Data are also scarce as regards the efficacy of drugs used currently in the treatment of patients with long COVID-19 or the possible complications of SARS-CoV-2 infections. The long-term consequences associated with a SARS-CoV-2 infection can only be surmised from what we know about other coronaviruses (e.g. SARS or MERS). This reasoning can, however, be subject to a high risk of error. There is no consensus on the percentage of patients prone to such post-infection symptoms.

No factors have been identified that predispose to developing the above syndrome. As the pandemic continued, long COVID-19 became a major and growing social concern. In order to establish management modalities for patients with long COVID-19 and define the magnitude of the problem, it is necessary to

undertake long-term observational research as a way to reliably assess the prevalence, severity, incidence and duration of symptoms, as well as establish the efficacy of the applied treatment. With the progress of the pandemic and a rising proportion of people with a history of COVID-19, the number of patients who require continuous multidisciplinary medical care and rehabilitation will keep growing, inevitably putting an even heavier burden on specialist health care, especially in the fields of pulmonology, cardiology, neurology and psychiatry. This alone demands creating optimal conditions for collecting medical data to better understand the reasons and long-term outcomes of the pandemic. Data thus obtained will make it possible on the one hand to streamline the health care policy, and on the other to optimise response to the future waves of the pandemic, which seem inevitable at this point.

3.3.2 Other emerging infectious diseases

The term “emerging infectious diseases” (EIDs) refers to communicable diseases whose incidence rates have increased over the past years, raising legitimate concerns that the number of cases will continue to grow in the near future. EIDs include novel diseases, re-emerging diseases or drug-resistant conditions. They constitute a real threat to human health and a serious challenge to the health care system. It is estimated that infectious agents that cause EIDs account for at least 12% of all infectious human pathogens. The appearance of an EID in the environment or in human population can result either from the evolution of an existing and known pathogen or from the dissemination of a wholly new, previously unknown pathogenic agent.⁸⁵ A special category of EIDs that merits a mention here are diseases which so far have not been classified as such, but scientific progress and new techniques of detecting pathogens have convinced researchers to revise this position. These include for example human herpesvirus 8 (HHV-8) or non-pathogenic GB viruses (hepatitis G virus). Moreover, developed countries have seen new phenomena replace epidemic infections as causes for concern – these are, for example, viral hepatitis C, coinfection of HIV and tuberculosis, or Lyme disease.⁸⁶ What is more, factor such as poor immunity, ageing populations, immunosuppressive treatment, large concentrations of people in urban agglomerations, natural disasters and wars facilitate the spreading of diseases. It must also be noted that over the past decade, the number of cases of parents refusing to vaccinate their children has grown 14-fold in Poland. The latest data from NIPH NIH - NRI indicate that this trend is intensifying, which could lead to the loss of population immunity to communicable diseases (e.g. measles) that have long been forgotten thanks to preventive vaccination programmes.⁸⁷ Another concern is the emergence of wholly new human infections, including zoonotic diseases transmitted from animals, a typical example of which is HIV, the cause of AIDS. Sadly, given the slowdown in developing new vaccines and antibiotics, and the absence of vaccines to many infections, communicable diseases have been and will remain a challenge due to their global nature and impact.

3.4. The impact of environmental contaminants on human health

The progress of civilisation brings about many changes to human life. Some of them have a direct impact on the human body through the exposure to polluted air, soil and water. Aggressors such as noise and

excessive radiation have a number of adverse health effects. The above elements constitute a major problem of the modern world. Our civilisation has reached a stage where human impact on the natural environment is far-reaching and omnipresent. As a consequence, new health concerns have emerged, often referred to as lifestyle diseases. Most of them either directly follow from environmental factors or are influenced by them. Environmentally-induced conditions not only contribute to poor quality of life and shorter life expectancy, but also incur considerable social costs.⁴⁸ It must be remembered that some environmental factors only cause effects after long periods of exposure. These include in particular chemical substances that accumulate in the body (e.g. cadmium) or hazardous agents that have a cumulative effect (e.g. ionising radiation or noise). Long-term exposure to environmental aggressors can have a debilitating effect on the immune system and hence increase susceptibility to further adverse impacts of environmental pollutants. Currently in Poland, access to reliable epidemiological data on how the environment contributes to the incidence of specific conditions and related mortality rates appears still to be debatable. It is therefore highly advisable to investigate the correlation between environmental pollution and the onset of certain diseases. In this context, it seems vital to invest in the development and utilisation of chemo- and bioinformatic methods that can be employed to identify the most significant threats, i.e. those that can be detected in the environment and are believed to have an adverse effect on human health. These methods, drawing from epidemiological and transcriptomic data, as well as the characteristics of these threats, will make it possible to define the pathways behind the pathologies observed, according to the concept of adverse outcome pathways (AOP). This approach, along with other alternative methods of risk assessment (known as New Approach Methodologies, NAMs) is currently being actively developed as a part of various initiatives and projects financed by the European Commission (PARC, EURION, ASPIS, Green Deal Projects). Actions undertaken within the biological monitoring in conjunction with environmental monitoring are consistent with European Union's policies, as illustrated by the initiation of the PARC programme. The 7-year programme's objectives include assessing public health risks from exposure to chemicals. The research community often raises concerns over the inconsistent methods of retaining the collected data. It is therefore expedient and highly desirable for the scientific community in Poland to contribute to the research being conducted in countries that are leading the way in exploring the influence of environmental conditions on population health. Fostering closer international cooperation would be beneficial in terms of developing more accurate prevention programmes.

The impact of microplastics on human health

A major emerging concern of today's world is the presence of microplastics in the environment. Microplastics are largely secondary products of the disintegration of plastic bottles or plastic bags due to UV radiation. They can accumulate in the human body, triggering inflammation and causing respiratory obstruction.^{49,50} Still, our understanding of the impact of microplastics on the human body is very limited, and most of what is known about their harmful effects is based on inferences from animal studies.

Among the most common compounds used in the manufacture of plastic are Bisphenol A (BPA) and brominated flame retardants. The International Agency for Research on Cancer (IARC) has recommended

that research should be undertaken on the potential carcinogenic effect of Bisphenol A.⁵¹ Few human studies have addressed the relation between long-term BPA exposure and cancer. Tarapore *et al.* have demonstrated a correlation between urine BPA levels and prostate cancer in 60 urology patients.⁵² What is more, 2017 saw the publication of the results of a Chinese case-control study on prostate cancer. The study demonstrated a correlation between BPA and prostate cancer in the population of Hong Kong.⁵³ On the other hand, a Polish case-control study showed no evidence of a relationship between BPA and the risk of post-menopausal breast cancer.⁵⁴

Undeniably, the studies carried out to date demonstrate that elevated levels of BPA in urine are associated with human prostate cancer and can be an independent diagnostic biomarker in this malignancy.⁵⁵ However, the causal relationship between BPA and breast cancer remains uncertain, even though some murine studies have suggested that BPA disturbs the balance of oestrogen in mice and that even limited exposure to BPA affects the morphogenesis of mammary glands.

Considering the above, it appears necessary to carry out a controlled human trial where follow-up should ideally begin as early in life as possible. Assessing BPA exposure on early developmental stages will enable an evaluation of the correlation between this exposure and the growing incidence rate of prostate cancer, breast cancer or liver cancer.

3.5. New risks to human health

New advancements in engineering give rise to new technologies. Nowadays, new solutions that facilitate and change our private and professional lives have penetrated every aspect of human existence. Faster and more advanced communication channels, including videoconference systems, e-mail, Internet messengers and social networks, have made professional communication easier than ever before, optimised working time and minimised the necessary office space. Tablets, computers and smartphones have become our close companions also beyond the working environment. This technological advancement is believed to be an advantage. However, the time spent interacting with new technologies has not been without consequences to our health. Scientists have identified a number of health issues caused by prolonged use of electronic devices. These include addiction, chronic fatigue, sleep disturbances, stress, depression and burnout syndrome.⁵⁶ All over the world, scientists have started to appreciate the need to study the negative effects of technology on human health.

In Poland, few research projects have addressed this topic. PubMed database returned no published research papers with the keyword “technostress.” On the other hand, a search on the impact of mobile phones (smartphones) generated 20 records, of which 10 focused on human health. It must be noted that Polish research to date has not addressed widely recognised health issues such as smartphone addiction, depression or so-called “phubbing” (interacting with one’s phone rather than other human beings).

The intensifying use of technologies at the office and the need to cope with new solutions have led to the emergence of a new phenomenon called technostress, an adaptive condition defined as an inability to contend with new computer applications and devices which affects mental well-being.⁵⁷ Another effect of

human interaction with technology is addiction. A study published by Salanova *et al.* in 2013 and 2014, which involved 1,000 ICT employees, defined technoadddiction as an excessive and compulsive use of ICT technologies everywhere and at all times, as well as excessive use of technologies over the long term. It also demonstrated technostress to be associated with anxiety and chronic fatigue.^{58,59} Technoadddiction and technostress have also been studied by researchers from the USA and Hong Kong. Their results confirmed the existence of a relationship between Internet addiction or addiction to social media and technostress. These effects are additionally mediated by cultural considerations.⁶⁰

A no less significant effect associated with chronic fatigue is professional burnout. A systematic review by Borle *et al.* (2021) included two studies on the correlation between technostress and burnout syndrome.⁶¹ An international study by Srivastava *et al.* (2015) investigated the impact of technostress on burnout in senior managers and executives. The authors concluded that new technologies and uncontrolled access to information significantly contribute to burnout in these professionals. Another study by Khedhaouria and Cucchi (2019) also demonstrated positive associations between technostress and burnout.

Poor sleep quality is believed to be another consequence of technostress. It must be pointed out, however, that data on this topic are still limited and the best source of information remains the study by Finnish researchers who conducted 32 detailed interviews and found sleep problems in 6 of the subjects.⁶²

Considering the paucity of Polish studies on the subject, research must be initiated to assess the impact of new technologies on human health, in particular with reference to the many foreign reports postulating the potential for a number of health issues stemming from long-term use of technologies. The best way to investigate the relationship between exposure and health effects would be to undertake a long-term cohort study. The first step, however, should be to design a cross-sectional trial that would be representative of the entire Polish population. The specific nature of the issue additionally requires research to be conducted in occupational cohorts consisting of social groups particularly exposed to new technologies at the workplace.

4. Selected tools, technologies and practices in epidemiological research

Besides the necessary expert-identified areas of direct support for epidemiological research, there are three other areas that can considerably promote the development of epidemiological projects. These are: omic analyses, utilisation of medical registries and BIG DATA streams, and fostering international collaborations. Discussed below are arguments for the need to have these areas addressed in the epidemiological research development plan.

4.1.1. Using innovative omic techniques in epidemiological research

Today's epidemiology draws from the so-called "omic research", which is analysis of the transcriptome (the set of all transcripts in the system), genome (the entire genetic material), proteome (the set of all proteins

produced by the system), and metabolome (the complete set of metabolites), as well as epigenetics (the study of changes in the chromatin or DNA structure which are not mutations and are caused by environmental factors).

Many observational studies in epidemiology exhibit a limited capacity to distinguish correlation from causation – i.e. be able to tell if a given exposure causes a disease or simply correlates with it (without contributing to its onset). Introducing advanced computing methods that use genetic diversity information is transforming the way we test hypotheses regarding how changing a trait suspected of inducing disease (e.g. by intervention, treatment or policy shift) positively affects a population. An example of this is using Mendelian randomization (MR), which draws from genomic data – single-nucleotide polymorphisms (SNPs) strongly associated with a putative exposure to test for and estimate a causal effect of the exposure. MR is gaining popularity in epidemiology, particularly in observational studies which use information on genetic variations reliably associated with a modifiable risk factor in order to provide evidence on the potential impact of that factor.

One of the most commonly used sets of statistical algorithms is referred to as genome-wide association studies (GWAS). This type of study has been successfully developing for over 15 years. A total of at least 5,700 GWASs have been conducted, focusing on approximately 3,300 traits (data up to 2019). To date, over a million subjects have participated in this type of studies globally.

GWAS is a multi-stage study of the entire genome, where 500,000 to more than a million polymorphisms (mainly single-nucleotide polymorphism, SNPs) are genotyped (by NGS or DNA microarrays). GWAS has contributed to the emergence of new concepts in big data analysis and new statistical methods with high potential for application in epidemiological research. The GWAS methodology, similarly to data mining, makes no *a priori* assumptions. No candidate genes or gene groups are identified as potentially associated with the phenotype of interest. The objective of GWAS is to use whole genome sequencing in order to obtain a list of molecular markers associated with the aetiopathogenesis of a given condition. What is also important in this model is that it enables investigation of interactions between genetic and environmental factors. The origin of many conditions explored with this approach is complex, multifactorial and often determined by such interactions. GWAS has provided evidence that most analysed phenotypic traits are influenced by thousands of polymorphic variants which individually carry very little risk of expressing a given phenotype. The challenge remains to define the combined effect of the identified genetic factors and their various combinations on phenotypic expression. Hence, causal reasoning in GWAS still offers a methodological challenge.

One of the limitations faced by GWAS is the low frequency of some polymorphic variants in the population (<5%). In order to be able to analyse data representative of relatively rare polymorphic variants, it is necessary to ensure a sufficiently numerous and phenotypically varied study sample. Such a sample would offer enough statistical power to analyse the genomic data collected. In practice, GWAS may need cohorts of even more than 10,000 cases, while available analyses are often based on samples of approx. 1,000. Other important quality criteria in GWAS include detailed characterisation of the analysed phenotype and

possibly differentiating endophenotypes and corresponding clinical subtypes. Meeting this requirement makes it possible to perform statistical analysis in more homogeneous groups, thus improving statistical power.

Currently available studies based on the GWAS model suggest that this approach shows much promising potential also in epidemiology. For example, genetic variants associated with pathological phenotypic traits can be used as control variables in epidemiological studies to account for significant genetic variation in the groups compared. GWAS results can also be used to predict individual risk of diseases based on genetic profiling. This type of profiling is used for genomic risk predictions, e.g. Genome-wide Polygenic Scores (GPS) or Polygenic Risk Scores (PRS). Such predictions have already been undertaken for diseases such as coronary artery disease, atrial fibrillation, type 2 diabetes mellitus, inflammatory bowel disease and breast cancer. Profiling can also be based on predicting monogenic risk estimated from rare but highly penetrant genetic mutations. It is expected that genomic risk prediction can soon be admitted in clinical practice as a stratification tool.

The potential benefits of GWAS include, among other things: understanding the biological determinants of different clinical phenotypes, estimating the heritability of genetic markers associated with pathological phenotypes, identifying associations between genetic markers, describing the relationships between genetic markers and environmental factors in terms of determining risk, and informing the development of new innovative drugs and new therapeutic uses for existing treatments.^{63,64,65,66,67,68,69,70}

Discussed below are examples of how genomic data can benefit epidemiology.

Oncology

Tumours originate from changes in the genome. The advances in DNA sequencing technologies are steppingstones to a new understanding of the mechanisms of carcinogenesis, giving rise to new methods of diagnostics and treatment of many types of cancer. An interesting new approach in cancer treatment is selecting the treatment regimen not on the basis of anatomical location of the tumour, but depending on what changes have been fixed in the genome of cancer cells. The mechanisms that can take advantage of omic (genomic) tools are described below.

Primary prevention of cancer (preventing onset)

Some environmental exposures trigger mutations within the tumour that can testify to the lifestyle and environmental factors that caused the tumour to develop in the first place. An excellent example is the mutation pattern in the *TP53* gene responsible for controlling the growth and division of cells. This gene is different e.g. in smokers vs. non-smokers who have developed lung cancer.

A vast majority of any cancer mutations have no functional impact. Their pattern can be a testament to the types of exposure experienced in the past. A similar phenomenon can be observed in the pattern of UV-induced mutations in skin melanoma or mutations caused by aflatoxin B1 in hepatic cancer. It is not to be expected that all mutations will be directly associated with exogenous exposures, but some of them will.

Identifying the causes of specific mutations and associating them with new types of cancer will be an important step towards improving our understanding of the origins of cancer.

Comparing sequencing data from large numbers of study cases, as in the International Cancer Genome Consortium and The Cancer Genome Atlas, enables a wider spectrum of analysis. An important characteristic of studies conducted so far is that patients have been recruited from individual sites, with a strong emphasis on collecting high quality biological samples and detailed clinical data, but with limited information on the environment or lifestyle. Having access to genomic sequences of a large, representative group of the Polish population would make it possible to take advantage of the following treatment methods, without limitation:

- sequencing selected samples according to the presence of a known or suspected carcinogenic factor in order to further specify mutation patterns for a given exposure;
- comparing colorectal cancer depending on diet: meat-rich versus vegetarian;
- comparing subjects with a history of high exposure to specific pesticides versus naive subjects with respect to multiple types of cancer suspected to have a causal link to that exposure.

The existing cancer screening programmes could be modified in the future so as to identify individuals at elevated genetic risk by using combinations of rare high-risk variants and many common low risk variants. A major breakthrough in cancer prevention would be identifying early cancer biomarkers that are:

- easy to quantify,
- sensitive to pre-symptomatic cancer (e.g. able to detect a large proportion of cases), and
- specific (give negative results in the vast majority of cancer-free cases).

Some of the already identified cancer biomarkers are used in attempts to predict disease. However, in today's diagnostics cancer biomarkers are only used as supportive measures. They are more widely utilised during the treatment process and as part of long-term follow-up afterwards. One of the recent examples of highly specific, sensitive and easily quantifiable biomarkers of preclinical disease are anti-HPV16 E6 antibodies in oropharyngeal cancer. This biomarker can be detected in the plasma of most people with HPV-associated oropharyngeal cancer up to 15 years before the onset of clinical symptoms and is not present in over 99% of comparable general population.

Early detection of plasma biomarkers would effectively reduce the incidence and mortality rates of many malignancies.

Below is a list of examples of tests and studies to be performed on biological material (e.g. blood) that would be beneficial in the investigation of the causes and early detection of cancers:

- genetic tests (mutations in *BRCA1*, *BRCA2*, *TP53* or *CHEK2* genes),
- searching for mutation patterns indicating past exposures to cancer risk factors,

- nutrigenomic research (*FTO* gene associated with obesity, genes associated with the assimilation and metabolism of individual nutrients, assessment of the risk of nutritional deficiencies and the efficacy of nutritional prevention of cancer – study of SNPs),
- saliva (and oral epithelial cells): genetic tests, microbiome sequencing, selective tests for pathogenic microorganisms.

One of the factors that can induce carcinogenesis are epigenetic changes, which originate from a variety of environmental factors and are partially reversible but are always reflected in modified genetic expression. Whatever the causes of different types of cancer, knowing the mechanisms governing epigenetic change could help develop new therapeutic methods which, combined with the existing, traditional modalities, could further advance the treatment process.

Asthma and allergies

Many epidemiological analyses demonstrate that the growing epidemic of allergies can be to a large extent attributable to the impact of human environment. The changes that occur on the epigenetic level can result from environmental factors, which could partially explain the effects of the environment on the development of allergies and asthma.⁷² Epigenetic changes in immune and respiratory epithelial cells can explain to some extent the correlation between the growing incidence of asthma and allergy on the one hand, and the impact of environmental factors on the human body on the other.

It has been demonstrated that many environmental agents including allergens, air and water pollutants or dietary ingredients can trigger epigenetic changes in the genome of immune cells, causing them to reprofile and increase production of type 2 cytokines responsible for allergic inflammation. Studies have also shown that exposure to house dust mite allergens and diesel exhaust particles reduces methylation levels of T2 (IL-4, IL-5) cytokine genes and increases methylation levels of T2 (IFN- γ) cytokine genes in Th CD4+ cells. What is more, diesel exhaust particles intensify the production of IgE against environmental allergens.⁷³ Similarly, pollutants such as carbon monoxide, nitrogen dioxide, ozone or fine particulate matter PM_{2.5} can increase methylation levels even 90 days after exposure, which fosters the development of T2 phenotype.⁷⁴ Understanding the role and importance of epigenetic changes in the pathogenesis of allergies and asthma can contribute in the future to the emergence of therapies based on modifying the epigenetic status of cells or tissues. Still, developing effective anti-allergic and anti-asthmatic treatment options that would entail modifying genes responsible for type 2 immune response will require extensive research and an in-depth understanding of the complexities of epigenetic mechanisms.

Mental and cognitive disorders

The episodic nature and spontaneous remission of many psychiatric conditions cannot be explained only by genetics. Another explanation could be provided by the periodic presence of specific environmental

factors that affect gene expression patterns. In theory, such changes can be brought about by reversible epigenetic regulation. This process, however, merits more research and verification.

Previous genetic studies have not identified many genes that could significantly predispose to mental issues, which suggests that environmental factors, including epigenetic changes, could also play a role. Epigenetic modifications are responsible for natural regulation of gene expression through changes in chromatin condensation at sites subject to translation or through methylation of gene promoters. Evidence shows, however, that post-translational histone modifications (triggered by epigenetic changes) regulate gene expression and can affect neuronal function and response to environmental factors such as gaining experience, learning and memorising.⁷⁵ In addition, *post mortem* examinations confirmed that patients with schizophrenia had higher DNA methylation levels compared to healthy people.⁷⁶ It has been suggested that understanding the causes of mental diseases requires applying many different research strategies on different levels: for example, association studies of SNPs can be combined with research on epigenetic regulation. Studies suggest that psychiatric medications for the most part affect epigenetic modifications, hence having an impact on target gene expression. In the future, a thorough understanding of the mechanisms behind epigenetic changes and the elaboration of methods to identify them will enhance our knowledge of the aetiopathologies involved in psychiatric diseases and offer an opportunity to markedly improve the quality of neuropsychiatric treatment.

4.1.2. The development and effective use of medical registries and BIG DATA

Working with large databases, known as “BIG DATA”, is currently the focus of research and a global trend in coordinated, collaborative epidemiological studies. One of such international initiatives is the Network on the Coordination and Harmonisation of European Occupational Cohorts (OMEGA-NET project), which is aimed at coordinating and integrating cohorts to investigate health and occupational exposures. The project originally only involved European countries. Currently, OMEGA-NET brings together a number of countries worldwide. The initiative corresponds with the recommendations of the National Heart, Lung, and Blood Institute and the US National Cancer Institute.

Another excellent example of making use of large volumes of data of various types is the Global Burden of Disease (GBD) study. The data are processed by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle. A special advantage of the GBD study is that it introduces new concepts and indicators representative of the multidimensional nature of health problems. The measures used by the GBD study provide answers to questions whose understanding is an essential prerequisite in order to make the right steps towards improving public health and add to the traditional methods of describing the epidemiological situation in a community. GBD is based on pooling many sources of data, often country-specific. To address the possible methodological disparities regarding the measurement techniques and/or the definitions used in different parts of the world, GBD has strategies in place to harmonise all input data so as to make them consistent and comparable. Estimates are updated to provide political and health decision makers, as well as other stakeholder groups, with the most up-to-date and

actionable information on population health. The above examples clearly illustrate how necessary it is to collect and regularly update large volumes of public health data.⁹³

Updating, expanding and creating new medical registries on the basis of periodic cross-sectional or retrospective studies should result in consolidating the existing databases. It will also make it possible to create new summaries based on BIG DATA. As a consequence, the health care system will be able to more effectively use medical registries managed by the Minister of Health. Periodic cross-sectional studies with consistent diagnostic standards and the same representative population group provide an opportunity for a large cohort study to be initiated. It must be borne in mind, however, that one of the fundamental characteristics of a cohort study is the inclusion of a healthy subject population.

In Poland, there is no study, or rather no central register of study subjects and no periodic research, on citizen health. Attempts have been made by the Ministry of Health, notably the *pacjent.gov.pl* website, where people can freely complete a survey questionnaire of the Profilaktyka 40 PLUS programme carried out by the NFZ or a healthy lifestyle survey proposed by NIPH NIH - NRI. This study, however, is not systemic and lacks a description of the entire methodology. An exemplary study of the kind, with a complete design, is the International Study of Asthma and Allergies in Childhood (ISAAC). The project's website describes the entire design, including the structure of the database.

In registry studies, an epidemiological standard is necessary which consists in using the same questions to accurately assess health or other aspects of life in the Polish population. This will make it possible not only to obtain reproducible results, but also to compare them between sites or even create a Polish database that could be the basis for cohort studies.

Another tangible benefit of developing databases and BIG DATA streams will be augmenting the number of therapies that draw from large volumes of data necessary for patient profiling and customising treatment. Our goal should be to foster optimum conditions for the development of epidemiological research that would use registry data or BIG DATA. Currently, this area is considerably underfinanced in Poland.

Once large volumes of data are available, they should serve to improve the precision of health programmes financed from public funds. The Epidemiological Research Plan for the Years 2023–2033 puts high hopes on the use of omic analyses. They constitute an innovative approach in reasoning and can guide new therapeutic options hitherto unavailable to patients. Hence, it appears reasonable to apply the results of these analyses in the ongoing prevention programmes in specific populations. It will make for more accurate predictions of morbidity trends.

4.1.3. Internationalisation of epidemiological research

The internationalisation of Polish epidemiological research should in particular involve cooperating with foreign research centres and undertaking parallel projects that would facilitate sharing experience and information as part of research collaboration. To this end, it seems indispensable to fund the participation of Polish teams in international internships, stipends, study visits etc. as part of long-term epidemiological studies using international platforms. Such funding would allow Polish teams to undertake large scale

epidemiological studies in Poland according to international standards. Another opportunity stemming from the collaborations formed and experience gained by Polish researchers is the possibility to publish results in prominent journals.

It is also vital that any large epidemiological trial become a showcase for the responsible research institution, which necessitates ensuring a suitable marketing strategy. Many cohort studies, such as The Danish National Cohort Study (DANCOS) or Nordoc – a 25-year longitudinal study of Norwegian doctors, have their own websites or actively promote their results on social media.

5. Strategic objectives of the epidemiological research support plan

By initiating the Epidemiological Research Plan for the Years 2023–2033, ABM establishes an organisational and financial framework for implementing an advanced and well substantiated epidemiological research programme with the following objectives:

- ➔ To promote high-quality nationwide research focused on essential health issues,
- ➔ To increase innovation in epidemiology with the use of omic methods,
- ➔ To develop and ensure effective use of medical registries and BIG DATA,
- ➔ To foster international collaboration in epidemiological research.

5.1. Specific objectives of the Plan

The above-listed strategic objectives will be accomplished through achieving the relevant specific objectives.

- 1 Strategic objective:** To promote high-quality nationwide research focused on essential health issues

An efficient health policy must be driven by reliable epidemiological information. This strategic objective will support projects focusing on key health challenges, in particular in areas where there are identifiable data deficits: cardiovascular disease, neurodegenerative diseases and dementia, psychiatric disorders, infectious diseases, pulmonology, oncology, new health concerns and environmental risks.

Projects can be entered by private and public institutions, provided that the results are not meant to be used directly for commercial purposes and the data are completely transparent. Data generated as part of the epidemiological projects will be made public on the Internet, and will be generally available for use, processing and sharing for any purpose.

Support under this objective will be provided to projects that ensure access to digital data. The form of presentation of the digitised data will naturally affect their dissemination. In view of the nature of the conditions and pathogens under consideration, this strategic objective will support projects that are based on large cohorts, ensure transparency and security of data, and are highly usable and distributable.

Specific objectives

- A. To promote research regarding the risk factors and prevalence of lifestyle diseases in the context of multimorbidity (e.g. in cardiology, oncology, pulmonology, allergology, infectious diseases, immunosuppression)

In order to ensure high quality of epidemiological projects, they should be carried out by specialised institutions with the highest research potential. Such potential can be found in medical universities, clinical

hospitals and research institutes supervised by the Minister of Health. The projects will be aimed at providing current data on specific diseases and implementing systemic improvements with regard to key health problems. Epidemiological research projects focusing on multimorbidity should be oriented towards lifestyle diseases, mainly in the fields of cardiology, oncology, pulmonology, allergology, infectious diseases and immunosuppression. These areas are particularly important from the epidemiological point of view and require support in terms of large cohort studies.

The principal health concerns of the Polish population discussed in Chapter 3 clearly illustrate the nature of multimorbidity. Epidemiological research targeted on multimorbidity will certainly result in collecting a large body of relevant data that will help to improve our understanding of this phenomenon. Currently, there are no reliable data based on population studies.

For this reason, the Agency is planning to use the epidemiological research development plan to fund calls for proposals targeted towards investigating multimorbidity in the Polish population. The collected data will serve future intensification of health care efforts and, as a consequence, optimisation and revision of clinical recommendations for the management of specific populations.

- B. To promote research on facilitating access to information on the impact of COVID-19 and post-COVID-19 symptoms on population health status

Since early 2020, there has been a major shift in the perceived importance of epidemiological risks. The emergence of a previously unknown, highly infectious and highly fatal virus SARS-CoV-2 has transformed every aspect of human life around the globe. Most people infected with SARS-CoV-2 experience mild or moderate respiratory symptoms, can be home-isolated and recover without the need for hospitalisation. However, the elderly and individuals with other comorbidities (especially chronic) such as cardiovascular disease, diabetes, chronic respiratory conditions or cancer, are at a higher risk of a severe course of SARS-CoV-2 infection. There are currently no known well-established determining factors of developing long COVID-19. It is therefore necessary to undertake long-term observational research as a way to reliably assess the prevalence, severity, incidence and duration of symptoms, as well as establish the efficacy of the applied treatment.

As part of this objective, efforts should be intensified to obtain epidemiological data that correlate with the impact of COVID-19 and post-COVID-19 symptoms on the health of the Polish population in the short and long term.

- C. To explore ways to improve access to reliable data enabling estimation of epidemiological indicators (e.g. incidence/prevalence) associated with new health concerns faced by the Polish population

Given the scarcity of research projects in Poland, it is necessary to initiate studies exploring the impact of new technologies on human health. All over the world, a growing number of reports directly address the health risks associated with technological devices, such as phubbing (interacting with one's phone rather than other human beings) or technostress. Excessive use of technologies can lead to addiction, chronic fatigue, sleep disorders, stress, depression and burnout. All these health issues can follow from

technostress.

This objective is primarily aimed at improving access to information on new health concerns in the Polish population. This can be translated into epidemiological indicators that will drive action in health care aimed at combating sleep disorders, burnout syndrome or the growing issue of phubbing.

There are practically no studies in Poland concerned with the new risks such as technostress, phubbing or their consequences.

Exploring these new concerns within the framework of epidemiological research will form a basis for revising strategic documents pertaining to public health in Poland. As a consequence, a better understanding of new epidemiological risks will help introduce effective methods to prevent addiction, chronic fatigue, sleep disorders, stress, depression, and burnout.

- D. To promote research on the impact of environmental risks (e.g. smog, noise) on the health of the Polish population

Health prevention is composed of many elements. Some of them are concerned with the direct influence of the environment on the health of a population. The rapid pace of civilisational progress exerts a negative impact on human health through air pollution, microplastics or noise.

It is therefore postulated that more opportunities should be created for epidemiological research verifying the degree to which the Polish population is affected by environmental pathogenic factors. This will allow to collect systematised information on the actual consequences of exposure to environmental factors and lay the foundation for future recommendations on measures to eliminate them.

2 Strategic objective: To increase innovation in epidemiology with the use of omic methods

Epidemiological research can be greatly supported by molecular genetics. All over the world many research projects are successfully carried out to verify the presumed relation between gene polymorphisms and diseases. Genetic studies can help explain the unknown causes of some idiopathic diseases, and combinations of many techniques can be used to explore the multifactorial origin of other conditions. They can enable personalised profiling of patients in order to better adapt the necessary treatment.

To date, over a million subjects have participated in this type of studies globally. To analyse data representative of relatively rare polymorphic variants, it is necessary to ensure a sufficiently numerous study sample. To this end, ABM plans to support experienced research facilities (public or private) that are able to design and perform epidemiological research which employs omic analyses to process the data collected. A prerequisite for private facilities to enter the calls for proposals is that the results must not be used directly for commercial purposes and the data must be completely transparent.

Specific objectives

- A. To improve access to reliable data on epidemiological indicators (e.g. incidence/prevalence) by using omic analyses

Reducing early mortality or incidence rates relies on accelerating the development of pharmaceutical and non-pharmaceutical technologies. Omic analyses can be used to support this goal by comprehensively contributing to e.g. characterising different clinical phenotypes or estimating the heritability of genetic markers associated with a phenotype. The relationship between an aetiological factor and pathogen has been investigated in a number of conditions, for example in allergies. This class of diseases has seen major progress over the last few decades. It has been demonstrated that many environmental agents including allergens, air and water pollutants or dietary ingredients can trigger epigenetic changes in the genome of immune cells. Understanding the role and importance of epigenetic changes in the pathogenesis of allergies and asthma can contribute in the future to the emergence of therapies based on modifying the epigenetic status of cells or tissues.

ABM intends to fund studies oriented directly towards finding a correlation between pathogenic factors and genes to better inform treatment. The population effect will be changed values of epidemiological indicators.

B. To promote epidemiological research that uses omic analysis to support preventive medicine

Researchers in other countries engage, among other things, in genome-wide association studies (GWAS). These studies aim at genotyping 500,000 to over a million polymorphisms. The objective is above all to use whole genome sequencing in order to obtain a list of molecular markers which may be closely associated with the aetiopathogenesis of a given condition. Besides defining correlations between genes and diseases, this type of research can also investigate the interactions between genetic factors and human environment. At the moment, no such epidemiological research is being conducted in Poland to inform preventive medicine. This will therefore be an innovative pathway.

It is anticipated that omic-based epidemiological research will enable the utilisation of the results in health care programmes and efforts that can directly reduce the rates of cancer, mental diseases or cognitive disorders in Poland. Considering the high prevalence of allergies and asthma in Poland, also in this area opportunity may arise to use omic analysis in support of preventive medicine. This objective will therefore serve to revise the existing prevention regimes or develop innovative solutions based on omic results.

3 Strategic objective: To develop and ensure effective use of medical registries and BIG DATA

Many medical registries are created worldwide for the purpose of collecting data on the health of societies. They give rise to an enormous body of data that can inform state health policies over a long-term horizon. There are also disease-specific medical registries that collect patient data. Fully functional tools are key to draw conclusions from the data collected. This facilitates prevention but can also directly guide curative medicine. Poland can boast few medical registries established to collect data. The problem is correlating the information they gather with e.g. data from Western Europe. The goal here should be to facilitate the comparisons between the Polish population's health status and that of the world at large. It appears, therefore, that it is necessary to update the existing registries and create new ones.

Registries contain large volumes of data, referred to as BIG DATA. Using such data is becoming an essential characteristic of a medical registry. The availability of funding for establishing the necessary resources is a must for creating a well-designed medical registry.

ABM plans to create opportunities for financing projects that will, as part of their resources, build new or update existing databases.

Specific objectives

A. To foster more effective use of medical registries by the health care system

So far, observations on the use of medical registries suggest that a wider range of health information should be collected from the Polish public. ABM's funding of registry research will contribute to expanding the existing medical registries. Then, they can directly correlate with data from international databases. The option to make references and comparisons between population data will pave the way for new solutions such as diagnostic regimens or health programmes for the Polish population. The above analysis of the present and future needs in terms of epidemiological research in Poland prominently emphasised the importance of the fields of cardiology, oncology, pulmonology, allergology and infectious diseases. Updating the existing registries or designing new ones in the above fields is bound to benefit comprehensive verifiability of data. In the future, complementary registry data can also be applied to retrospective epidemiological research.

B. To promote therapies based on BIG DATA necessary for patient profiling and implementing personalised treatment

Currently in Poland, access to BIG DATA exchange is limited. An important limiting factor is the underfunding of research infrastructure necessary to collect and analyse large volumes of data. Better funding of the essential technical and organisational resources will help intensify the use of BIG DATA. Particular emphasis should be put on information from the fields of cardiology, oncology, pulmonology, allergology and infectious diseases. No less important is collecting data on neurodegenerative diseases, dementia and addiction to new technologies (e.g. technostress, phubbing), to mention just a few. Data are visibly lacking in all these areas.

Intensifying efforts to ensure support for health policies by using aggregated BIG DATA streams as part of collecting information on diseases should directly translate into developing personalised treatment options.

4 Strategic objective: To foster international collaboration in epidemiological research

No research effort can succeed without the appropriate resources in the form of experience, knowledge, planning skills and a capacity to develop standardised documentation. Combining these elements skilfully will determine the future success or failure of a study. This is why it is so important to support researchers and provide them with the right conditions to produce well-designed study projects. ABM's efforts under the epidemiological research development plan will cater for the individual professional development needs of

potential research group members and foster lasting international cooperation between scientific research facilities. These measures are bound to bring tangible benefits in the form of better experience, mastery in developing methodologies and more international recognition for Polish research institutions.

Specific objectives

- A. To enhance competence in epidemiological research groups with regard to planning and management of studies on large patient populations

Personnel is the key asset of any research project. This is particularly true for planning and handling epidemiological trials that require suitable competence levels.

ABM-funded internships and study visits at foreign epidemiological research facilities will improve the international position of Polish research groups and help them gain the necessary experience to carry out future epidemiological research in Poland.

- B. To promote the participation of Polish teams in international epidemiological research

Polish scientific institutions are not operating at their full potential. Injecting more funds into their teams in order to establish international cooperation with foreign research institutions will foster experience sharing and mutual learning.

- C. To promote the potential of Polish epidemiological research centres

Funding internships, study visits or stipends is a way to ensure gaining relevant experience. As a result, research groups will improve their skills in designing and carrying out large scale epidemiological studies. With such enhanced potential, the Polish research community will be able to take the lead in international epidemiological studies.

- D. To enhance the contribution of Polish data in European and international registries

More experience in conducting epidemiological research in accordance with a strictly defined methodology will result in a better quality of implemented projects. It will also foster cooperation with foreign institutions in the framework of international research. Another tangible benefit will be the possibility to have data from Polish registries published in prominent international journals.

- E. To promote correlation between Polish and international epidemiological data

The data collected in Polish registries often do not correspond with the internationally accepted assumptions. This creates problems when comparing study results from populations in Poland and Western Europe.

Cooperation with foreign research institutions and the know-how obtained from joint epidemiological projects will therefore bring advancements in the methodologies used in Polish research, thereby ensuring more alignment in terms of study design.

Appendix 1 contains a detailed presentation of all the objectives along with their respective outcomes, tools, implementation systems and estimated allocation values for each strategic objective.

6. Plan implementation and monitoring

The Epidemiological Research Plan for the Years 2023–2033 is primarily aimed at providing scientific evidence regarding the major health concerns that determine the structure of morbidity in the Polish society. Epidemiological research results should inform the implementation of reasonable and effective measures in health promotion and prevention as part of the health care system. The future efforts under the Plan and their outcomes must also be aligned with the existing strategies employed in epidemiological research and public health in a broad sense.

The progress of the Plan will be monitored with specific indicators:

- on the strategic objective level,
- on the project level.

The Plan will be carried out by monitoring the indicators listed below.

Indicator	Outcome measure
Number of subjects involved in epidemiological research financed by ABM	Minimum 130,000 subjects
Total number of sites conducting epidemiological studies under strategic objectives 1 and 2	Minimum 13 sites
Total number of epidemiological studies co-funded under strategic objectives 1 and 2	Minimum 13 studies
Number of publications on the impact of COVID-19 and post-COVID-19 symptoms on the health of the Polish population	Minimum 5 publications
Number of studies on the impact of lifestyle diseases in the context of multimorbidity	Minimum 4 studies
Number of studies assessing epidemiological indicators associated with new health concerns	Minimum 2 studies
Number of studies on the health impact of environmental risks	Minimum 2 studies
Number of studies assessing epidemiological indicators with the use of omic analyses	Minimum 3 studies
Number of epidemiological studies that use omic analysis to support preventive medicine	Minimum 2 studies

Number of newly established or modified medical registry databases	Minimum 2 newly established/modified databases
Number of newly established or modified treatment regimens drawing from BIG DATA analysis	Minimum 2 newly established/modified treatment regimens
Number of health programmes financed from public funds on the basis of omic analysis results in specified populations	Minimum 3 programmes
Number of internships and study visits by Polish research groups as part of international cooperation	Minimum 30 people participating in internships/study visits
Number of Polish teams participating in international epidemiological research	Minimum 5 research groups
Number of publications based on epidemiological research performed jointly with foreign groups	Minimum 10 publications

Projects will be implemented by way of monitoring pre-determined indicators (project implementation period), such as:

- Number of ongoing epidemiological studies,
- Number of individuals involved in epidemiological research,
- Number of investigated subject areas.

Financial considerations

Strategic objective	Estimated allocation value (PLN)
To promote high-quality nationwide research focused on essential health issues	180 million
To increase innovation in epidemiology with the use of omic methods	250 million
To develop and ensure effective use of medical registries and BIG DATA	150 million
To foster international collaboration in epidemiological research	20 million
Total	600 million

7. References

1. WHO. *Multimorbidity. Technical Series on Safer Primary Care*. Vol Geneva: Wo.; 2016.
2. The Academy of Medical Sciences. Multimorbidity: a priority for global health research Overview and key messages. *Academy of Medical Sciences*. 2018;(April).
3. du Vaure CB, Ravaud P, Baron G, Barnes C, Gilberg S, Boutron I. Potential workload in applying clinical practice guidelines for patients with chronic conditions and multimorbidity: A Systematic analysis. *BMJ Open*. 2016;6(3). doi:10.1136/bmjopen-2015-010119
4. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *The Lancet*. 2012;380(9836). doi:10.1016/S0140-6736(12)60240-2
5. Wiesner G, Bittner E. Zur Inzidenz und Prävalenz von Mehrfachkrankheiten in Deutschland. *Arbeitsmedizin Sozialmedizin Umweltmedizin*. 2005;40(9).
6. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *The Lancet Public Health*. 2018;3(7). doi:10.1016/S2468-2667(18)30091-4
7. Schäfer I, Kaduszkiewicz H, Nguyen TS, van den Bussche H, Scherer M, Schön G. Multimorbidity patterns and 5-year overall mortality: Results from a claims data-based observational study. *Journal of Comorbidity*. 2018;8(1). doi:10.1177/2235042x18816588
8. Head A, Fleming K, Kypridemos C, Pearson-Stuttard J, O'Flaherty M. Multimorbidity: The case for prevention. *Journal of Epidemiology and Community Health*. 2021;75(3). doi:10.1136/jech-2020-214301
9. Laskowski I. Rola prywatnych ubezpieczeń zdrowotnych w systemie ochrony zdrowia w obliczu zmian demograficznych w Polsce. *Problemy Zarządzania*. 2017;15(3):117-129.
10. Banerjee A, Hurst J, Fottrell E, Miranda JJ. Multimorbidity: Not just for the west. *Global Heart*. 2020;15(1). doi:10.5334/GH.835
11. Hurst JR, Dickhaus J, Maulik PK, et al. Global Alliance for Chronic Disease researchers' statement on multimorbidity. *The Lancet Global Health*. 2018;6(12). doi:10.1016/S2214-109X(18)30391-7
12. Kudesia P, Salimmarouny B, Stanley M, et al. The incidence of multimorbidity and patterns in accumulation of chronic conditions: A systematic review. *Journal of Multimorbidity and Comorbidity*. 2021;11. doi:10.1177/26335565211032880
13. van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: An analysis of the European Heart Failure Pilot Survey. *European Journal of Heart Failure*. 2014;16(1). doi:10.1002/ehf.30
14. Siga O, Wizner B, Piotrowicz K, Fedyk-Lukasik M, Grodzicki T. The prevalence and determinants of multimorbidity in hospitalized patients with heart failure. *Folia medica Cracoviensia*. 2017;57(2).
15. Nguyen H, Manolova G, Daskalopoulou C, Vitoratou S, Prince M, Prina AM. Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. *Journal of Comorbidity*. 2019;9. doi:10.1177/2235042x19870934
16. The Lancet. Making more of multimorbidity: an emerging priority. *The Lancet*. 2018;391(10131). doi:10.1016/S0140-6736(18)30941-3
17. Willadsen TG, Bebe A, Køster-Rasmussen R, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity – a systematic review. *Scandinavian Journal of Primary Health Care*. 2016;34(2). doi:10.3109/02813432.2016.1153242
18. Onder G, Palmer K, Navickas R, et al. Time to face the challenge of multimorbidity. A European perspective from the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). *European Journal of Internal Medicine*. 2015;26(3). doi:10.1016/j.ejim.2015.02.020
19. Haith MM, Benson JB. *Encyclopedia of Infant and Early Childhood Development*. Vol 1-3.; 2008. doi:10.5860/choice.46-0041
20. Pawankar R, Holgate ST, Canonica GW, Lockey RF, Blaiss MS. *World Allergy Organization (WAO) White Book on Allergy: Update 2013*. Vol 43.; 2016.
21. Agache I, Akdis CA. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases. *Journal of Clinical Investigation*. 2019;129(4). doi:10.1172/JCI124611
22. Fuchs O, Bahmer T, Weckmann M, et al. The all age asthma cohort (ALLIANCE) - from early beginnings to chronic disease: A longitudinal cohort study. *BMC Pulmonary Medicine*. 2018;18(1). doi:10.1186/s12890-018-0705-6
23. Epton MJ, Town GI, Ingham T, et al. The New Zealand Asthma and Allergy Cohort Study (NZA2CS): Assembly, demographics and investigations. *BMC Public Health*. 2007;7. doi:10.1186/1471-2458-7-26
24. Rajaei A, Masquelin ME, Pohlgeers KM. Pediatric Allergy: An Overview. *Primary Care - Clinics in Office Practice*. 2021;48(3). doi:10.1016/j.pop.2021.04.006
25. Brozek G, Lawson J, Szumilas D, Zejda J. Increasing prevalence of asthma, respiratory symptoms, and allergic diseases: Four repeated surveys from 1993-2014. *Respiratory Medicine*. 2015;109(8). doi:10.1016/j.rmed.2015.05.010
26. Dubovyi A, Chelimo C, Schierding W, Bisnyuk Y, Camargo CA, Grant CC. A systematic review of asthma case definitions in 67 birth cohort studies. *Paediatric Respiratory Reviews*. 2021;37. doi:10.1016/j.prrv.2019.12.005
27. Barber AT, Loughlin CE. Pediatric Pulmonology 2020 year in review: Asthma. *Pediatric Pulmonology*. 2021;56(8). doi:10.1002/ppul.25510
28. Innes Asher M, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. *European Respiratory Journal*. 2020;56(6). doi:10.1183/13993003.02094-2020
29. Dharmage S. C., Perret J. L., Custovic A. Epidemiology of Asthma in Children and Adults. *Frontiers in Pediatrics*. 2019;7(JUN).
30. Agache I, Annesi-Maesano I, Bonertz A, et al. Prioritizing research challenges and funding for allergy and asthma and the need for translational research—The European Strategic Forum on Allergic Diseases. *Allergy: European Journal of Allergy and Clinical Immunology*. 2019;74(11). doi:10.1111/all.13856
31. North ML, Brook JR, Lee EY, et al. The Kingston Allergy Birth Cohort: Exploring parentally reported respiratory outcomes through the lens of the exposome. *Annals of Allergy, Asthma and Immunology*. 2017;118(4). doi:10.1016/j.anai.2017.01.002

32. Lodge CJ, Lowe AJ, Dharmage SC. EuroPrevall: Insights into the allergic disease epidemic. *Thorax*. Published online 2018. doi:10.1136/thoraxjnl-2018-211660
33. Ostrowska M, Woźniak R. *Analiza Ryzyka Wystąpienia Zjawiska Stresu i Wypalenia Zawodowego Wśród Funkcjonariuszy Policji*. Oficyna Wydawnicza AFM; 2018.
34. Zgliczyńska M, Zgliczyński S, Ciebiera M, Kosińska-Kaczyńska K. Occupational burnout syndrome in Polish physicians: A systematic review. *International Journal of Environmental Research and Public Health*. 2019;16(24). doi:10.3390/ijerph16245026
35. Misiótek A, Gorczyca P, Misiótek H, Gierlotka Z. The prevalence of burnout syndrome in Polish anaesthesiologists. *Anaesthesiology Intensive Therapy*. 2014;46(3). doi:10.5603/AIT.2014.028
36. Wirkus Ł, Babicka-Wirkus A, Opora R, Stasiak K. Burnout among probation officers in Poland and the role of preferred styles of coping with stress. *International Journal of Environmental Research and Public Health*. 2021;18(1). doi:10.3390/ijerph18010355
37. Basinska BA, Däderman AM. Work values of police officers and their relationship with job burnout and work engagement. *Frontiers in Psychology*. 2019;10(MAR). doi:10.3389/fpsyg.2019.00442
38. UNICEF Poland. *W trosce o przyszłe pokolenia. Dzieci w krajach bogatych w kontekście Celów Zrównoważonego Rozwoju*. [Original title: Building the Future. Children and the Sustainable Development Goals in Rich Countries.]; 2017
39. Supreme Audit Office. *Dostępność leczenia psychiatrycznego dla dzieci młodzieży w latach 2017–2019*. [Access to psychiatric treatment for children and adolescents in the years 2017–2019.]; 2020
40. Biechowska D, Orłowska E. Neuropsychologiczna charakterystyka wybranych zespołów otępiennych. *Polski Przegląd Neurologiczny*. 2012;8(2).
41. Hańczyc P, Sochocka M, Leszek J. *Opieka medyczna nad osobami starszymi z chorobami neurodegeneracyjnymi w erze postępującej cyfryzacji: raport sierpień 2020* [Medical care in the elderly with neurodegenerative diseases in the age of advancing digital transition: Report, August 2020]; 2020
42. Szczudlik A, Barcikowska-Kotowicz M, Gabry T. *Sytuacja osób chorych na chorobę Alzheimera w Polsce. Raport RPO* [Situation of Alzheimer's disease patients in Poland. Report by the Polish Ombudsman]; 2016
43. Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *Journal of the Royal Society of Medicine*. 2021;114(9). doi:10.1177/01410768211032850
44. Borkowski L, Fal A, Filipiak K, et al. *Charakterystyka Choroby COVID-19, Objawy Oraz Skutki Zdrowotne. Rekomendacje i Doświadczenia Polskich Klinikistów.*; 2021.
45. Carfi, A., Bernabei, R., Landi F& G. Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *The BMJ*. 2020;369.
46. Mandal S, Barnett J, Brill SE, et al. Long-COVID: A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax*. 2021;76(4). doi:10.1136/thoraxjnl-2020-215818
47. Tenforde MW, Kim S, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020. *MMWR*. 2020;69(30).
48. *Wpływ stanu środowiska na zdrowie* [The impact of natural environment on human health]; 2015
49. Wang J, Tan Z, Peng J, Qiu Q, Li M. The behaviors of microplastics in the marine environment. *Marine Environmental Research*. 2016;113. doi:10.1016/j.marenvres.2015.10.014
50. Wright SL, Thompson RC, Galloway TS. The physical impacts of microplastics on marine organisms: a review. *Environmental Pollution (Barking, Essex : 1987)*. 2013;178. doi:10.1016/j.envpol.2013.02.031
51. International Agency for Research on Cancer. Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2020–2024. *IARC Monographs On The Evaluation Of Carcinogenic Risks To Humans*. 2020;(April 2014).
52. Tarapore P, Ying J, Ouyang B, Burke B, Bracken B, Ho SM. Exposure to bisphenol a correlates with early-onset prostate cancer and promotes centrosome amplification and anchorage-independent growth in vitro. *PLoS ONE*. 2014;9(3). doi:10.1371/journal.pone.0090332
53. Tse LA, Lee PMY, Ho WM, et al. Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. *Environment International*. 2017;107. doi:10.1016/j.envint.2017.06.012
54. Trabert B, Falk RT, Figueroa JD, et al. Urinary bisphenol A-glucuronide and postmenopausal breast cancer in Poland. *Cancer Causes and Control*. 2014;25(12). doi:10.1007/s10552-014-0461-8
55. Rahman A, Sarkar A, Yadav OP, Achari G, Slobodnik J. Potential human health risks due to environmental exposure to nano- and microplastics and knowledge gaps: A scoping review. *Science of the Total Environment*. 2021;757. doi:10.1016/j.scitotenv.2020.143872
56. European Parliament DG for IP of the UGR. *The Mental Health of Workers in the Digital Era : How Recent Technical Innovation and Its Pace Affects the Mental Well-Being of Workers.*; 2020.
57. Bondanini G, Giorgi G, Ariza-Montes A, Vega-Muñoz A, Andreucci-Annunziata P. Technostress dark side of technology in the workplace: a scientometric analysis. *International Journal of Environmental Research and Public Health*. 2020;17(21). doi:10.3390/ijerph17218013
58. Salanova M, Llorens S, Ventura M. Technostress: The dark side of technologies. In: *The Impact of ICT on Quality of Working Life*. ; 2014. doi:10.1007/978-94-017-8854-0_6
59. Salanova M, Llorens S, Cifre E. The dark side of technologies: Technostress among users of information and communication technologies. *International Journal of Psychology*. 2013;48(3). doi:10.1080/00207594.2012.680460
60. Brooks S, Schneider C, Wang X. Technology addictions and technostress: An examination of Hong Kong and the U.S. In: *AMCIS 2016: Surfing the IT Innovation Wave - 22nd Americas Conference on Information Systems*. ; 2016.
61. Borle, P., Reichel, K., Niebuhr, F., & Voelter-Mahlknecht, S. (2021). How are techno-stressors associated with mental health and work outcomes? A systematic review of occupational exposure to information and communication technologies within the technostress model. *International Journal of Environmental Research and Public Health*, 18(16), 8673. doi.org/10.3390/ijerph18168673
62. Salo M, Pirkkalainen H, Koskelainen T. Technostress and social networking services: Explaining users' concentration, sleep, identity, and social relation problems. *Information Systems Journal*. 2019;29(2). doi:10.1111/isj.12213
63. Uffelmann E, Huang QQ, Munung NS, et al. Genome-wide association studies. *Nature Reviews Methods Primers*. 2021;1(1):59. doi:10.1038/s43586-021-00056-9

64. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726). doi:10.1038/s41586-018-0579-z
65. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: Consensus, uncertainty and challenges. *Nature Reviews Genetics*. 2008;9(5). doi:10.1038/nrg2344
66. Khera A v., Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature Genetics*. 2018;50(9). doi:10.1038/s41588-018-0183-z
67. LaBianca S, LaBianca J, Pagsberg AK, et al. Copy Number Variants and Polygenic Risk Scores Predict Need of Care in Autism and/or ADHD Families. *Journal of Autism and Developmental Disorders*. 2021;51(1). doi:10.1007/s10803-020-04552-x
68. Kramer I, Hoening MJ, Mavaddat N, et al. Breast Cancer Polygenic Risk Score and Contralateral Breast Cancer Risk. *American Journal of Human Genetics*. 2020;107(5). doi:10.1016/j.ajhg.2020.09.001
69. Leonenko G, Sims R, Shoai M, et al. Polygenic risk and hazard scores for Alzheimer's disease prediction. *Annals of Clinical and Translational Neurology*. 2019;6(3). doi:10.1002/acn3.716
70. Hachiya T, Kamatani Y, Takahashi A, et al. Genetic Predisposition to Ischemic Stroke: A Polygenic Risk Score. *Stroke*. 2017;48(2). doi:10.1161/STROKEAHA.116.014506
71. Flis S, Flis K, Splawiński J. Modyfikacje epigenetyczne a nowotwory. *Nowotwory*. 2007;57(4).
72. Kabesch M, Michel S, Tost J. Epigenetic mechanisms and the relationship to childhood asthma. *European Respiratory Journal*. 2010;36(4). doi:10.1183/09031936.00019310
73. Liu J, Ballaney M, Al-Alem U, et al. Combined inhaled diesel exhaust particles and allergen exposure alter methylation of T helper genes and Ige production in vivo. *Toxicological Sciences*. 2008;102(1). doi:10.1093/toxsci/kfm290
74. Prunicki M, Stell L, Dinakarandian D, et al. Exposure to NO₂, CO, and PM 2.5 is linked to regional DNA methylation differences in asthma. *Clinical epigenetics*. 2018;10. doi:10.1186/s13148-017-0433-4
75. Dmitrzak-Węglarz M, Hauser J. Mechanizmy epigenetyczne w chorobach psychicznych i zaburzeniach funkcji poznawczych. *Psychiatria*. 2009;6(2).
76. Veldic M, Kadriu B, Maloku E, et al. Epigenetic mechanisms expressed in basal ganglia GABAergic neurons differentiate schizophrenia from bipolar disorder. *Schizophrenia Research*. 2007;91(1-3). doi:10.1016/j.schres.2006.11.029
77. Gürel E. SWOT Analysis: A theoretical review. *Journal of International Social Research* 10(51):994-1006 August 2017DOI: 10.17719/jisr.2017.1832 Dostęp 18.10.2020 r., s. 994.
78. Website of *Przegląd Epidemiologiczny*: <http://www.przeglepidemiol.pzh.gov.pl/media/niezbednik/Badania%20kohortowe.pdf> Access on 28 Feb 2022
79. Website of *Przegląd Epidemiologiczny*: <http://www.przeglepidemiol.pzh.gov.pl/badania-kliniczno-kontrolne> Access on 01 Apr 2022
80. *Demographic situation in Poland up to 2020. Death and mortality*; GUS 2022
81. *Cancer in Poland in 2019*; KRŃ 2021
82. Website of the National Health Fund, epidemiology records – diabetes mellitus: <https://shiny.nfz.gov.pl/cukrzyca/> Accessed on 27 May 2022
83. Website of the National Health Fund: <https://statystyki.nfz.gov.pl/> Accessed on 12 Jan 2021
84. Zejda JE., Wysocki MJ.: Zdrowie Publiczne w projektach badawczych finansowanych przez Ministerstwo Nauki i Szkolnictwa Wyższego – realizacja i potrzeby. *Przegląd Epidemiologiczny* 2010, 64(3): 405-411.
85. Poglód R., Rosiek A, Łętowska M. Nowo pojawiające się choroby zakaźne w aspekcie bezpieczeństwa krwi. *Acta Haematologica Polonica*, 44:(2013);284-293.
86. Directorate general for internal policies policy department a: economic and scientific policy. Communicable Diseases: EU Response to HIV, Tuberculosis and Hepatitis C. 2016.
87. Website of NIPH NIH - NRI: <https://szczepienia.pzh.gov.pl/faq/jaka-jest-liczba-uchylen-szczepien-obowiazkowych/> Accessed on 21 Apr 2022
88. al. Rezaei N. et. Introduction on Primary Immunodeficiency Diseases. [In:] Rezaei N. Aghamohammadi A., Notarangelo L. *Primary Immunodeficiency Diseases*. Berlin, Springer, 2017.
89. Tangye SG Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhender E, Picard C, Puck J, Torgerson TR, Casanova JL, Sullivan KE. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 40(1):24-64, 2021
90. Bucciol G Moens L, Bosch B, Bossuyt X, Casanova JL, Puel A, et al. Lessons learned from the study of human inborn errors of innate immunity. *J Allergy Clin Immunol*. 143(2):507–527, 2019.
91. Zhang Q Frange P, Blanche S, Casanova JL. Pathogenesis of infections in HIV-infected individuals: insights from primary immunodeficiencies. *Curr Opin Immunol*. 48:122–133., 2017.
92. Winter Litzman J. Primary immunodeficiencies in adults. *Vnitř Lek*. 2019, strony 65(2):109-116.
93. Website of AOTMiT: <https://www.aotm.gov.pl/projekty-aotmit/gbd/metodologia-global-burden-of-disease/> Accessed on 03 Jun 2022