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Scoping study on evidence to tackle high-burden under-researched medical conditions

Discussion paper

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Scoping study on evidence to tackle high-burden under-researched medical conditions - Discussion paper

European Commission
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Scoping study on evidence to tackle high-burden under-researched medical conditions

Discussion paper

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1. Summary

The European Commission (EC) supports the improvement of health and healthcare across the European Union (EU). This is in part done by allocating funding for research and innovation to, amongst others, increase our understanding of specific medical conditions and to stimulate advances in diagnosis, prevention and treatment. However, some medical conditions fail to be sufficiently recognised, diagnosed, prevented or treated, and may therefore be under-researched. These conditions can however, pose a considerable burden on patients and society. The aim of the current study is to explore the definition, identification and research needs of high-burden under-researched medical conditions in the EU.

What are high-burden under-researched medical conditions – a working definition

Within this study, high-burden under-researched medical conditions are defined as: “Diseases or conditions that receive insufficient research funding relative to the expected level of funding based on their burden.” This working definition, derived from literature and stakeholder consultation, is based on the assumptions that the burden stems (partly) from lack of evidence regarding the conditions, and that conditions with a high burden for patients, should receive a higher share of the total funding for medical research, than conditions with a low burden. Rare diseases (i.e. diseases affecting less than 1 in 2000 European citizens) did not fall within the scope of the current study, as the EC has specific funding for rare diseases.

Methodological approach to identify high-burden under-researched conditions

Since there is no gold standard on how to identify high-burden under-researched medical conditions, four complementary perspectives were used to compose a list of possible high-burden under-researched medical conditions in the EU. In the first perspective, the amount of EU funding per group of medical conditions (based on the International Classification of Diseases, version 11) was examined. The five groups of medical conditions that received the least EU funding were selected. In the second perspective, the amount of funding was related to the burden of medical conditions, expressed in prevalence, disability adjusted life years (DALYs), years of life lost (YLL), and mortality (based on the Global Burden of Diseases study). For each of these burden metrics, the 10 most relatively under-funded (groups of) conditions were selected for the list. In addition, (groups of) conditions mentioned in the top 50 of all burden metrics (i.e. prevalence, DALY, YLL, and deaths) were identified for the list of high-burden under-researched medical conditions. In the third perspective, a short literature search in PubMed was carried out to identify why (with what complaints) patients visit their general practitioner (GP). This perspective led to an overview of common complaints, symptoms or conditions for which European citizens visit their GP and may thus be considered high-burden. In the fourth and last perspective, stakeholders were asked to indicate any additional high-burden under-researched medical conditions, leading to 20 additional conditions. Conditions were excluded from the final list of high-burden under-researched medical conditions if: a) it concerned a rare disease, b) there was no evident knowledge gap concerning aetiology and treatment for the particular condition, and c) the funding received was relatively high.

Twelve possible high-burden under-researched groups of medical conditions

Twelve groups of conditions were identified as possibly high-burden and under-researched. Within these groups of medical conditions, several individual diseases or conditions were identified. Box 1 presents the final list of all the identified possible high-burden under-researched medical conditions in this study.

Box 1: the final list of possible high-burden under-researched medical conditions

Main groups of disorders <i>(conditions further detailed in this report)</i>
Mental disorders (Depression or anxiety; Self-harm; Autism)
Disorders of the blood and organ system (Chronic kidney disease; Cirrhosis and other chronic liver diseases; Cystitis/urinary tract infection; Gallbladder and biliary diseases; Abdominal pain Haemoglobinopathies and haemolytic anaemias)
Musculoskeletal disorders (Arthritis (not back); Injuries; Low back pain; Fibromyalgia)
Headache disorders (Tension-type headache; Migraine)
Fatigue / weakness (Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS))
Sleep-wake disorders
Skin and subcutaneous diseases (Dermatitis; Hidradenitis Suppurativa; Genital Lichen Sclerosus; Lichen Planus)
Gynaecological diseases (Pregnancy, childbirth or the puerperium; Endometriosis)
Conditions related to sexual health
Developmental anomalies
Immune related diseases (Allergy (food allergy); Autoimmune diseases; Mast cell activation syndrome (MCAS))
Other: Postural tachycardia syndrome (POTS); Chronic Lyme disease; Hypermobile Ehlers Danlos Syndrome (EDS)
Note that for some diseases or conditions that are generally considered not to be under-funded, certain population groups could be underserved and there is therefore a need to better consider the diversity of the affected population. Furthermore, it is recommended to keep on monitoring the threat of and attention to infectious diseases, as well as the budget allocated to and the burden of post COVID-19, as factors such as globalisation, antimicrobial resistance, influx of migrants, and climate change could make these themes even more relevant in the future.

Stakeholders identified prevention, basic or fundamental research, clinical research and implementation research as important research areas. In addition, stakeholders underlined the importance of cohorts, biobanks, large databases like genetic / imaging data, as well as clinical trial networks. To increase research activities in high-burden under-researched medical conditions, stakeholders considered overall that it is important to create more / better national, EU, and international funding opportunities, stimulate the creation of large research networks, increase accessible incentives to do research on these medical conditions,

stimulate the organisation of specific conferences in the medical areas, and stimulate researcher mobility.

Ongoing research and monitoring is required

This exploratory study led to a list of possible high-burden under-researched groups of medical conditions and individual diseases or conditions. A strength of the current study is that multiple methods (perspectives) were applied to come to the identification of possible high-burden under-researched medical conditions. However, each of these perspectives has its own limitations. The major limitations are that with the definition, sources and data used in this study, only a part of (i) the full landscape of high-burden medical conditions, (ii) research and development resources, and (iii) the burden of diseases specifically due to lack of scientific evidence is described.

The identified disease groups may be used as a starting point to further explore specific conditions within these groups. As research priorities change over the years and the European Union is only one of many players in the field of health research funding, we recommend a number of future activities in this area of research.

First, we recommend future activities in this field to focus on specific areas of diseases and dedicate resources to rigorously investigate which conditions within the identified groups of diseases are high-burden due to lack of scientific evidence to effectively address them, quantify their impact on individuals, society and healthcare systems, study the research and innovation initiatives undertaken over the past years, and consult extensively with experts and other stakeholders in the field to understand what type of research activity is urgently needed. This approach will allow for a more in-depth analysis within disease groups, as opposed to the broad scoping research performed here, which is needed when determining knowledge gaps within specific disease areas.

Second, we recommend future activities in this field to include information on research input and output from outside the EU. When certain high-burden under-researched conditions are already (scheduled to be) targeted by funding bodies other than those from the EC, this may influence the priorities to be set within EU. Taking funding from outside the EU Framework Programmes for Research and Innovation into account will result in a more valid evaluation of medical conditions that may be under-researched and enables (global) prioritisation and appropriate distribution of resources. Third, we recommend to pay more attention to the diversity of affected populations. Within some diseases or conditions that are generally considered not to be under-researched, certain population groups could very well be underserved. The systematic evaluation of this diversity in terms of age, gender, ethnic background and other aspects in which human beings differ from one another needs to be taken into account when setting research priorities.

This study provides a first impression of the areas in which more support seems to be needed. We recommend that the findings of this study be further explored and considered when designing topics in future work programmes, to offer opportunities for support to diseases and regions where they are needed the most.

2. Introduction

2.1. Issue at stake

Research and innovation is essential to deliver improved diagnostic, preventive and therapeutic strategies. The European Commission (EC) therefore funds research projects on a variety of medical conditions via framework programmes for research and innovation. Deciding on the amount of resources that should be attributed to certain medical conditions is not an easy task. State of the art with regards to knowledge on physiology, pathology or treatment may vary considerably between medical conditions. At the same time, the burden that medical conditions pose on European citizens varies between conditions, but also varies within the population, across countries, ethnicities and genders. Some of these conditions that pose a considerable burden on European citizens may be insufficiently researched and underfunded by the European Commission's framework programmes. Which diseases, conditions or syndromes it concerns is currently unknown. Therefore, the European Commission (Directorate-General for Research and Innovation (DG RTD)) has tasked the EUHealthSupport consortium to identify those under-researched conditions that have a high burden for citizens of the European Union (EU). Insight into these high-burden under-researched medical conditions could lead to improved policies and practices to better tackle these conditions and hopefully alleviate the burden on patients and society.

2.2. Background

In the past, various studies have been conducted on the topic of under-researched medical conditions. They demonstrate a mismatch between research and development needs in terms of burden of disease and research and development activities in the form of funding, clinical trial conduct, drug innovation or other metrics of research output (1-4). A study from the United States showed that the National Institute of Health (NIH) spending appeared to be based primarily on the level of spending for that disease in prior years, despite changes in burden of disease (5). Atal and colleagues identified for instance that in non-high-income regions, the conduct of randomised controlled clinical trials (RCTs) was misaligned with the distribution of major causes of burden, in particular infectious diseases and neonatal disorders in Sub-Saharan Africa and South Asia (6). Another study from the United States showed that globally, the conditions most understudied relative to disease burden were injuries, nutritional deficiencies, and respiratory infections (7). Recently, the German Federal Ministry of Education and Research (BMBF) launched a call to support projects studying 'the unknown patho-mechanisms of individual diseases with a high burden'¹. To date, no studies were found that have the aim to identify high-burden under-researched conditions in the EU.

2.3. Aim

The aim of this discussion paper is to provide insight into high-burden under-researched medical conditions in the European Union, as well as possible clarifications on why or in what respect certain medical conditions can be considered under-researched. Given the limited time and resources available, and considering that no gold standard for the identification of high-burden under-researched medical conditions exists, the study described in this discussion paper is of an explorative nature and focuses on funding by the European Commission.

¹ <https://www.gesundheitsforschung-bmbf.de/de/11004.php>; and <https://www.bmbf.de/bmbf/en/research/health-research/pooling-research-to-tackle-common-diseases/pooling-research-to-tackle-common-diseases.html>

3. Methodology

The following steps were taken to compose a list of possible high-burden under-researched medical conditions:

- Defining high-burden under-researched medical conditions;
- Selection of high-burden under-researched medical conditions using four leading perspectives:
 - Perspective 1: Matching levels of EU research funding with medical conditions, as categorised in the International Classification of Diseases (ICD-11);
 - Perspective 2: Matching levels of EU research funding with high-burden medical conditions, as documented in the Global Burden of Diseases (GBD) study;
 - Perspective 3: Matching levels of EU research funding with medical conditions identified as why people most frequently consult their general practitioner (GP);
 - Perspective 4: Stakeholders' views on the identified high-burden under-researched medical conditions;
- Integrating the conditions that were obtained from the four perspectives into one list of possible high-burden under-researched medical conditions.

Defining high-burden under-researched medical conditions

There is no common definition of high-burden under-researched medical conditions. To determine how these high-burden under-researched medical conditions are best defined, two strategies were pursued:

- An explorative (non-systematic) literature search to identify how high-burden under-researched medical conditions are defined in scientific studies;
- An internet search and stakeholder consultation to determine how other research-funding organisations in Europe, Canada and the US define high-burden under-researched medical conditions.

Fourteen studies were reviewed (6, 8-20) and definitions from two funding organisations were retrieved (the Research Council of Norway, and the German Federal Ministry of Education and Research / DLR Project Management Agency) (21). In general, these definitions determined which diseases or areas of diseases are under-researched or under-funded by analysing the expected level of funding or research output for a specific disease in relation to its burden. Based on this, high-burden under-researched medical conditions in this study are defined as:

“Diseases or conditions that receive insufficient research funding relative to the expected level of funding based on their burden.”

Within this working definition the expected level of funding is based on whether there is a balance between the contribution of the burden on patients that the disease or condition imposes relative to the total burden on the European population, and the share of the total budget a specific disease or condition receives relative to the total funding for medical research.

In this study, medical conditions are limited to conditions in the European setting. As rare diseases are funded through dedicated European research funds, and because they require a different approach, rare diseases are considered outside the scope of this study and will

hence be excluded. In this study, a rare disease will be defined as affecting no more than 1 person in 2,000².

Selection of high-burden under-researched medical conditions

Identification of high-burden under-researched medical conditions was explored using four perspectives, which is illustrated by Figure 3.1 and of which the methodology is discussed below.

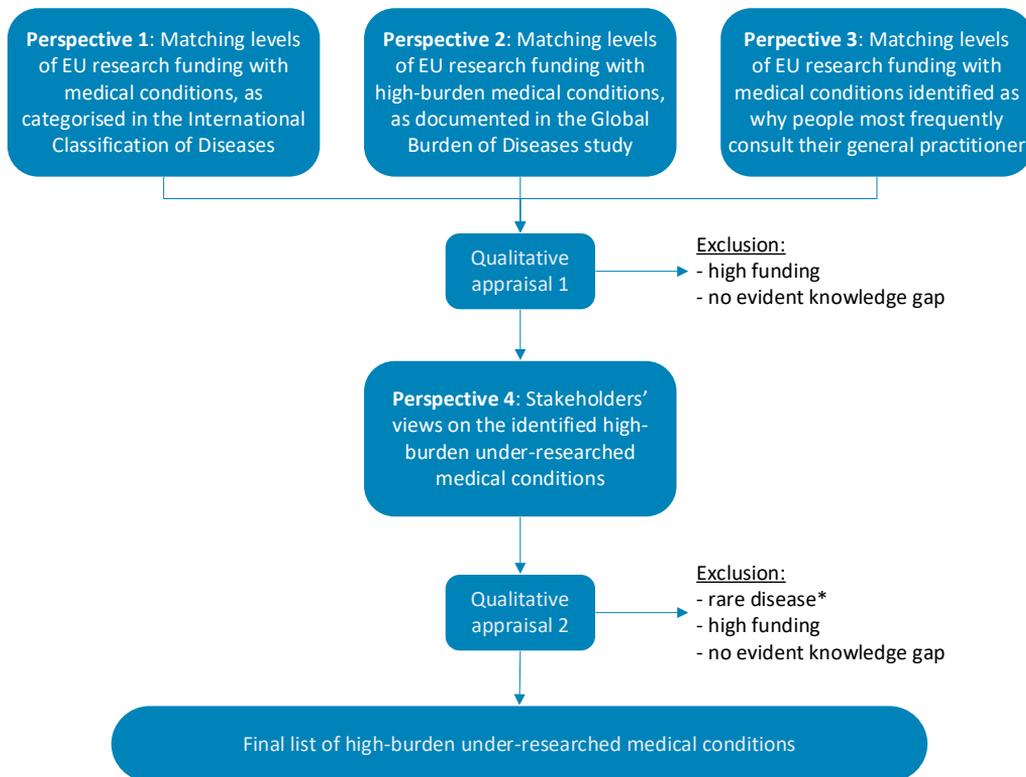


Figure 3.1. Overview of the selection process to come to a list of high-burden under-researched conditions

* Rare diseases in perspectives 1, 2 and 3 were not excluded in qualitative appraisal round 1, but during the selection process.

Perspective 1: Matching levels of EU research funding with medical conditions, as categorised in the International Classification of Diseases (ICD-11)

EC funded projects were identified through the Community Research and Development Information Service (CORDIS) database, which is the European Commission’s primary source of results from the projects funded by the EC’s framework programmes for research and innovation³. A CORDIS database file was downloaded from the online open CORDIS database for all projects under the Horizon 2020 Programme within the filter ‘domain of

² https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en

³ <https://cordis.europa.eu/en>

application: health'⁴. This resulted in 1,580 projects to be screened and a total of 812 projects that were considered relevant for this study.

The disease(s)/condition(s) that were the topic of research in these projects were classified according to the corresponding code of the 11th revision of the International Classification of Diseases (ICD-11). Also the amount of (the EC's contribution to) funding for each project was linked to the ICD-11. Eventually, this led to a dataset in which for each ICD code the total number of projects and funding from the screened projects could be extracted. The five ICD-11 chapters that received the lowest amount of funding were identified as potentially under-researched in this first approach. (For strengths and limitations of this approach, see section 5: discussion).

Perspective 2: Matching levels of EU research funding with high-burden medical conditions, as documented in the Global Burden of Diseases (GBD) study

Considering the measures that were seen as being frequently used in relative similar studies found in the literature (1, 5, 6, 9-16, 18-20, 22-26) and based on the availability of information in the Global Burden of Disease (GBD) database⁵, it was decided to approach the burden of diseases in this study with the following measures: prevalence, disability adjusted life years (DALYs), years of life lost (YLL), and mortality (death). These measures were obtained from the GBD for the year 2019 for the European Union.

Information was available for 364 'causes', or medical conditions. Yet, not all of these causes were considered relevant for this study. As such, causes defined as rare diseases not compatible with the ICD (e.g. addressing 'communicable diseases' without further specification), too specifically defined for the information obtained in CORDIS (e.g. 'cirrhosis and other chronic liver diseases due to NAFLD'), not related to diseases/conditions but rather a general risk-factor, and causes that are subcategories of groups of diseases that were classified as 'other', were eliminated. This resulted in 195 diseases and groups of diseases for which prevalence and burden information was obtained from the GBD.

Subsequently, analyses using Excel were executed to determine the relative funding versus the prevalence/burden of each of these diseases and disease groups. For each disease the percentage of the burden metric (i.e. prevalence, DALY, YLL, death) as part of the total was calculated, as well as the percentage of the funding as part of the total. Next the funding difference was determined as illustrated below. This calculation was done based on the assumption that, ideally, the percentage of funding the disease has received should be equal to the percentage of contribution to the total burden.

$$\text{Burden (in \%)} = \frac{\text{absolute number of burden metric}}{\text{sum of absolute numbers of burden metrics}} * 100\%$$

$$\text{Funding (in \%)} = \frac{\text{funding for disease}}{\text{total amount of funding for all included diseases}} * 100\%$$

⁴ From the CORDIS database, we selected projects that were assigned the tag "Health" as domain of application. The applied filter resulted in a collection of projects reflecting Cordis publications in the health area and a semi-automatic classification of health research projects based on the European Science Vocabulary (EuroSciVoc) taxonomy. The rationale behind this choice is that these projects are considered to contribute to the health of EU citizens. However, this approach has its limitations, as it does not cover all areas related to health, missing areas such as fundamental research.

⁵ Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020. Available from: <https://vizhub.healthdata.org/gbd-results/>.

Funding difference: Δ per disease (in %) = Funding – burden

Where:

$\Delta = 0$ means funding equals burden

Positive Δ = funding > burden

Negative Δ = funding < burden

Thereafter, all funding differences (Δ) were sorted from lowest to highest for all four metrics. Here, the lowest numbers represent the most under-funded diseases in the list. For all four metrics, the 50 diseases or disease groups with the lowest numbers (i.e. highest mismatch between funding and burden) were listed. Diseases or disease groups that were mentioned in the top 50 of all burden metrics (i.e. prevalence, DALY, YLL, and deaths) were identified for the list of under-funded high-burden medical conditions. In addition, for each burden metric the 10 most relatively under-funded diseases or disease groups were identified for the list⁶. (For strengths and limitations of this approach, see section 5: discussion).

Perspective 3: Diseases and conditions for which people visit their GP

To identify those conditions that represent a high burden for patients but are poorly recognised by the first and second perspectives described above due to a lack of knowledge or definition, a short literature search in PubMed was carried out to identify why (with what complaints) patients visit their general practitioner (GP) (see Annex C for more details on the search terms and the selection process). This perspective led to an overview of common complaints, symptoms or conditions for which European citizens visit their GP and may thus be considered high-burden. (For strengths and limitations of this approach, see section 5: discussion).

Perspective 4: Stakeholders' views on the identified high-burden under-researched medical conditions

The fourth perspective was drawn from the consultation of stakeholders in the field, including: (inter)national funding bodies, ministries of health, scientific organisations in specific medical fields, patient organisations in the respective medical fields and industry. An overview of the number of invited and the number of responding stakeholders per stakeholder type, is provided in table G1 in Annex G. Stakeholders were asked:

- a) if they agree with the working definition of high-burden under-researched medical conditions and are aware of other working definitions;
- b) whether they recognised the listed disease (groups) retrieved from the first three perspectives as being under-researched;
- c) what types of research and actions should be undertaken to address the knowledge gaps for the listed disease (groups);
- d) if they could list conditions that are under-researched in specific groups (e.g., women, persons with a migration background etc.);

⁶ Additionally, a funding ratio was also calculated per disease: funding ratio (in %) = $\frac{\text{funding}}{\text{burden}} * 100\%$. However, since the total amount of funding was zero for a considerable amount of diseases in the screened projects, this metric was not able to discriminate between burden levels for non-funded conditions and was not used to select relevant conditions

- e) if they were aware of other high-burden under-researched medical conditions that were not included in the list.

The survey is included in Annex F.

Qualitative appraisal

To integrate the four perspectives into one list of possible high-burden under-researched medical conditions, two rounds of qualitative appraisals were performed. The first qualitative appraisal was performed on the preliminary list of high-burden under-researched medical conditions based on the integrated findings of perspectives 1, 2 and 3. This preliminary list was composed of all disease groups, diseases or conditions that emerged as high-burden and possibly under-researched from one of three perspectives.

After this first appraisal, the preliminary list was used in perspective 4, the stakeholder survey. The survey yielded additional information on medical conditions perceived as high-burden and under-researched. This new information was appraised in a second qualitative appraisal round.

The methodology of the two qualitative appraisal rounds was the same and consisted of two steps. In the appraisals, a distinction was made between identified disease groups and identified individual diseases. First, the four disease groups (together being 20% of all listed disease groups) that received the highest amount of funding according to the projects screened in CORDIS were considered for exclusion from the shortlist, based on the relative high amounts of funding they already received. In addition, those disease groups that were considered not having an evident knowledge gap in the scientific literature (based on the availability of knowledge on aetiology and treatment options) were considered for exclusion as well. Second, those individual diseases that did not fall under the already excluded disease groups in the first step were listed according to amount of CORDIS funding of the screened projects. One individual disease with the highest amount of funding (receiving six times more funding than the second-highest) was also excluded from the shortlist, based on this high amount and not having an evident knowledge gap. (Groups of) diseases/conditions mentioned in the survey that are rare diseases were excluded in the second round appraisal exercise.

4. Results

The selection of high-burden under-researched medical conditions was composed based on four perspectives, as described in the Methodology section.

The results of the separate perspectives are summarised below and presented in more detail in Annex A to H. The integration of findings from the different perspectives that result in a final listing of high-burden under-researched medical conditions is summarised in Annex I.

Outcomes of perspective 1: Matching levels of EU research funding with medical conditions, as categorised in the International Classification of Diseases

This perspective showed that the least funded ICD-11 chapters based on the screened projects in CORDIS are:

- Conditions related to sexual health
- Developmental anomalies
- Pregnancy, childbirth or the puerperium
- Sleep-wake disorders
- Diseases of the blood or blood-forming organs

Annex A provides insight into the distribution of the EC research funding of the screened projects among the ICD-11 chapters.

Outcomes of perspective 2: Matching levels of EU research funding with high-burden medical conditions as documented in the Global Burden of Diseases (GBD) study

From this perspective, the conditions listed in Table 4.1 were identified and included in the preliminary list. Annex B is complementary to this table and provides a more detailed insight into the Δ outcomes (% funding - % burden) of the diseases/conditions identified, based on the listing within the 50 diseases/conditions with the lowest outcomes on all four metrics (table B.1), and based on the listing within the 10 diseases/conditions with the lowest outcomes on at least one of the metrics (tables B.2-B.5).

Table 4.1 Conditions included based on Δ outcomes (% funding - % burden) with data from the Global Burden of Disease study

These diseases/conditions that were for all four metrics (prevalence, DALY, YLL, deaths) listed in the top 50 most under-funded diseases are:	The diseases/conditions that were in the top 10 most under-funded diseases using at least one of the four metrics are:
<ul style="list-style-type: none"> • Chronic kidney disease • Chronic obstructive pulmonary disease (COPD) • Cirrhosis and other chronic liver diseases • Gallbladder and biliary diseases • Injuries • Ischemic heart disease 	<ul style="list-style-type: none"> • Cardiovascular diseases (DALY, YLL, deaths) • Caries of permanent teeth (prevalence) • Chronic obstructive pulmonary disease (DALY, YLL, deaths) • Gynaecological diseases (prevalence) • Headache disorders (prevalence) • Haemoglobinopathies and haemolytic anaemias (prevalence) • Hypertensive heart disease (deaths) • Injuries (prevalence, DALY, YLL) • Intracerebral haemorrhage (deaths) • Ischemic heart disease (DALY, YLL, deaths) • Ischemic stroke (DALY, YLL, deaths) • Low back pain (DALY) • Mental disorders (DALY) • Migraine (prevalence) • Musculoskeletal disorders (DALY) • Neoplasms (YLL, deaths) • Oral disorders (prevalence) • Periodontal diseases (prevalence) • Self-harm (YLL) • Skin and subcutaneous diseases (prevalence) • Stroke (DALY, YLL, deaths) • Tension-type headache (prevalence) • Total cancers (YLL, deaths) • Tracheal, bronchus, and lung cancer (DALY, YLL, deaths)
<p><i>DALY: Disability Adjusted Life Years ; YLL: Years of Life Lost</i></p>	

Outcomes of perspective 3: Matching levels of EU research funding with medical conditions identified as why people most frequently consult their general practitioner

Based on the systematic review of Finley and colleagues (2018) and a report from the Netherlands based on nationally representative data (Nielen et al., 2021), the (groups) of reasons, symptoms and health complaints listed in Table 4.2 were identified (27, 28). Annex C provides more details on the search terms and the selection process.

Table 4.2 Diseases, conditions and health complaints selected based on the third perspective

Diseases and conditions for which people visit their GP
<ul style="list-style-type: none">• Abdominal pain• Acute otitis media• Acute upper respiratory tract infection• Arthritis (not back)• Back pain• Cough• Cystitis/urinary tract infection• Depression or anxiety• Dermatitis• Diabetes mellitus• Fatigue/weakness• Hypertension

Initial list based on the first three perspectives

Annex D provides an overview of the initial list of high-burden under-researched medical conditions in which all three perspectives are included and provides a rationale for why certain conditions, diseases or disease groups were (not) taken further to the stakeholder survey. It is important to underline that the conditions that were not included in the stakeholder survey might still be in need of attention with respect to certain areas, even though these conditions were not considered to be under-researched based on our working definition. For instance, it could be that within these conditions or disease groups, specific populations are under-researched.

Table 4.3 presents the combined list of high-burden under-researched medical conditions based on perspective 1 to 3 and after appraisal of scientific and additional information on burden of diseases. Annex E provides a case description as an example of the process for the qualitative appraisal based on the first two perspectives.

Table 4.3 Initial list of high-burden under-researched medical conditions based on perspective 1 to 3 and the first appraisal round

High-burden under-researched medical condition
Mental disorders <i>(including but not limited to depression or anxiety and self-harm)</i>
Disorders of the blood and organ system <i>(including but not limited to chronic kidney disease, cirrhosis and other chronic liver diseases, cystitis/urinary tract infection, gallbladder and biliary diseases, abdominal pain, haemoglobinopathies and haemolytic anaemias)</i>
Musculoskeletal disorders <i>(including but not limited to arthritis (not back), injuries, low back pain)</i>
Headache disorders <i>(including but not limited to tension-type headaches, migraine)</i>
Fatigue/weakness
Sleep-wake disorders
Skin and subcutaneous diseases <i>(including but not limited to dermatitis)</i>
Gynaecological diseases <i>(including but not limited to pregnancy, childbirth or the puerperium)</i>
Conditions related to sexual health
Developmental anomalies

Outcomes of perspective 4: Stakeholders’ views on the identified high-burden under-researched medical conditions

A total of 44 responses to the survey were received, a response rate of 20%. Responses reflected the views of patients and citizens (17), academia (9), public funding bodies (national or international), EU Member State representatives (6), and healthcare professionals (5). Responses originated from individuals and (international) organisations or associations from the following countries: Austria (1), Australia (1), Belgium (2), Croatia (1), Denmark (2), France (5), Germany (2), Greece (1), Hungary (1), The Netherlands (6), Poland (1), Spain (1), Sweden (2), Switzerland (2), Ireland (2), Latvia (6), Malta (1), United Kingdom (2), United States (4).

Views on the list of under-researched conditions and the types of research and actions needed

Results of the stakeholder survey did not warrant to exclude any of the diseases or conditions from the list of high-burden under-researched medical conditions, see Table G.2 in Annex G. There was variation between disease groups in what type of research respondents deemed necessary to close the evidence gap, see Annex G table G.3 for more detail. Prevention, basic or fundamental research, clinical research and implementation research were often mentioned as important research areas. Furthermore, there was variation between disease groups in the minimal research requirements that were considered necessary to make progress. Stakeholders underlined the importance of cohorts, biobanks, large databases such as genetic/imaging data, as well as clinical trial networks. To increase the research

activities, the stakeholders considered overall that it is important to create more/better national, EU, and international funding opportunities, stimulate the creation of large research networks, increase incentives (other than financial) to conduct research on these medical conditions, make incentives sufficiently accessible to carry out research on these medical conditions, stimulate the organisation of specific conferences in the medical areas, and stimulate researcher mobility.

Perceived additional high-burden under-researched medical conditions

The stakeholders had various suggestions for other high-burden under-researched conditions that were not part of the list. These suggestions are listed in Table 4.4.

Table 4.4 Diseases and conditions that were mentioned in the stakeholder survey as additional high-burden under-researched medical conditions

Diseases and conditions that were mentioned by stakeholders
Allergy (specific food allergy)
Autism
Autoimmune diseases
Chronic Lyme disease
Endometriosis
Fibromyalgia
Genital Lichen Sclerosus and Lichen Planus
Hidradenitis Suppurativa
High-burden infectious diseases for which there are no effective treatments
Hypermobile Ehlers Danlos Syndrome (EDS)
Inborn errors of metabolism
Mast cell activation syndrome (MCAS)
Metastatic breast cancers
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
Neglected tropical diseases (emerging health threats in Europe such as Malaria, Dengue, and various other infectious and parasitic diseases)
Neurodegenerative diseases
Oncological diseases of autoimmune origin
Ovarian cancer
Post COVID-19 condition (Long COVID)
Postural tachycardia syndrome (POTS)

In addition to diseases and conditions listed in Table 4.4, the following fields were mentioned as being under-researched: frailty; ageism; violence; social inequalities in health; prevention; public health genomics; orphan drugs; safety of medicines in pregnancy; and multiple chronic conditions.

Stakeholders acknowledged general knowledge gaps for specific groups in the population, including women, elderly, persons with a migration background and socially vulnerable persons. Specifically mentioned by respondents to the survey were: young female adolescents, older women, people with limited health literacy, people with multimorbidity and children.

Composing a list of high-burden under-researched medical conditions

Perspectives 1 to 4 all provide information to the search for high-burden under-researched medical conditions. However, each of these perspectives has its strengths and limitations (see section 5 for discussion). Hence, a number of diseases and disease groups that are included in one of the four perspectives may from another perspective not be a high-burden under-researched medical condition as defined in this study.

For example, cardiovascular diseases and cancers were identified as relatively under-funded conditions in the second perspective due to their high burden of disease, although high amounts of funding are attributed to these disease categories. Because this group of diseases poses such a high burden to patients, it still listed high on the list of conditions that are relatively under-funded⁷. However, considering the amount of funding these disease categories receive, they are generally not regarded as under-funded.

Another reason why conditions that have been identified in one of four perspectives may in fact not be a high-burden under-researched medical condition as defined in this study is because there is no clear knowledge gap, as the aetiology and treatment of the condition is known. For example, for caries, as identified in the second perspective as being highly prevalent, the aetiology is known and it is well treatable (29). Similarly for COPD, identified in the second perspective as a condition with a high burden in terms of DALY, YLL and mortality, there does not seem to be a pressing scientific knowledge gap that justifies further study based on our definition (30).

A qualitative appraisal of each of the identified disease groups or individual diseases or conditions resulted in exclusion of those conditions that seem to be generously funded by EU programmes already, or those that are scientifically understood in terms of aetiology and treatment options. See Annex D and H for a summary of results of this qualitative appraisal for the first three perspectives and the fourth perspective, respectively. Annex I provides an overview of the identified diseases/conditions and the appraisal outcomes categorised per perspective.

This has resulted in a final list of high-burden under-researched medical conditions as listed in Table 4.5.

⁷ Based on the calculation in the second perspective: Δ outcomes = % funding - % burden, where a lower outcome gives a higher rank as high-burden under-researched medical condition

Table 4.5: The final list of high-burden under-researched medical conditions identified through perspectives 1 to 4, followed by the qualitative appraisal

Main group of disorders	Main groups further detailed
Mental disorders	<ul style="list-style-type: none"> - Depression or anxiety - Self-harm - Autism
Disorders of the blood and organ system	<ul style="list-style-type: none"> - Chronic kidney disease - Cirrhosis and other chronic liver diseases - Cystitis/urinary tract infection - Gallbladder and biliary diseases - Abdominal pain - Haemoglobinopathies and haemolytic anaemias
Musculoskeletal disorders	<ul style="list-style-type: none"> - Arthritis (not back) - Injuries - Low back pain - Fibromyalgia
Headache disorders	<ul style="list-style-type: none"> - Tension-type headache - Migraine
Fatigue / weakness	<ul style="list-style-type: none"> - Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
Sleep-wake disorders	
Skin and subcutaneous diseases	<ul style="list-style-type: none"> - Dermatitis - Hidradenitis Suppurativa - Genital Lichen Sclerosus - Lichen Planus
Gynaecological diseases	<ul style="list-style-type: none"> - Pregnancy, childbirth or the puerperium - Endometriosis
Conditions related to sexual health	
Developmental anomalies	
Immune related diseases	<ul style="list-style-type: none"> - Allergy (food allergy) - Autoimmune diseases - Mast cell activation syndrome (MCAS)
Other	<ul style="list-style-type: none"> - Postural tachycardia syndrome (POTS) - Chronic Lyme disease - Hypermobile Ehlers Danlos Syndrome (EDS)
<p>Note that for some diseases or conditions that are generally considered not to be under-funded, certain population groups could be underserved and there is therefore a need to better consider the diversity of the affected population. Furthermore, it is recommended to keep on monitoring the threat of and attention to infectious diseases, as well as the budget allocated to and the burden of post COVID-19, as factors such as globalisation, antimicrobial resistance, influx of migrants, and climate change could make these themes even more relevant in the future.</p>	

The main groups of disorders (left side of the table) originate from the ICD-11, with headache disorders and fatigue/weaknesses classified as subcategories. Further details of main groups (right side of the table) originate from either perspective 2, 3 or 4.

5. Discussion

There is no gold standard or guideline on how to identify high-burden under-researched medical conditions. The current study can be seen as a starting point, providing insight into the main groups of diseases that are relatively under-researched. Additional research into these disease groups is required to identify high-burden under-researched diseases or conditions more specifically. A first exploration has been provided here by conducting a stakeholder analysis and a qualitative appraisal of all findings, providing more insight on disease-level.

The methodology that has been used in this study was considered the most solid in light of the available time and resources. It has strengths, but also several limitations. Below, the major challenges have been described and further strengths and weaknesses of the different approaches have been listed in Table 5.1.

The CORDIS database has limitations for the identification of under-researched conditions

The limitations of the CORDIS database in mapping and monitoring medical research has been addressed by various researchers in the past (31-34). It has been emphasised by these researchers that more transparency in CORDIS is needed to evaluate whether funding priorities are related to societal needs and burden of disease and whether funded research has produced information that is useful to improve the health of European citizens.

As recently pointed out by Gallo and colleagues, a classification system in CORDIS that offers multiple matching keys and which allows projects to be classified not only by disease category but also by level of research⁸ and/or research domain⁹ would be appropriate in order to allow critical assessment of funds allocated (31). Good research mapping, which is fundamental for showcasing research output, would require a classification system common to research funder (31, 35, 36).

The first two perspectives are based on a classification exercise that started with the downloaded projects from the CORDIS database. For this classification exercise, project descriptions from the project title, teaser, abstract and key words were used. Some diseases that were not mentioned in the title, teaser or abstract but did receive funding within a project may have been missed. Also, the diseases described in the GBD might have been too specific for the project description in CORDIS. In that case, a disease mentioned in the GBD might have been classified as being more under-funded than actually is the case. Yet, this potential limitation seems to be mitigated in the results, as often both the more specific diseases listed in the GBD and the more 'parental' disease groups are listed in the tables in this report. It was assumed that for projects that covered multiple diseases or disease groups, the funding was spread equally over the number of mentioned diseases/conditions, which in reality may not be the case. For 109 projects out of the 812 (13%) the budget was split in two ICD-codes, 12 (1%) projects in three, 3 (0.4%) projects in four and 2 (0.2%) projects in five.

In our study, we used the domain of application 'Health' as a selection criterion (filter) for searching projects. In hindsight it would have been better to use the field of science 'medical

⁸ For instance basic research versus applied or implementation research.

⁹ For instance according to the following categorisation: 1. Aetiology, pathology, diagnostics; 2. Epidemiology, determinants, demography; 3. Intervention development, clinical trials; 4. Palliative care, end-of-life care; 5. Economic, personal and societal consequences and costs; 6. Ethical and legal aspects; 7. Data availability and options for exchange or linkage.

and health sciences'. The latter search resulted in many more hits (over 9,000) and would be more comprehensive, but not manageable in the time available for this study.

ICD chapters are not comparable

When looking at the ICD chapters, the least funding (in absolute numbers) was given to chapters covering the following diseases/conditions: conditions related to sexual health, developmental anomalies, pregnancy, childbirth or the puerperium, sleep-wake disorders, and diseases of the blood or blood-forming organs. It should, however, be noted that some ICD chapters consist of considerably fewer diseases than others, which may (partially) explain the difference in the total amount of funding. For instance, the chapter of sleep-wake disorders (Chapter 7 in ICD-11) covers far fewer diseases compared to the chapter covering diseases of the nervous system (Chapter 8). In addition, it should be noted that this analysis is based on chapter averages. For example, chapter 6 of ICD-11: "Mental, behavioural or neurodevelopmental disorders" was listed as one of the chapters with the most funding. Yet, mental disorders, which falls under this chapter was listed in the top 10 of most under-funded based on DALYs. In this example, this discrepancy might be caused by, for example, the fact that dementia, which received on all four metrics a higher percentage of funding compared to the burden, falls under this chapter as well.

The definition of the burden of disease is limited

For determining the disease burden, it was decided to only use data from the Global Burden of Disease study, as this study comprises a very large number of conditions whilst using the same methodology to assess DALYs for each of these conditions. This ensures comparability among the conditions. A limitation of the GBD study, however, is that it does not include the social and economic consequences of a condition, the impact it has on healthcare, on personal costs (i.e., because of job loss), on discrimination or exclusion etc. Furthermore, trends in the burden of a disease and intergroup differences are not addressed in the Global Burden of Diseases study. This underestimates the importance of, for instance, ageing-related diseases and diseases that predominantly occur in a subgroup (i.e., migrants, women, people with a lower socioeconomic position).

Potentially under-funded diseases might have been missed in perspective 2 if no prevalence, DALY, YLL and/or death information was available in the GBD. In addition, to link the GBD information to the total amount of funding under the Horizon 2020 health project, ICD definitions had to be matched to the GBD while this was not always possible as some cases were not one-to-one comparable and required a sum of multiple ICD categories.

With using DALY information, it should be noted that there could be a variability in disability weight per country. It also can vary over time. Yet, we tried to mitigate this risk of unfair comparison by using only GBD information. In addition, we used it in combination with hard indicators, such as prevalence and death.

Furthermore, the GBD database does not cover all diseases. It only includes diseases that can be diagnosed and defined. It is therefore possible that not all high-burden conditions could be identified based on the approach of perspective 2 and that we might have missed the conditions that are especially in need of funding, e.g. because of underdiagnosis.

Lastly, prevalence was used in the current study as one indicator of burden of disease. However, it might not in all cases be a very good indicator for the burden of a disease, as it leads to the identification of conditions that are highly prevalent, such as caries, but that do not necessarily pose a high burden on patients or society, or for which there is no evident knowledge gap.

Limited qualitative appraisal

This exploratory study was not powered to systematically screen all factors that are important to take into account when composing a preliminary list of high-burden under-researched medical conditions. However, an attempt was made to integrate the four perspectives into one list, by a qualitative appraisal of each of the identified disease groups or individual diseases or conditions and excluding those that are scientifically understood in terms of aetiology and treatment options. The qualitative appraisal that was performed on the integrated list of perspectives 1 to 3 and on the additional findings from perspective 4 was not exhaustive. A conservative approach was taken regarding the exclusion of individual diseases, although some individual diseases (e.g. stroke, ischemic heart disease) that fell under a broader disease group (i.e. 'cardiovascular diseases') in the GBD study, were excluded because of the substantiated exclusion of the broader disease group. The evaluation of all identified disease groups and separate diseases and conditions that were identified in this study need further in-depth review to determine research needs. Also, further study to identify specific diseases within identified disease groups is needed. Future work in this area would require the formulation of clear and fair cut-off values to determine if a disease (group) is (too) highly funded, or whether there is a knowledge gap present.

The criteria used to determine research needs are limited

Research needs can be based on other criteria than on the burden of disease. This was also mentioned by the experts who filled out the stakeholder survey. There might not be a direct relation between burden of disease and funding received, for instance because little is known about the burden of a disease or there might be high-burden diseases for which there are few research gaps, e.g., diabetes and COPD. A previous study, using a similar methodology, found a significant relation between funding and burden and highlighted the fact that comparison of actual and predicted funding based on different measures of disease can alter conclusions as to whether a disease is over- or under-funded (37). Other criteria could for instance be the preventability of a disease, whether or not it is a public concern or the size of the gap in robust scientific evidence.

Furthermore, research-investment needs differ per disease (group). Even if a disease with a high burden is already generously funded, it may still be relatively under-researched from the perspective of certain research areas. Taking the example of diabetes and COPD again, more research into prevention and behaviour change could help to reduce its incidence.

A suggestion would be to base the need for research related to a specific disease on the availability of a minimum required knowledge base in the following areas: 1. Aetiology, pathology, diagnostics; 2. Epidemiology, determinants (risk factor complexity), demography; 3. Clinical research: intervention development, quality of life, clinical trials; 4. Palliative care, end-of-life care; 5. Economic, personal and societal consequences and costs; 6. Ethical and legal aspects; 7. Data availability and options for exchange or linkage.

Other funding streams

There are other funding streams, besides the funding programmes of the European Commission, that may already have met a large part of the research needs, including national funding streams for academic institutes; funding by national and international charities, often with a focus on a specific disease (e.g., diabetes, multiple sclerosis) or on a wider group of diseases (e.g., cancers); funding of research by the medical and pharmaceutical industry, often clinical research focusing on treatment possibilities for patients of diseases with a high prevalence. These alternative funding streams need to be taken into account when investigating whether a disease is under-funded.

The Global Observatory on Health R&D¹⁰ is a comprehensive source of information and analyses on global health R&D for human diseases. It builds on existing data/reports from a range of sources, and gathers new information to help monitor health R&D and decision-making related to health R&D gaps, priorities for new investments in health R&D and capacity strengthening needs for health R&D. Although the scope of this database is global rather than European, the data on funds attributed to specific diseases worldwide as collected in the World RePORT¹¹ may nevertheless help to gain insight into alternative funding streams.

Research funding also depends on the availability and quality of researchers and research infrastructures. Good research groups will attract money from several sources and there is a limit to the amount of time that researchers will invest in applying for funding. Saturation of research capacity is therefore not unthinkable. A lack of clinical and research expertise and the necessary infrastructure, data collection and patient availability will limit the potential of researchers on less prevalent diseases to attract funding by high-quality applications.

Disease-transcending research gaps

There are certain disease-transcending problems or gaps in research. This concerns for instance: the lack of relevant infrastructures (costly equipment); patients that are reluctant to participate in research (for instance in the field of psychiatry); a lack of sufficient high-quality research capacity; a lack of good and FAIR (findable, accessible, interoperable, re-usable) disease registries; barriers in the accessibility and reuse of data (privacy issues, ownership); inappropriate health service infrastructure; neglect of multimorbidity/ comorbidity; experimental treatments that are too expensive; relevant medical expertise that is scarce or absent; ethical constraints (e.g., patients that are not able to consent); political constraints (e.g., abortion, euthanasia). For most of these problems, support programmes and funding strategies at EU level that extend to several diseases might be helpful.

¹⁰ <https://www.who.int/observatories/global-observatory-on-health-research-and-development>

¹¹ <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/investments-on-grants-for-biomedical-research-by-funder-type-of-grant-health-category-and-recipient>

Table 5.1 Strengths and limitations of the four perspectives

Perspective	Strengths	Limitations
1: Matching levels of EU research funding with medical conditions, as categorised in the International Classification of Diseases (ICD-11)	Internationally recognised classification of projects according to disease (group) it covers	A selection of 'health' projects has been extracted ¹² , while there may be more Horizon 2020 funded projects related to health not labelled as health-projects.
	Provides insight into the clustering of EC funding across ICD categories	No data on prevalence and burden of diseases/conditions
		Manual assignment of projects into ICD categories by one researcher. Ideally, two independent researchers would have classified the projects into ICD categories.
		Level of detail of the ICD classification results in high-level, non-specific results. A second step for each high-level condition would be needed to identify specific conditions within that group. Projects were categorised by ICD-11 code based on abstract, keywords and teaser, not the full proposal
2: Matching levels of EU research funding with high-burden medical conditions, as documented in the Global Burden of Diseases (GBD) study	Validated burden of disease statistics specific for countries within the European Union	Not all diseases/conditions are included in the GBD
	Inclusion of four different burden metrics	Only well-defined diseases and conditions are included
3: Matching levels of EU research funding with medical conditions identified as why people most frequently consult their general practitioner (GP)	In contrast to the GBD and ICD approach, this could allow the discovery of poorly recognised conditions	Limited by the number of thorough studies investigating this, but it could uncover poorly recognised disorders and hint at their burden
		Is more focused on symptoms rather than the potentially underlying diseases/conditions
4: Stakeholders' views on the identified high-burden under-researched medical conditions	Open opportunity to point attention towards high-burden under-researched conditions	Some stakeholder groups were overrepresented/underrepresented

¹² From the CORDIS database, we selected projects that were assigned the tag "Health" as domain of application. The rationale behind this choice is that these projects are considered to contribute to the health of EU citizens. However, this approach has its limitations, as it does not cover all areas related to health, and is missing areas such as fundamental research.

6. Conclusions & recommendations

This exploratory study led to a list of high-burden under-researched medical diseases, conditions and disease groups. The disease groups that are identified as being high-burden but under-funded, include: mental disorders; disorders of the blood and organ system; musculoskeletal disorders; headache disorders; fatigue / weakness; sleep-wake disorders; skin and subcutaneous diseases; gynaecological diseases; conditions related to sexual health; developmental anomalies; immune related diseases; and a group composed of other remaining individual conditions. In addition, perceived research gaps related to addressing the needs of specific population groups, demographic trends and environmental changes that will require attention in the near future were identified.

The groups of conditions identified in this study may be used as a starting point to further explore specific conditions within these groups. The adopted methodological approach needs to be further refined and validated in future studies and more time and resources would need to be allocated to take account of the full research landscape, its total funding, as well as the true burden of diseases.

Focus future work towards specific areas of diseases

This work was performed based on a request of the EC to get support in designing topics in future work programmes that will address the gaps in robust, scientific evidence needed to develop policies and practice to address high-burden under-researched medical conditions. As can be appreciated from the work reported here, it is not easy to provide this type of information, taking into account all disease areas for the entire EU region. To make it more manageable for future exercises, we recommend to focus future work towards specific areas of diseases. This can be done by focussing on more homogenous groups of conditions and within these groups, explore burden, impact and research and innovation activities undertaken. This approach will allow a more in-depth stakeholder consultation and more specific direction on the type of research and/or research priorities that are urgently needed. Alternatively, one can focus on those conditions that have already been demonstrated as being high-burden and under-researched and explore more in-depth their burden, impact and research and innovation activities. To further refine the methodological approach reported here, lessons could be drawn from the more mature academic field of health research priority setting (38, 39). Viergever et al. have created a tool which helps those seeking to undertake a health research priority setting exercise to make an informed choice as to which comprehensive approach to use, or provides assistance for creating a high quality priority setting process without use of an existing approach (38). Nine common themes for good practice are listed that deserve to be considered in any health research prioritisation exercise. In such future exercises, global data sources could be taken into account to be able to prioritise research needs. The database on funds attributed to specific diseases worldwide as collected in the World RePORT by the Global Observatory on Health R&D may help to gain insight into alternative funding streams and provide a more complete picture of research gaps, in Europe and beyond (40). In addition, more attention towards the systematic evaluation of other aspects of diseases are required to enable priority setting, including for example societal costs of medical conditions, but also the differences in burden of disease within the population taking into account age, gender, ethnic background and many other aspects in which human beings differ from one another.

This study provides a first impression of the areas in which more support seems to be needed. We recommend that the findings of this study be further explored and considered when designing topics in future work programmes, to offer opportunities for support to diseases and regions where they are needed the most.

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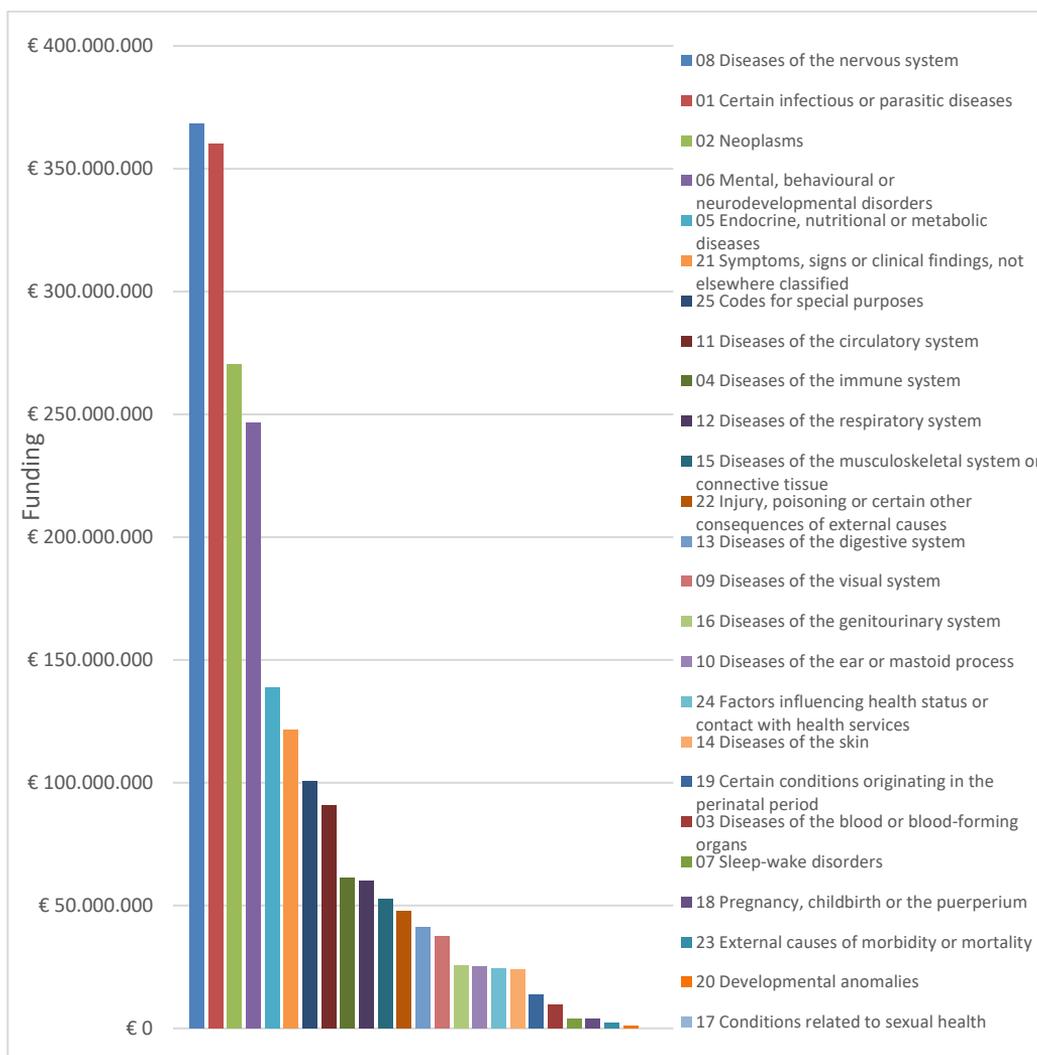
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Annex A – Perspective 1: Matching levels of EU research funding with medical conditions

Figure A.1 shows the distribution of EU research funding of the screened projects among the International Classification of Diseases (ICD-11) chapters. The five chapters with the lowest amount of funding in this exercise were identified for the preliminary list. As the majority of the chapter 'External causes of morbidity and mortality' was considered outside the scope of this study, this chapter was ignored in this perspective.

Figure A.1: Distribution of EU research funding of the screened projects among ICD-11 chapters



Annex B – Perspective 2: Matching levels of EU research funding with high-burden medical conditions

In the second perspective, (groups of) diseases/conditions available for which burden information was available in the Global Burden of Diseases (GBD) were identified for the preliminary list if they were either part of the 50 diseases/conditions with the lowest outcomes on Δ (% funding - % burden) on both prevalence, DALY, YLL and deaths (table B.1), or part of the 10 diseases/conditions with the lowest Δ outcomes on prevalence (table B.2), DALY (table B.3), YLL (table B.4), or death (table B.5).

Table B.1: Diseases/conditions that were listed within the 50 lowest outcomes of % funding - % burden (Δ) on prevalence, DALY, YLL, and deaths (“top 50”; sorted on alphabetical order)

GBD cause name	Δ (% funding - % prevalence)	Δ (% funding - % DALY)	Δ (% funding - % YLL)	Δ (% funding - % death)
Chronic kidney disease	-0.88	-0.23	-0.41	-0.70
Chronic obstructive pulmonary disease (COPD)	-0.55	-1.41	-1.61	-1.95
Cirrhosis and other chronic liver diseases	-1.64	-0.56	-1.15	-0.65
Gallbladder and biliary diseases	-0.52	-0.22	-0.13	-0.17
Injuries	-3.06	-2.47	-1.88	-0.53
Ischemic heart disease	-0.44	-4.21	-7.06	-8.37

Table B.2: Diseases/conditions that were listed within the 10 lowest outcomes of % funding - % burden (Δ) on prevalence (“top 10 prevalence”)

GBD cause name	% Funding	% Prevalence	Δ (% funding - % prevalence)	Funding ratio ¹
Oral disorders	0.18	5.69	-5.51	0.03
Headache disorders	0.04	4.95	-4.91	0.01
Tension-type headache	0	4.07	-4.07	0
Caries of permanent teeth	0	3.61	-3.61	0
Injuries	1.56	4.62	-3.02	0.34

Skin and subcutaneous diseases	1.02	3.70	-2.65	0.28
Gynaecological diseases	0.20	2.57	-2.35	0.08
Haemoglobinopathies and haemolytic anaemias	0	2.07	-2.07	0
Migraine	0.04	2.08	-2.03	0.02
Periodontal diseases	0.08	1.75	-1.67	0.05

¹ % funding / % prevalence

Table B.3: Diseases/conditions that were listed within the 10 lowest outcomes of % funding - % burden (Δ) on DALY (“top 10 DALY”)

GBD cause name	% Funding	% DALY	Δ (% funding - % DALY)	Funding ratio ¹
Cardiovascular diseases	3.98	9.10	-5.13	0.44
Ischemic heart disease	0.03	4.23	-4.21	0.01
Injuries	1.60	4.07	-2.47	0.39
Mental disorders	0.90	3.22	-2.32	0.28
Musculoskeletal disorders	2.31	4.47	-2.15	0.52
Low back pain	0.39	2.27	-1.87	0.17
Stroke	0.63	2.50	-1.87	0.25
Tracheal, bronchus, and lung cancer	0.23	2.07	-1.84	0.11
Ischemic stroke	0.01	1.58	-1.57	0.01
Chronic obstructive pulmonary disorders	0.12	1.52	-1.41	0.08

¹ % funding / % DALY

Table B.4: Diseases/conditions that were listed within the 10 lowest outcomes of % funding - % burden (Δ) on YLL (“top 10 YLL”)

GBD cause name	% Funding	% YLL	Δ (% funding - % YLL)	Funding ratio ¹
Cardiovascular diseases	3.98	14.19	-10.21	0.28
Ischemic heart disease	0.03	7.08	-7.056	0.00
Neoplasms	11.85	15.74	-3.89	0.73
Total cancers	11.85	15.61	-3.76	0.76
Tracheal, bronchus, and lung cancer	0.23	3.56	-3.33	0.06
Stroke	0.63	3.71	-3.08	0.17
Injuries	1.60	3.49	-1.88	0.46
Ischemic stroke	0.01	2.23	-2.23	0.00
Chronic obstructive pulmonary disease	0.12	1.73	-1.61	0.07
Self-harm	0	1.23	-1.23	0

¹ % funding / % YLL

Table B.5: Diseases/conditions that were listed within the 10 lowest outcomes of % funding - % burden (Δ) on deaths (“top 10 deaths”)

GBD cause name	% Funding	% death	Δ (% funding - % death)	Funding ratio ¹
Cardiovascular diseases	3.98	17.30	-13.32	0.23
Ischemic heart disease	0.03	8.40	-8.37	0.00
Stroke	0.63	4.62	-4.00	0.14
Ischemic stroke	0.01	3.20	-3.19	0.00
Tracheal, bronchus, and lung cancer	0.23	2.79	-2.56	0.08
Chronic obstructive pulmonary disease	0.12	2.07	-1.95	0.06
Neoplasms	11.85	13.40	-1.55	0.88

Total cancers	11.85	13.24	-1.39	0.90
Hypertensive heart disease	0	1.26	-1.26	0
Intracerebral haemorrhage	0	1.14	-1.14	0

¹ % funding / % deaths

Annex C – Perspective 3: Matching levels of EU research funding with most frequent health conditions presented during GP visits

A rapid literature search was conducted in PubMed, based on the search strategy as displayed in Table C.1. This led to seven papers that included a list of most common reasons, symptoms and/or health complaints for which people visit their general practitioner (GP) or primary care provider. One of these papers concerned a systematic review (Finley et al., 2018), which provided a ranking of most common reasons for primary care visits in developed countries. The ranking from this systematic review was used as input for the third perspective in the current study (based on five studies from Australia, England and Wales, Sweden, and the United States).

In addition to this systematic review, it was decided to add information from a recent report of the Netherlands Institute of Health Services research (Nivel) that provides insight into the most common reasons for people to contact their general practitioner (GP) (Nielen et al., 2021). Given the gatekeepers' role of GPs in the Dutch healthcare system, all Dutch citizens are registered at a GP practice and can only access non-emergency hospital care after a referral of their GP. Therefore, the national representative data that was used in the Nivel report provide an accurate picture of common health problems in the total population.

Table C.2 provides an overview of the most common health problems that are presented during contact with the GP as based on the systematic review of Finley and colleagues and the Nivel report.

Table C.1: Search terms used to search in PubMed

#	Search terms
1	GP visits AND (Europe OR Canada OR USA)
2	frequent health complaints AND GP
3	(primary care OR GP) AND prevalent AND health
4	(primary care OR GP) AND prevalent AND health AND visits
5	(primary care OR GP) AND prevalent AND health complaints AND visits
6	utilization AND (primary care or GP)
7	frequent utilization AND (primary care or GP)
8	common health problem AND utilization AND (primary care or GP)
9	(common OR frequent) health problem AND utilization AND (primary care or GP)
10	(common OR frequent OR prevalent OR utilization) AND (primary care or GP)
11	(primary care OR GP) AND visits AND (prevalent OR common) conditions
12	(primary care OR GP) AND (prevalent OR common) conditions
13	GP visits AND primary care routine data
14	common complaint AND (GP OR primary care)

15	common complaint AND visit AND general practitioner
16	(symptoms OR conditions) AND (primary care OR GP) AND (common OR frequent)
17	(GP OR primary care) AND visits AND reasons
18	Reasons for GP visits

Table C.2: Most common health problems for which people contact their GP

Finley et al., 2018*	Nivel report*
Hypertension	Cystitis/Urinary Tract Infection
Upper respiratory tract infection, unspecified	Essential hypertension without organ damage
Depression or anxiety	Diabetes mellitus
Back pain	Acute upper respiratory tract infection
Arthritis (not back)	Fatigue/weakness
Dermatitis	Cough
Acute otitis media	Depression
Diabetes	Anxiety Disorder/Anxiety State
Cough	Other localized abdominal pain
Medication	
Urinary tract infection	

* Some of the listed reasons to visit a GP that did not concern a specific symptom or condition, including: routine health maintenance (from the list of Finley et al., 2018), medication (from the list of Finley et al., 2018), and excessive cerumen (from the Nivel report). These reasons for visiting the GP were therefore not added to the list of conditions from this perspective.

Annex D – (Appraisal of) preliminary list of high-burden under-researched medical conditions

All identified (groups of) diseases/conditions from perspectives 1 to 3 were grouped and categorised, to form together the preliminary list of high-burden under-researched medical conditions based on the first three perspectives (table D.1). Each (groups of) diseases/conditions were appraised in a qualitative appraisal. Where the (groups of) diseases/conditions were appraised for further exclusion, a summary of the rationale is put at the right side of table D.1. Table D.2. provides the list of all (groups of) diseases that were not excluded in the appraisal. Those (groups of) diseases/conditions listed were included in the stakeholder survey.

Table D.1: Preliminary list of high-burden under-researched medical conditions, including source of inclusion and rationale for exclusion of conditions, disease (groups) based on perspectives 1-3

No.	Condition, disease or disease group	Source / perspective that caused inclusion in the list		Rationale for <u>exclusion</u> from the shortlist
1	Mental disorders	GBD	DALY	
	Depression or anxiety	GP		
	Self-harm	GBD	YLL	
2	Cardiovascular diseases	GBD	DALY, YLL, deaths	Exclude from list: - Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)
	Ischemic heart disease	GBD	Top50, DALY, YLL, deaths	
	Ischemic stroke	GBD	DALY, YLL, deaths	
	Stroke	GBD	DALY, YLL, deaths	
	Intracerebral haemorrhage	GBD	Deaths	
	Hypertensive heart disease	GBD	Deaths	
	Hypertension	GP		
3	COPD	GBD	Top50, DALY, YLL, deaths	Exclude from list: - No evident scientific knowledge gap
4	Acute upper respiratory tract infections	GP		Exclude from list: - No evident scientific knowledge gap
	Acute otitis media	GP		
	Cough	GP		
5	Disorders of the blood and organ system	ICD		
	Chronic kidney disease	GBD	Top50	
	Cirrhosis and other chronic liver diseases	GBD	Top50	

	Diabetes mellitus	GP		Exclude from list: - Highly funded compared to other diseases in the list (highest funded of all individual diseases) - No evident scientific knowledge gap
	Cystitis/urinary tract infection	GP		
	Gallbladder and biliary diseases	GBD	Top50	
	Abdominal pain	GP		
	Haemoglobinopathies and haemolytic anaemias	GBD	Prevalence	
6	Total cancers	GBD	YLL, deaths	Exclude from list: - Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)
	Neoplasms		YLL, deaths	
	Tracheal, bronchus, and lung cancer		DALY, YLL, deaths	
7	Musculoskeletal disorders	GBD	DALY	
	Arthritis (not back)	GP		
	Injuries	GBD	Top50, prevalence, DALY, YLL	
	Low back pain	GBD & GP	DALY	
8	Headache disorders	GBD	Prevalence	
	Tension-type headache	GBD	Prevalence	
	Migraine	GBD	Prevalence	
9	Fatigue/weakness	GP		
10	Sleep-wake disorders	ICD		
11	Oral disorders	GBD	Prevalence	Exclude from list: - No evident scientific knowledge gap
	Caries of permanent teeth	GBD	Prevalence	
	Periodontal diseases	GBD	Prevalence	
12	Skin and subcutaneous diseases	GBD	Prevalence	
	Dermatitis	GP		
13	Gynaecological diseases	GBD	Prevalence	
	Pregnancy, childbirth or the puerperium	ICD		
14	Conditions related to sexual health	ICD		
15	Developmental anomalies	ICD		

Annex E – Case description of process of the first and second perspectives and the qualitative appraisal

This annex describes a case description of the process of the first and second perspectives and the qualitative appraisal.

Several steps have been undertaken to serve as a basis for the first two perspectives. This case description will use the disease group of cardiovascular diseases as an example for this process.

From CORDIS project description into ICD code

In the screened projects in CORDIS, various projects were found in the field of cardiovascular diseases. All of these projects were classified at the most detailed ICD-11 code as possible within chapter 11 of the 'Diseases of the Circulatory system'. For instance, projects were classified as: Acute Myocardial Infarction (BA41), or Aortic dissection (BD50). Other projects were broader in their scope and project description and could only be classified into a broader ICD-11 category or classified under the level of the ICD-11 chapter 'Diseases of the Circulatory system'.

From ICD-11 code to input for perspective 1 and 2

In total, 52 projects were classified under ICD-11 chapter 'Diseases of the circulatory system'. Together, they received a funding of €90,790,524, based on the screened projects. This was the information provided in the first perspective, where it ended up in the upper segment of chapters with the highest total funding.

In the second perspective, several cardiovascular diseases were available in the GBD database. For instance: aortic aneurysm, myocarditis, ischemic stroke, as well as the entire group of cardiovascular diseases. For each of these (groups of) diseases, the total funding based on the screened projects were retrieved via the ICD-11 classifications, described in the step above. Then, the percentage of funding and burden was calculated. For the example of the group of cardiovascular diseases, it is presented as follows:

$$\text{Funding (in \%)} = \frac{\text{funding for disease}}{\text{total amount of funding for all included diseases}} * 100\% = \frac{90,790,524}{2,366,651,739} = 3.836\%$$

Similarly, the percentage was calculated for all four burden metrics:

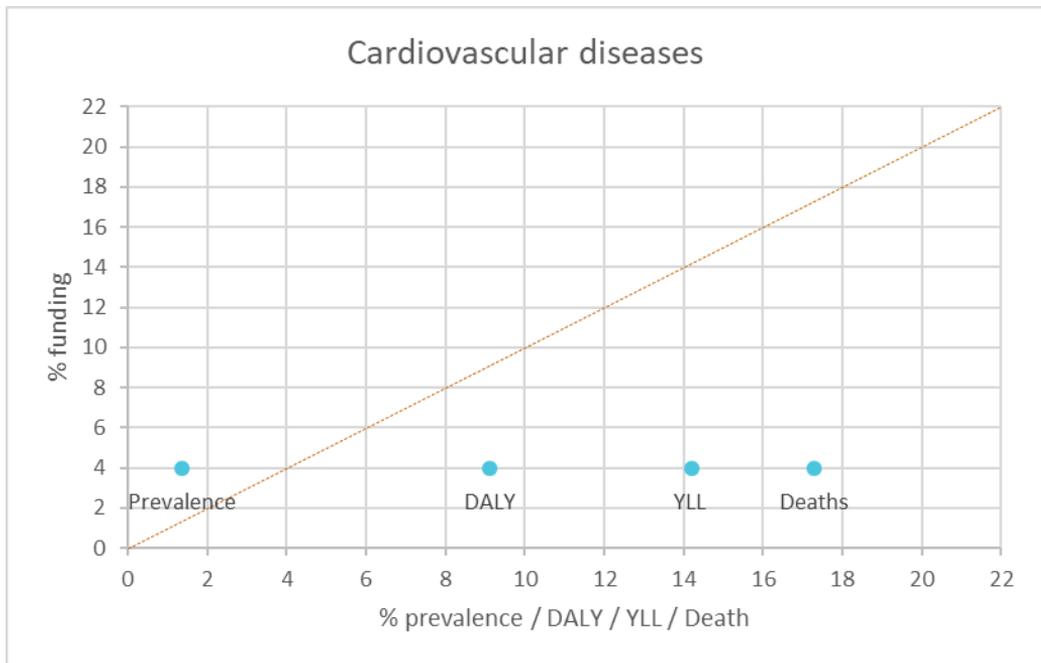
$$\text{Prevalence (in \%)} = \frac{\text{prevalence of disease}}{\text{total prevalence of all included diseases}} * 100\% = \frac{59,945,560}{4,428,969,769} = 1.353\%$$

$$\text{DALY (in \%)} = \frac{\text{DALY of disease}}{\text{total DALY of all included diseases}} * 100\% = \frac{29,748,374}{326,744,665} = 9.104\%$$

$$\text{YLL (in \%)} = \frac{\text{YLL of disease}}{\text{total YLL of all included diseases}} * 100\% = \frac{26,529,719}{186,931,365} = 14.192\%$$

$$\text{Death (in \%)} = \frac{\text{Deaths of disease}}{\text{total deaths of all included diseases}} * 100\% = \frac{2,004,436}{11,587,845} = 17.298\%$$

Then, the Δ was calculated of % funding - % burden, which was 2.5%, -5.3%, -10.4%, and -13.4%, respectively. It is presented graphically as follows.



When the Δ outcomes were sorted ascendingly with all other GBD inputs, it appeared three times (for DALY, YLL, death) in the list of the 50GBD inputs with the lowest Δ outcomes. Furthermore, for all these three burden metrics (DALY, YLL, death), it was within the lowest 10 of Δ outcomes. Based on this, the group of cardiovascular diseases was initially identified as potentially a high-burden under-researched medical condition.

Appraisal of identified conditions, diseases and disease groups

In the appraisal of the identified conditions, diseases and disease groups from the four perspectives, cardiovascular diseases was among the 4 highest funded groups of diseases in the list. Therefore, it was decided to not further include the group of cardiovascular diseases in the list of identified high-burden under-researched medical conditions.

Annex F – Perspective 4: Stakeholder survey

Selected stakeholders were approached by e-mail and asked to participate in an online survey.

Under-researched, high-burden for patients medical conditions

This is the MS-Word version of a stakeholder survey, which is circulated via the online survey tool EUSurvey.

You are kindly invited to participate in a survey conducted by the EUHealthSupport consortium, in the context of a study supported by the European Commission's Directorate General for Research & Innovation (DG RTD).

The aim of this survey is to incorporate your opinion in an ongoing scoping study on high-burden under-researched conditions in Europe and beyond.

At this stage, we would like to capture your views on the information collected so far, and to gain more understanding what the underlying reasons might be why certain conditions are under-researched, e.g. they might have an unclear origin, an underlying mechanism that is not sufficiently understood, or may be inaccurately diagnosed.

To this end, the Commission has tasked EUHealthSupport to survey governmental funding agencies, large funding bodies and other key stakeholder groups – among others umbrella associations in the healthcare field.

Your contribution will be very much appreciated and will take approximately 15 minutes of your time. The results of this consultation will be summarised in a report, which will be submitted to the European Commission in the fall of 2022. If you have any questions about this consultation or the study itself, please contact [email-address].

Thank you for your contribution.

About this study:

Several consecutive activities have been undertaken to come to a preliminary list of possibly under-researched and high-burden diseases and conditions: research projects related to health under the Horizon 2020 programme have been mapped with their amount of funding and the disease (group) or condition they address; this was related to the burden of these disease (groups) and conditions; a literature search identified common reasons for people to visit their general practitioner; and additional literature research provided insight into the knowledge base available for disease (groups) and conditions identified. This consultation aims to capture key stakeholders' views on how this subject is approached by others, to

reflect on the list of disease (groups) and conditions that we have identified as being potentially under-researched and high-burden in past and ongoing EU Research Framework Programmes and to provide the opportunity to share your views on how this subject should be further addressed.

About us:

The EUHealthSupport Consortium is composed of Nivel (Netherlands institute for health services research; Lead), RIVM (National Institute for Public Health and the Environment of the Netherlands), Royal College of Surgeons in Ireland (RCSI), infeurope S.A., the Association of Medical Schools in Europe (AMSE) and Leginda GmbH, under the Single Framework Contract 'Chafea/2018/Health/03 - for the provision of support services for managing expert groups in the field of (public) health'. More information is available at www.euhealthsupport.eu.

[Outline](#)

This consultation starts with some background questions (part I). This will be followed by part II, in which we present our working definition on high-burden, under-researched medical conditions. Here, we ask you to reflect upon this working definition and inform us on whether and how the topic of high-burden under-researched medical conditions is currently being addressed in your organisation or country (if applicable).

Part III presents you with our preliminary shortlist of high-burden under-researched medical disease (groups) and conditions on which we would like your reflection. We would also like to hear from you what type of research would be needed to help close the research gap that exists for these disease (groups) and conditions. Finally, we ask for your thoughts about other diseases or conditions that may be under-researched while posing a high-burden on patients/society.

[Part I: Background questions](#)

1. Please indicate which **group of stakeholders** you primarily represent or consider yourself to be part of.
 - EU Member State representative
 - Public funding bodies (national or international)
 - Philanthropic funding bodies
 - Healthcare professionals
 - Academia
 - Industry
 - Patients or citizens
 - Other

1a. If other, please specify:

2. Are you answering on behalf of an organisation?

- Yes > Q2b
- No > Q2a

2a. In which country do you live? > Q3

2b. Please provide the name of this organisation.

Note that all answers to this survey will be reported anonymously, but that we might consider adding a list of responding organisations as an annex to the final report.

2c. What is your (organisation's) disease / condition area of expertise, if any?

2d. Please indicate at which **geographical level** your organisation is predominantly active.

- Local or regional level within one country > Q2e
- National level within one country > Q2e
- European level (covering multiple European countries) > Q3
- International level (other or wider than Europe) > Q3

2e. In which **country** is your organisation based?

Part II: Views on working definition

In this study, we defined high-burden under-researched diseases or conditions as *those diseases or conditions that receive insufficient research funding relative to the expected level of funding based on their burden.*

With this definition, we aim to identify those medical conditions where the research funding is insufficient to close the gap in robust scientific evidence needed for improved policies and practices to tackle these medical conditions. This can result in a lack of knowledge that hampers adequate preventive, diagnostic and therapeutic strategies, while the disease poses a considerable burden on patients in terms of incidence/prevalence, mortality or quality of life.

3a. What is your reflection on our working definition?

In case your organisation or country has its own definition of high-burden under-researched medical conditions, or in case you have suggestions for another definition or an addition to the above- mentioned definition, please mention this here as well.

3b. If you are aware of (national) research or R&I initiatives that have been undertaken to address under-researched conditions in Europe over the last 5 years, please let us know here. *If relevant, please provide links to any public document that describes or explains how under-researched conditions are defined or addressed in that initiative*

Part III: Views on high-burden under-researched (groups of) diseases and conditions

In this study, several consecutive activities have been undertaken to come to a preliminary list of possibly under-researched and high-burden diseases and conditions: research projects related to health under the Horizon 2020 programme have been mapped with their amount of funding and the disease (group) or condition they address; this was related to the burden of these disease (groups) and conditions; a literature search identified common reasons for people to visit their general practitioner; and additional literature research provided insight into the knowledge base available for disease (groups) and conditions identified. This has resulted in a preliminary overview of possibly under-researched disease (groups) and conditions that are high-burden for patients in the EU (shown below). What we would like to know from you is: a) Do you recognise these disease (groups) and conditions as being under-researched? b) What type of research do you think is especially needed? and c) What other high-burden diseases may be under-researched that are not included in the list?

The following list of disease (groups) and conditions have been identified as possible under-researched and high-burden to patients in Europe:¹³

(please note that the research underlying the creation of this list has its limitations; this list is debatable and therefore your expert opinion is needed)

- Mental disorders
 - Mental disorders
 - Depression or anxiety
 - Self-harm
- Disorders of the blood and organ system
 - Chronic kidney disease
 - Cirrhosis and other chronic liver diseases

Diabetes mellitus¹³

- Cystitis / urinary tract infection
- Gallbladder and biliary diseases
- Dyspepsia
- Abdominal pain
- Hemoglobinopathies and hemolytic anaemias
- Musculoskeletal disorders
 - Musculoskeletal disorders
 - Arthritis (not back)
 - Injuries
 - Low back pain
- Headache disorders
 - Headache disorders
 - Tension-type headaches
 - Migraine
- Fatigue / weakness
- Sleep-wake disorders
- Skin and subcutaneous diseases
 - Dermatitis

Sense organ diseases¹³

- Gynaecological diseases
 - Pregnancy, childbirth or the puerperium
- Conditions related to sexual health

¹³ The final qualitative appraisal was based on amount of funding and evident research gap; as these criteria were systematically checked after the survey had been sent, one disease group was initially excluded, but should have been included, based on funding and/or evident research gap. This concerns developmental anomalies. Three conditions were included that should have been excluded. This concerns: diabetes mellitus, dyspepsia, and sense organ diseases.

3. Do you recognise the disease (groups) and/or conditions in the above list as being under-researched?
- Yes, all of the disease groups on the list
 - Yes, part of the disease groups on the list > Q4
 - No, none of the disease groups on the list
 - I don't know
4. Please specify which disease (groups) and/or conditions should not be included in the list:
- You will be given the opportunity to suggest disease (groups) and/or conditions that should be included but are not part of the above list later on.*
5. Please select a maximum of three (groups of) diseases / conditions from the list below on which you consider yourself to be an expert.¹⁴
- Mental disorders (including, but not limited to: depression or anxiety and self-harm)
 - Disorders of the blood and organ system (including, but not limited to: chronic kidney disease, cirrhosis and other chronic liver diseases, diabetes mellitus¹⁴, cystitis / urinary tract infection, gallbladder and biliary diseases, dyspepsia¹⁴, abdominal pain, hemoglobinopathies and haemolytic anaemias)
 - Musculoskeletal disorders (including, but not limited to: arthritis (not back), injuries, low back pain)
 - Headache disorders (including, but not limited to: tension-type headaches, migraine)
 - Fatigue / weakness
 - Sleep-wake disorders
 - Skin and subcutaneous diseases (including, but not limited to: dermatitis)
 - Sense organ diseases¹⁴
 - Gynaecological diseases (including, but not limited to: pregnancy, childbirth or the puerperium)
 - Conditions related to sexual health

[For each of the disease groups that are selected by the respondent, Q5a – Q5d will follow.]

¹⁴ The final qualitative appraisal was based on amount of funding and evident research gap; as these criteria were systematically checked after the survey had been sent, one disease group was initially excluded, but should have been included, based on funding and/or evident research gap. This concerns developmental anomalies. Three conditions were included that should have been excluded. This concerns: diabetes mellitus, dyspepsia, and sense organ diseases.

5a. Can you indicate whether you think this is indeed an under-researched (group of) disease(s) with a high burden for patients?

- I am certain** that this is an under-researched high burden (group of) diseases > *Q5b*
- I suspect that this may be an under-researched high burden (group of) diseases > *Q5b*
- I am not sure that this group is an under-researched high burden (group of) diseases > *Go to next disease group*
- I am certain that this group is NOT an under-researched high burden (group of) diseases > *Go to next disease group*

5b. What type of research would be primarily needed to close the evidence gap allowing for improved policies and practices to tackle these medical conditions?

- Prevention
- Basic or fundamental research
- Clinical (incl. diagnostic and/or treatment)
- Implementation
- Other

Please specify:

- I don't know

5c. What are in your opinion the minimal research requirements needed for this type of research, to make a real impact?

- Cohorts
- Biobanks
- Large databases like genetic/ imaging data
- Clinical trial networks
- Other

Please specify:

5d. What do you think should be improved in order to increase the research activities?

- Create more / better national, EU, and international funding opportunities
- Increase incentives (other than financial) to do research on these medical conditions

Please specify what type of incentives you have in mind:

- Make incentives sufficiently accessible to do research on these medical conditions

Please specify how you would envision incentives can be made sufficiently accessible:

- Stimulate the organisation of specific conferences in the medical areas
- Stimulate researcher mobility
- Stimulate the creation of large research networks
- Other

Please specify:

6a. Could you indicate which other conditions, diseases or disease groups you would consider to label as ‘under-researched’ and high burden to patients, in need of robust scientific evidence for improved management of these medical conditions? *If relevant, please provide links to any public document that describes or explains how under-researched conditions are defined or addressed in your country. Please be aware that rare diseases are not within the scope of this study.*

- No > Q7
- Yes

Please specify:

6b. Can you think of any (European) Research Networks on these conditions?

- No
- Yes

Please exemplify for all the disease (groups) and/or conditions that you have specified:

6c. Can you think of ways to enhance the research capacity in Europe for these conditions?

- No

- Yes

Please exemplify for all the disease (groups) and/or conditions that you have specified:

6d. Can you think of any possible reasons explaining why these medical conditions are understudied and underrepresented in EU-funded projects?

- No
- Yes

Please exemplify for all the disease (groups) and/or conditions that you have specified:

7. Are there in your opinion any disease (groups) and/or conditions with significant knowledge gaps related to specific population group(s)? *E.g. for women, elderly, persons with a migration background, socially vulnerable persons, etc.*

8. Are there any final comments that you would like to make?

Thank you for your cooperation.

Annex G – Perspective 4 : survey results

Table G.1: Response rate per type of stakeholder

Type of stakeholder	Number invited	Number responded	Response rate
Academia	3	9	300%
EU Member State representative	29*	6	21%
Healthcare professionals	28	5	18%
Patients or citizens	33	17	48%
Public funding bodies (national or international)	29	7	24%
Industry	3	0	0%
Philanthropic	5	0	0%
TOTAL	130	44	34%

* SGPP and NCD sub-group members from 29 countries (EU MS plus Norway and Iceland) were invited, which included in most cases multiple representatives per country (the invitation was sent to 115 persons or functional email addresses). However, as in general one coordinated response per country is requested in these types of surveys, the number of countries that were approached is presented in the table.

Table G.2: Perceptions of stakeholders regarding the list of high-burden under-researched conditions

Disease (groups)	Frequency of being considered as <u>not</u> under-researched
Mental disorders	3
<i>depression or anxiety</i>	2
<i>self-harm</i>	1
Disorders of the blood and organ system	2
<i>chronic kidney disease</i>	3
<i>cirrhosis and other chronic liver diseases</i>	1
<i>cystitis/urinary tract infection</i>	1
<i>gallbladder and biliary diseases</i>	1
<i>abdominal pain</i>	2
<i>haemoglobinopathies</i>	1
<i>haemolytic anaemias</i>	1
Musculoskeletal disorders	1
<i>arthritis (not back)</i>	3
<i>injuries</i>	2
<i>low back pain</i>	2
Headache disorders	2
<i>tension-type headaches</i>	0
<i>migraine</i>	0
Fatigue/weakness	0
Sleep-wake disorders	1
Skin and subcutaneous diseases	1
<i>dermatitis</i>	1
Gynaecological diseases	3
<i>pregnancy</i>	1
<i>childbirth or the puerperium</i>	1
Conditions related to sexual health	1

Table G.3: Number of stakeholders that: a) consider a specific disease group as under-researched; b) endorse types of research needed to close the knowledge gap; endorse specific research requirements; endorse requirements to increase research activities

Disease group	Nr. of stakeholders	Under-researched condition?	Type of researched considered needed to close knowledge gap	Minimal research requirements	Requirements to increase research activity
Mental disorders	13	10 certain 3 suspects	11 Prevention 9 Basic or fundamental research 9 Clinical research 4 Implementation	9 Cohorts 7 Large databases 7 Clinical trial networks 3 Biobanks	10 More/better national, EU, and international funding opportunities 8 The stimulation of the creation of large research networks 5 The increase of incentives (other than financial) to do research on these medical conditions 5 Making incentives sufficiently accessible to do research on these medical conditions 4 The stimulation of researcher mobility 3 The stimulation of the organisation of specific conferences in the medical areas
Disorders of the blood and organ system	10	5 certain 2 suspects 2 not sure 1 not specified	5 Prevention 5 Basic or fundamental research 2 Clinical research	7 Cohorts 4 Biobanks 4 Large databases 3 Clinical trial networks	6 Create more/better national, EU, and international funding opportunities 4 Make incentives sufficiently accessible to do research on these medical conditions 3 Stimulate the creation of large research networks 2 Increase incentives (other than financial) to do research on these medical conditions 1 Stimulate researcher mobility
Musculoskeletal disorders	5	3 certain 2 suspects	4 Basic or fundamental research 4 Clinical research 3 Prevention	4 Biobanks 4 Large databases 3 Cohorts 3 Clinical trial networks	4 Create more/better national, EU, and international funding opportunities 2 Stimulate the creation of large research networks 2 Increase incentives (other than financial) to do research on these medical conditions

			1 Implementation		2 Make incentives sufficiently accessible to do research on these medical conditions 1 Stimulate researcher mobility
Headache disorders	3	2 certain 1 suspects	2 Basic or fundamental research 2 Clinical research 1 Prevention 1 Implementation	1 Clinical trial networks	2 Create more/better national, EU, and international funding opportunities 2 Increase incentives (other than financial) to do research on these medical conditions 2 Make incentives sufficiently accessible to do research on these medical conditions 2 Stimulate the creation of large research networks 1 Stimulate the organisation of specific conferences in the medical areas 1 Stimulate researcher mobility
Fatigue / weakness	6	5 certain	6 Clinical research 5 Basic or fundamental research 2 Implementation 1 Prevention	5 Cohorts 4 Biobanks 4 Clinical trial Networks 3 Large databases	6 Create more/better national, EU, and international funding opportunities 5 Stimulate the creation of large research networks 3 Make incentives sufficiently accessible to do research on these medical conditions 3 Stimulate researcher mobility 2 Stimulate the organisation of specific conferences in the medical areas 2 Increase incentives (other than financial) to do research on these medical conditions
Sleep-wake disorders	5	4 certain 1 suspects	4 Basic or fundamental research 3 Prevention 3 Clinical research 3 Implementation	3 Cohorts 3 Large databases 1 Clinical trial networks	5 Create more/better national, EU, and international funding opportunities 5 Stimulate the creation of large research networks 2 Make incentives sufficiently accessible to do research 2 Stimulate the organisation of specific conferences in this field 2 Stimulate researcher mobility

Skin and sub-cutaneous diseases	12	10 certain 1 suspects 1 not specified	6 Clinical research 4 Prevention 4 Basic or fundamental research 2 Implementation	7 Large databases 7 Clinical trial networks 6 Cohorts 4 Biobanks	9 Stimulate the creation of large research networks 6 Create more/better national, EU, and international funding opportunities 6 Stimulate researcher mobility 5 Make incentives sufficiently accessible to do research on these medical conditions 4 Increase incentives (other than financial) to do research on these medical conditions 4 Stimulate the organisation of specific conferences in the medical areas
Gynaecological diseases	3	2 certain 1 suspects	2 Basic or fundamental research 2 Clinical research 2 Implementation research	2 Large databases 2 Clinical trial networks 1 Cohorts 1 Biobanks	2 Create more/better national, EU, and international funding opportunities 2 Stimulate the creation of large research networks 1 Increase incentives (other than financial) to do research on these medical conditions 1 Stimulate researcher mobility
Conditions related to sexual health	2	1 certain 1 suspects	2 Prevention 1 Clinical research 1 Implementation research	2 Clinical trial networks 1 Cohorts 1 Biobanks 1 Large databases	1 Stimulate the creation of large research networks 1 Create more/better national, EU, and international funding opportunities

Annex H – Perspective 4: (Appraisal of) list of high-burden under-researched medical conditions from stakeholder survey

All identified (groups of) diseases/conditions mentioned by the responding stakeholders from the survey were grouped, categorised and included in the already existing list based on perspectives 1-3 (table H.1). Those (groups of) diseases/conditions added by survey, were also appraised in a qualitative appraisal. Where the (groups of) diseases/conditions were appraised for further exclusion, a summary of the rationale is put at the right side of table H.1. Table H.2. provides the list of all (groups of) diseases that were not excluded in the appraisal. These form the final list of high-burden under-researched medical conditions in this study.

Table H.1: List of high-burden under-researched medical conditions including the stakeholder perspective, including source of inclusion and rationale for exclusion of conditions, diseases or disease groups for perspective 4

No.	Condition, disease or disease group	Perspective		Rationale for exclusion from the shortlist
1	Mental disorders	GBD	DALY	
	Depression or anxiety	GP		
	Self-harm	GBD	YLL	
	Autism	Survey		
2	Disorders of the blood and organ system	ICD		
	Chronic kidney disease	GBD	Top50	
	Cirrhosis and other chronic liver diseases	GBD	Top50	
	Cystitis/urinary tract infection	GP		
	Gallbladder and biliary diseases	GBD	Top50	
	Abdominal pain	GP		
	Haemoglobinopathies and haemolytic anaemias	GBD	Prevalence	
3	Musculoskeletal disorders	GBD	DALY	
	Arthritis (not back)	GP		
	Injuries	GBD	Top50, prevalence, DALY, YLL	
	Low back pain	GBD & GP	DALY	
	Fibromyalgia	Survey		
4	Headache disorders	GBD	Prevalence	
	Tension-type headache	GBD	Prevalence	

	Migraine	GBD	Prevalence	
5	Fatigue/weakness	GP		
	Myalgic encephalomyelitis / Chronic fatigue syndrome (ME/CFS)	Survey		
6	Sleep-wake disorders	ICD		
7	Skin and subcutaneous diseases	GBD	Prevalence	
	Dermatitis	GP		
	Hidradenitis suppurativa	Survey		
	Genital lichen sclerosus	Survey		
	Lichen planus	Survey		
8	Gynaecological diseases	GBD	Prevalence	
	Pregnancy, childbirth or the puerperium	ICD		
	Endometriosis	Survey		
9	Conditions related to sexual health	ICD		
10	Developmental anomalies	ICD		
11	Immune related diseases			
	Food allergy	Survey		
	Autoimmune diseases	Survey		
	Mast cell activation syndrome (MCAS)	Survey		
12	Other			
	Postural tachycardia syndrome (PoTS)	Survey		
	Chronic Lyme disease	Survey		
	Hypermobile Ehlers Danlos Syndrome (EDS)	Survey		
	Inborn errors of metabolism	Survey		<i>Exclude from list: - Rare disease</i>
	Neoplasms: ovarian cancer, metastatic breast cancer, oncological diseases of autoimmune origin	Survey		<i>Exclude from list: - See table D.1 category 2</i>
	Neurodegenerative diseases	Survey		<i>Exclude from list: - Highly funded compared to the other disease groups in the</i>

				<i>list (within highest 4 (20%) of funded groups)</i>
	Infectious diseases	Survey		<i>Exclude from list: - Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)</i>
	Post COVID-19 condition (long COVID)	Survey		<i>As this study focused on Horizon2020 project, unable determine the amount of funding and attention for post COVID-19</i>

GBD: Global Burden of Disease database (2nd perspective); GP: general practitioner (3rd perspective); ICD: International Classification of Diseases (1st perspective); Top50: listed in the top 50 lowest Δ outcome (%funding - %burden); DALY: Disability Adjusted Life Years; YLL: Years of Life Lost

Table H.2: Final list of high-burden under-researched medical conditions (based on perspectives 1-4)

No.	Condition, disease or disease group	Perspective	
1	Mental disorders	GBD	DALY
	Depression or anxiety	GP	
	Self-harm	GBD	YLL
	Autism	Survey	
2	Disorders of the blood and organ system	ICD	
	Chronic kidney disease	GBD	Top50
	Cirrhosis and other chronic liver diseases	GBD	Top50
	Cystitis/urinary tract infection	GP	
	Gallbladder and biliary diseases	GBD	Top50
	Abdominal pain	GP	
	Haemoglobinopathies and haemolytic anaemias	GBD	Prevalence
3	Musculoskeletal disorders	GBD	DALY
	Arthritis (not back)	GP	
	Injuries	GBD	Top50, prevalence, DALY, YLL
	Low back pain	GBD & GP	DALY
	Fibromyalgia	Survey	
4	Headache disorders	GBD	Prevalence
	Tension-type headache	GBD	Prevalence
	Migraine	GBD	Prevalence
5	Fatigue/weakness	GP	

	Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)	Survey	
6	Sleep-wake disorders	ICD	
7	Skin and subcutaneous diseases	GBD	Prevalence
	Dermatitis	GP	
	Hidradenitis suppurativa	Survey	
	Genital lichen sclerosis	Survey	
	Lichen planus	Survey	
8	Gynaecological diseases	GBD	Prevalence
	Pregnancy, childbirth or the puerperium	ICD	
	Endometriosis	Survey	
9	Conditions related to sexual health	ICD	
10	Developmental anomalies	ICD	
11	Immune related diseases		
	Food allergy	Survey	
	Autoimmune diseases	Survey	
	Mast cell activation syndrome (MCAS)	Survey	
12	Other		
	Postural tachycardia syndrome (PoTS)	Survey	
	Chronic Lyme disease	Survey	
	Hypermobility Ehlers Danlos Syndrome (EDS)	Survey	

GBD: Global Burden of Disease database (2nd perspective); GP: general practitioner (3rd perspective); ICD: International Classification of Diseases (1st perspective); Top50: listed in the top 50 lowest Δ outcome (%funding - %burden); DALY: Disability Adjusted Life Years; YLL: Years of Life Lost

Annex I – Perspectives 1-4: Overview of qualitative appraisals categorised per perspective

Table I.1: Summary table of qualitative appraisal perspectives 1-4

Perspective	Main consideration to exclude the condition	In final list
Perspective 1: Matching levels of EU research funding with medical conditions, as categorised in the International Classification of Diseases		
Conditions related to sexual health		X
Developmental anomalies		X
Pregnancy, childbirth or the puerperium		X
Sleep-wake disorders		X
Diseases of the blood or blood-forming organs		X
Perspective 2: Matching levels of EU research funding with high-burden medical conditions, as documented in the Global Burden of Diseases (GBD) study		
Cardiovascular diseases (DALY, YLL, deaths)	Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)	
Caries of permanent teeth (prevalence)	Within excluded group of oral disorders	
Chronic kidney disease		X
Chronic obstructive pulmonary disease (COPD) (DALY, YLL, deaths)	No evident scientific knowledge gap	
Cirrhosis and other chronic liver diseases		X
Gallbladder and biliary diseases		X
Gynaecological diseases (prevalence)		X
Headache disorders (prevalence)		X
Haemoglobinopathies and haemolytic anaemias (prevalence)		X
Hypertensive heart disease (deaths)	Within excluded group of cardiovascular diseases	
Injuries (prevalence, DALY, YLL)		X
Intracerebral haemorrhage (deaths)	Within excluded group of cardiovascular diseases	
Ischemic heart disease (DALY, YLL, deaths)	Within excluded group of cardiovascular diseases	
Ischemic stroke (DALY, YLL, deaths)	Within excluded group of cardiovascular diseases	
Low back pain (DALY)		X
Mental disorders (DALY)		X
Migraine (prevalence)		X

Musculoskeletal disorders (DALY)		X
Neoplasms (YLL, deaths)	Within excluded group of total cancers	
Oral disorders (prevalence)	No evident scientific knowledge gap	
Periodontal diseases (prevalence)	Within excluded group of oral disorders	
Self-harm (YLL)		X
Skin and subcutaneous diseases (prevalence)		X
Stroke (DALY, YLL, deaths)	Within excluded group of cardiovascular disorders	
Tension-type headache (prevalence)		X
Total cancers (YLL, deaths)	Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)	
Tracheal, bronchus, and lung cancer (DALY, YLL, deaths)	Within excluded group of total cancers	
Perspective 3: Matching levels of EU research funding with medical conditions identified as why people most frequently consult their general practitioner (GP)		
Abdominal pain		X
Acute otitis media	Within excluded group of acute upper respiratory tract infection	
Acute upper respiratory tract infection	No evident scientific knowledge gap	
Arthritis (not back)		X
Back pain		X
Cough	Within excluded group of acute upper respiratory tract infection	
Cystitis/urinary tract infection		X
Depression or anxiety		X
Dermatitis		X
Diabetes mellitus	Highly funded compared to other diseases in the list (highest funded) in combination with no evident scientific knowledge gap	
Fatigue/weakness		X
Hypertension	Within excluded group of cardiovascular disorders	
Perspective 4: Stakeholders' views on the identified high-burden under-researched medical conditions		
Hidradenitis Suppurativa		X
Allergy (specific food allergy)		X
Inborn errors of metabolism	Mostly rare diseases	
Ovarian cancer	Within excluded group of total cancers	

Genital Lichen Sclerosus and Lichen Planus		X
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)		X
Postural tachycardia syndrome (POTS)		X
Chronic Lyme disease		X
Fibromyalgia		X
Endometriosis		X
Metastatic breast cancers	Within excluded group of total cancers	
High-burden infectious diseases for which there are no effective treatments	Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)	*
Post COVID-19 condition (long COVID)	Emerging disease, amount of funding cannot be established yet based on CORDIS	*
Autoimmune diseases		X
Oncological diseases of autoimmune origin	Within excluded group of total cancers	
Neurodegenerative diseases	Highly funded compared to the other disease groups in the list (within highest 4 (20%) of funded groups)	
Hypermobile Ehlers Danlos Syndrome (EDS)		X
Mast cell activation syndrome (MCAS)		X
Autism		X
Neglected tropical diseases (emerging health threats in Europe such as Malaria, Dengue, and various other infectious and parasitic diseases)	Funding via other EU programme	

* Not included in the list of possibly high-burden under-researched medical conditions but recommended to take into account based on a diversity of factors, including: needs of underserved population groups, globalisation, antimicrobial resistance, influx of migrants, climate change, which could make these themes relevant in the future.

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A number of medical conditions are insufficiently recognised, diagnosed and treated due to a lack of knowledge, and may be under-researched, even though they are a major burden for patients and society. The EUHealthSupport Consortium conducted exploratory research for the European Commission into these so-called 'high-burden under-researched medical conditions'.

Four complementary perspectives were used to identify conditions with a high disease burden that may be under-researched. This resulted in the identification of 12 groups of conditions:

1. Mental disorders
2. Disorders of the blood and organ system
3. Musculoskeletal disorders
4. Headache disorders
5. Fatigue / weakness
6. Sleep-wake disorders
7. Skin and subcutaneous disorders
8. Gynaecological disorders
9. Conditions related to sexual health
10. Developmental anomalies
11. Immune-related diseases
12. Others

The findings of this study can guide policy makers in designing programmes for diseases and conditions where more research is needed, with a view to improve health and healthcare in the EU.

Studies and reports

