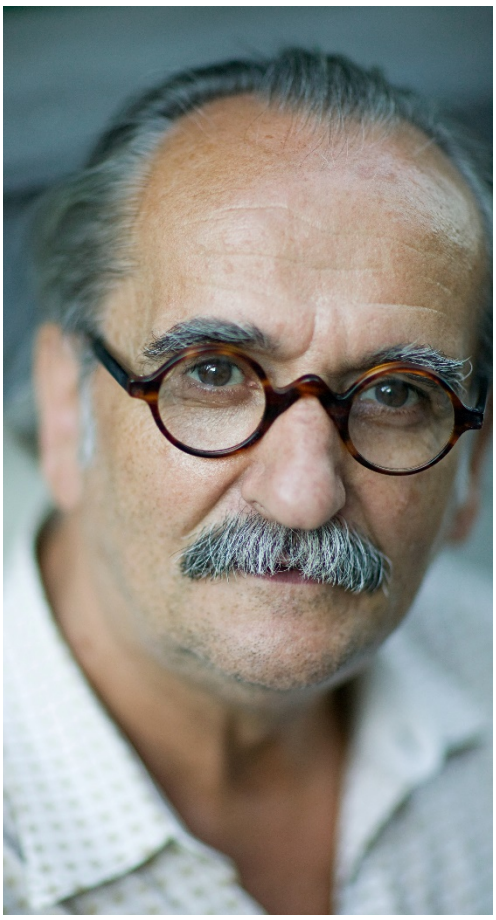

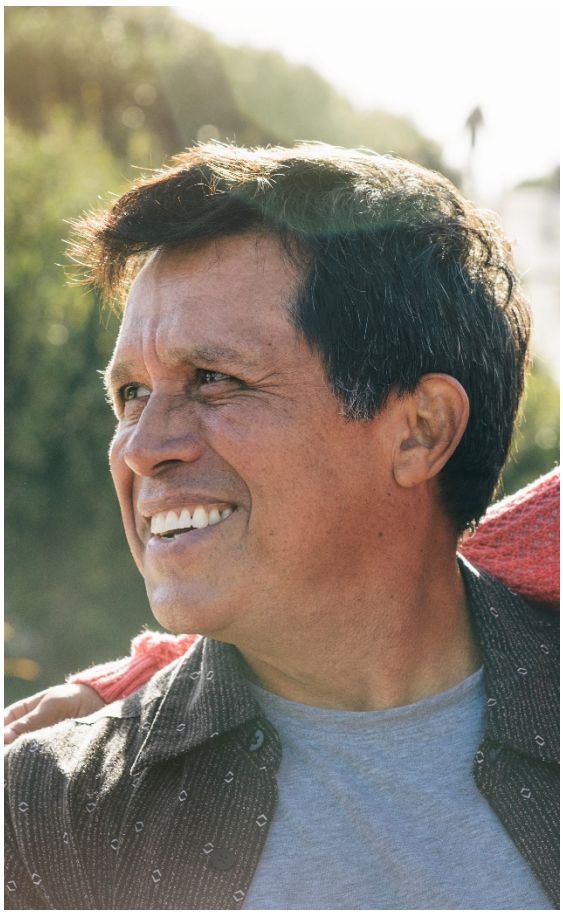

Multiple Chronic Conditions
THE GLOBAL STATE

Dr. Cother Hajat, Emma Stein, Dr. Derek Yach

Acknowledgements

The purpose of this work is to quantify the health, economic, and patient burden of multiple chronic conditions (MCC) and define potential areas for innovation and intervention. The authors of this work include:

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- Emma Stein, MPH
- Derek Yach, MBChB, MPH

The authors would like to acknowledge the support and direction provided for this work by Dr. Sandeep Kishore, Dr. Richard Smith, Dr. Venkat Narayan, Dr. Rachel Nugent, and Dr. Anthony Rodgers. We would also like to thank the interviewees who participated in the stakeholder consultation for the terminology of MCC.

This initiative was supported by Teva Pharmaceuticals. The content of the report has been developed by the authors independently of Teva.

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Executive Summary

Globally, one in three adults has multiple chronic conditions (MCC). This work was conducted to quantify the health, economic, and personal burden of MCC and to define potential areas for innovation and interventions to reduce its impact.

The increasing burden from chronic disease, which falls disproportionately on low-income countries, is a global priority. Worldwide, three in five of all deaths are attributable to four major chronic conditions–cardiovascular disease (CVD), cancer, chronic lung diseases, and diabetes. One in three adults suffer from more than one chronic condition. Furthermore, certain chronic diseases occur together more frequently in clusters, a phenomenon which occurs more in developing countries.

Studies exploring the impact of MCC on healthcare costs and resources show a high cost burden for healthcare systems globally, with an individual's healthcare costs doubling with each additional chronic condition they suffer. This burden will only grow with the increasing number of older adults and the onset of risk factors for chronic disease at younger ages. Moreover, patients with MCC and their caregivers face significant burdens, including increased costs and deterioration of quality of life. While the challenge and need are great, there is also opportunity to introduce cross-sector efforts to improve patient quality of life and alleviate costs related to MCC.

Definitions and Data

There is no agreed taxonomy for those suffering with more than one chronic condition, with several terms used interchangeably to describe such patients. Multimorbidity, MCC, and polychronic disease (PCD) are the most widely used.

What constitutes a chronic disease and which ones are included in MCC vary across the literature with studies including between four to 147 conditions. The lack of a consistent term and definition has led to considerable differences in prevalence and burden estimates by up to threefold.

As part of this work, a literature search and stakeholder consultation with 36 healthcare providers and public health professionals suggests that multiple chronic conditions (MCC) is the preferred term across multiple geographies and languages. Further agreement as to which conditions should be included is required.

Data used in this report include academic literature searches and 'snowballing' to identify additional articles and reports. Other data repositories were reviewed for primary data, including the World Health Organization (WHO) and the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study.

Key Findings

This report is the first comprehensive review of the burden and impact of multiple chronic conditions (MCC) globally, reporting on the taxonomy, epidemiology, and burden on patients, health systems, and economies, and presenting strategies for how these may be tackled. A summary of the key findings is presented in the box below.

Key Report Findings

- The prevalence of MCC, although highly dependent on definitions, is about one in three adults globally and ranges between 16% and 58% of adults in developed countries.
- The top chronic conditions contributing to disease burden globally include ischemic heart disease (IHD), stroke, lung cancer, depression, diabetes, and back and neck pain.
- Low-income countries (LICs) and lower middle-income countries (LMICs) have a similar noncommunicable disease (NCD) burden to high-income countries (HICs), while simultaneously also suffering from the burden of communicable disease (e.g., diarrhea, HIV/AIDS and tuberculosis (TB)).
- The five leading global risk factors for chronic disease are high blood pressure, high fasting glucose, smoking, high total cholesterol, and high body mass index.
- Certain chronic diseases cluster together more frequently (e.g. Cardiovascular Disease (CVD) and stroke with depression, TB with diabetes, and HIV/AIDS with CVD).
- MCC is associated with substantially greater increases in healthcare costs and resource utilization. Healthcare expenditures double with each additional chronic condition due to elevated rates of primary care and specialist physician access, emergency department presentations, hospital admissions, and polypharmacy.
- The impact of MCC on patients and families is profound, including deterioration of patients' quality of life, significant out-of-pocket expenses, difficulties with medication adherence, inability to continue work, symptom control (chronic pain, in particular), and a considerable toll on caregivers.
- The increasing proportion of older adults in the population and of younger adults with MCC who will live to advanced ages has implications for policies and funding.
- Current research and research funding, healthcare system infrastructure, and healthcare delivery systems are not well-equipped to tackle the burden and future impact of MCC.

Health Burden from Chronic Conditions

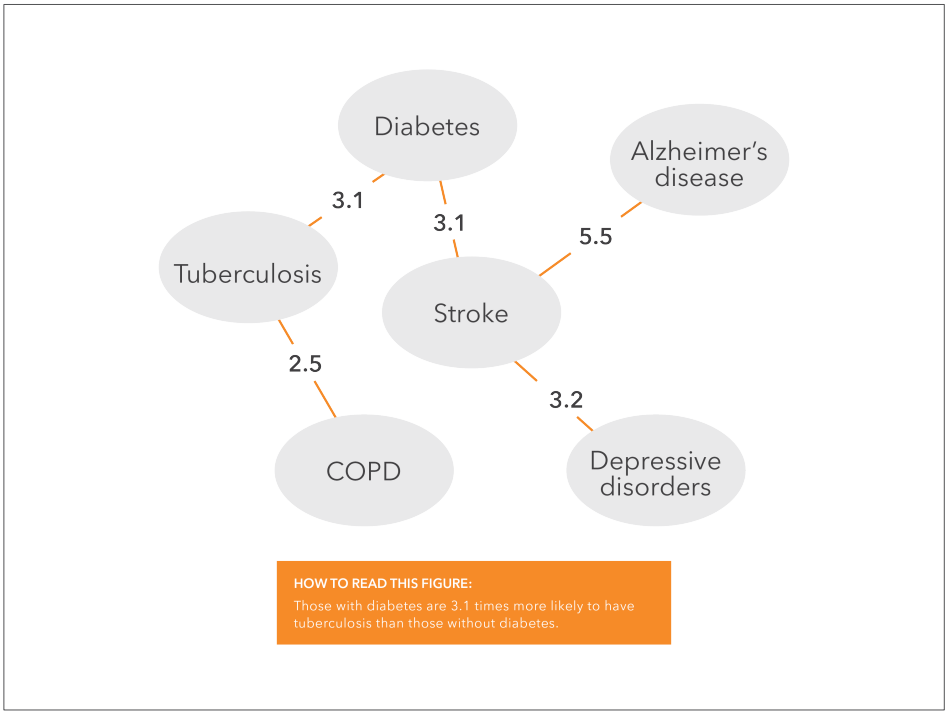
The prevalence of MCC is highly dependent on its definition and the number of conditions considered. Estimates range from 16% to 58% in United Kingdom studies and 26% in United States studies (for between 10 to 114 conditions included). Among Americans 65 years of age and older, as many as three in four have MCC.

Using the composite measure of disability adjusted life years, (DALYs), the top conditions contributing to mortality and morbidity are widely reported. In LMICs, the top diseases include the same NCDs, as well as communicable diseases, such as diarrhea, HIV and malaria, and road traffic injuries. Trends over the last 25 years include a reduction in DALYs for IHD but DALYs for diabetes, low back pain, chronic kidney disease, and depression remain largely unchanged since 1990.

The leading global risk factors of high blood pressure, high fasting glucose, smoking, high total cholesterol, and high body mass index contribute to both mortality and morbidity from chronic diseases, and are similar for developed and developing countries. Furthermore, they are all highly amenable to prevention, highlighting the importance of prevention as a tool in tackling MCC.

Chronic Disease Clusters

Certain chronic diseases occur together more frequently by virtue of independently high prevalence rates, common risk factors, or a synergistic relationship between the two. The most widely reported clusters, some of which are illustrated in the figure below, include CVD and stroke coexisting with depression, and CVD and diabetes coexisting with long-term communicable conditions in developing countries, such as TB and diabetes, and HIV/AIDS and CVD.



This phenomenon of MCC is not widely reported despite the markedly different cost and personal burdens on patients and healthcare systems. Furthermore, there are additional complexities in the treatment of certain conditions occurring together; these include different screening and prevention requirements, greater risk of drug-drug interactions, reduced efficacy of medications, a lack of joint guidelines, and a greater tendency to see specialists over primary care physicians. By tackling these clusters, rather than the individual diseases, interventions and systems can directly address the difficulties faced by such patients, including through medication design, approaches to screening and detection, and care guidelines.

Impact of Multiple Chronic Conditions on Patients, Families, and Economies

MCC is associated with substantially greater increases in healthcare costs and resource utilization; healthcare expenditures are found to double with each additional chronic condition. Reasons for this include elevated rates of primary care and specialist physician access, emergency department visits, hospital admissions (e.g., frequency of admissions, bed days), and polypharmacy.

The impact on patients and families is profound, including deterioration of patients' quality of life, significant out-of-pocket expenses, difficulty with medication adherence, inability to continue work, symptom control, and a considerable toll on caregivers.

Unmet Needs and Challenges

Despite the increasing burden of NCDs, intervention funding and political action are not commensurate. Prevention and control of NCDs have been recognized, but there are major disparities between the burden of disease and funding allocated. This disparity is particularly problematic in LICs and LMICs.

Rates of chronic disease are increasing rapidly, especially in LICs. As the burden of MCC increases, healthcare costs, risk of death, and poor functional health also rise. Unfortunately, traditional health systems and major disease programs rarely address chronic diseases that occur together, instead adopting a single-disease framework. The shift from a single-disease focus to MCC will require a broad multidisciplinary application of behavioral and social science to all areas of health and medicine.

Recommendations and Areas for Intervention

Key Recommendations

Despite MCC affecting one in three adults globally and the large burden this places on healthcare resources, the scale of the problem is not reflected in the response, namely:

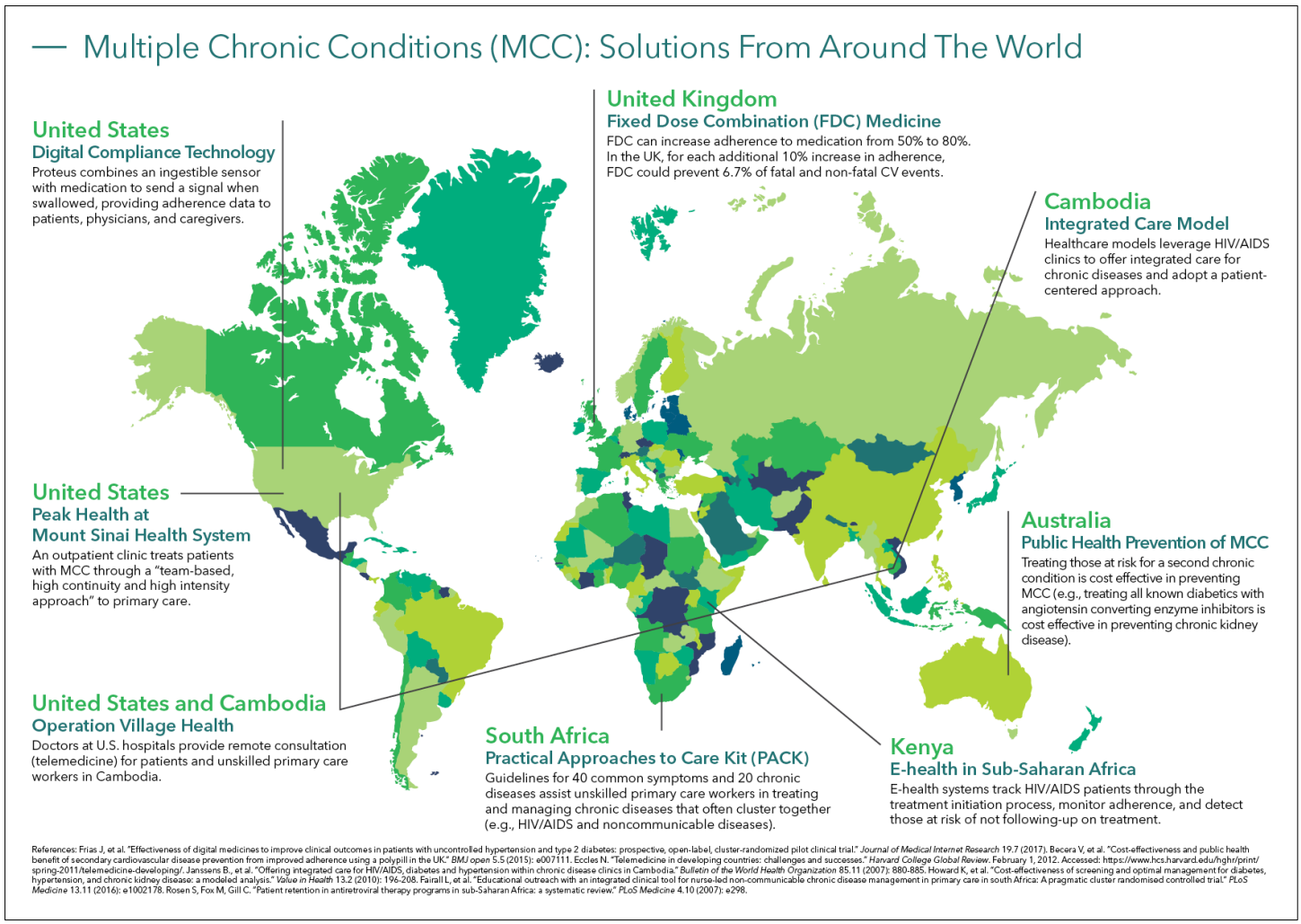
Key Recommendations

1. The evidence base for MCC is currently sparse, together with the necessary research funding to tackle this issue going forward. Due to the high prevalence and burden, as well as the inevitable increase due to population aging and increases in risk factors at earlier ages, further attention to MCC is urgently required.
2. There is no agreed taxonomy for MCC such that the descriptions of its burden are widely heterogeneous due to differing terms, definitions, and inclusion criteria. Consensus is required for the term itself, the definition of which chronic conditions should be included, and what constitutes a chronic condition. Further caution is required to differentiate which risk factors, diseases, and symptoms fit within the definition, and on the relationship between simultaneously occurring diseases (e.g., between correlation and causation).
3. Avoidance of chronic diseases through improvements to lifestyle behaviors such as smoking, diet, and physical activity remains the mainstay of primary prevention. Secondary prevention through disease management and control of established risk factors also plays a significant role. Economic evaluations are required to establish the most cost-effective approaches and interventions to reduce MCC burden.
4. Data reporting and monitoring systems do not include MCC. Some of the most widely used health data repositories, such as the WHO and GBD databases, only deal with single chronic conditions and do not yet report on MCC. Administrative data, such as hospital electronic medical records and financial (claims) data also do not deal adequately with MCC due to the lack of specific coding. This format of data reporting is not conducive to subsequent identification or analyses of MCC patients. The ability to report on multiple primary diagnoses in future coding systems should be considered.
5. Healthcare delivery systems are set up to manage chronic conditions individually, and not for the holistic or coordinated care of a MCC patient. Healthcare teams that have responsibility for community care as well as in the clinic, care guidelines that tackle symptoms as well as conditions, and also deal with more than one condition at a time, would assist with the provision of more patient-centric care. These are even more needed—but complex to deliver—in developing countries, where long-term infectious conditions co-exist alongside NCDs and access to healthcare is not guaranteed.
6. Healthcare payment mechanisms that reward positive health outcomes (e.g., value-based care) rather than activity-based funding (e.g., the fee-for-service approach in the United States) may help in achieving improved MCC patient outcomes.

Areas for Intervention

Interventions for MCC with proven health and cost outcomes are lacking. Certain interventions have started to show early impact, including the use of fixed dose combination pills to improve medication adherence and tackle undertreatment, cross-condition and symptom-based management guidelines, and community models of healthcare delivery. Additional funding is needed for research on MCC and interventions to address it. Future approaches should involve healthcare systems and key stakeholders, such as health insurers and pharmaceutical manufacturers, and focus on the concerns and difficulties of patients living with MCC.

Examples of case studies of interventions that show early signs of being capable of tackling the burden of MCC are shown in the map below.



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This work has outlined key challenges of MCC and promising areas for targeting this growing issue. The hope is that this work will lead to recommendations for tangible actions and interventions to address the impact of MCC.

Section 1: Introduction

Investment in Noncommunicable Diseases

Three in five of all global deaths are attributed to four major noncommunicable diseases (NCDs) – cardiovascular disease (CVD), cancer, chronic lung diseases, and diabetes.[1] The increasing burden of NCDs, which falls disproportionately on low-income countries (LICs), has made the prevention and management of these diseases a global priority. In 2011, the United Nations convened a High-Level Meeting on NCDs calling for "whole-of-society, whole-of-government, and multi-stakeholder action to prevent and control NCDs."[2] The 66th annual World Health Assembly endorsed the World Health Organization Action Plan for the prevention and control of NCDs between 2013 and 2020.[3] A recent report by the National Academy of Medicine focuses on strategies to better serve high-need patients.[4] The burden is apparent, priorities have been set, and it is now time for the development of innovative patient-centered approaches to the delivery of health services globally.

Purpose of the Report

The purpose of this report is to quantify the health, economic, and patient burden of multiple chronic conditions (MCC) and to highlight potential areas for innovation and intervention. The report offers clarity on the often-confused terminology used to describe patients with two or more chronic conditions. Variation in terminology and corresponding definitions make it difficult to quantify the extent of the problem among patients, economies, and healthcare systems. Recommendations for terminology are offered.

Using recent global estimates from the Global Burden of Disease, Injuries, and Risk Factors (GBD) study and other sources, the report describes the burden of chronic diseases globally and in countries of differing income levels. These estimates provide a sense of major contributors to disability adjusted life years (DALYs), mortality, and risk. Clusters of chronic diseases that commonly occur together are discussed, particularly as they pertain to solutions for reducing the burden of MCC.

The report highlights economic, social, and personal implications of MCC globally and offers preliminary calls-to-action, as well as emerging solutions, technologies, and models, to address the growing burden of MCC.

The Patient's Perspective

The impact of disease on the patient, as well as their caregiver, remains underexamined. Yet, for patients with MCC, their conditions are deeply ingrained in every aspect of their lives. This includes their ability to work, remain productive, and lead an independent life, as well as the burdens they face due to financial constraints and out-of-pocket expenses related to healthcare costs.

A few cases are highlighted to demonstrate the extent to which MCC impacts patients' and the caregivers' lives (Box 1, Box 3). The patient perspectives are compiled based on market research and focus group studies and represent multiple patients to highlight specific themes identified in the literature.[5] A caregiver profile also details the impact of MCC on those caring for patients (Box 2). These profiles highlight the emotional and physical toll on patients with MCC and their caregivers, as well as the challenges they face.

PATIENT PROFILE: CHRONIC LUPUS

The patient perspective on managing multiple chronic conditions

Joe, 62 years old

"I think improving is possible but you've got to keep realistic expectations. I know that I have a lot of things that will get better but aren't going to fix themselves. You have to realize that you're going to have bad days, you're going to have good days."

On Multiple Chronic Conditions

"My life used to be so different. I used to have the energy to leave the house, go to work, and see my friends. Now my life revolves around my conditions - and the pain. There is constant pain - both from my conditions themselves and from my medications. There is no end in sight."

Joe has chronic lupus. In the last year, Joe has also been **diagnosed with seven different chronic conditions**. He used to work part time, but had to give that up when his disease got worse. Sometimes he struggles to get out of bed, and on days like this, he has to make an active choice to get up for his wife.

His kids recently got him tickets to a concert. It was sweet, but it was hard for him to enjoy the concert, as he was thinking he would rather be in bed resting. Joe has **stopped seeing many of his friends** and no longer engages in the same social activities he did before he became sick. He was most recently **diagnosed with depression** after he spent five whole days in his bed when his wife was away.

Lupus started as a peripheral part of his life, then became very central. Managing it can be a huge task. He takes many different medications, and he doesn't believe they are very helpful. Sometimes **he won't take his medications for three days** until his wife encourages him to.

Box 1. Patient profile: chronic lupus

CAREGIVER PROFILE

The caregiver perspective on caring for someone with multiple chronic conditions

Judith, 33 years old

"My mom has her bad days and lashes out, which is a big drain on me. She comes first, of course, but I also value my own health. It's a vicious cycle. I need to be healthy to have the energy to look after her, but in looking after her, I often neglect my own health."

For Judith, taking care of her mother, who suffers from arthritis and chronic pain, takes up the majority of her life. **Judith's mother relies on her for a lot** and her mother's illness has made considerable demands on Judith's time

Judith values her own health because it gives her the strength and energy to carry on, and the ability to be patient, and to focus on her mother's needs. However, the responsibility **can wear Judith down** to the point where she isn't thinking about her own health. It can be a detrimental cycle – she needs to be well to look after her mom, but looking after her mom can make her neglect her own well-being.

Judith feels guilty for taking time to herself. As a result, she has not been dating or keeping in touch with her friends. She hasn't had time to make the effort mainly because her caregiver duties overwhelm her.

As an only child, Judith feels a big responsibility to influence her mom's health. This can be easier with her physical health (e.g., medication, diet) than her mental well-being. When she can't control her mom's mental health, Judith feels helpless and frustrated.

Box 2. Caregiver profile

PATIENT PROFILE: HYPERTENSION AND HYPERLIPIDEMIA

The patient perspective on managing hypertension and hyperlipidemia concurrently

David, 56 years old

"After a period of time, you know what the situation is. You know what you need to be on the lookout for. You've been diagnosed and treated, so you adapt to it. Now I'm in the management and maintenance mode."

On Multiple Chronic Conditions

Even though David was not able to recognize any symptoms of his high cholesterol (hyperlipidemia), he knows the medications will improve his health. David trusts his doctor and says they always agree on the best treatment strategy. David is now on two medications; his simple medication regimen means he never misses them.

David has suffered from high blood pressure (hypertension) for nearly a decade. He has a partial blockage of a cardiac artery, something he **has lived with for a long time now**.

He was recently diagnosed with high cholesterol and his doctor prescribed a cholesterol-lowering medication. Since this diagnosis, David **adopted healthy habits** he can get used to, such as cutting out red meat and eating more vegetables.

He sees himself as having the most influence to change his situation (versus his doctor). He accepts these conditions will be with him throughout his whole life. However, **he still feels positive he can manage the conditions** and perhaps get to a point where he needs less medication.

Box 3. Patient profile: hypertension and hyperlipidemia

As noted in the patient profile for Joe (Box 1), those with certain chronic conditions, such as systemic lupus erythematosus (SLE or lupus), suffer enormously from chronic pain and often take multiple medications to treat multiple diseases and symptoms. As a result, they may be unable to work, which can have a harmful impact on their quality of life and social relationships. Depression is not uncommon among patients with these mental, physical, and social disabilities. The depression, along with high quantities of medications, can negatively impact a patient's adherence to medication. Conversely, patients who have greater control over their diseases, a strong and trusting relationship with their physician, and a simple medication regimen are often more adherent to their medication. Those who care for individuals with MCC also face an enormous burden, not only on their mental health, but also on their physical health.

Section 2: Terminology, Data Sources, and Availability

Terminology

Commonly used synonyms for the presence of two or more chronic conditions include multiple chronic conditions (MCC), multimorbidity and polychronic disease (PCD). To properly describe the prevalence and burden from MCC, consistency in terminology is critical. The National Academy of Medicine recently proposed taxonomy for high need patients that include patients with MCC in addition to major complex chronic conditions, children with complex needs, non-elderly disabled, frail elderly, and those with advancing illness.[4] However, no single consensus exists for the taxonomy or definitions to be employed in defining those with MCC. This section discusses the findings of a systematic search for common terms and the findings of a stakeholder consultation on the most common terms found in the search.

Systematic Search for Commonly Used Terms

The term PCD is not commonly used in academic literature, and seems to be predominantly used within the healthcare provider and pharmaceutical industries.[6,7,8,9] Polychronicity is also a homonym, sharing the same spelling as the word used to describe the preference for multitasking.[10] The term multimorbidity emerged as a complement to the term comorbidity, often defined in relation to a primary (or index) condition. While used globally, multimorbidity is not well defined and is not specific to chronic conditions, often referring to the coexistence of health conditions in general. The term MCC refers to the presence of two or more chronic conditions in an individual and of the terms, is most commonly used in the academic literature. Notably, it is also used by the United States Department of Health and Human Services and the Centers for Medicare & Medicaid Services.[11]

Stakeholder Consultation on Terminology

The most commonly used terms identified in the systematic search were shared and tested for expert opinions and personal usage by global healthcare professionals (HCPs) and public health professional (PHPs) in six countries to ascertain the most appropriate terms. The research sought to:

- Identify terms used to describe patients with two or more chronic conditions
- Qualitatively assess reactions to six commonly used terms: multiple chronic conditions, multimorbidity, comorbidity, polychronic conditions, polychronic diseases, and polychronicity
- Determine inconsistencies in meanings between different languages

Methods

In-depth interviews were conducted in six countries (France, India, Israel, Peru, Russia, and United States), with 18 HCPs and 18 PHPs who were predetermined to have sufficient professional experience related to the purpose of this study. Eligibility criteria for HCPs included:

- Treat chronic patients
- Spend more than 75% of their time in direct patient care
- Identify as one of the following specialties: internists/primary care physicians, neurologists, respiratory/pulmonologists, pain specialists, or oncologists

PHPs included former representatives of national ministries or departments of health, administrators and experts at leading public health non-governmental organizations (NGOs), and academic researchers focused on chronic disease, but there were no specific eligibility criteria. A predetermined list of terms was presented to respondents to gauge reactions and preferences based on a combination of perceived accuracy, understandability, and resonance.

Results

Figure 1 reports the rankings overall and shows the overwhelming preference for the term MCC, ranked highest by respondents in each country. The data also demonstrate lack of preference for the terms polychronicity, polychronic conditions, and polychronic diseases in all countries.

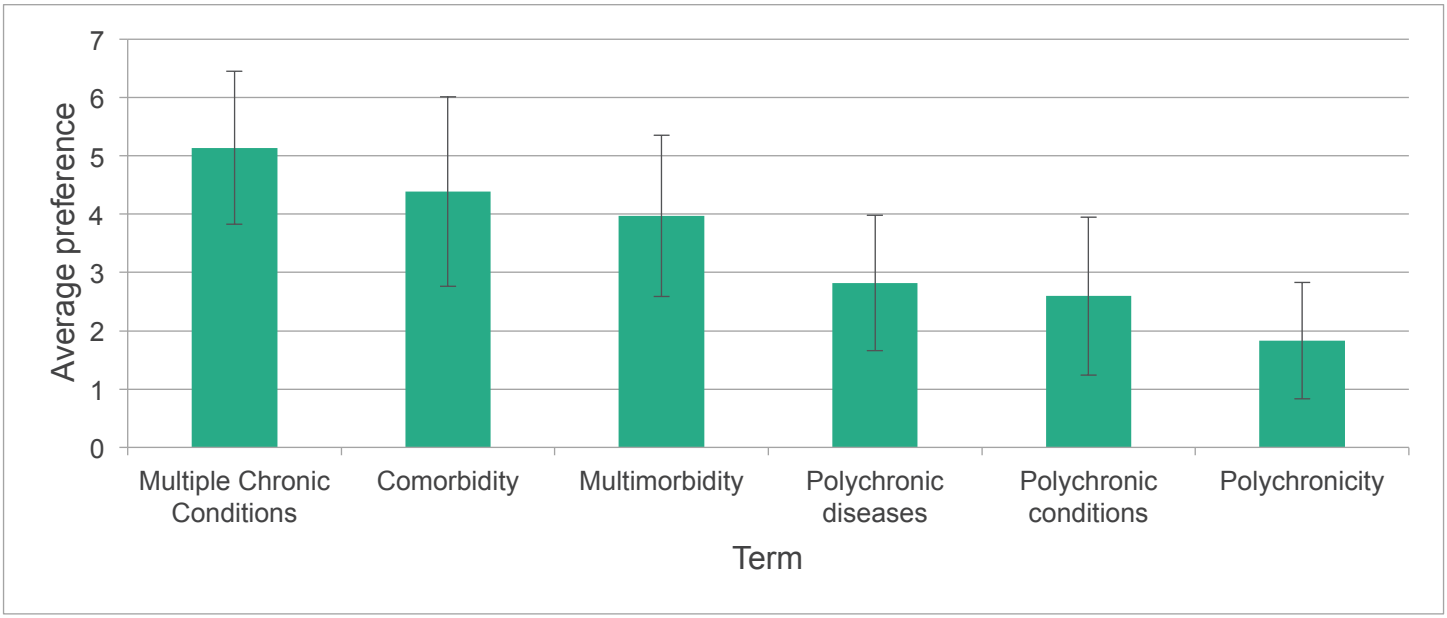


Figure 1. Average preference for terms (6 = most liked, 1 = least liked) used to describe patients with two or more chronic conditions among HCPs and PHPs (n = 36)

In addition to ranking the terms, respondents also shared reactions to each, including perceived definitions, elicited emotions, positive or negative connotations, related conditions, interpretations, and comments on ease of understanding. Table 1 provides a summary of qualitative responses across all countries for each term.

Term	Global Insights
Multiple Chronic Conditions	• **Widely used** in all regions • Very natural and **easily understood**, even for lay audiences • Very **popular**, often used in medical articles, materials, reviews, and guidelines • Does not distinguish whether the chronic diseases are **interconnected**
Multimorbidity	• When used properly, denotes a patient with **two or more** chronic conditions • **Not widely understood**, eliciting a variety of reactions • Insinuates **end-stage diseases**, rather than manageable conditions
Comorbidity	• Widely used to describe patients with **one primary chronic condition** and **multiple associated chronic conditions** • Commonly used and very familiar • Could be considered **too focused**, as it refers to a primary, or index, condition
Polychronic Conditions	• **Unfamiliar term** that is rarely used • While not preferred, most people could **figure out** what it means • **Not** a term respondents are **using now** or **envision using** in the future
Polychronic Disease	• **Unfamiliar term** that is rarely used; used incorrectly • Perceived as **grammatically incorrect** in some languages • Ambivalence of wording **elicited** feelings of uncertainty • **Could sound more pleasant** to patients compared to other terms
Polychronicity	• **Not fully understood**; does not immediately bring to mind patients with two or more chronic conditions • **Not a medical term** • If used in proper context, some could **guess the meaning** • This means multiple time points and is used to describe the **duration** of chronic disease, rather than the number of chronic conditions

Table 1. Summary of attitudes toward terminology

Summary

MCC is the preferred term of the six terms presented to 36 expert interviewees. In general, respondents felt all terms, with the exception of comorbidity, were synonymous. Comorbidity, well recognized, was deemed to refer to one main condition, whether chronic or acute. Polychronic disease, polychronic conditions, and polychronicity were unfamiliar to all respondents, and while most could guess their meaning based on the context, respondents indicated they were not likely to use them. Respondents from non-English speaking countries expressed a preference for using the original English terminology—a common practice with complex medical terms. There were no major differences in receptivity to the terms when translated to English, highlighting the ability to select a term, translate it into various relevant languages, and maintain consistent meaning and receptivity.

The authors recommend using the term MCC, which is unambiguous and has been used in both academic and non-academic settings across the globe.[12,13,14,15]

Definitions of Multiple Chronic Conditions

The lack of a single definition for MCC has resulted in considerable heterogeneity in prevalence estimates. This report presents estimates, where appropriate, but it is important to consider that estimates of prevalence and consequences of MCC are highly dependent on the number of chronic conditions considered. The simplest definition of MCC is the presence of two or more chronic conditions, but what constitutes a chronic condition is variable across the literature. Most studies utilize a diagnosis count to identify concurrent chronic conditions (i.e. two or more chronic conditions), thereby ignoring the relationship between the chronic conditions included in the study. Various indices have also been used to quantify MCC, which assess the severity of chronic diseases. Perhaps the most well-known is the Charlson Comorbidities Index (CCI) and its adaptations, established to predict mortality in hospital patients.[16] Other indices have been derived from medical data, medication groups, or diagnoses groups, such as the medication-based Chronic Disease Score (CDS),[17] which groups individual diagnosis codes, by organ system, into 23 diagnostics categories.[18] Other indices include the ambulatory case-mix system,[19] which groups patients into three morbidity burden groups and the Clinical Classification Software (CCS), which groups diagnosis codes into clinically-homogenous categories.[20] However, the CCI and other available measures are not widely or consistently used in the reporting of MCC, as is seen throughout the report.

In some instances, MCC describes co-occurring conditions, generally including diseases, symptoms, and risk factors. Other studies define MCC as disease endpoints (e.g., ischemic stroke or cancer) and do not include risk factors (e.g., hypertension) that have led to the disease or symptoms (e.g., low back pain) that have resulted from the disease. A review of 115 MCC studies highlighted significant heterogeneity, with the number of conditions considered in the definition ranging from 4 to 147.[21] Risk factors were included in 85% of the individually-developed definitions, whereas 62% of articles included symptoms. The specific role of risk factors, diseases, and symptoms, while equally important to the patient, should be considered when quantifying the burden of MCC.

Condition Versus Disease; Chronic Versus Noncommunicable Diseases

The terms condition and disease are used synonymously for the purpose of this report (i.e., where the report refers to a condition, unless otherwise specified, it is referring to the disease endpoint).

The terms chronic disease and NCD have traditionally been used synonymously, despite the fact that they refer to overlapping but different sets of conditions. The World Health Organization (WHO) defines NCDs as conditions that "tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behaviours factors."[22] The main types of NCDs are cardiovascular disease (including heart attack and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma) and diabetes. However, as infectious diseases, such as HIV and tuberculosis (TB), become more treatable, they also increasingly have longer durations. This results in an overlap between infectious and chronic conditions. To date, there is a lack of consensus on the use of chronic disease versus NCD, and the two terms are used interchangeably despite their different meanings. As the use of this terminology remains inconsistent, there may be resulting variation in what individual data sources and authors have defined as chronic conditions.

Data Sources and Availability

Data used for the report include searches conducted of academic literature and 'snowballing' to identify other referenced articles and reports. Other data repositories, such as the WHO and the GBD study developed by the Institute of Health Metrics and Evaluation (IHME), were sourced for primary data.

The GBD study is the most comprehensive global epidemiological study to date, quantifying the magnitude of health loss from hundreds of diseases, injuries, and risk factors in more than 120 countries by sex and age. The GBD dataset utilizes DALYs, which represent one lost year of healthy life, and is a combination of years lived with disability (YLD), a measure of morbidity, and years of life lost (YLL), a measure of mortality. The sum of DALYs characterizes the gap between a population's current health status and an ideal health status.

The data in this report were collected through high-quality epidemiological research. It is important to note however, that the data do not represent the results of a meta-analysis or systematic review, but rather an effort to collect methodologically-sound data across diverse geographic regions, income-levels, ages, and chronic diseases.

A limitation of most data pertaining to MCC, including GBD data, is that the data only consider individual chronic conditions on the assumption of an additive effect. In fact, as explored in this report, the economic burden is not a simple additive burden, but rather increases exponentially with each additional chronic condition. Failure to consider chronic conditions that occur together as a cluster will inevitably lead to incorrect, and likely lower estimates, of the burden of MCC.

Distinguishing Between Risk Factors, Diseases, and Symptoms

A patient's medical-seeking behavior can be prompted by the presence of a risk factor, disease, or symptom, and may be the most meaningful characteristic of the patient's experience. In order to describe the extent of the problem of MCC, it is essential to distinguish between risk factors, diseases, and symptoms.

Risk Factors are characteristics, attributes, or exposures that increase the likelihood of developing a disease (i.e., hypertension increasing the risk of stroke). Hypertension and hyperlipidemia are the most common risk factors, due to the fact they are established diseases and they have high prevalence rates. The inclusion of risk factors into the MCC definition may lead to estimates that reflect future illness but not necessarily the current burden of disease in a population.

Diseases are associated with a specific diagnosis code and are manifestations of end-organ damage as a result of risk factors.

Symptoms are expressions of disease (such as low back pain). Due to their impact on patients' lives, symptoms are the most frequently mentioned part of the disease process in patient self-reported surveys. They are often included in definitions of MCC because of their impact and burden on daily functional status. The expression of symptoms is critical to the process of diagnostics, as their expression is what often leads patients to seek medical help.

Box 4. Distinguishing between risk factors, diseases, and symptoms in defining MCC

Estimates of MCC can also differ due to differences in setting (higher in primary care setting versus general population), age of the sample (as MCC increases dramatically with age), observation period (longer observation period is associated with more conditions), and categories of disease (e.g., CVD as one category versus ischemic heart disease (IHD) and ischemic stroke as separate diseases). Finally, it is important to note the strength of the study design. Observational studies can include cohort or cross-sectional studies. Cross-sectional studies collect observations at a single point in time and can only infer associations. Cohort studies collect observations over time and can establish causation, providing support for the sequences of risk factors, diseases, and symptoms.

Chronic Disease Progression

Figure 2 illustrates the directional relationship between underlying determinants, modifiable and non-modifiable risk factors, intermediate risk factors, chronic disease endpoints and disease symptoms.

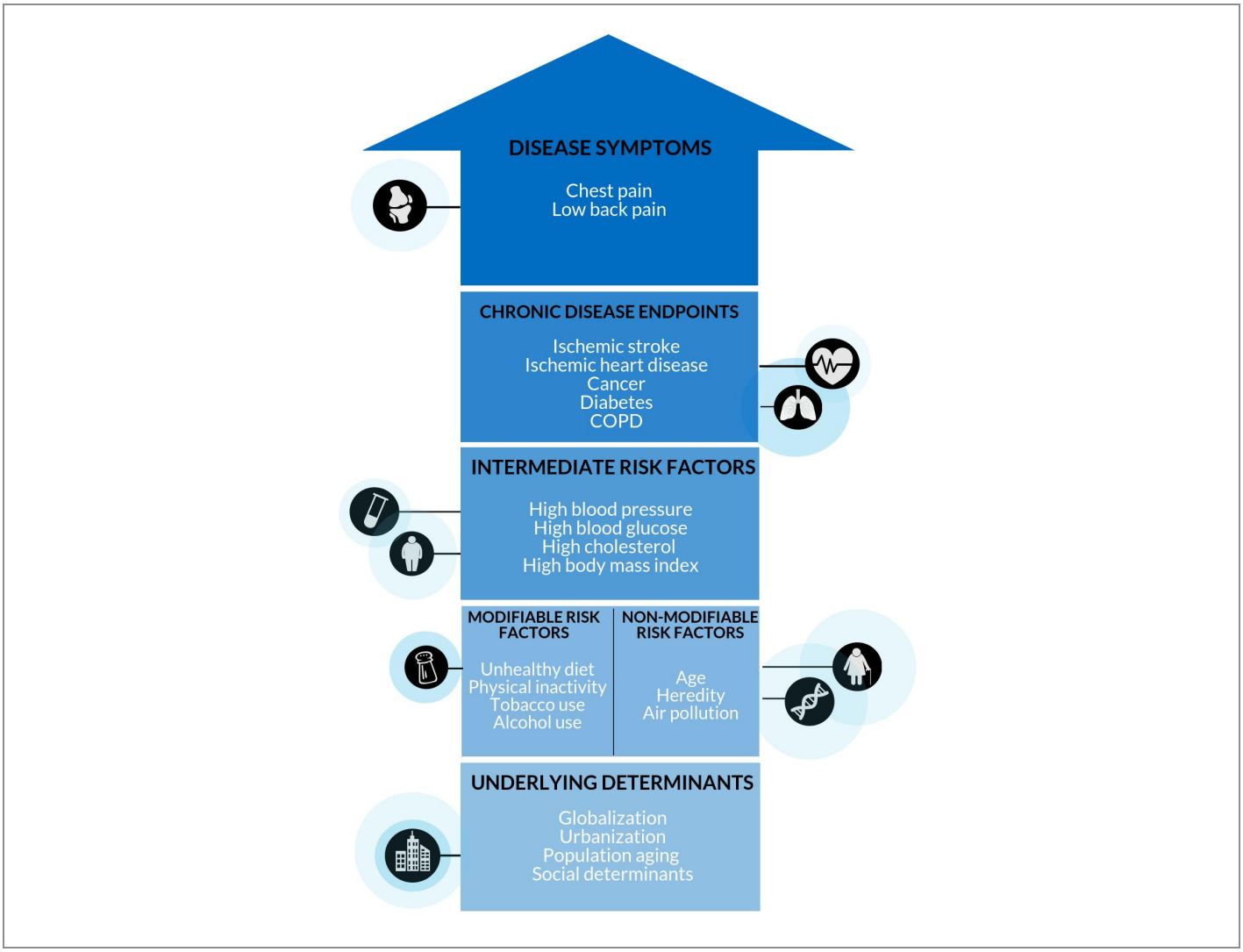


Figure 2. Directionality of chronic disease progression

Symptoms, such as chest and low back pain would not typically have an International Classification of Diseases (ICD) diagnosis code in and of themselves.

Modifiable risk factors, such as smoking and excess alcohol intake, are risk factors for numerous chronic conditions such as ischemic stroke, IHD, and cancer, and are prime targets for preventive interventions. Modifiable risks are more amenable to change than risks factors such as age, heredity, and air pollution, which are equally important, but not changeable by individuals or preventative measures. Other risk factors may also be considered disease endpoints, such as diabetes and hypertension.

Chronic disease endpoints are the manifestation of end-organ damage as a result of the risk factors, for example, IHD as a result of smoking, which produces the symptom of chest pain.

The categories are not mutually exclusive and conditions do not always fall neatly into only one category. This work focuses on quantifying chronic disease endpoints rather than pure risk factors or symptoms. Healthcare systems treat conditions, rather than symptoms or risk factors, and this work focuses on quantifying chronic disease endpoints rather than pure risk factors or symptoms to align with the nomenclature of healthcare systems globally. Prevention efforts, on the other hand, deal with both risk factors and their resultant disease endpoints. Although symptoms are more of a priority for the patient than the risk or condition itself, they are difficult to identify, quantify, monitor, and tackle, although some efforts are being made in this regard.

The relationship between risk factors and diseases, and also between two or more diseases themselves, can take several forms (Figures 3a-d), such that:

1. **A disease of interest may be caused by another disease.**
   As illustrated in figure 3a, one disease of interest can be caused by another disease. For example, poor glucose control due to diabetes leads to atherosclerotic narrowing of blood vessels and increased risk of stroke.

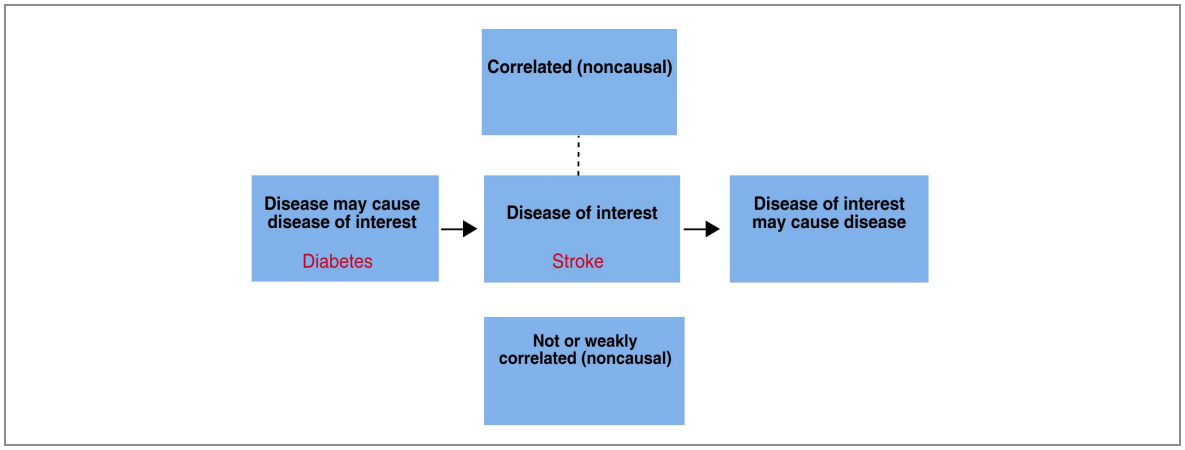


Figure 3a. Disease of interest may be caused by another disease

2. **Two diseases may be correlated with a common causal link.**
   As shown in Figure 3b, two diseases may occur together because they share similar risk factors. For example, both stroke and Alzheimer's disease share risk factors of poor diet and a sedentary lifestyle.[23]

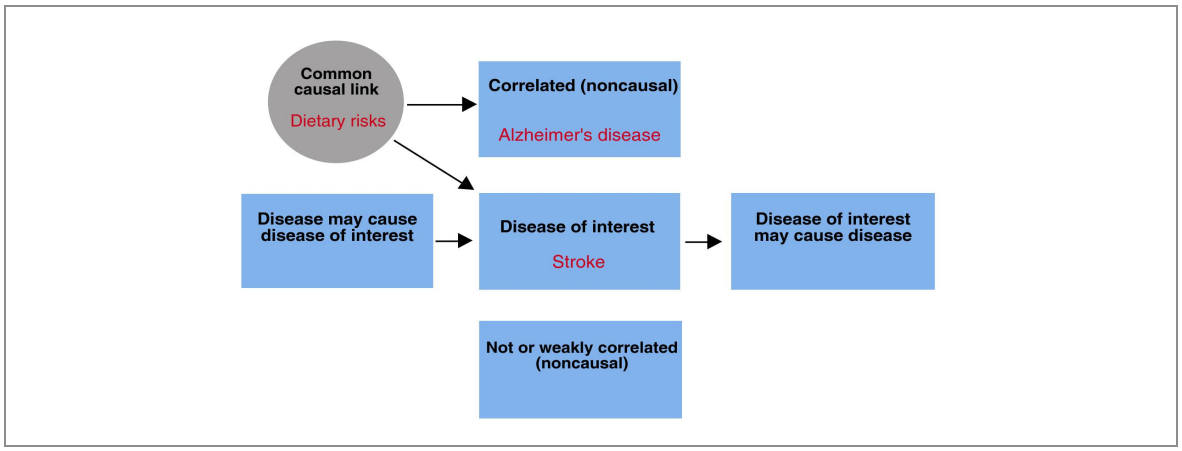


Figure 3b. Two diseases may be correlated with causal link

3. **The disease of interest may cause another disease.**
   As highlighted in Figure 3c, the disease of interest may lead to another disease. For example, depression may be caused by both biological and psychosocial factors following a stroke, such as dysphasia or the absence of social support.[24,25]

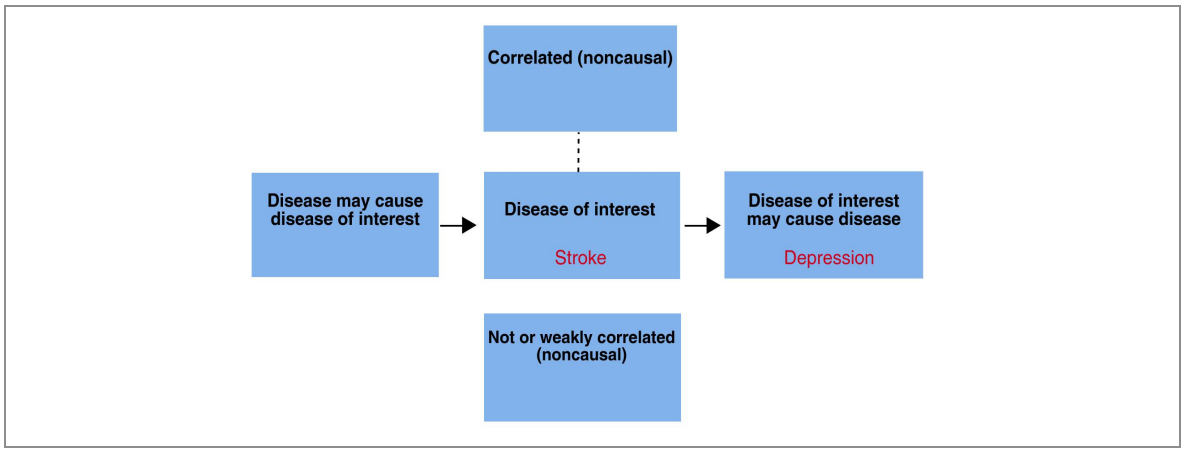


Figure 3c. Disease of interest may cause another disease

4. **Two diseases may have no causal link and have only weak or no significant association.**
   As shown in Figure 3d, diseases may occur together simply due to high prevalence rates, but are noncausal. For example, stroke and low back pain are both common diseases and therefore, are often observed together, but neither disease causes the other.

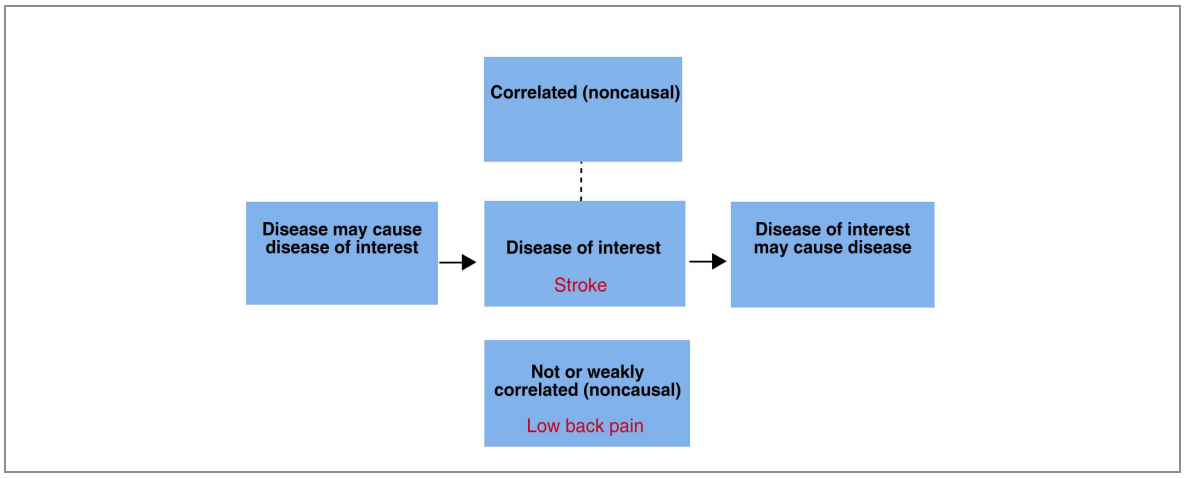


Figure 3d. Two diseases may have no causal link and only weak or no significant association

Each step in the process is not as linear as illustrated in Figure 2. In fact, the pathways are complex and the categories are not mutually exclusive. To illustrate the complexity, consider the progression of ischemic stroke. A low-income woman may be unable to afford healthy foods, and therefore relies on energy-dense, nutrient-poor foods with excess sodium. The sodium consumption eventually leads to high blood pressure, which over time, causes a stroke. Alternatively, a middle or high-income man may be exposed to increasing urbanization, which leads to both physical inactivity and consumption of fast foods. These risk factors may lead to high body mass index (BMI) and obesity, which pose a strong risk for the development of diabetes; the presence of diabetes could eventually lead to stroke. While both individuals in this example suffered the same disease endpoint (stroke), the pathways and risks were different and nonlinear.

In other examples, consider the progressions of IHD and depression. A middle-aged woman may have an increased likelihood of developing depression due to a positive family history of mental health problems and also develop high blood pressure as a result of excess sodium intake. Her depression may exacerbate poor adherence to her blood pressure medication, which could eventually lead to the disease endpoint of IHD. Alternatively, a middle-aged man may have high blood pressure due to a sedentary lifestyle and obesity, and may develop IHD. The effects of IHD, including an initial diminished ability to be physically active, may trigger depression. Depression and heart disease have a bi-directional relationship, and either can be a risk factor or disease endpoint. The complexity of the progression of chronic disease necessitates unique interventions that consider the etiologic relationship between risk factors and diseases.

Section 3: The Epidemiology of Chronic Diseases

Global Burden of Chronic Diseases

The top conditions contributing to combined mortality and morbidity (using DALYs) in high-income countries (HICs) include IHD, stroke, lung cancer, depression, diabetes, and back and neck pain.[26] Similarly, in lower middle-income countries (LMICs), top diseases include IHD, stroke, diabetes, and depression, but additionally include communicable diseases, such as diarrhea, HIV/AIDS and malaria, as well as road traffic injuries.

	Global average	Russia	Turkey	Italy	Canada	USA	Germany	UK	Chile	Peru	Poland	Argentina	France	Israel	Mexico
Percent with chronic condition (%)	**60**	**65**	**65**	**66**	**67**	**65**	**64**	**64**	**57**	**54**	**62**	**51**	**55**	**53**	**48**
High blood pressure/ hypertension	18	**22**	15	**22**	20	**23**	**28**	19	**14**	**8**	**24**	15	**13**	14	**12**
High cholesterol	16	11	**8**	**25**	17	**23**	18	19	14	15	**20**	16	**12**	**19**	**11**
Migraines	16	19	**23**	19	12	13	**11**	14	15	**20**	18	**10**	18	12	15
Depression/anxiety	16	**22**	**25**	16	**21**	**21**	14	**21**	18	13	**10**	**11**	13	**8**	**11**
Chronic pain	15	**24**	**11**	13	14	17	**28**	15	**9**	**9**	**26**	**10**	12	11	**10**
Arthritis/rheumatism	9	12	6	10	**15**	**18**	8	**17**	**4**	**3**	**14**	**5**	9	3	**4**
Diabetes	8	6	11	9	**12**	10	**11**	8	8	6	7	7	8	7	7
Asthma	7	4	**12**	7	9	9	6	**11**	7	8	6	5	9	7	4
Reproductive/ sexual health issues	4	**10**	7	6	3	5	3	4	3	4	4	2	3	3	4
Chronic lung disease/ emphysema/chronic bronchitis/COPD	3	4	4	3	4	5	**7**	2	2	1	3	3	2	2	1
Coronary artery disease	2	5	1	1	1	2	**5**	2	0	1	**5**	2	2	2	1
Other mental condition	2	1	1	1	2	**5**	**7**	**6**	1	0	2	1	1	2	1
Cancer	2	1	2	2	2	2	2	2	1	1	3	1	2	2	0
Congestive heart failure	1	2	1	1	1	2	2	1	1	0	1	1	1	1	1
Bipolar disorder/ schizophrenia	1	1	1	1	2	3	2	1	1	1	1	0	1	1	1
Epilepsy	1	1	3	0	1	1	1	1	0	0	1	1	1	0	1
Multiple sclerosis	1	2	0	1	0	1	1	1	0	0	1	0	1	0	0
Cystic fibrosis	0	1	1	0	0	0	0	2	0	0	0	0	0	0	1
Parkinson's disease	0	1	1	0	0	1	1	0	0	0	0	1	0	0	0
Hemophilia	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Other	7	7	9	5	6	7	8	7	7		6	7	7	6	4

Table 2. Prevalence of chronic conditions in a range of LICs, LMICs, UPMICs, and HICs

Note: Self-reported data: red cells–high prevalence of chronic conditions; green cells–low prevalence of chronic conditions

Figures 4-6 illustrate the burden of the 15 leading chronic diseases, according to the GBD study, across income levels, risk factors, and time.

In Figure 4, which highlights the relative contribution of risk factors to specific chronic diseases, the dark green demonstrates the high percentage of IHD attributed to various risk factors. Osteoarthritis, Alzheimer's disease, and low back pain on the other hand, are not attributed to many modifiable risk factors, but are primarily age-related and therefore less modifiable. Distinguishing the modifiable risk factors from non-modifiable risk factors (as illustrated in Figure 2) is critical for developing effective interventions that prevent disease onset. For example, the increasing burden of IHD with age can be attributed to several well-known modifiable risk factors, but the increasing burden of Alzheimer's disease with age is a result of the aging process and the burden of other chronic diseases.

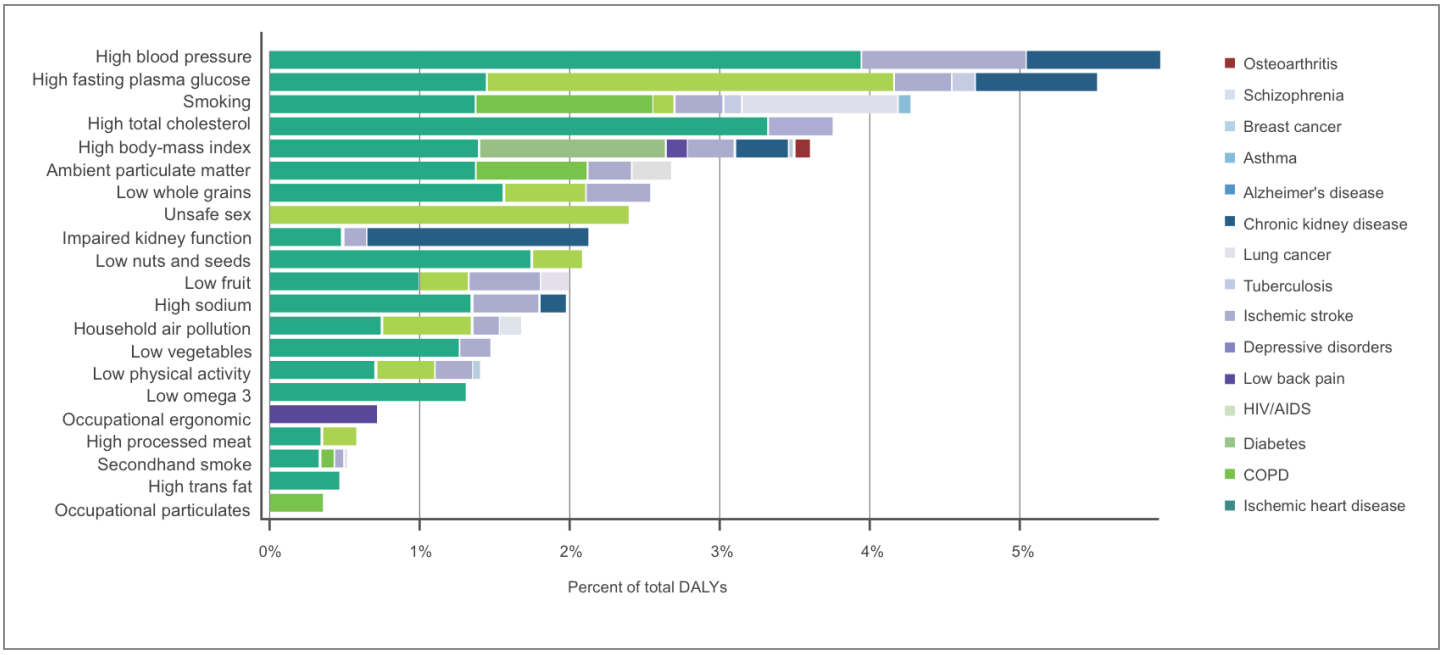


Figure 4. Global leading risks for chronic diseases by age-standardized DALYs as a percent of total DALYs (2015)
Abbreviations: DALYs (disability adjusted life years); COPD (chronic obstructive pulmonary disease)

Figure 5 illustrates the global burden of chronic disease, from 1990-2015, as measured in DALYs. The shift over time highlights the reduction in chronic disease DALYs due to IHD, which has resulted from an increase in the prevalence of, but a reduction in mortality from, IHD. DALYs for diabetes, low back pain, chronic kidney disease, and depression remain mostly unchanged since 1990.

Figure 6 demonstrates the burden of chronic disease by country income level in 2015. LMICs, such as India, have the highest IHD burden, as measured by DALYs. The combined burden of chronic disease as measured by DALYs is greatest in LICs and is largely attributed to HIV/AIDS. While socioeconomic status (SES) of these countries' populations can explain the variation in HIV/AIDS and IHD, the burden of other diseases appears to function independently of SES. The burden of low back pain, depression, and arthritis, which are prevalent among 8%, 4%, and 3% of the global population respectively, are relatively homogenous across SES. As populations age, these conditions are likely to coexist with other major conditions. Other chronic conditions and symptoms, such as depression and back pain, also significantly contribute to DALYs in countries of all income levels.

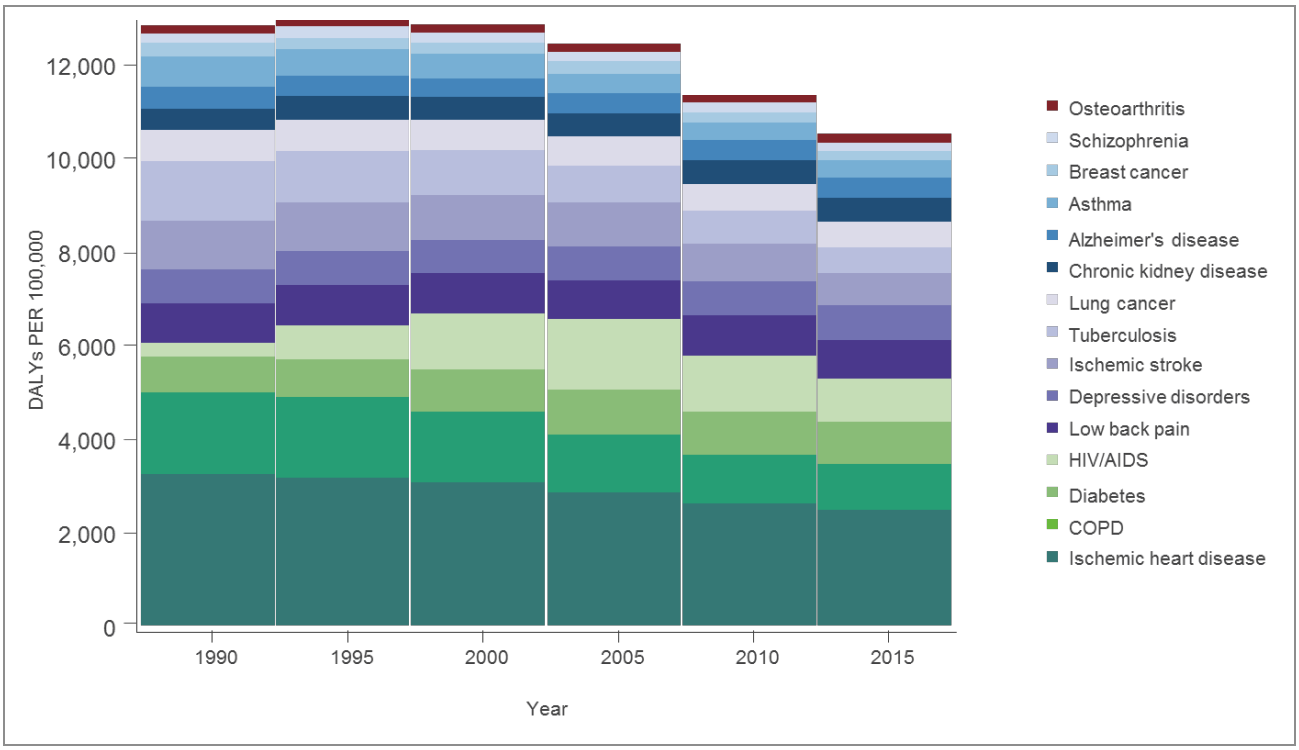


Figure 5. Change over time in age-standardized DALYs (rate per 100,000) for leading chronic conditions (1990-2015)

Abbreviations: DALYs (disability adjusted life years); COPD (chronic obstructive pulmonary disease)

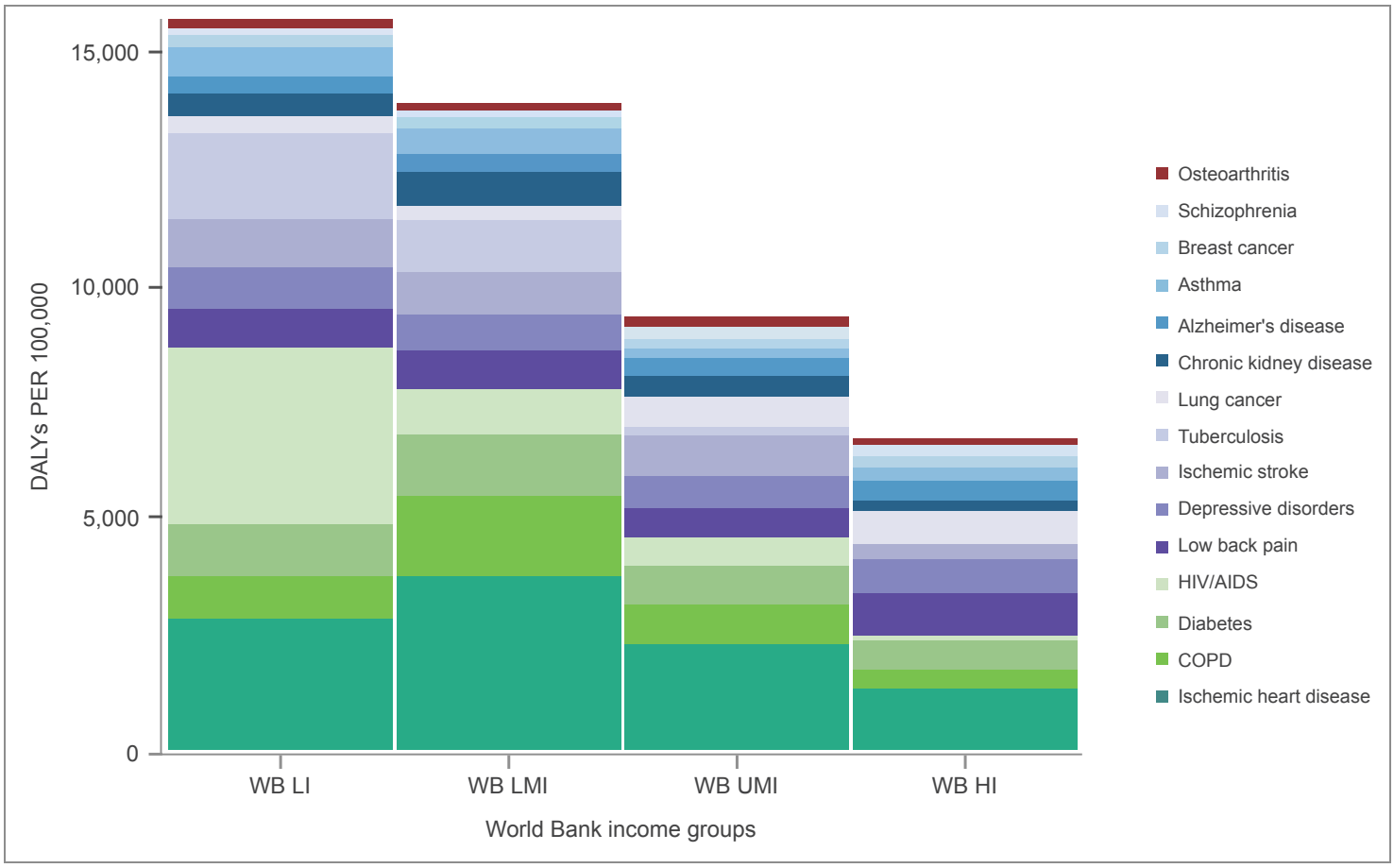


Figure 6. Age-standardized DALYs (rate per 100,000) for leading chronic diseases (1995-2015) for World Bank country income groups

Abbreviations: DALYs (disability adjusted life years); WBI LI (World Bank low-income countries); WB LMI (World Bank lower middle-income countries); WB UMI (World Bank upper middle-income countries); WB HI (World Bank high-income countries)

Chronic Diseases Attributable to Major Risk Factors

Table 2 illustrates global age-standardized DALYs for the top 15 chronic diseases attributed to each risk factor from the GBD study. The chronic diseases are listed according to global burden (in DALYs).

	Top Chronic Conditions Globally														
Risk factors	**CVD**	**IHD**	**COPD**	**Diabetes**	**HIV/ AIDS**	**Low back pain**	**Depressive disorders**	**Ischemic stroke**	**TB**	**Tracheal, bronchus, lung cancer**	**CKD**	**Alzheimer's disease and dementia**	**Asthma**	**Breast cancer**	**Osteo-arthritis**
High systolic blood pressure	2,848.42	1350.7						375.62			303.90				
High cholesterol	1,287.18	1137.14						150.03							
Diet high in sodium	**1050.71**	465.86						150.96			61.86				
Diet low in whole grains	**960.43**	536.00		187.16				150.08							
High body mass index	951.91	477.84		428.50		45.83		108.38			126.43			11.49	34.51
Smoking	894.81	471.00	406.20	48.21				111.90	39.24	356.77			28.73		
High fasting plasma glucose	831.89	498.57		925.82				132.00	52.42		280.39				
Diet low in fruits	**825.70**	344.55		112.67				163.83		64.50					
Ambient particulate matter pollution	**751.95**	470.74	257.20					100.92		90.89					
Diet low in vegetables	**646.55**	437.13						70.62							
Diets low in nuts and seeds	**600.84**	600.84		115.82											
Diet low in seafood (omega-3 fatty acids)	**454.56**	454.56													
Household air pollution (solid fuels)	**449.27**	261.26	203.18					61.94		49.99					
Low physical activity	328.89	246.90	134.59					81.98						18.23	
Impaired kidney function	257.66	147.9						46.49			478.35				
Alcohol use	126.03			-39.49				6.62	64.08					12.65	
Occupational ergonomic						**251.98**									

Table 3. Age-standardized DALYs (rate per 100,000) for risks attributable to leading chronic conditions (2015)
Abbreviations: CVD (cardiovascular disease–includes both ischemic heart disease and ischemic stroke); IHD (ischemic heart disease); COPD (chronic obstructive pulmonary disease); TB (tuberculosis); CKD (chronic kidney disease)

Despite the magnitude of DALYs that are attributed to major risk factors, it is critical to distinguish modifiable risk factors compared with non-modifiable risk factors. For example, exposure to ambient air pollution was the fifth-ranking risk factor for mortality in 2015. However, a reduction in air pollution is not a feasible clinical or public health intervention,[27] whereas dietary factors, also responsible for a large proportion of CVD, are amenable to modification at both an individual and environmental level. Furthermore, there is strong evidence for dietary interventions that have successfully reduced the incidence and mortality from CVD.[28,29] While changing and sustaining dietary habits is difficult outside of the study setting, there are many real-world success stories.[30]

Table 2 highlights the predominance of dietary risks (high sodium, low whole grains and low fruit) and metabolic risks (high blood pressure and high fasting glucose) that contribute to CVD. It also demonstrates the level of known risk factors for various diseases. For example, Alzheimer's disease has few known risk factors, whereas IHD is highly attributed to several behavioral risk factors.

Smoking contributes to the burden of eight of the 15 leading chronic diseases, whereas high sodium only contributes to CVD and chronic kidney disease (CKD).

A selection of risk factors are discussed in further detail below and highlighted in Table 2.

1. **CVD and Dietary Risk**
   All dietary risks together contribute to a total of 3,073.5 CVD DALYs (rate per 100,000) and 8.9% of total CVD DALYs, greater than those attributed to high systolic blood pressure (SBP), the leading risk factor for CVD. Dietary interventions, such as Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet, promote health and target many of the dietary risks that increase CVD risk. The Mediterranean diet emphasizes consumption of fruits, vegetables, whole grains, fish, legumes, nuts, and monounsaturated fats, while reducing intake of meat, and alcohol. The DASH diet is characterized by similar dietary patterns, with increased consumption of fruits and vegetables, moderate intake of dairy and animal protein, and higher intake of plant proteins. Studies have reported reduced risk of CVD among individuals who adhere to the DASH or Mediterranean diet.[31,32]

2. **Low Back Pain and Occupational Ergonomic Risk**
   The only known risks for low back pain documented by GBD are high BMI and occupational ergonomic risk. The burden of low back pain that is attributed to occupational ergonomic factors is 248.96 DALYs (rate per 100,000), which is less than 1% of total DALYs.

   Low back pain represents 1.5% (in LICs) to 5.5% (in HICs) of total DALYs, a similar proportion to diabetes. In 2010, low back pain ranked highest in terms of disability (years lost to disability), and sixth in terms of overall burden (DALYs). The DALYs increased from 58.2 million in 1990 to 83 million in 2010.[33] As populations around the world age, so does the burden of low back pain, but few contributing factors are amenable to prevention. The non-specific symptoms coupled with the inability to identify risk factors make low back pain a major cause of disability worldwide.

3. **CVD and Air Pollution (Household and Ambient Air Pollution)**
The DALYs from CVD attributed to ambient particulate matter pollution and household air pollution from solid fuels are illustrated in Figure 7 by World Bank income levels. There is an inverse relationship between CVD DALYs attributed to air pollution and country income level; LICs have greater CVD DALYs and a greater proportion of CVD DALYs attributed to household air pollution from solid fuels. Air pollution accounts for 3.17% of total CVD DALYs, the fourth largest contributor after dietary risks, high blood pressure, and high total cholesterol.[34] The biological mechanisms that account for the relationship between air pollution and CVD include a direct effect of pollutants on the cardiovascular (CV) system, blood and lung, and indirect effects mediated by pulmonary oxidative stress.[35]

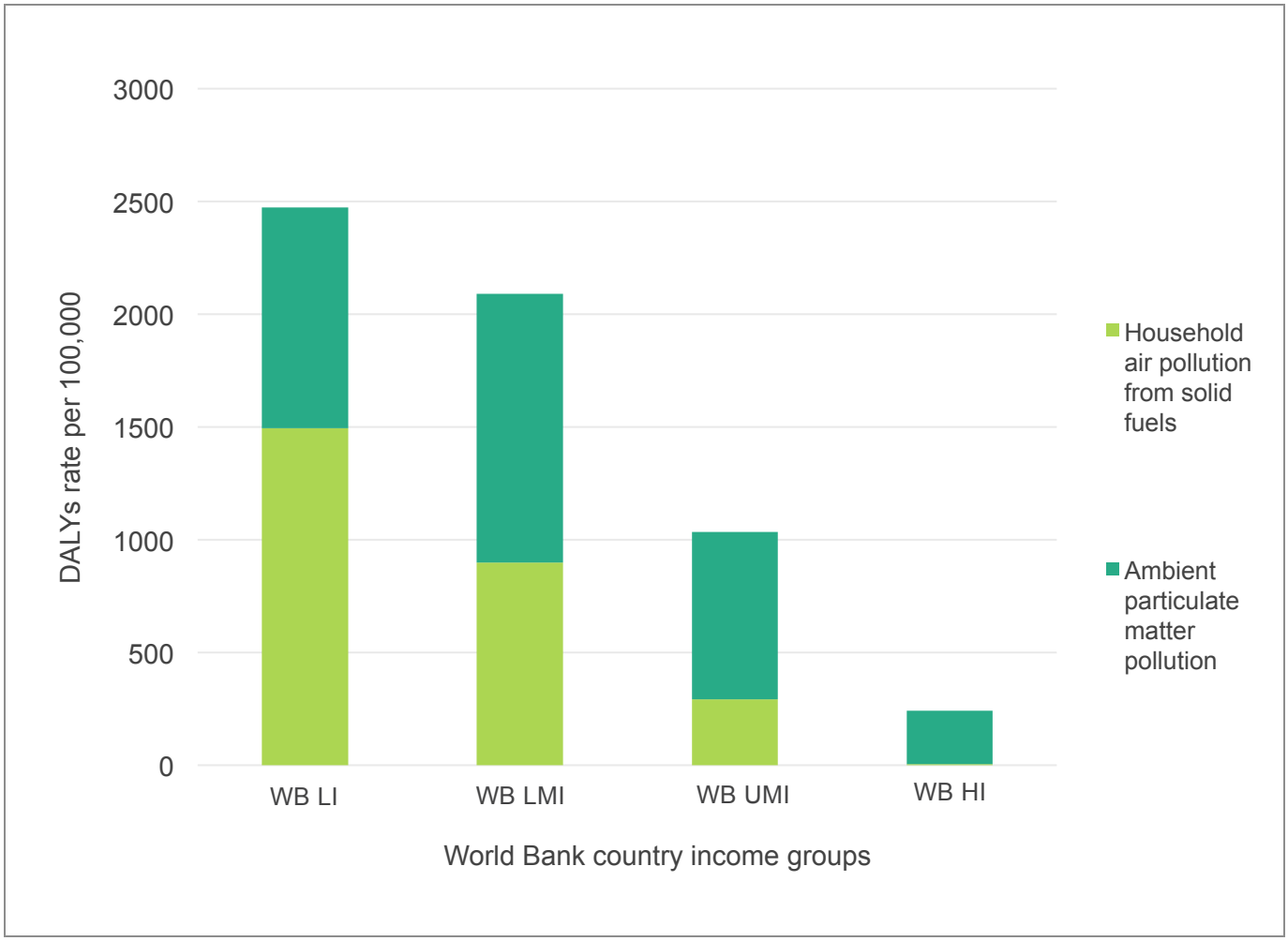


Figure 7. DALYs (rate per 100,000) attributable to air pollution for World Bank country income groups (2015)
Abbreviations: DALYs (disability adjusted life years); WBI LI (World Bank low-income countries); WB LMI (World Bank lower middle-income countries); WB UMI (World Bank upper middle-income countries); WB HI (World Bank high-income countries)

Section 4: The Epidemiology of Multiple Chronic Conditions

Prevalence of Multiple Chronic Conditions

Prevalence estimates for MCC are highly heterogeneous. Methodological differences, including the number of chronic conditions included in the count, have led to estimates that may vary up to threefold. No global prevalence estimates for MCC exist, and most national studies vary by definition and age. Most studies based in the United States use a list of 20 chronic diseases classified by the Department of Health and Human Services (HHS), while other reviews include 40 health diseases and up to 140 conditions.[36] United Kingdom prevalence estimates for MCC range from 16% (for 17 chronic conditions considered) to 58% (for 114 chronic conditions considered).[37] When including 10 physical chronic conditions, approximately 25.5% of the United States population were reported to have MCC, and the prevalence increases to 50% of adults 45 to 65 years, and up to 81% of adults older than 65 years.[42] For adults over 50 years, rates of MCC vary from 45% in China to 71% in Russia. [38] The degree of heterogeneity of the findings suggests market research and other self-reported sources may underestimate the burden, while the academic literature, if more accurate, suggests rates that are up to twofold higher than self-reported rates.

Prevalence of MCC by Chronic Disease Type

The Australian Bureau of Statistics Health Survey from 2011–2012 reported on the proportion of individuals with MCC by their first chronic disease, among a group of eight chronic diseases (arthritis, asthma, back problems, cancer, chronic obstructive pulmonary disease (COPD), CVD, diabetes, and mental health conditions).[39] The study reported considerable heterogeneity of MCC prevalence according to primary chronic condition among those less than 45 years of age, but this diminished considerably for those older than 45 years. More than half of those less than 45 years of age with cancer, COPD, or arthritis had MCC. Compared to men, significantly more women with cancer had MCC, a difference largely attributed to increased rates of mental health and back pain among female cancer patients.[39]

Figure 8 presents findings from a sample of more than 1.6 million United States Medicare beneficiaries (65-74 years of age) in 2005.[40] The results illustrate the highest proportion of beneficiaries with MCC is observed among those with CKD, 82.1% of which have at least one other secondary chronic condition. The most common secondary conditions were heart failure and diabetes (observed in 52% and 51% of those with CKD, respectively). For those with diabetes, depression, and cancer, individuals were more likely to only have the primary condition (e.g., 47.3% of those with diabetes only had diabetes).

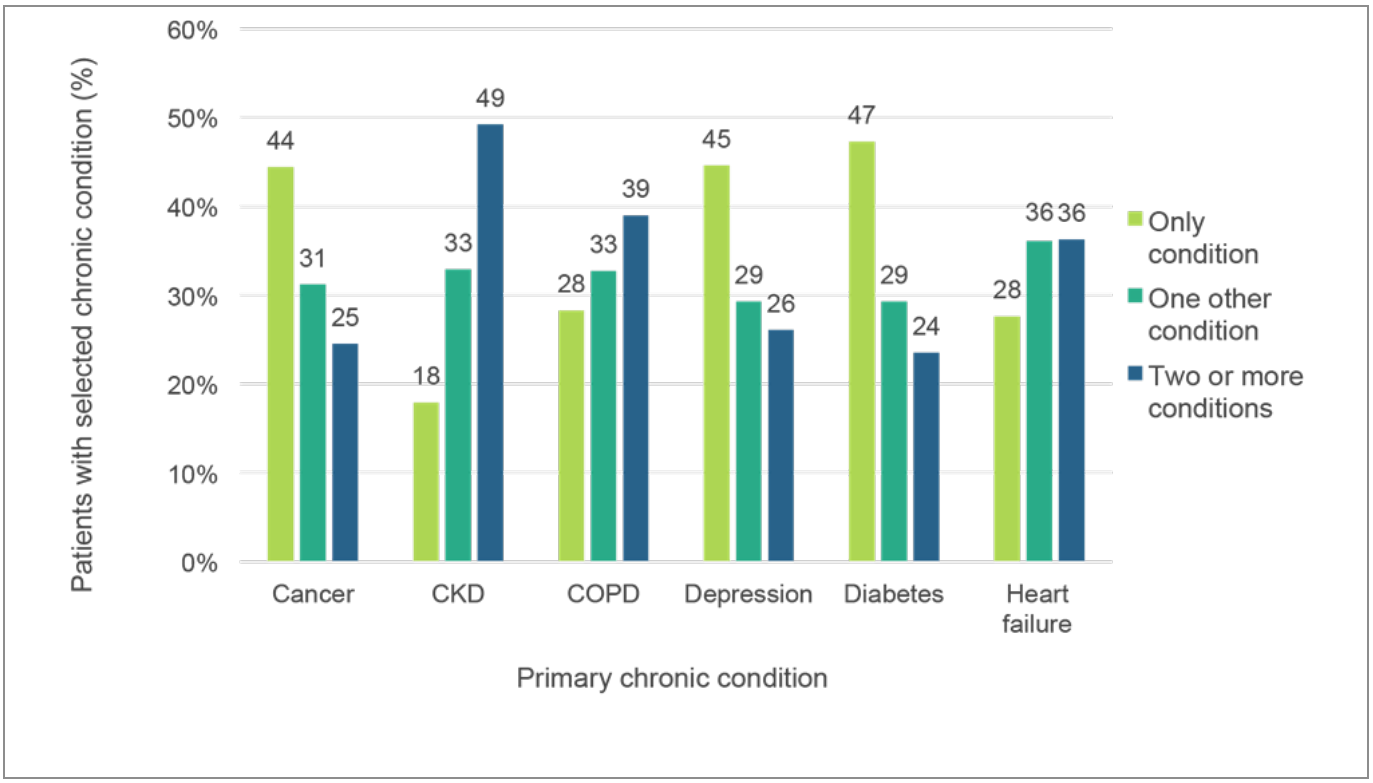


Figure 8. Proportion of Medicare beneficiaries with multiple chronic diseases by selected chronic disease (2005)[40]

Abbreviations: CKD (chronic kidney disease); COPD (chronic obstructive pulmonary disease)

MCC and Demographics

In 2012, American women were more likely than men to have MCC between the ages of 18 and 64 years.[41] Women were more likely than men to have two diseases (14.5% versus 13.0%) or three diseases (12.6% versus 10.7%). This may be attributed to a greater tendency for health-seeking behavior among women.[42]

Figure 9 illustrates the 2012 prevalence of MCC by age and SES in Maccabi Healthcare Services, Israel's second largest healthcare system. Approximately 38% of this population (all ages) is considered to have MCC, a higher rate than has been documented in Scotland and the United States.[43] Figure 9 highlights the increasing prevalence of MCC with age and the inverse relationship of MCC with SES among those 25 to 75 years of age.

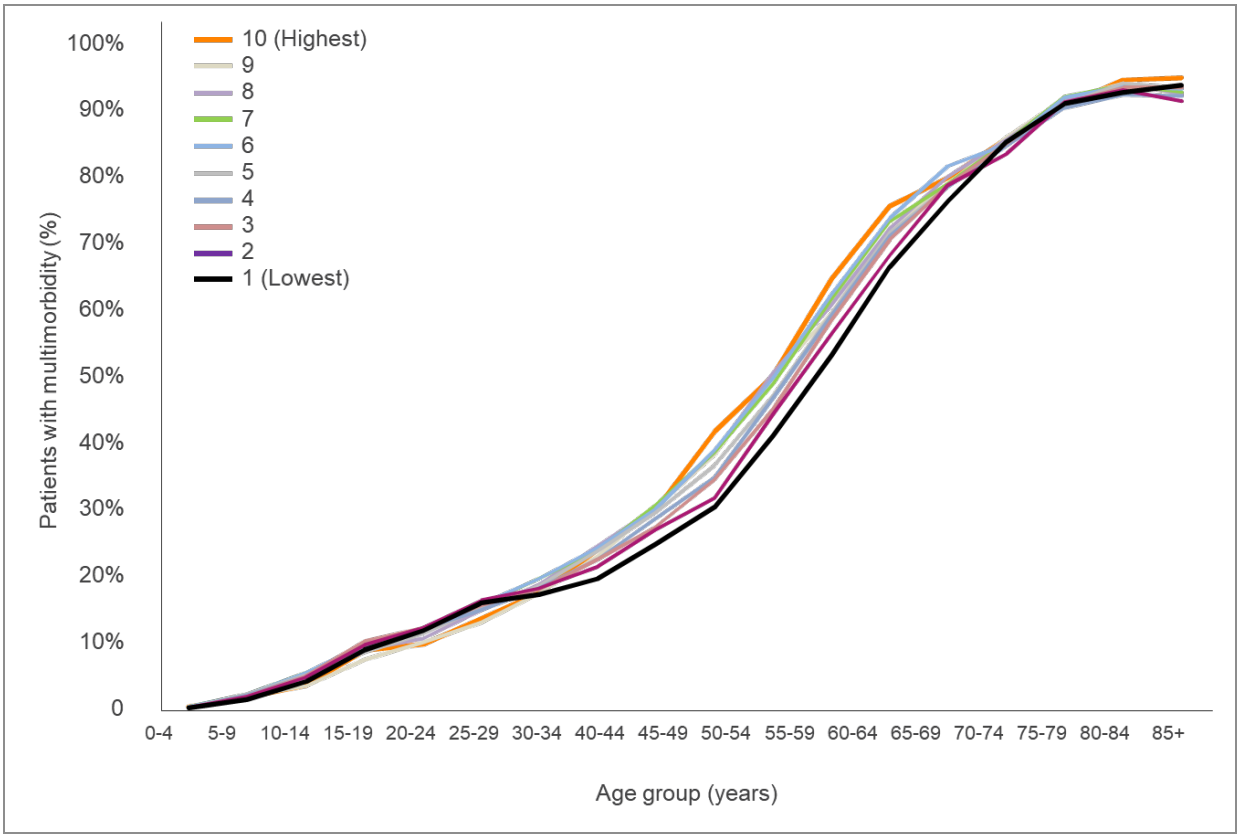


Figure 9. Prevalence of chronic diseases by socioeconomic status among Israeli adults (2012)[43]

The relationship between SES and MCC is highly dependent on geography and age. Figure 10 is based on chronic disease data from 28 countries of the World Health Survey (adults older than 17 years), illustrates prevalence ratios of MCC across SES (using education as a proxy), according to age groups in LICs and MICs.[44]

In most countries, there is a strong, negative relationship between SES and MCC among adults under 55 years (i.e., as SES increases, MCC decreases), which is most pronounced in Western Europe, Eastern Europe, and Central Asia. However, this relationship is not consistent for adults older than 55 years, with no, or only weak, relationships observed in all regions, other than Southeast Asia, where a positive relationship is observed (i.e., as SES increases, the prevalence of MCC also increases).[44] This finding is consistent with studies that reported greater chronic disease prevalence (obesity, CVD, and MCC) among higher SES groups in India.[45,46] This geographic and age pattern may reflect the distribution of key risk factors for chronic diseases–unhealthy diet, physical inactivity, tobacco use, and alcohol consumption–which occur more frequently among wealthier populations in developing countries and poorer populations in developed countries.

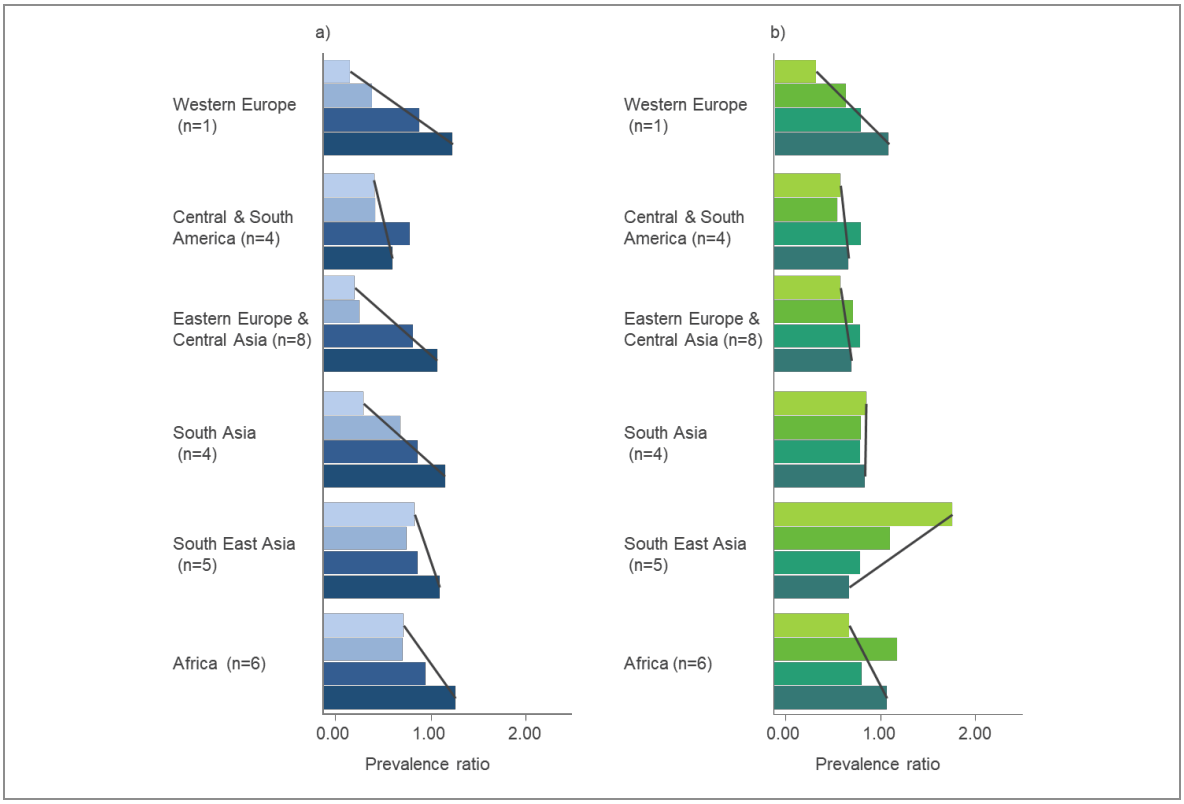


Figure 10. a) Socioeconomic gradient of MCC prevalence (2003) by regions for age < 55 years b) Socioeconomic gradient of MCC prevalence (2003) by regions for age ≥ 55 years[44]

Note: Lightest blue/green (category 1) – higher education; darkest blue/green (category 4) – less than primary school education; MCC prevalence ratios are based on prevalence of MCC compared to third category (set to1)

Chronic Disease Clusters

Certain chronic conditions occur together more frequently due to independently high prevalence rates, common risk factors, or a synergistic relationship between the two. The most widely reported clusters include CVD and stroke with depression, and in developing countries, a NCD with a long-term communicable disease (e.g., CVD and HIV/AIDS, or diabetes and TB).

There is a severe paucity of published information on clusters of chronic conditions and their impact on patients, health systems, and healthcare costs. One systematic review of MCC clusters provides a useful summary, but the authors stated limitations due to heterogeneity in study design, setting, age, and even the definition used for MCC.[47]

Table 3 provides a summary of available evidence for chronic disease clusters for the leading global chronic diseases by DALYs. The data represent relative risk, odds ratios, or hazard ratios. The table only presents chronic conditions and does not include observed clusters of risk factors (e.g., hypertension, high cholesterol). By tackling these clusters, rather than the individual diseases, interventions and systems can directly address the difficulties faced by such patients, including through medication design, approaches to screening and detection, and care guidelines. Moreover, as detailed in Table 4, healthcare costs for MCC patients increase exponentially and are expected to be greater than the additive effect of treating patients with each individual chronic condition. As one in three adults have more than one chronic condition, current estimates of healthcare costs for chronic disease are likely to underestimate the true costs for such patients. Furthermore, there are additional

complexities in the treatment of certain conditions occurring together, which are detailed more in the examples provided alongside Table 4. These include different screening and prevention requirements, greater risk of drug-drug interactions, reduced efficacy of medications, a lack of joint guidelines, and a greater tendency to see specialists over primary care physicians.

Primary Condition	Secondary Condition	Risk
COPD	Depressive disorders[48]	RR = 1.4
	TB[49]	OR = 2.5
Diabetes	CVD[50]	RR = 1.2
	COPD[51]	HR = 1.2
	Depressive disorders[52]	OR = 1.6
	Ischemic stroke[53]	RR = 1.9, RR = 3.1
	TB	OR = 3.1,[54] HR = 2.1[55]
	Asthma[51]	HR = 1.1
	Osteoarthritis[56]	HR = 1.46
HIV/AIDS (on ART)	CVD[57]	OR = 2.0
HIV/AIDS (not on ART)	CVD[57]	OR = 1.6
Depressive disorders	CVD[58]	RR = 1.2
	IHD[58]	RR = 1.5
	Diabetes[59]	RR = 1.2
	Low back pain[60]	RR = 1.9
	Ischemic stroke[58]	RR = 1.4
	Alzheimer's disease[61]	RR = 1.9
Ischemic stroke	Depressive disorders[62]	RR = 3.2
	Alzheimer's disease[63]	RR = 5.5
CKD	CVD[64]	RR = 1.2
Asthma	CVD[65]	RR = 2.1
Breast cancer	CVD[66]	RR = 1.7
Osteoarthritis	Diabetes[56]	HR = 1.4
	Alzheimer's disease[67]	HR = 1.3

Table 4. Clustering and strength of association between common chronic conditions, ranked by global DALYs
Abbreviations: OR (odds ratio); RR (relative risk); ART (antiretroviral therapy); IHD (ischemic heart disease); TB (tuberculosis); COPD (chronic obstructive pulmonary disease); CVD (cardiovascular diseases–includes ischemic heart disease and ischemic stroke); CKD (chronic kidney disease)

Specifically Studied Chronic Condition Clusters

1. **Tuberculosis and Diabetes Mellitus**
   A systematic review of 13 observational studies indicated that diabetes mellitus (DM) is associated with more than a threefold increased risk of developing TB.[68,69] Subgroup analyses revealed this relationship was significantly stronger in non-North American countries. The mechanism of the increased risk is unclear, as is whether the higher risk is due to reactivation of dormant TB or the acquiring of new infections. Some cross-sectional studies have shown a positive correlation between presence of latent TB and diabetes.[70,71] Whether the latent TB is more likely to reactivate has not yet been reported. Furthermore, TB patients who have diabetes are less responsive to anti-TB medication.[72]

   The association between TB and diabetes is bi-directional; patients with TB are also at higher risk of developing glycemic dysfunction and diabetes.[54] The biological mechanism for this remains unclear and it may be the anti-TB medication, rather than the TB itself, that causes glycemic dysfunction. It is also unclear whether the glycemic dysfunction is transient or translates to increased diabetes risk beyond the TB treatment period.

2. **Tuberculosis and Chronic Obstructive Pulmonary Disease**
   A systematic review of studies evaluating TB and COPD suggested the two chronic diseases occur together more frequently than alone. Studies have demonstrated that COPD patients have a threefold higher risk of developing TB, [73] and COPD is an independent risk factor for developing TB (Table 4).[74] This could be due to their common risk factors of smoking, low SES, biomass fuel exposure and/or vitamin D deficiency.

3. **Depression and Chronic Diseases**
   One study that examined the clustering of depression with other chronic diseases in a sample of adults 50-74 years of age reported depressive symptoms increase with the number of chronic conditions.[75] The prevalence of depressive symptoms was 10.5% with no conditions, 14.4% with one condition, 20.8% with two conditions, 30.1% with three conditions, 37.3% with four conditions, and 58.3% with five conditions.[75] Research from the World Health Survey demonstrate the prevalence of depression in respondents with chronic diseases is significantly higher than in those without.[76] Respondents with depression have the lowest health scores (an indicator of poor to excellent health) among all chronic disease conditions (including asthma, angina, arthritis and diabetes). Furthermore, the clustering of depression with any other chronic condition incrementally worsens health compared to depression alone or any combination of chronic conditions without depression. The reduction in health score from the combination of diabetes and depression is significantly greater than the sum of the two conditions separately, suggesting conditions do not merely add up, but co-occurrence of depression interacts to exacerbate and worsen health. The findings of the study also demonstrate disease status has a greater impact on health score than SES.

4. **HIV/AIDS and Cardiovascular Disease**
   While the introduction of antiretroviral therapy (ART) has reduced global risk of HIV/AIDS-related mortality, it has increased risk of CVD among HIV/AIDS patients. A meta-analysis of studies examining this relationship reported a substantially increased pooled relative risk (RR) of CVD of 1.61 (95% CI: 1.43-1.81) for HIV/AIDS patients compared to HIV/AIDS-uninfected people.[57] HIV/AIDS patients on ART treatment have an increased risk of CVD compared to both individuals with HIV who are not being treated (RR = 1.52; 95% CI: 1.35-1.70) and HIV/AIDS-uninfected people (RR = 2.0; 95% CI: 1.70-2.37). CVD risk also depends on the duration of ART treatment; CVD risk may be higher after initiating ART, which may be mediated by an increase in dyslipidemia, a reduction in insulin sensitivity, and increased body fat redistribution.[77]

5. **Diabetes and Stroke**
   While the increased risk of stroke among patients with diabetes is well reported, the magnitude of risk varies by study population. One study comparing risk of stroke in diabetes patients between two cohort studies of different populations found that Japanese American men in the Honolulu Heart Program had a RR of stroke of 1.9 (95% CI: 1.5-2.4), whereas American men in the Framingham study had a higher relative risk of stroke of 3.1 (95% CI: 1.6-5.8).[78] This difference in risk could not be explained by differing risk factor profiles alone.

Section 5: The Impact of MCC on Patients, Families and Economies

Introduction

MCC is associated with substantially greater, near exponential, increases in healthcare costs and resource utilization.[16] Increased healthcare costs have been linked to elevated rates of primary care and specialist physician visits, medication use, emergency department presentations, and hospital admissions (frequency of admissions and bed days),[16] as further detailed in Table 4.

Older age, undesirable lifestyle factors, and low SES have been consistently associated with the development of chronic disease, and in particular, MCC.[16] Three important and interrelated challenges to contemporary healthcare policy are:[12]

- Aging nature of population demographics
- Development of chronic diseases at younger ages
- Socioeconomic inequities in the distribution of MCC and its effects

These challenges are great and have policy implications, including funding for sustainable healthcare services.

The scarcity of robust economic evaluations of MCC represents a considerable challenge for resource allocation decision making to reduce the MCC burden in already resource-constrained healthcare systems. Although the literature is sparse, one systematic review and several published studies are summarized below. However, of the 35 articles, some articles are old. In addition, the definition of what constituted a chronic condition varied, not allowing for comparisons between studies. Definitions were only specified in 11 studies, study duration ranged from 3 -12 months, and studies may or may not have specified functional limitations or need for medical care.[12] This important topic warrants further verification through economic evaluations that are more recent and cover a broader range of topics.

Determining Costs from Multiple Chronic Diseases

As illustrated in Figures 3a-d, diseases that occur alongside a disease of interest may be classified in various ways.[16]

1. A disease of interest may be caused by another disease.
2. Two diseases may be correlated with a causal link.
3. The disease of interest may cause another disease.
4. Two diseases may have no causal link and have only weak or no significant association.

Differences in the categorization of correlation and causal relationships between chronic conditions have been demonstrated to have substantial effects on cost of illness estimates.[16] Failing to adjust for diseases that are correlated but have no causal relationship may lead to an overestimation of the cost of the illness of interest, whereas failing to adjust for the cost of diseases caused by the condition of interest may lead to an underestimation of the cost of the illness of interest. Although literature in the field is still emerging, it is likely that some combinations of chronic diseases may have a disproportionate impact on healthcare utilization compared to the sum of their individual disease burdens.[16] However, there is already strong evidence that the greater the number of chronic

diseases, the higher the healthcare costs. Table 4 provides a summary of studies on excess costs, patterns of usage, physician access, medication use, bed utilization, out-of-pocket healthcare costs, and cost effectiveness of MCC interventions.[12]

Cost

Almost all studies asserted a positive association between MCC and healthcare utilization outcomes (including physician visits, hospitalizations, and use of medications) and healthcare cost outcomes (including medication, out-of-pocket, and total healthcare expenditures). In particular, utilization and cost significantly increased with each additional chronic condition consistently, as shown in Figure 11. Several studies observed a near exponential relationship, in which expenditures approximately doubled with each additional chronic condition.[40,79] This suggests costs do not simply add up, but several concurrent chronic conditions may interact in some way, leading to higher costs.

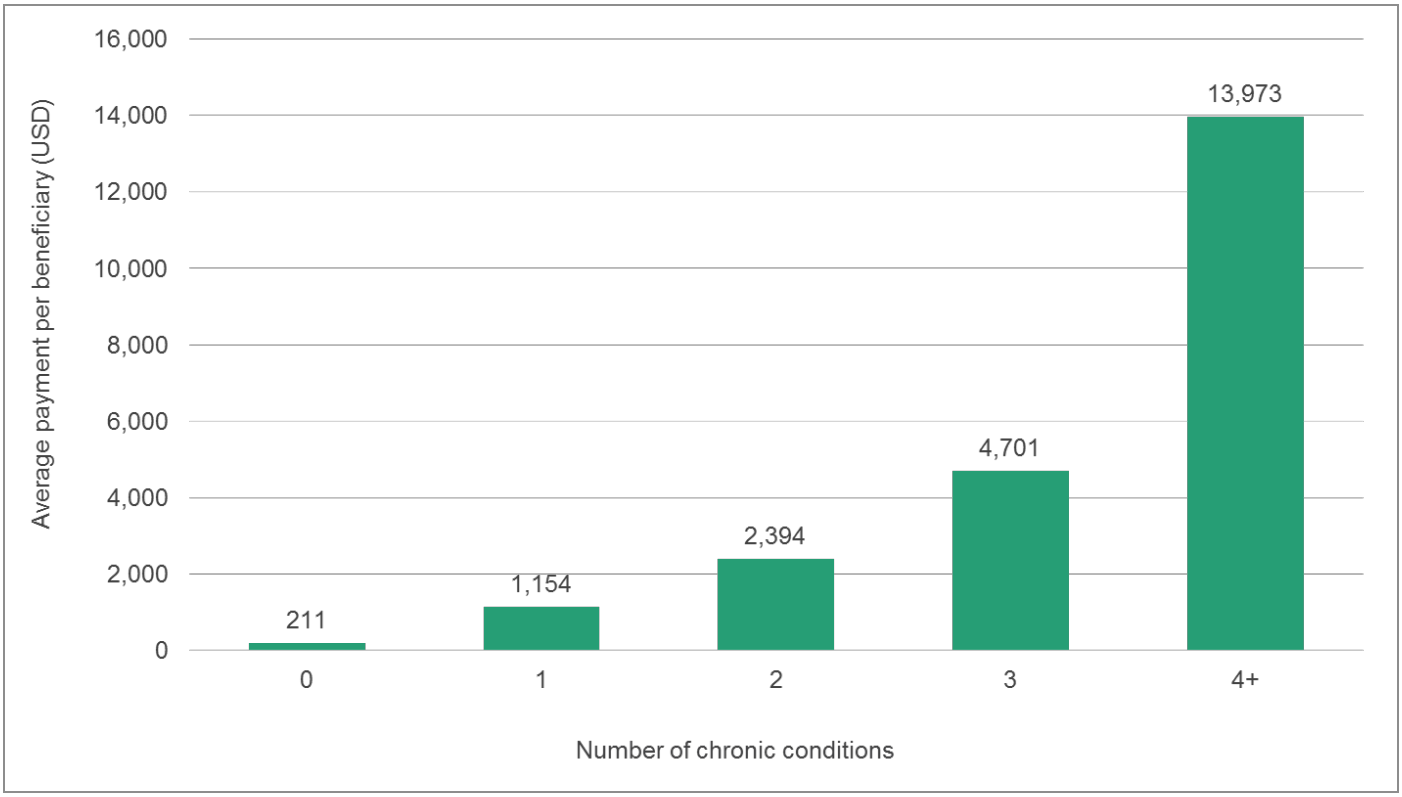


Figure 11. Annual average Medicare expenditures by number of chronic conditions (1999)[79]

Patterns of Usage

MCC is associated with higher levels of health resource utilization across resource types including medications, primary care, and outpatient specialist visits, as well as emergency department presentations and hospitalizations.[16]

Figure 12 represents the odds of incurring a hospital admission for an adverse event by number of chronic conditions.[79] The greater use of non-emergency care and preventable conditions suggest some of the access utilization is avoidable.

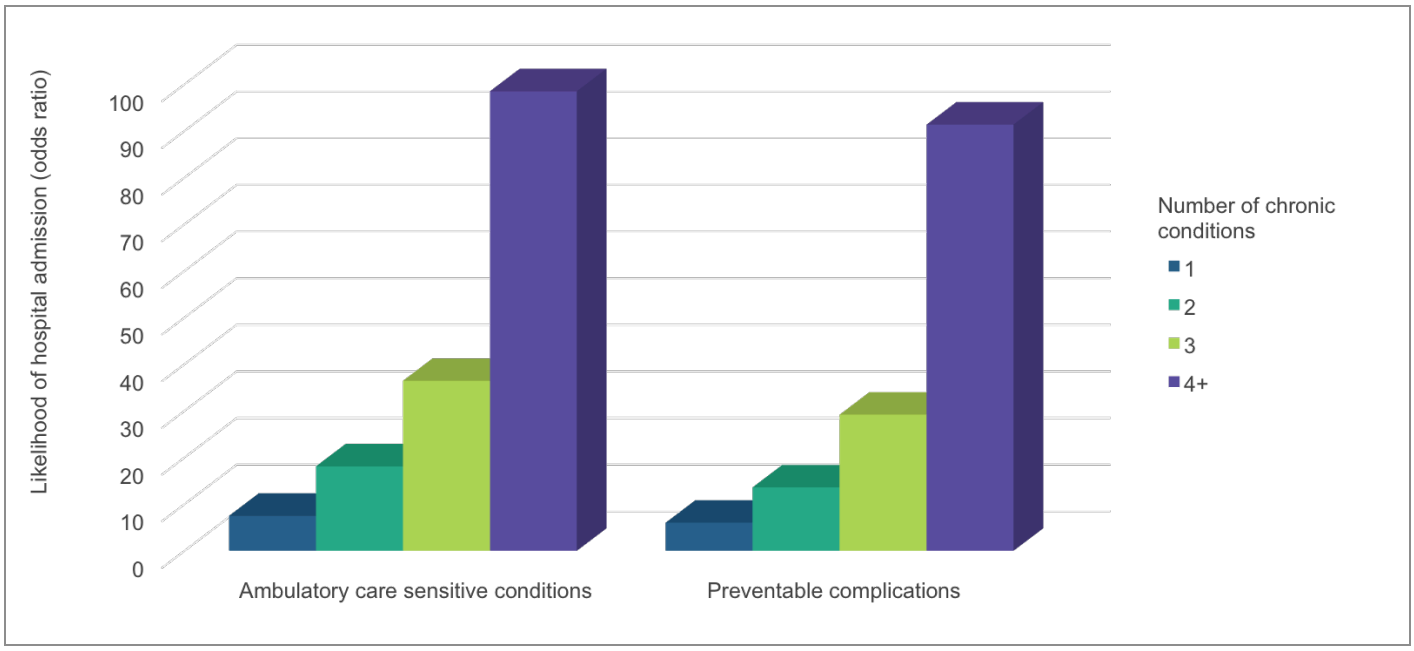


Figure 12. Odds of incurring a hospital admission for an adverse event by number of chronic conditions (1999)[79]

There is considerable variation in the magnitude of resource utilization increases reported between studies, health systems, and data sources. In terms of healthcare utilization, evidence points to more complex inpatient and outpatient care scenarios, such as disproportionately high use of specialist services, visits to a multitude of physicians,[80] and confronting physicians with more problems at each visit.[81] MCC patients use significantly more prescription medications (polypharmacy) and have higher prescription drug expenditures.[82,83]

Patient factors that determine cost and healthcare utilization include age and living arrangements (e.g., living alone), which are positively associated with hospital use,[84,85,103,104,105] female gender, and supplementary insurance. These factors are associated with an increased use of prescription medications,[83,101,108] independent of the number of chronic conditions.

Physician Access

Older adults with MCC have been reported to have between two and five times as many physician appointments as their peers without chronic diseases.[40,86,87] A Canadian study reported 51% greater use of physician services for each additional chronic disease.[84] People with MCC are also more likely to see a specialist physician for a chronic condition that would usually fall within the scope of a primary care service.[19]

Medication Use

Several studies have found patients with three or more comorbidities utilize prescription medications costing 6.6 times more, on average, than peers without comorbidities, and 2.1 times more than peers with one or two comorbidities.[20,88]Among Medicare beneficiaries in the United States, people with five or more comorbidities used eight more prescriptions for each additional comorbidity during their last year of life.[108]

Bed Utilization

Greater emergency department presentations and hospital admissions are also reported among those with MCC. Older adults in the United States with three or more chronic diseases utilized 25 times as many hospital bed days, during 14.6 times as many hospital admissions, than peers without any chronic diseases.

Out-of-Pocket Healthcare Costs

Individual patients are also impacted by elevated costs of MCC if they are responsible for expenses associated with their healthcare usage.[16] For example, out-of-pocket costs are 2.1 times higher for older adults with MCC than those without MCC.[89] Further, out-of-pocket costs for people with MCC are increasing at a faster rate than wage growth or broader consumer inflation levels. This has the potential to adversely affect the lives of the most vulnerable members of society, particularly those without adequate health insurance coverage or access to universal healthcare systems.[16]

With increases in aging and YLD, it is projected that patients will live with MCC for longer periods. As such, disproportionate increases in out-of-pocket expenses in relation to salaries require attention.

Cost Effectiveness of Multiple Chronic Conditions Interventions

Literature on cost effectiveness of interventions that address two or more chronic conditions is sparse, and studies that do exist highlight methodological problems with such research. A Cochrane systematic review published in April 2012 examined the effect of primary care and interventions in community settings for people with MCC, and identified ten trials for inclusion; however, there were no accompanying economic evaluations.[90] The authors postulated cost savings were plausible based on favorable intervention effects related to pharmaceutical use and reductions in chronic disease risk factors, but this cost effectiveness was not specifically reported. The paucity of cost-effectiveness data to inform allocation decisions related to MCC remains a concern.[90]

Regarding primary prevention, long-term or lifetime modeling of potential attainment of health benefits (and costs) may be required to demonstrate tangible health benefits and large reductions in health service utilization for some MCC interventions.[91,92] Unfortunately, long-term modeling may also come with untenable levels of uncertainty, including about how long lifestyle behavior change interventions will last.[12] Studies examining secondary prevention would require many years of ongoing intervention and follow-up among large samples before benefits could be directly observed, including outcomes such as myocardial infarction (MI) or stroke.[93,94,95]

Future studies should aim to investigate the incremental cost of providing services to patients with MCC through an integrated model, compared to via a non-integrated model or greater prevention. Both improved patient outcomes and reduced cost, and preferably a combination of the two, should be the aim of a successful healthcare delivery model for MCC.

Study & Country	Description & Year	Impact
Healthcare Costs		
Fishman et al. (1997) United States[96]	Cross-sectional study with diagnostic and procedural data (1992) from Group Health Cooperative (GHC) of Puget Sound (Washington State, U.S.)	Each additional chronic condition resulted in an expected increase in annual healthcare costs of 80% to 300%, depending on age, sex, and chronic condition profile.
Hoffman et al. (1996) United States[97]	Cross-sectional study with data from the 1987 National Medical Expenditure Survey (household component)	In comparison with elders with acute conditions only ($2,713 USD), those with one chronic condition had annual healthcare costs about 1.8 times ($4,887 USD), and those with two or more chronic conditions had costs about 3.6 times as high ($9,881 USD).
Crystal et al. (2000) United States[98]	Cross-sectional study with 1995 Medicare Current Beneficiary Survey data (use and cost files)	The number of chronic conditions was significantly and positively associated with total healthcare costs, annual out-of-pocket expenses, and out-of-pocket expenses as percentage of income (persons without chronic conditions spent 13.8% of their income; those with five or more chronic conditions spent 25.5%).
Hwang et al. (2001) United States[99]	Cross-sectional study with 1996 Medicare Expenditure Panel Survey data (household component)	Out-of-pocket expenses increased with each additional chronic condition and were about twice as high for elders with two chronic conditions, compared with those without chronic conditions. This association was found for out-of-pocket expenses for prescription drugs, home health, office visits, hospital use, and medical equipment, but not for out-of-pocket expenses for dental services and vision aids.
Physician Usage		
Hessel et al. (2000) Germany[100]	Cross-sectional study with data from a household survey by the Leipzig University, Germany, March/April 1996	The number of medical conditions was significantly and positively associated with the annual number of physician visits and number of medications taken on a daily basis (chronic conditions were the strongest predictor in each of the multiple regression analyses).
Bed Utilization		
Chan et al. (2002) Australia[101]	Cross-sectional study with data from a household survey in the Randwick Municipality of Sydney (Australia), March 1998-June 1999	Multiple chronic conditions (three or more) was a strong and significant predictor of emergency department admissions.
Ionescu-Ittu et al. (2007) Canada[102]	Cross-sectional study with random sample drawn from provincial administrative databases in Quebec, Canada, 2000-2001	Comorbidity was a significant independent predictor of emergency department use. In a multivariate analysis, comorbidity had a comparatively weak effect on emergency department use: One additional score on the Charlson Comorbidity Index increased the rate of emergency department use by 7% and one additional score on the chronic disease score increased department use by 4%.

Landi et al. (2004) Italy[103]	Observational cohort study with administrative data from six Italian home health care agencies (longitudinal data), 1997-2002	Elders with any hospital admissions (at baseline) had significantly more chronic conditions (3.9) than those without hospital admissions (3.2). In a multivariate analysis, elderly persons with five or more chronic conditions were more than twice as likely to incur an hospital admission, compared with those without chronic conditions (during one-year follow-up).
Librero et al. (1999) Spain[104]	Cross-sectional study with administrative (hospital discharge) data from Valencia Health Service, Spain, 1993-1994	Results from logistic regression with age comorbidity interaction: patients 65 to 79 years of age in the highest morbidity group (5+) had significantly lower chances of being hospitalized (OR 0.51) than those without chronic conditions, whereas patients with moderate morbidity burden (1 to 2) had significantly higher chances (OR 1.24).
Condelius et al. (2008) Sweden[105]	Cross-sectional study with administrative registry data (2001) from four municipalities in southern Sweden	In multivariate analyses, the number of chronic conditions was significantly associated with acute and total number of admissions, and (less strongly) with planned hospital admissions.
Chu and Pei (1999) Hong Kong[106]	Prospective case–control study with emergency admissions (using administrative data) at Queen Mary Hospital of Hong Kong, 1996	Compared with controls, readmission cases had significantly more chronic conditions (3.1 vs. 2.6). Number of chronic conditions was a significant risk factor for early, unplanned readmission in a multivariate analysis (OR 1.30).
Medication Use		
Fahlman et al. (2006) United States[107]	Retrospective review (cross-sectional) of retail and mail order prescription claims data from Medicare+Choice (collected between January 1998 and December 2000), United States	Beneficiaries with higher numbers of comorbidities had significantly greater numbers of prescriptions (8 prescriptions for each additional comorbidity) and higher annual prescription drug expenditures and out-of-pocket expenses.

Table 5. Summary of studies related to cost and healthcare utilization for patients with MCC, adapted from Lehnert (2011)[12]

Future Work on Multiple Chronic Conditions Healthcare Costs

Geographic Variation in Healthcare Costs

The impact of MCC on healthcare costs and resources will likely differ greatly across health systems, geographic regions, disease combinations, and person-specific factors (e.g., social disadvantage and age).[12,84,108,109,110,111] Most studies exploring the impact of MCC on healthcare costs and resources to date have been generated from relatively few health systems and regions. Investigations to understand the impact of MCC on healthcare utilization in other health systems and regions would be useful for informing policy and practice in those, and similar, systems.

Clusters of Diseases

Existing studies have concentrated on few chronic condition combinations, or risk factors, with limited consideration of the potential impact of intervening in two conditions together (i.e., concordant disease combination) versus two conditions separately (i.e., discordant disease combination).[90,93,112,113,114,115,116,117] In particular, the clustering of specific diseases is increasingly recognized but remains poorly studied, such as the bi-directional relationship between TB and DM in developing countries.

Healthcare Resource Allocation

Health services research to quantify the effects of resource allocation decisions on patient health and healthcare costs at a systems level may be among the most important and influential research that can occur in the field of MCC.

Healthcare Data Reporting

Administrative data offers huge potential for the study of the epidemiology and cost of MCC. One barrier to its use for this purpose, however, is the lack of specific coding. While it may be possible to develop algorithms to enable some analytic output from administrative data,[118] this has proved difficult and limited to date. The International Classification of Diseases Framework (ICD9 and ICD10),[119] which is among the most commonly-used systems for reporting healthcare episode diagnoses globally, requires the reporting of one primary diagnosis. While secondary diagnoses may be added, they are not instructive as to the conditions relevant to the patient episode. The ability to report multiple conditions as primary diagnoses should be considered for future data coding systems.

Payment Mechanisms and Financial Incentives

Most payment policies do not provide financial incentives and instead reimburse healthcare providers for discrete medical interventions on a fee-for-service basis. Alternative models, such as value-based purchasing and shared care approaches, recognize and reward the broader assessment and engagement of medical and social needs, which is an important prerequisite to the holistic management of MCC patients.[4]

Issues Related to Polypharmacy

Poor Adherence

Poor adherence to medication is a well-known consequence of taking multiple medications, referred to as polypharmacy. Aside from quantity of medications, poor adherence is also influenced by medication regimens, depression, and type of chronic condition. A review of 76 studies assessing compliance to medication, measured by electronic monitoring devices, showed overall compliance of 71%, as well as declines in adherence with an increase in number of daily doses. Adherence rates were 79% with one medication dose, 69% with two doses, 65% with three doses, and 51% with four doses.[120] Another meta-analysis reported that depressed patients have threefold odds of being non-adherent to medical treatment, compared with non-depressed patients.[121] Other major predictors of poor adherence include cognitive impairment, lack of symptoms, inadequate follow-up or discharge, side effects of medication, high complexity of treatment, and cost of medication.[122] For secondary prevention (among those with history of CVD), younger age, depression, and complex drug treatment are associated with lower medication adherence.[123]

Adverse Drug Events and Drug Interactions

Adverse drug reactions are defined as reactions that are noxious and unintended and which occur at dosages normally used in humans for prophylaxis, diagnosis, or therapy.[124] Polypharmacy increases the risk of adverse drug reactions from 13% for two medications to 58% for five medications. Seven or more medications further increase the risk to 82%.[125] Polypharmacy also increases the risk of drug-drug interactions. Elderly patients are disproportionately affected; approximately 35% to 60% are at risk of drug-drug interactions, but this increases with the number of medications, reaching approximately 100% with eight or more medications.[126] The most common interactions reported in elderly patients are aspirin and peptic ulcer disease, calcium channel blockers and heart failure, and beta blockers and diabetes.[127]

Undertreatment

Undertreatment, or underprescribing, is also a common consequence of polypharmacy. In an elderly sample, those with polypharmacy were 4.8 times more likely to be undertreated, compared with those using four or less medications.[128] The most frequently undertreated medications and conditions in the elderly population are laxatives for morphine use, beta-adrenoceptor blockers for myocardial infarction, ACE (angiotensin-converting enzyme) inhibitors for heart failure, coumarin derivatives for atrial fibrillation, and bisphosphonate or raloxifene for osteoporosis. The use of fixed dose combination pills has been shown to reduce undertreatment.[129]

Section 6: Discussion and Recommendations

Discussion

This report is the first comprehensive review of the burden and impact of MCC globally, reporting on the taxonomy, epidemiology, and burden on patients, health systems, and economies, and presenting strategies for how these may be tackled. A summary of the key findings is presented in Box 5.

Key Report Findings

- The prevalence of MCC, although highly dependent on definitions, is about one in three adults globally and ranges between 16% and 58% of adults in developed countries.
- The top chronic conditions contributing to disease burden globally include IHD, stroke, lung cancer, depression, diabetes, and back and neck pain.
- LICs and LMICs have a similar NCD burden to HICs, while simultaneously also suffering from the burden of communicable disease (e.g., diarrhea, HIV/AIDS, and TB).
- The five leading global risk factors for chronic disease are high blood pressure, high fasting glucose, smoking, high total cholesterol, and high body mass index.
- Certain chronic diseases cluster together more frequently (e.g. CVD and stroke with depression, TB with diabetes, and HIV/AIDS with CVD).
- MCC is associated with substantially greater increases in healthcare costs and resource utilization. Healthcare expenditures double with each additional chronic condition due to elevated rates of primary care and specialist physician access, emergency department presentations, hospital admissions, and polypharmacy.
- The impact of MCC on patients and families is profound, including deterioration of patients' quality of life, significant out-of-pocket expenses, difficulties with medication adherence, inability to continue work, symptom control (chronic pain in particular), and a considerable toll on caregivers.
- The increasing proportion of older adults in the population and younger adults with MCC who will live to advanced ages, has implications for policies and funding.
- Current research and research funding, healthcare system infrastructure, and healthcare delivery systems are not well equipped to tackle the burden and future impact of MCC.

Box 5. Key report findings

MCC is common in all countries and across all income levels, affecting one in three adults globally, and is set to become more common as the population ages and risk factors are acquired at earlier ages. Developing countries face the continued problem of infectious diseases that are increasingly long term and chronic due to improved treatment, such as TB and HIV/AIDS, in addition to NCDs. Women appear to have higher rates of MCC than men due to differing health-seeking behavior and disease patterns. The association between SES and chronic disease appears complex and understudied, and evidence to date points to a negative association in adults under 55 years of age, no association (or only a weak one) in adults older than 55 years, and a positive association in some Southeast Asian countries.

Risk factors leading to the chronic conditions that contribute most to MCC, namely high blood pressure, high fasting glucose, smoking, high total cholesterol, and high body mass index, are all highly amenable to modification. The vital role of prevention through lifestyle behavior change is further emphasized by the potential to impact MCC and the burden on healthcare systems. Further economic evaluations of different interventions would provide timely and useful tools for the development of future MCC-related health policy.

The clustering of certain chronic conditions more than others warrants urgent and careful consideration, in light of the strength of such associations (odds ratios greater than three), and the potential to have considerable impact through relatively small shifts in healthcare delivery. Conditions that seem to co-occur most frequently include depression alongside CVD in developed countries and TB and HIV/AIDS alongside CVD in developing countries. Depression warrants particular attention through further recognition, prevention and screening practices, and prescribing practice for drug-drug interaction and adherence rates, particularly among healthcare teams who may currently only manage CVD. The relatively recent phenomenon of coexistence and clustering of chronic infectious conditions, often with high endemicity in some regions, together with highly prevalent NCDs, such as diabetes and CVD, represents a serious threat of failing to manage these conditions and increasing their prevalence. This is further complicated by poor healthcare access in such regions.

There is scarce data on the economic burden of MCC. This report relies on some studies that are dated or restricted to a narrow range of conditions. As such, conclusions on the economic impact of MCC require further verification. Nevertheless, studies to date point to the excess cost burden of MCC being largely underestimated and overlooked. This is despite the opportunity for cost savings to be tremendous, with relatively small changes in healthcare system delivery to lessen reliance on specialist care and inpatient stays. Further work is required to delineate the potential savings from various cost drivers of MCC, such as polypharmacy, inpatient bed days and specialist care, in order to better inform healthcare policy.

In estimating the economic impact of multiple conditions, it is essential to differentiate between correlation and causal relationships, as this has been demonstrated to have substantial effects on cost of illness estimates. Although literature in the field is still emerging, it is likely specific combinations of chronic diseases may have a disproportionate impact on healthcare utilization, compared to the simple addition of the individual disease burdens.[22] Existing databases frequently employed for economic evaluations, such as the GBD study, assume an additive model from single conditions and may be underestimating the true cost burden.[130]

The impact on patients' lives also remains understudied and can be profound, including deterioration in patients' quality of life, significant out-of-pocket expenses, difficulties with medication adherence, inability to continue work, symptom control (chronic pain, in particular), and a considerable toll on caregivers. Interventions that adopt a more holistic approach (e.g., dealing with a patient's symptoms in addition to the disease itself) are more likely to succeed.

Limitations of This Report

The absence of agreed-upon taxonomy relating to MCC, including a specific designated term, as well as a definition of what constitutes a chronic condition and which conditions are to be included in MCC, has led to considerable heterogeneity in the reporting of MCC prevalence and burden. Further heterogeneity is seen when the data are self-reported, compared with the use of verified data.

The major repositories of epidemiological health data, such as the WHO and the GBD study, in addition to administrative data sources, such as hospital EMR and claims data, do not collect or report on MCC. While there is some ability to derive this information from these data sources, the complexity of MCC may be missed. For example, the cost of MCC is exponential, according to several studies, and would not be captured through derivation algorithms.

While this review has sought to be comprehensive, the paucity of studies on some aspects of MCC, such as economic burden, has led to the reliance on fewer than the ideal number of studies, rendering a risk of non-representation of the findings. Where this is the case, the authors recommend verification of the findings through future research. This section discusses some approaches and strategies for action and intervention. However, this area remains undeveloped. While the recognition and activity in this field, particularly in some developing countries, is encouraging, there are relatively few reports or case studies with proven outcomes to date. Economic evaluations of interventions that would produce both improved health and reduced cost outcomes are urgently required to inform future health policy related to MCC.

Unmet Needs and Challenges

Despite the increasing burden of NCDs around the world, intervention funding and political action are not proportionate. Prevention and control of NCDs have been recognized, yet NCDs receive a small proportion of funding compared to their burden. This disparity is particularly problematic in LICs and LMICs. For example, in 2010, HIV/AIDS accounted for 3.7% of the disease burden in LICs and MICs, whereas NCDs accounted for 49.8% of the burden. The development assistance for health, which includes grants, loans, and goods and services, allocated just 2.3% to NCDs, but 45.9% to HIV/AIDS.[131] The lack of attention to chronic diseases in developing countries exacerbates poverty, hinders economic development, and continues to take the lives of millions of people.

Rates of chronic disease are increasing rapidly, especially in LICs. As the MCC burden increases, so too, do healthcare costs, risk of death, and poor functional health. Among Americans 65 years of age and older, as many as three out of four have MCC. Many of these chronic conditions increase with age, and as the population ages, the MCC burden will continue to increase. Chronic diseases cluster together due to independently high prevalence rates, common risk factors, or a synergistic relationship between the two. Unfortunately, traditional health systems and major disease programs rarely address chronic diseases that occur together, instead adopting a single-disease framework. For example, reports have indicated that physicians greatly underestimate the presence of depression in cancer patients primarily because oncology visits are focused only on physiologic treatment and symptom management of cancer.[132] Over the last twenty years, advances in psycho-oncology research have made depression screening more common. The shift from a single-disease focus to consideration of other chronic diseases was the result of a successful, broad multidisciplinary application of behavioral and social science that must be applied to all areas of health and medicine.[133]

NCDs are preventable, and sufficient research has highlighted critical areas for investment. There is a need for multisectoral collaboration, with efforts by countries, health systems, organizations and stakeholders at local, national, regional, and global levels. Public-private partnerships are critical for collective and effective decision making, and for providing strategies to address the complexity of MCC. Innovative strategies, from telemedicine and algorithmic medicine, to pharmaceutical developments, have set the stage for actors and multisectoral collaborations to achieve prevention of

NCDs and control of MCC. Key recommendations for future areas of work and research in the field of MCCs are summarized in Box 14.

Opportunities for Action and Intervention

While there are relatively few examples of interventions that have reported positive outcomes to date, some potential examples are reported. These emerging solutions represent the multidisciplinary effort required to prevent and control MCC and address its many challenges of disease burden, functional health, quality of life, and healthcare costs, as well as issues related to polypharmacy (poor adherence, undertreatment, and adverse drug events).

Reducing the burden of MCC will require action by healthcare providers as well as the pharmaceutical industry, policymakers, the digital health industry, and the broader community. There have been some promising advances, particularly in the field of high technology solutions. However, few efforts report sustained improvements in both health and cost outcomes.

Developing countries face the double burden of infectious diseases becoming chronic alongside more traditional NCDs, which necessitates a rapid transition away from the current vertical program management to cross-condition management and greater continuity of care. Learnings from the successful delivery of HIV programs can be leveraged to enhance the provision of NCD services. Some examples include HIV treatment screening in HIV-infected patients in Malawi,[134] integrated primary care services for NCDs and HIV in Kenya,[135] and medication adherence clubs funded by the NIH and the United States President's Emergency Plan for AIDS Relief (PEPFAR).[136]

Many other sectoral opportunities exist, some of which are detailed below. These include measures for prevention, health systems and professionals, and smarter and tailored development of medication and patient support systems, as well as technological advances.

1. Public Health Prevention

Prevention of chronic conditions is most impactful in terms of both cost and health outcomes, but also the most difficult to achieve. Potential interventions would predict groups with one chronic disease at risk of developing additional chronic conditions.

1.1) Predicting Groups at Risk of Multiple Chronic Conditions

Prevention of MCC involves the development of methods to predict which groups of people will develop chronic diseases.

Studies examining the cost of preventing a second chronic disease among those with a chronic disease have demonstrated cost effectiveness. Among adults with newly diagnosed type 2 diabetes, long-term aspirin use is cost effective for preventing CV events.[137] Over a lifetime, aspirin users gained 0.31 life-years (LY) or 0.19 quality-adjusted life years (QALYs) over non-aspirin users, at an incremental cost of $1,700 USD. The incremental cost-effectiveness ratio (ICER) of aspirin use was $5,428 USD per LY gained or $8,801 USD per QALY gained.

Additional studies have examined the cost effectiveness of screening for diabetes and the use of ACE inhibitors for prevention of CKD. Treating all known diabetics with ACE inhibitors was both less costly (average lifetime savings of $623 USD per patient) and more effective than current treatment (0.124 additional QALYs per patient).[138] Primary care screening for individuals 50 to 69 year of age, as well as intensive treatment of diabetes, had an incremental cost-effectiveness ratio of $10,416 USD per

QALY gained. These results suggest screening of diabetes and the use of ACE inhibitors can prevent CKD among those with diabetes.

Another cost-effectiveness study examined screening for atrial fibrillation (AF) using iPhone electrocardiogram (iECG) and subsequent warfarin prescriptions for stroke prevention.[139] In a sample of community adults, prevalence of AF was 6.7%. The incremental cost-effectiveness ratio of extending iECG screening to the community, based on 55% warfarin prescription adherence, would be $4,066 USD per QALY gained and $20,695 USD for preventing one stroke. Sensitivity analyses indicated cost effectiveness improved with increased treatment adherence. The authors concluded screening with iECG in pharmacies with an automated algorithm is both feasible and cost effective for prevention of a chronic disease such as stroke. These benefits may be bolstered by complementary strategies to increase medication adherence.

2. Healthcare Systems

Healthcare systems should develop models of care and systems that facilitate cross-condition management.

2.1) Care Guidelines

One case study of how care guidelines have improved MCC outcomes is the use of Practical Approach to Care Kit (PACK) guidelines in conjunction with British Medical Journal Best Practice.[140] PACK is uniquely designed for primary care providers in low-resource settings, where a lack of specialized care further hinders management and control of chronic conditions. The interventions are designed to address high prevalence of chronic infectious diseases (e.g., TB) and chronic non-infectious diseases (e.g., DM) in LICs. PACK helps clinicians integrate the care of a patient with multiple problems and prompts diagnosis of MCC. Randomized controlled trials have assessed the effectiveness of PACK in improving health outcomes and strengthening health systems (Box 6).

PACK was developed to improve global health by addressing unskilled primary care workers in LMICs. It aims to provide symptom-based care with a management plan for one or more chronic diseases. The evidence-based guidelines include 40 common symptoms and 20 chronic diseases (including TB, HIV/AIDS, chronic respiratory disease, chronic diseases of lifestyle, mental health, musculoskeletal diseases, epilepsy, women's health, and palliative care).

In summary, studies assessing PACK found modest but significant improvements in screening, referrals, and prescribing. The symptom-based guidelines empower non-physician prescribing and can be an effective strategy for cross-condition management.

Trials Assessing Practical Approach to Care Kit		
Study (objective)	**Methods**	**Results**
Fairall et al., 2005 (to evaluate the effect of educational outreach program on detection of TB and effects on care)[141]	Cluster randomized controlled trial (RCT) in South Africa, 2-6 educational outreach sessions delivered to nurse practitioners	Greater prescriptions for corticosteroids (OR= 1.90, 95%CI: 1.14 to 3.18), referrals to a doctor among those who were severely ill (OR= 2.59, 95%CI: 1.06, 6.19), and TB diagnoses (OR = 1.72, 95%CI: 1.04, 2.85) compared to clinics with no new training. No difference in prescriptions of antibiotics (OR = 1.01, 95%CI: 0.74, 1.38), or sputum screening for TB (OR=1.22, 95% CI: 0.83, 1.80) between the two groups.
Zwarenstein et al., 2011 (assessed education outreach program of staff to improve care for patients with HIV/AIDS)[142]	Outreach for public primary care clinics for HIV/AIDS in eight clinics, control (seven clinics)	Patients referred to program in intervention clinics more likely to receive co-trimoxazole prophylaxis (OR=1.95, 95%CI: 1.11-3.40). There was no increased enrollment in the HIV/AIDS and ART program through testing in primary care.
Fairall et al., 2008 (assessment of nurse-prescribing antiretroviral therapy (ART) in South Africa)[143]	Followed patients in public sector ART project for 20 months	ART was associated with lower mortality (HR=0.14; 95%CI: 0.11, 0.18) and increased presence of TB (HR=0.61; 95%CI: 0.46, 0.81).
Fairall et al., 2016 (assessed NCD education outreach on prescribing and treatment of NCD patients in South Africa)[144]	Cluster RCT in 38 care clinics; trial expanded to include mental health and NCDs, increased prescribing provisions and NCD care for nurses	No differences in treatment intensification of hypertension (RR =1.08; 95%CI: 0.94, 1.24), diabetes (RR=1.1; 95% CI: 0.97, 1.24), or chronic respiratory disease (RR= 1.08; 95% CI: 0.75, 1.55) or detection of depression (RR= 0.76; 95% CI: 0.53, 1.10), but there were no reports of harm from nurses expanded scope of practice.

Box 6. Trials investigating the impact of PACK guidelines on health outcomes

2.2) Community-Based Care

The successful management of disease for MCC patients, in particular, relies on the provision of healthcare delivery in the patients' own environment, as well as the coordination with social care provision. While healthcare models are gearing up to provide such care, a few models of successful implementation are reported below.

Health Quality Partners

Health Quality Partners developed an intervention for improved management of Medicare beneficiaries with complex chronic conditions. Through the program, registered nurse care coordinators focus on changing patient behavior with frequent in-person contact with both patients and physicians. Patient education includes condition-specific self-monitoring training. According to the National Academy of Medicine, the program has reported reductions in average monthly Medicare expenditures by 21%.[4]

Impact

This program provides a collaborative care approach for older adults suffering from depression. Primary care physicians work with depression care managers (e.g., nurses, social workers, or psychologists supported by other paraprofessionals) to develop and implement treatment plans including antidepressant medication and/or short-term counseling. The care manager also educates patients about depression and coaches them in self-care. The care providers utilize ongoing measurement and tracking of outcomes with a validated depression screening tool (e.g., Patient Health Questionnaire-9) and adapt care to the patients' changing symptoms. In reported outcomes, total healthcare costs for patients were $3,300 USD lower per patient on average than those of patients receiving usual primary care.

Box 7. Health quality partners

Mount Sinai Peak Health Program

In 2010, the Mount Sinai Health System in New York established Peak Health, an outpatient clinic that targets patients with MCC by taking a "team-based, high continuity and high intensity approach" to primary care.

Patients with three or more chronic conditions, psychosocial complexities, and a recent history of hospitalization are either referred by providers or recruited to the program. Patients are assigned to one of four identical care teams (pods), each comprised of a nurse practitioner or physician who works alongside other nursing staff, social workers, care coordinators, and administrative staff. Each care team supports a relatively small number of patients (fewer than 100) to promote a high level of continuity and strong social care support.

Patients receive a risk assessment and individual plan to address medical and social drivers of readmission risk. The team follows up frequently with the patient and their caregivers at clinic and home, and connects them to clinical and non-clinical services to help address challenges such as adherence, activation, access, and other psychosocial complexities. The frequent patient contact in their own environment ensures real-time problem solving and coaching.

Each patient agrees to concrete, tailored goals with their care team (e.g., reduction of HbA1c for diabetes patients). This patient-centered approach strengthens motivation to attain the goals. Upon achieving goals, patients 'graduate' from the program and return to their usual primary care provider.

Box 8. Mount Sinai Peak Health Program highlights

2.3) Integrated Chronic Condition Care

In LICs, where populations face a double burden of NCD (e.g., CVD or diabetes) and HIV/AIDS, integrated care must address both. Chronic diseases are on the rise in HIV-infected countries, and recent evidence points toward a link between HIV infection, treatment, and NCD onset.

Cambodian Integrated Care

- Program offered integrated care for HIV/AIDS, diabetes, and hypertension within chronic disease clinics in Cambodia to build efficiency through multidisciplinary chronic disease care team, reduce barriers to HIV/AIDS care, and reflect high chronic disease burden.
- Clinics were set up locally in provincial referral hospitals in Siem Reap and Takéo. They provided treatment for HIV/AIDS, hypertension, and diabetes, as well as counseling activities to encourage medication adherence and lifestyle modifications with psychosocial support.
- This approach demonstrates care for HIV/AIDS patients can be leveraged to address MCC, and integrated care is feasible and well received. Doctors became specialized in chronic disease and, over time, adopted a patient-centered approach. Existing functions developed for HIV/AIDS care—specifically adherence support—were valuable in supporting diabetes care.

Box 9. Cambodian integrated care model[145]

3. Health Professionals

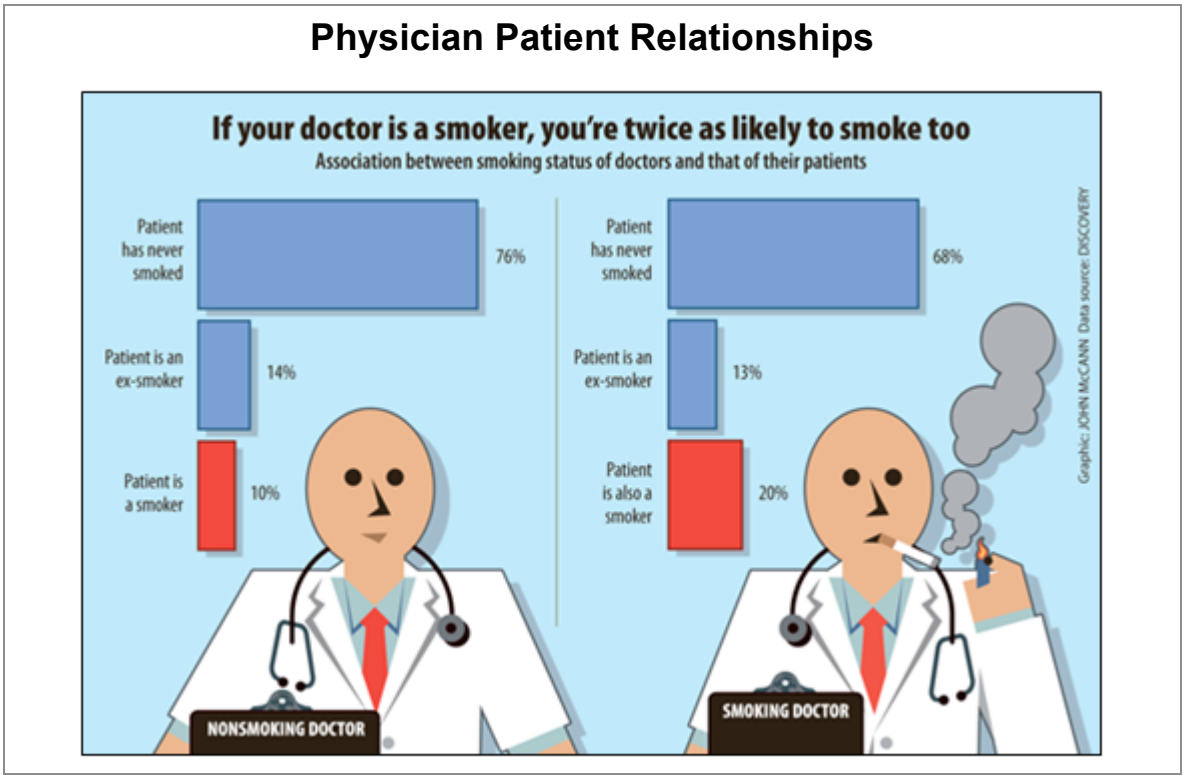
3.1) Team-Based Care

Team-based care is a core component of most healthcare system-level interventions for reducing MCC burden. Examples include the PACK guidelines and the Mount Sinai Peak Health Program.

3.2) Improved Understanding of Physician-Patient Relationships

3.21) Discovery Health Study on Physician Health Habits and Patient Impact

Physician-patient relationships, including time, rapport, communication, and trust, can impact the health of patients with MCC. Evidence suggests that physicians have a unique influence on their patients that extends beyond treatments provided and that they may influence patient lifestyle choices (Box 10). In a study of South African doctors by Discovery Health,[146] smoking rates among patients of non-smoking doctors were 10%, compared with 20% among patients of smoking doctors. Similarly, inactive doctors had more physically inactive patients (56%) compared with doctors who were highly active (50%).



Box 10. Impact of a doctor's lifestyle behaviors on those of their patients

The Vitality Age is a composite score that measures health status and lifestyle, where the difference between an individual's actual age and their Vitality Age (Vitality Age differential) is an indication of overall health status. Discovery Health data highlighted a 5.9% increase in patients with a Vitality Age greater than their actual age from the best doctor tertile (doctors with a Vitality Age equal to or less than their actual age) to the worst (doctors with a Vitality Age three or more years greater than their actual age). The authors suggest modifying the lifestyle behavior of physicians would have a positive impact on their patients' lifestyle choices and subsequent health status.

3.22) Physician-Patient Consultation and Prolonged Opioid Use

Physician prescribing patterns can have a significant impact on the degree of polypharmacy and the subsequent health of patients, including the likelihood of opioid dependence. In a large sample of Medicare recipients who visited the emergency department and had not used prescription opioids in the six months prior, there was significant variation in opioid prescriptions between physicians practicing in the same hospital.[147] The intensity of a physician's opioid prescribing, characterized as high or low, was positively associated with the likelihood that their patient would become long-term opioid users over the next 12 months. Patients treated by high-intensity prescribers were 1.30 (95% CI: 1.23-1.37) times as likely to be long-term opioid users at 12 months, compared to those treated by low-intensity prescribers.[147] These results suggest the likelihood of long-term opioid dependence may be increased by a single initial consultation with a physician who is more likely to prescribe either opioids or a higher dose.

In both of these examples, appropriate training and education of physicians, together with tools to support best practice, may indirectly and positively influence their patients' health outcomes.

4. Pharmaceutical Development and Delivery Innovation

4.1) Combination Pills/Polypill Approach

Medications do not work when patients do not take them. For patients with chronic diseases, adherence to, or compliance with, medication is very low, often dropping to just 50% after six months.[148] In the United States, 33% to 69% of medication-related hospital admissions are due to poor adherence, resulting in healthcare system costs of approximately $100 billion USD a year.[149,150] Efforts to increase adherence to medication among those with chronic conditions could dramatically improve health and reduce healthcare costs.

The polypill, also known as fixed-dose combination (FDC) medicine, combines multiple medications into a single pill. FDC medicine has been used across more than 32 countries to treat HIV/AIDS, malaria, TB, and more (Box 11). Further innovations have created a polypill for prevention of CVD, and studies have successfully shown how a single pill, combining a statin, aspirin, and one or more antihypertensive drugs, can reduce CVD events by as much as 80%.[151] The effectiveness of polypills is based on increased medication adherence. A review of polypill adherence, including fixed dose drugs for hypertension, TB, diabetes, and HIV/AIDS, demonstrated a 26% reduced risk of noncompliance among those prescribed polypills, compared to free-drug component regimen.[152]

Fixed Dose Combination Medicine

FDC medicine aims to simplify the treatment regimen and increase likelihood of adherence. It has predominantly been studied in primary prevention, but may be applied to treatment regimens and secondary prevention.

Adherence:

- TB: A randomized controlled trial (RCT) that compared compliance to TB medication between a FDC medication and the same medications separately found no difference at 8 weeks (96.5% versus 98.1%), but higher adherence in the FDC group at 6 months (88.5% versus 87.3%; p > .05).
- HIV: Those taking FDC medication are 1.46 (95%CI: 1.00, 2.13) times more likely to adhere to medication, compared with those on non-FDC medications.
- CVD: Use of the FDC medication was associated with 1.41 times more improved outcomes (reduced systolic blood pressure; no change in LDL cholesterol).

Cost Implications:

- Over ten years, scale-up of FDC medication programs could avert 17.9 million deaths, equivalent to 20%. The cost over this period would range from $0.43 USD to $0.99 USD per head in LICs and from $0.54 USD to $2.39 USD across LMICs and UMICs.
- CVD:
  - In the United States, 15.4 million Americans would be eligible for a FDC medication for secondary prevention of CVD, which could reduce 10-year incidence of CHD by 32% and stroke by 30%. To our knowledge, there have been no long-term evaluations of a FDC medication for secondary prevention of CVD.
  - Cost-effectiveness modeling in acute MI patients suggests that for each 10% increase in adherence, 6.7% of all CVD events are avoided and adherence to medication increases by 20%.

Box 11. The fixed-dose combination (FDC) medicine approach[153,154,155]

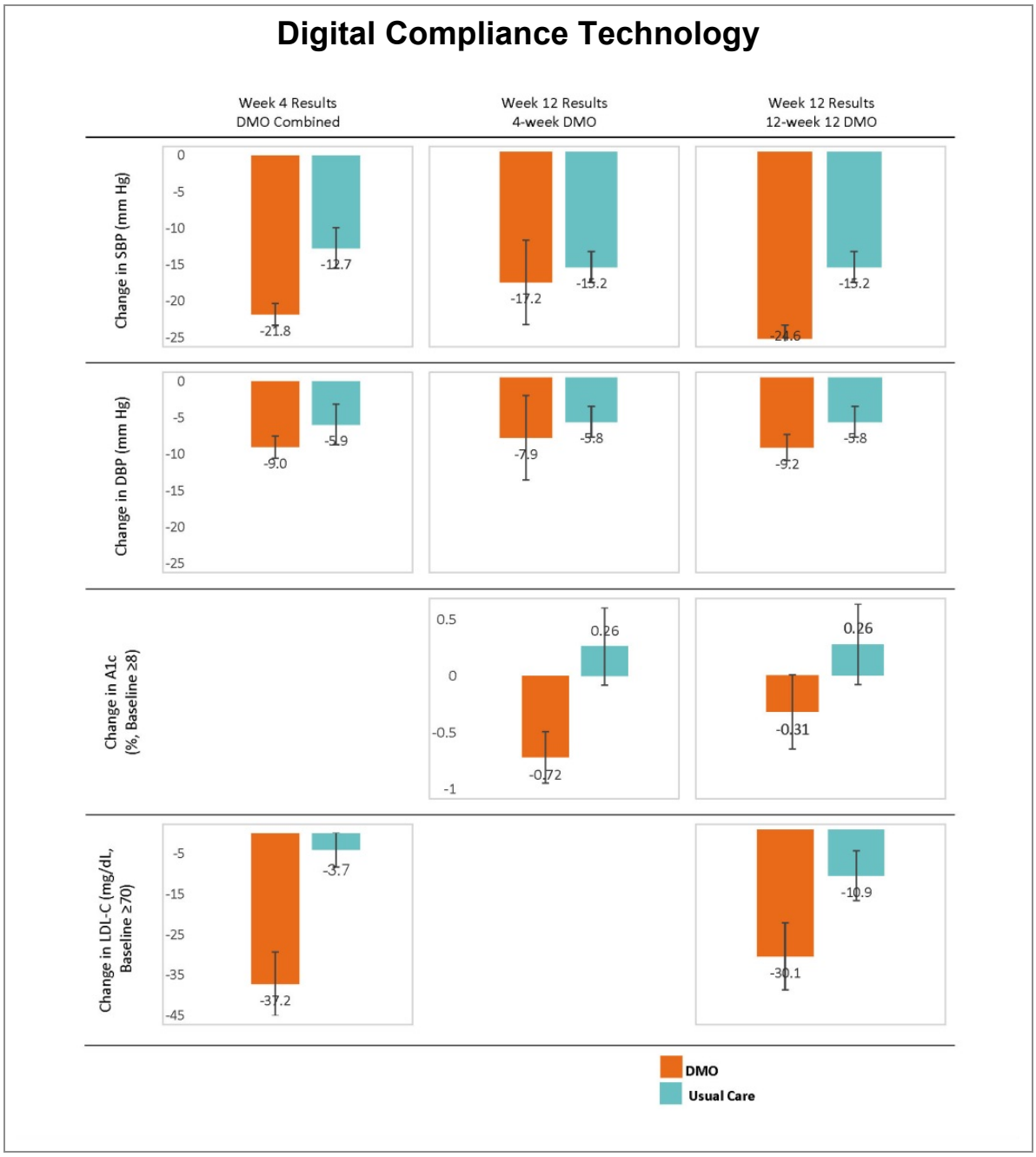
A RCT assessed compliance to medication between a FDC medication and the same medication prescribed separately for TB and found no difference in compliance at 8 weeks (96.5% versus 98.1%), but a higher adherence rate in those taking the FDC medication at 6 months (88.5% versus 87.3%; p > .05).[156] Among patients with HIV, those who took the FDC medication were 1.46 (95%CI: 1.00, 2.13) times as likely to adhere to medication, compared to those taking the medication as separate pills.[157] Among patients with type 2 diabetes, FDC medication resulted in 10% to 13% higher adherence compared to loose-pill combination therapy for patients starting combination therapy.[158]

The polypill has been well studied among those with hypertension and at risk of CVD, but little research exists on use of the polypill for secondary prevention of CVD. One study found that among those with established CVD, the polypill was associated with 1.41 times better outcomes (reduced systolic blood pressure; no change in LDL cholesterol).[159] Cost-effectiveness models for FDC pills have shown that for each additional 10% increase in adherence, the polypill can prevent 6.7% of fatal and non-fatal CV events.[160] This modeling approach, using a sample of UK patients with history of MI and a mean age of 64.7, suggests this scenario could improve adherence to medication by 20%.

Despite the promise of FDC medicines, implementation of the approach has been limited. Documented barriers include physician reluctance to prescribe FDC, as the use of combination medicines is perceived to replace efforts to promote healthy lifestyles.[161] The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE) trial provides evidence that lifestyle measures of those on FDC medication are not adversely affected.[162] Large-scale implementation barriers include reluctance of pharmaceutical companies to invest in FDC medicines—which are created from low-cost generic drugs.[161] Government investment may provide necessary support for companies to develop affordable FDC medicines, which has been done successfully for other conditions, such as malaria and HIV/AIDS. The success of FDC medicine in other medical areas suggests partnerships and investments by academics, international health agencies, research funding bodies, governments, regulators, and pharmaceutical manufacturers can make scaling up FDC medicine for CVD a viable possibility.

4.2) Digital Compliance Technology

Methods of drug delivery have evolved since the days of traditional syringes. Today, companies are developing innovative capsules that promote medication adherence and prevent subsequent consequences of poor compliance. The FDA has accepted the first digital medicine drug application. The tablet combines Otsuka's Abilify, an atypical antipsychotic drug, with Proteus' ingestible sensor, which sends a signal when swallowed, providing adherence data.[163] The technology has the ability to share information with professionals and caregivers, with patient consent. This new mechanism allows for objective information to be communicated between the patient and the physician, improving concordant decision making and tailored treatment. With this efficacy information, medicine can be tailored to reflect unique needs and patterns of medication adherence among certain groups of patients with chronic disease clusters (Box 12). Box 12 illustrates results of a small study (n=109) of patients with uncontrolled hypertension and type 2 diabetes who used Proteus' digital medicine sensors (digital medicine offering). The results indicate those using the ingestible sensor had better CV outcomes than those with usual care.



Box 12. Clinical results week 4 for combined DMO groups, week 4 DMO, and week 12 DMO[164]
Abbreviations: DMO (digital medicine offering); SBP,(systolic blood pressure); DBP (diastolic blood pressure); HbA1c (glycated hemoglobin); LDL-C,(low-density lipoprotein cholesterol)

5. Technology

5.1) Telemedicine

Access to timely, acceptable, and affordable healthcare remains a fundamental determinant of good health, yet timely medical attention is rare. Patients wait up to 109 days in the United States for a family medicine doctor appointment.[165] New telehealth companies are addressing this issue by developing telemedicine services that provide kiosks or stations in the workplace, allowing employees to connect with a physician within minutes via phone or video. Most importantly, on-demand physician support brings top health services to hospitals or cities with a shortage of physicians. New digital platforms have been developed to link physicians with hospitals in need. Nomad Health,[166] for example, allows hospitals to search and connect with physicians that have specific credentials.

Telemedicine in the form of remote monitoring could meet the needs of chronic disease patients who require monitoring and long-term support. Remote monitoring can allow individuals with MCC to remain maximally functional and independent, understand and better manage their diseases, and remain safely in their homes. Providing on-demand care could deliver the support older patients need and may reduce utilization of hospital resources.

In resource-poor settings, telemedicine may play an important role connecting skilled primary care providers in developed countries with unskilled primary care providers in developing countries. The Center for Connected Health is a non-profit organization in Boston that runs Operation Village Health, a project that provides health services to two Cambodian villages.[167] Using a multitude of modern technologies, including transmitting information via text, audio, and video, doctors at Massachusetts General Hospital and Brigham and Women's Hospital provide remote consultations for patients in Southeast Asia. Telemedicine also eliminates travel expenses for specialists and patient transfers, which are significant costs and barriers for patients in resource-constrained settings.

5.2) Algorithmic Medicine

The pervasive use of technology has led to an enormity of data, 2.5 quintillion bytes per day.[168] The growing databases of research, patient health information, physical activity trackers, and more have provided artificial intelligence with an abundance of information to deliver critical healthcare insights. Pharmaceutical companies have the opportunity to develop advanced algorithms that can predict which patients will benefit from specific drugs or adhere to medications, as well as the likelihood of drug-drug interactions. The combination of human insight with the advanced cognitive capabilities of computer algorithms has the ability to transform chronic disease management.

IBM Watson Health is one of the first data repositories to partner with numerous drug companies and hospitals to deliver technological insights by mining large-scale data to solve complex health equations. One of the consequences of MCC and subsequent polypharmacy is drug-drug interactions. As the number of medications prescribed increases, so does the risk of drug-drug interactions, which makes it difficult for physicians to identify all possible interactions. When medications exceed ten or 15, physicians will be unable to determine the optimal set of medications and doses to maximize gains and minimize side effects. IBM Watson Health uses data to analyze possible drug-drug interactions for different people, genetic makeups, and classes of drugs.

IBM Watson Health can also better manage patient outcomes by engaging patients and providing personalized care. Using evidence-based communications that promote specific health outcomes, IBM Watson Health can provide the outreach necessary to ensure care does not end when patients leave the hospital. Collective data on specific diseases and outcomes allows for targeted outreach and disease management.[169]

Healthcare Technology Applications in Low-Resource Settings

Technological advances can play a unique role in low-resource settings, helping to address diverse population needs in remote settings and provide support for poorly-skilled healthcare workers. For resource-poor settings, which face unique obstacles to managing MCC patients, e-health systems can be an economically viable and sustainable solution. Although research in developing countries is scarce, the following e-health functions have been found to have a positive impact in LICs:[170]

- Ability to track patients though treatment initiation process, monitor adherence, and detect those at risk for loss to follow-up (particularly important given follow-up rate of up to 76% for HIV patients in Africa)[171]
- Tools to decrease communication times between institutions
- Ability to electronically monitor and remind patients of healthcare needs or treatments (e.g., South African text message system may increase TB treatment completion rates)

Box 13. Healthcare technology application in low-resource settings

Key Recommendations

Despite MCC affecting one in three adults globally and the large burden on healthcare resources, the scale of the problem is not reflected in the current response. Detailed in Box 14 are key recommendations for future areas of work and research in the field of MCC.

Key Recommendations

1. The evidence base for MCC is currently sparse, as well as the necessary research funding to tackle this issue going forward. Due to the high prevalence and burden, as well as the inevitable increase due to population aging and increases in risk factors at earlier ages, further attention to MCC is urgently required.
2. There is no agreed taxonomy for MCC such that the descriptions of its burden are widely heterogeneous due to differing terms, definitions and inclusion criteria. Consensus is required for the term itself, the definition of which chronic conditions should be included, and what constitutes a chronic condition. Further caution is required to differentiate which risk factors, diseases, and symptoms fit within the definition, and on the relationship between simultaneously occurring diseases (e.g., between correlation and causation).
3. Avoidance of chronic diseases through improvements to lifestyle behaviors such as smoking, diet, and physical activity remains the mainstay of primary prevention. Secondary prevention through disease management and control of established risk factors also plays a significant role. Economic evaluations are required to establish the most cost-effective approaches and interventions to reduce MCC burden.
4. Data reporting and monitoring systems do not include MCC. Some of the most widely used health data repositories, such as the WHO and GBD databases,[130,172] only deal with single chronic conditions and do not yet report on MCC. Administrative data, such as hospital electronic medical record and financial (claims) data also do not deal adequately with MCC due to the lack of specific coding. This format of data reporting is not conducive to subsequent identification or analyses of MCC patients. The ability to report on multiple primary diagnoses in future coding systems should be considered.
5. Healthcare delivery systems are set up to manage individual chronic conditions individually and not for the holistic or coordinated care of a MCC patient. Healthcare teams that have responsibility for community care as well as in the clinic, care guidelines that tackle symptoms as well as conditions, and also deal with more than one condition at a time, would assist with the provision of more patient-centric care. These are even more needed—but complex to deliver—in developing countries, where long-term infectious conditions coexist alongside NCDs and access to healthcare is not guaranteed.
6. Healthcare payment mechanisms that reward positive health outcomes (e.g., value-based care) rather than activity-based funding (e.g., the fee-for-service approach in the United States) may help in achieving improved MCC patient outcomes.

Box 14. Key recommendations

Conclusion

Existing data suggest approximately one in three adults suffer from two or more chronic conditions, and multiple chronic conditions (MCC) occurs in 16% to 57% of all adults in developed countries. Developing countries are increasingly facing the double burden of long-term communicable conditions alongside chronic conditions, with clustering and causality between many common conditions. From the relatively sparse research on the topic, MCC has been shown to be associated with substantially greater increases in healthcare costs and resource utilization. The increasing proportion of older adults in the population, and younger adults with MCC who will live to advanced ages, has implications for policies and funding.

Several actions can be taken to better estimate the scale of MCC. These include establishing agreed-upon terminology and definition of MCC and developing turnkey classification of MCC within common medical data sources. Additionally, more research is needed to capture MCC patient concerns, such as the presence of chronic pain and the inability to continue work.

Research funding for noncommunicable diseases remains disproportionately low, and research funding for MCC is not widely reported. Quantifying the amount of research funding available for MCC will be a starting point to justify additional resources for this highly-prevalent challenge.

Interventions for MCC are lacking. Research on existing initiatives to increase medication adherence (e.g., fixed dose combination medication) and multi-condition management (e.g., patient-based guidelines) has shown promising impact. There is a need for healthcare providers to urgently rethink and test new models of healthcare provision to prepare for future escalating costs of managing MCC in aging populations.

This paper has outlined key challenges of MCC and promising areas for targeting this growing issue. The hope is that this work will lead to recommendations for tangible actions and interventions to address the impact of MCC. In addition to the involvement of healthcare systems and key stakeholders, such as health insurers and pharmaceutical manufacturers, any future approaches should consider the concerns and challenges of patients living with MCC.

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