

# Global Alliance for Chronic Diseases Researchers' Statement on Multi-Morbidity

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**We present the first Global Alliance for Chronic Diseases (GACD) Researchers' Statement on Multi-Morbidity. The GACD network is an alliance of multidisciplinary health-care professionals, researchers and health-research funders. We aim to reduce the impact of non-communicable diseases (NCDs) through a focus on implementation research in low and middle-income countries (LMICs), and vulnerable populations in high-income countries (HICs).**

*Case Vignette: Maria is fifty. She lives in the suburbs of a large LMIC city remote from the nearest health-centre and earns money by washing clothes. She has elderly relatives at home and her partner is unemployed. She has obesity, hypertension, chronic obstructive pulmonary disease (COPD) and depression. How do these conditions interact to affect health and social outcomes? How does treatment for one condition affect the outcome or progression of the others? How can she access holistic community-based health-care? Who cares for her relatives when she is unwell and how will the family earn money when she can't work? How can the impact of her health-conditions be minimised, both for her and her family? Such are the challenges in detection and management of non-communicable disease multi-morbidity in low- and middle-income countries.*

## Introduction

An ageing population develops an increasing number of NCDs. Consequent to improvements in public health measures (such as improved sanitation), preventive measures (such as vaccination) and global vertical initiatives aimed at reducing mortality from infectious diseases (particularly pneumonia and gastroenteritis) global life expectancy has improved. Global Burden of Disease data highlight that 70% of global deaths are attributable to NCDs, whilst 80% of premature deaths from NCDs occur in LMICs [1]. In LMICs multi-morbidity from NCDs, acute and chronic infections, developmental problems from childhood and malnutrition all add to the overall burden of adult ill-health. NCDs often co-exist as 'multi-morbidity' which is most simply defined as the presence of two or more long-term physical or mental health conditions. **We argue that multi-morbidity has not been adequately recognised in current policy and**

**funding priorities and therefore in research, healthcare provision and healthcare education.** Moreover, multi-morbidity research in the field has been hampered by the absence of an agreed definition across investigators.

## **The GACD Network**

The GACD is an alliance of international funding agencies working together on common areas of research that are of high global importance [2]. Our projects bring together a network of researchers active in LMICs and vulnerable populations in HICs. The GACD develops and facilitates innovative research and funding collaborations between LMICs and HICs in the fight against chronic diseases. We focus on researching NCDs, and implementation science, to improve health in disadvantaged populations and real-world settings. Previous GACD funding calls have focused on hypertension, diabetes, chronic respiratory diseases and mental health and, most recently, scale-up in hypertension and diabetes – our first example of a cross-disease funding call.

The GACD Network recognised the importance of multi-morbidity, and the specific need for multi-morbidity research in LMIC and vulnerable populations in HICs. Following discussions at the 2017 Annual Scientific Meeting, we formed a multidisciplinary Multi-Morbidity Working Group. Our Network embraces the practical challenges of delivering multi-morbidity research and care, and we aim to influence others to drive these aims. Our expertise is cross-specialty, from primary through tertiary care, and multi-stakeholder, from clinicians and academics, to NGOs, funders and policy advisors. At the end of this document we present a first GACD Researchers' Statement on multi-morbidity, incorporating three high-level strategic objectives. Our Statement is aligned with the UN Political Declaration on the Prevention and Control of NCDs which recognised NCDs as a global health and development priority and committed governments to take urgent action to address this growing crisis. We are also aligned with the 2030 Agenda for Sustainable Development Goals (SDGs) agreed in 2015, to reduce premature NCD mortality by one third [3], which is of profound importance for cost-effective implementation of Universal Health Care [4]. We present our Statement ahead of the 2018 (Third) United Nations General Assembly High-Level meeting on NCDs and urge, in particular, a greater focus on multi-morbidity.

## **The Challenge of Multi-Morbidity**

Whilst developing our Statement, the UK Academy of Medical Sciences (AMS) issued a report entitled 'Multimorbidity: a priority for global health research' [5]. The AMS proposed the addition of chronic and/or life-long infectious disease to the definition of multi-morbidity. The GACD supports that inclusion as both NCD and long-duration infectious diseases need long-term treatment and care. The AMS report makes a clear distinction between multi-morbidity and co-morbidity, the latter focusing on a specific index condition and greater precision in the use of these related terms is required. Individual conditions in multi-morbidity often cluster - perhaps through shared risk factors (termed 'concordant multi-

morbidity’). Where components of multi-morbidity appear unrelated and/or require different management approaches the term ‘discordant multi-morbidity’ may be applied. **We argue that in LMIC (as in HICs), in addition to simple co-existence, there may be reciprocal interactions between NCD multi-morbidity and acute events including infections that are poorly studied.**

There is abundant evidence highlighting increased use of health services by those suffering from multi-morbidity [6], and improved quality of life in patients receiving integrated care for chronic diseases [7]. Despite developments in integrated care, there is the need for better coordinated service provision across different health systems, generation of evidence-based guidelines to manage multi-morbidity including mental health, and greater investment in health promotion and prevention strategies to tackle multi-morbidity [8]. People living with multi-morbidity can visit any level of healthcare facility, so all healthcare professionals should be trained about the possibilities of multi-morbidity and know how to approach this. We particularly recognise the importance of multi-morbidity involving physical and mental health. We have summarised some of the evidence around the prevalence, importance and challenges of multi-morbidity in hypertension, diabetes and cardiovascular diseases, chronic respiratory diseases and mental health – the initial areas of GACD research focus – together with that in chronic infection and cancer in the Appendix. These sections highlight the rich body of data describing isolated diseases in contrast to the multi-morbidity approach promoted in this statement. We strongly advocate for utilising a multi-morbidity approach in characterising NCDs.

## **Barriers to Holistic Health Care**

Major barriers to holistic health care are the lack of comprehensive, co-ordinating primary health care generally, and siloed specialty knowledge focused on treating the disease rather than the individual. The major effect of this is on people living with multi-morbidity (see Box). This may be perpetuated by training programmes for health-professionals, and the training of informal health workers such as Community Health Workers and Volunteers being developed and delivered by specialised professionals. How best to deliver expert multi-morbidity prevention and management in primary health care settings in LMICs remains a major challenge. Notably, however, many simple and effective interventions such as diet, exercise and inhaled tobacco, indoor and outdoor pollution exposure reduction could have a major impact on many aspects of multi-morbidity. Addressing multi-morbidity using integrated chronic disease management in Primary Health Care in LMIC will help improve health systems whilst developing opportunities for efficiencies, particularly when such systems are weak or fragmented.

**BOX:** Barriers to implementation of UHC for multi-morbidity due to the current disease-specific focus:

Cost and inconvenience to see multiple specialists, and lack of both specialists and expert multi-morbidity generalists

Lack of awareness of the consequences of interventions on multi-morbidity

Poly-pharmacy

Missed holistic health-promotion opportunities

No evidence base to make decisions in multi-morbidity

Health provider anxiety dealing with multi-morbidity

## **Common Themes**

These summaries from our initial areas of focus in GACD research have empowered the GACD Multi-Morbidity Working Group to identify six common themes:

1. The relevance of multi-morbidity to all health-care professionals.
2. The general under-recognition of multi-morbidity in health-care provision and research, including research to explore new models of care delivery.
3. The absence of evidence-based guidelines on approaches to managing patients with multi-morbidity leading to under- mis-and over-treatment (in part driven by the absence of primary evidence due to exclusion of many people with multi-morbidity from efficacy trials).
4. The need to provide greater access to expert, pro-active holistic primary care that integrates NCDs.
5. The need for better integration of health-care education, both to health-care providers and also to patients and their families, specifically in relation to multi-morbidity including how best to access current models of care.
6. The need for further research assessing interventions that address the challenge of multi-morbidity in LMIC settings, for example low-cost combination interventions and holistic prevention programmes.

## **Recommendations**

We have presented a case for a greater focus on multi-morbidity, specifically in relation to NCDs in LMICs. Our current disease-specific research and care-delivery approaches are hindering research and patient care, and our ability to

maximise improvements in health outcomes. Only by doing this will we be able to achieve the SDG targets, especially 3.4 (NCDs), 3.5 (with links to mental health) and long-term communicable diseases (3.3). There is also the opportunity to improve maternal mortality (3.1) outcomes. This will require collaborative working cutting across traditional boundaries.

***Thus, the GACD research network believes that a greater focus on multi-morbidity is overdue and necessary to successfully improve global healthcare outcomes – the first GACD Researchers’ statement on multi-morbidity.***

We stress the following three strategic objectives:

- 1. Greater policy awareness and focus on multi-morbidity** through integrated proactive chronic care, rather than systems that address single NCDs. Practical examples of this would include support for education, training and guideline development that focus on multi-morbidity, and policies which make implementation of simple universal interventions around diet, exercise and reduced exposure to tobacco, indoor and outdoor air pollution and alcohol attractive, effective and practical to implement.
- 2. Changes to the way that research is commissioned, funded and delivered** when considering NCDs in LMICs – particularly the promotion of working across and between traditional disease, primary care and specialist boundaries. Pragmatic trial designs are one approach to ensure the effects of interventions are considered holistically, in the situations in which they arise and are treated, using shared data dictionaries of disease and broad outcome definitions.
- 3. Health systems research aligned with Universal Health Coverage.** In particular, greater consideration of the role of pro-active Primary Care and (where appropriate) Community Health Workers in developing knowledge and skills to deliver effective integrated multi-morbid NCD care. Addressing multi-morbidity will help improve health systems and efficiencies, particularly when such systems are weak or fragmented.

With regard to research funding, we are not explicitly arguing for greater funding (though this would be welcome), rather that funding models strongly encourage research across traditional boundaries and single disease siloes. The GACD is already leading this, with the latest call in relation to ‘scale up’ of multi-morbid hypertension and diabetes research in partnership with relevant stakeholders and delivery organisations, our shared data dictionaries and multidisciplinary working groups. The GACD aims to use its network to begin to reduce the impact of multi-morbidity and, ultimately, to improve the lives of people living with multi-morbidity such as Maria.

**This statement reflects the perspectives of researchers from the GACD but does not necessarily reflect the perspective of the funding agencies.**

## **Appendix**

We have summarised below some of the evidence around the prevalence, importance and challenges of multi-morbidity in hypertension, diabetes and cardiovascular diseases, chronic respiratory diseases and mental health – the initial areas of GACD research focus.

### **1. Hypertension, Diabetes and Cardiovascular Diseases**

The prevalence, detection rate and effective control of hypertension varies considerably across LMIC settings [9]. Hypertension is the leading global risk for mortality [10] principally, through increased rates of ischemic heart disease [11], heart failure [12], and stroke [13].

Diabetes is also common in many LMIC, the prevalence in some countries is as high as 25% [14]. Diabetes is also a major risk factor for cardiovascular and renal disease. Cardiovascular disease is the major cause of death in people with diabetes and pre-diabetes [15]. Hypertension increases the risk of renal and cardiovascular complications in diabetes [16]. Both hypertension and diabetes often remain undiagnosed for a number of years, perhaps until complications ensue. The ‘metabolic syndrome’ is a clustering of risk factors, such as central obesity, insulin resistance, dyslipidaemia and hypertension that together culminate in increased risk of type 2 diabetes mellitus and cardiovascular disease. Shifting dietary and lifestyle habits, away from normal cultural practices to the adoption of a more ‘Western’ Lifestyle and diet further increase the global prevalence of these conditions.

Due to genetic, lifestyle and environmental factors, hypertension and diabetes tend to cluster together, further increasing the likelihood of multi-morbidity. Treatments for both are centred around the same lifestyle modifications, which are low cost, and based on education of patients and raising community awareness of these conditions together with, where necessary, challenging cultural norms on perceptions of ideal body shape.

Both hypertension and diabetes have been associated with higher prevalence of certain cancers (and excess mortality from cancer), chronic obstructive lung disease, and dementia. Diabetes increases the severity of some chronic infections such as tuberculosis, melioidosis, and dengue virus infection [R17]. Conversely, when multi-morbid with other conditions, hypertension and DM become more difficult to manage. For instance, diabetic patients with mental health disorders require more emergency and hospital visits associated with increased healthcare costs [18]. HIV and the use of antiretroviral therapy [19], as well as cancer and the use of chemotherapy and/or radiation [20], have been shown to increase cardiovascular disease events.

### **2. Chronic Respiratory Diseases**

Asthma and chronic obstructive pulmonary disease are highly prevalent; asthma being twice as common but causing fewer deaths than COPD which has an age-standardised prevalence of 3% in males and 2% in females [21]. COPD prevalence is driven by exposure to tobacco smoke, and indoor and outdoor air pollution.

Many people living with chronic respiratory disease such as asthma and chronic obstructive pulmonary disease (COPD) remain undiagnosed, and consequently under-treated.

People living with COPD serve to highlight the challenge of multi-morbidity, receiving many other diagnoses and treatments, often dying with respiratory disease, not of it [22], leading to misclassification and omission from medical records and death statistics. Mechanistically, aside from exposures such as smoking, the links between respiratory conditions and co-morbid conditions are not fully understood. Independent of exposures such as tobacco smoke, indoor and outdoor pollution, chronic systemic and pulmonary inflammation are present in all stages of respiratory conditions, suggesting a potential mechanistic link to other chronic conditions such as ischaemic heart disease and osteoporosis. The lack of a correct diagnosis for their co-morbid condition often complicates the management of the respiratory disease, and vice-versa.

There have been few general population assessments that systematically identify the distribution of co-morbidities in prevalent chronic respiratory diseases. Data from the UK General Practice Research Database (GPRD; now Clinical Practice Research Datalink, CPRD) have been analyzed to quantify baseline rates of co-morbidities in patients with asthma or COPD compared with matched controls [R23]. In both COPD and asthma, the total sum of diagnoses related to major organ systems was higher than in controls. Among incident COPD patients, a frequency > 1% within the first year after diagnosis was observed for angina, cataracts, bone fractures, osteoporosis, pneumonia, and respiratory infections. Amongst incident asthma patients, the occurrence of events was lower likely due to the younger age distribution. In addition, there is evidence suggesting undertreatment in the context of multi-morbidity with, for example, under use of  $\beta$ -blockers in patients with COPD and ischaemic heart disease [24], despite evidence that such use is generally safe.

### **3. Mental Health**

Around one in three people will have mental illness at some point during their lifetime [25]. The reciprocal links between mental health and chronic physical health conditions are well known. Mental disorders are risk factors for hypertension, diabetes and stroke [26]. In turn, diabetes and cardiovascular complications such as myocardial infarction are associated with increased risk of depression and anxiety which have led to treatment protocols including psychological assessment being provided for those with chronic physical conditions [27]. A bi-directional association between HIV and mental disorders has also been established such that depression and other neurocognitive deficits can be due to HIV [28]. There is an increased risk of suicide amongst those suffering from disability and chronic disorders due to a number of illnesses including malignancies [29].

Mental disorders are associated with increased mortality from a number of chronic physical diseases. Appropriate treatment involving both physical and psychological management with a specific focus on treatment adherence is

therefore vital in reducing mortality amongst those suffering from multi-morbidity involving a mental health diagnosis [30]. Quality of life in old age, palliative and end of life care are all specific domains of health care that are related to ensuring better mental health status of individuals at such stages, so that the individual can function better and suffer less.

Co-morbid mental disorders in patients with other chronic disorders are often missed by healthcare workers due to lack of awareness, leading to inadequate management of the patient's illness. This has implications both for the undiagnosed or poorly managed mental disorder, and also impacts treatment adherence for the physical illness. GACD researchers have begun to assess the implementation of novel approaches to multi-morbidity and demonstrated the impact of proactively identifying mental health diagnoses, for example using screening Apps in primary care [31].

#### **4. Cancer**

Smoking, obesity, unhealthy diet, lack of physical activity and alcohol excess – major risk factors for non-malignant NCDs – are also risk factors for many types of cancer. Multi-morbidity affects cancer prevention, diagnosis, treatment and clinical as well as economic outcomes [32]. This includes participation in screening, and delayed recognition of early symptoms and signs. Patients with COPD, for example, are at increased risk of lung carcinoma over and above that expected through shared exposure to risk-factors such as tobacco smoke [33]. Cancer therapies can result in multi-morbidity, for example hypertension and cardiac dysfunction. As in other areas of medicine, patients with multi-morbidity are often excluded from clinical trials, making interpretation of clinical evidence challenging. As cancer care improves, managing multi-morbidity in cancer survivors becomes increasingly important.

#### **5. Chronic Infections including HIV-AIDS**

There has been a growing awareness of the co-existence and potential for interactions between NCDs and chronic infectious diseases, such as HIV and TB, as patients with chronic and/or life-long infections experience the life-prolonging benefits of anti-infective therapies. While much of the data on this interaction in HIV comes from high-income countries because of the longer duration of exposure to anti-retroviral therapy (ART) and increased capacity for research, patients in LMICs are starting to see a higher prevalence of NCDs amongst HIV patients as they age [34]. In addition to the expected increases in NCDs with the advancing age of patients with HIV, certain types of ART are known to increase the risk for metabolic diseases, and the chronicity of HIV infection is known to increase inflammation and thus potentially increase the risk of NCDs [35]. As large scale HIV programmes continue to demonstrate the ability to prolong the lives of patients in LMICs, the issue of multi-morbidity will grow in importance [36].

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