Thank you for your consideration of our submission for this important topic. We are a team of researchers in multimorbidity from Australia, Belgium and Canada.

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* Is this input submitted as an organisational or individual response? This input is submitted by organizations from Australia, Belgium and Canada.

* Are you happy for your response to be published by the Academy? Yes.
1. There is no standard definition of ‘multimorbidity’ – various different definitions are used. Which definitions (or aspects of definitions) do you think are most helpful to efforts to describe and understand multimorbidity?

As stated and widely recognized by the research community in multimorbidity, no standard definition of ‘multimorbidity’ has been established in the scientific literature. With the increasing number of publications on multimorbidity-related topics (building the knowledge base) come an increasing number of multimorbidity definitions (clouding the knowledge base). A lack of standard definition may stem from the lack of consensus on the ‘nomenclature’ of multimorbidity or the ‘multiples’ that are included within the definition itself. Essentially, there is no consensus on the pieces of the definition, let alone the entirety of the definition. This relates to the underlying challenge of defining, and then measuring, health issues (whether these are defined as diseases, conditions, problems or symptoms). Many published studies do not discuss the rationale of their underlying definition or measure or multimorbidity within the publication. In fact, some studies assess only somatic diseases whereas other studies include mental health, psychosocial issues and a broad range of physiological and psychosocial risk factors in their definition and measurement of multimorbidity. A 2013 bibliometric analysis that reviewed the definition used in publications focused on multimorbidity indicated that only 51% of the published studies using the term ‘multimorbidity’ provided a definition, and among these 233 papers, 13 different definitions were used (Almirall and Fortin, 2013). Previous use of indices of multimorbidity have proven to be difficult for wide use due to a number of factors, including proprietary programs, lack of adaptability and lack of comprehensiveness. In fact, many of these indices were developed and advocated for based on their association with a small set of outcomes, such as cost or mortality.

Based on a systematic review of the multimorbidity literature and expert consensus, the European General Practice Research Network has proposed a definition: “any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor” (Le Reste et al., 2013). This definition speaks to the conflict between providing a definition that is comprehensive enough to capture the clinical reality of multimorbidity and a definition that is specific enough for the development of functional measures or tools. From the clinical perspective, many would argue that none of the current measures of multimorbidity are completely suitable. This is because of the complex
nature of multimorbidity. Moreover, different measures of multimorbidity seem to relate differently to different outcomes. So, while measures are required, these measures will not necessarily align with the ‘clinical definition of multimorbidity’, nor will these measures be perfectly valid across all potentially relevant outcomes. As such, measurement is required but has to be done to suit the context of the study. This means that multimorbidity measurement must be pragmatic.

To date, little work has been done to consistently compare and contrast aspects of definitions. To conduct this comparison in a meaningful way, the research and clinical communities should find common ground on a sound clinical definition which then relates to a pragmatic, patient-centred, valid and reliable measure of the concept of multimorbidity that holds across databases and outcomes. Although not ideal, a single definition of multimorbidity may not consistently perform with high validity and reliability in all contexts. Therefore, if deemed necessary, preference is needed for measures in the appropriate context and that perform well with relevant outcomes. However, a single measure should ideally be created and validated to allow for application and comparison in different data sources, across international contexts. For example, this definition should be easily adaptable to clinical, administrative and survey datasets and to the diagnostic coding that is used (e.g., ICD-9 codes, ICD-10 codes, ICPC-2 codes and Read codes). Once again, this measurement should achieve a widely-approved balance in both comprehensiveness (e.g., including all important conditions or diseases) and efficiency (e.g., particularly for use in large secondary databases) when measuring the burden of multimorbidity.

While this definition can be readily applied to research studies, it is important that this measurement be adaptable to the contexts of the individual research studies. For example, if a study in Canada was looking to understand the challenge of multimorbidity among patients with headaches, the approved international measure for multimorbidity must be easily adapted to survey data collection and the condition of "headaches" must be easily incorporated into the definition and measurement. As previously stated, this measure should be easily adapted to the needs of a research study. This study will produce comparative findings, which are also tailored to the individual study. Once the approved measure of multimorbidity has demonstrated high levels of validity and reliability, this is the measure that should be advocated by the multimorbidity research community.
6. What should the definition of ‘multimorbidity’ be? How would this definition improve research and/or treatment?

This question is directly related to the previous question and there is much work to be done to establish common ground between a clinically and methodologically sound definition of multimorbidity, with the integration of participant or patient perspectives. One example of common ground between clinical and methodological relevance is the consideration of the number of conditions or diseases that should be included in the operationalization of the multimorbidity definition. When multimorbidity-related research was first being published, research focused almost exclusively on those participants or patients living with two or more conditions or diseases (2+). Due to the rise in those living with 2+ conditions or diseases, movement towards a focus on those participants or patients with three or more conditions or diseases (3+) has indicated an important shift in both the measurement and interventions for individuals with multimorbidity. In fact, a definition that focuses on 3+ conditions or diseases performs better in terms of face validity among clinicians (this is what clinicians often think of when they talk about multimorbidity) and specificity for the identification of those who require complex needs interventions (this would allow for interventions to be more targeted).

While this criterion in the definition of multimorbidity can be more easily agreed upon (and publications can still display results stratified by 2+ and 3+ conditions or diseases, if desired), the challenge remains in establishing ‘what’ conditions or diseases to include. Many measures focus on conditions or diseases that are completely chronic in nature. However, in the context of clinical care, the temporary addition of an acute condition or the ongoing management of more cyclic conditions can make a patient’s care more complex; in some cases, in a similar way to the addition of another chronic condition or disease. In contrast, the definition of ‘chronicity’ has been more readily used in the multimorbidity literature. Once again, this distinction speaks to the need for common ground to be established between clinical and research communities, with the integration of participant or patient perspectives. The importance of the clinical and patient perspectives speaks to the identification of the exact level of burden from conditions and diseases, whether they are chronic, acute or cyclic in nature. These need to be appropriate pieces within the broader multimorbidity puzzle.
Some researchers have advocated for a definition or measure of multimorbidity based on the outcome of interest, such as hospitalization or mortality. However, there is a need for a pragmatic measure that will perform well across outcomes (compromising the achievement of a ‘perfect’ relationship between multimorbidity and a single outcome). Understanding and assessing the burden for patients with multimorbidity needs to go along with the adaptive nature of the multimorbidity definition. As such, an enhanced multifactorial understanding of diseases and care burden would be beneficial. The current lack of adaptive measurements means that only generic instruments can be used in the multimorbidity population which causes inability to show improvements in intervention research (Smith et al., 2012). While this conversation moves beyond the definition of multimorbidity, this step will be crucial to informing intervention research for this population of individuals, and subsequently improving the treatment or management of those living with multimorbidity.

Ultimately, the definition of multimorbidity must be comprehensive, pragmatic, parsimonious and patient-centred. This is not an easy feat, and of course, this is something that is lacking in the international research community. A call for existing measures of multimorbidity and a process of identifying the measure that fulfills expectations may help to engage relevant stakeholders.

7. What are the priorities for research about the prevalence, burden and determinants of multimorbidity?

To establish a cross-national understanding of the burden of multimorbidity, a consistent and comprehensive definition of multimorbidity is needed. Indeed, this need was reflected in the previous two questions and responses in this submission. A study conducted by Harrison et al. (2014) indicated that if only twelve of the most prevalent chronic conditions were measured, the prevalence estimate of multimorbidity defined as 2+ chronic diseases would be significantly lower (two-thirds) than the true estimate when multimorbidity was defined as 3+ chronic diseases. As such, researchers should include as many chronic conditions as possible, while maintaining parsimony in their definition of multimorbidity. Interestingly, this relates to the elusiveness of the clinical definition of multimorbidity. The definition of multimorbidity must have face validity clinically (in a multidisciplinary setting), but then a pragmatic measure should be established by the research community. Indeed, researchers must be pragmatic in the
measurement of multimorbidity as no measure will achieve perfect sensitivity and specificity. Once again, this pragmatic measure must take into account the study context. The priorities for research regarding the prevalence of multimorbidity were the primary focus in this response. The priorities for research regarding burden and determinants require a more extensive response and are not included in this submission.

**Prevalence:** Ideally, the conditions or diseases in the selected measure of multimorbidity should be accessible and assessed across different datasets and different geographic locations. Moving beyond the conduct of consistent research studies, valid comparisons of multimorbidity require specific criteria made explicit in publications. According to Stewart et al. (2013), the criteria for comparability of multimorbidity studies include commonality in: 1) the definition of multimorbidity; 2) the definition of chronicity; 3) the level at which chronic diseases are defined (e.g., transient ischemic heart attack or cerebrovascular disease; split or lumped); 4) the list of chronic diseases that will be considered; and 5) the study population and data source being used (e.g., clinical, administrative or survey data).

1. **The definition of multimorbidity.** This refers to the number of conditions required for a participant or patient to have multimorbidity (2+ or 3+ chronic conditions). As discussed above, the estimated prevalence found using 2+ chronic conditions is significantly higher than that found using 3+ chronic conditions. To ensure comparability across studies that have been published to date, and future studies, researchers should report prevalence estimates using both definitions.

2. **The definition of chronicity.** This refers to firstly whether only chronic conditions are being included and secondly, if it is only chronic conditions, how ‘chronic’ is defined. Much of the multimorbidity literature to date has focused on the study of multiple ‘chronic’ conditions. However, this inclusion criterion is still being debated. As mentioned above, the addition of an acute or cyclic condition can increase the complexity of a patient’s care; this situation would be important to account for from the clinical and patient perspectives. From an epidemiological or methodological perspective, when measuring the prevalence of multimorbidity, chronic conditions are considered to be most important due to their long-term nature. There are two major ways in which stakeholders can decide whether a condition is “chronic” or not. The first approach is that conditions can be selected from a list of defined chronic conditions, either drawn up by the researcher team or using an already
published and internationally recognised list (such as O’Halloran et al., 2004). The second approach is to have a clinician, or team of clinicians using a Delphi technique, decide whether a particular condition is chronic or not using a predefined set of criteria (e.g., expected to last longer than six months). The advantage of the first approach is that the results are more easily standardized and reproducible, which allows for comparison with other studies that has utilized the same approach. However, the advantage of having a clinician decide on the final list of conditions or diseases to include is that it moves more toward capturing multimorbidity in the relevant context (e.g., the clinician may identify a condition that is missed by a pre-established list).

3. **The level at which chronic diseases are defined.** Traditionally, the disease entities that were counted when measuring multimorbidity were discrete, individual chronic conditions. One of the issues though is how to count very similar chronic conditions or the sequelae of chronic conditions. Some clinicians or researchers may consider them to be one condition while other clinicians or researchers may consider them to be two separate conditions. A similar issue would be conditions that evolve over time, receiving a different code in the medical record as the disease progresses. A simple review of the medical record by a program may count the disease as two conditions, when it is really just one condition. To avoid this from occurring, care is required by the researchers, but this technique has limitations in large secondary datasets. Some multimorbidity researchers have instead counted ‘groups’ or ‘clusters’ of like conditions. Grouping like conditions has the advantage of only counting the conditions once in both examples provided above, providing consistency in measurement. However, considerable care is needed to appropriately group these conditions together and to not apply subjective labels to these similar clusters. This is often done using methodological approaches such as latent growth curve analysis and exploratory factor analysis. Examples of more conservative approaches to counting clusters are the grouping of Cumulative Illness Rating Scale (CIRS) domains or the chapters of the ICD-9 or ICPC-2 classification systems.

4. **The list of chronic diseases that will be considered.** As discussed above, the number of conditions or groups of conditions that are considered in the definition of multimorbidity can significantly affect the eventual prevalence estimates. The combination of differences between definitions, as well as the differences between
datasets and research contexts creates a muddled understanding of multimorbidity. A measurement of multimorbidity that allows for more comprehensive and consistent assessment of multimorbidity, regardless of research context and maintaining parsimony, will be crucial to clarifying the multimorbidity puzzle.

5. **The study population and data source being used (e.g., clinical, administrative or survey data).** Comparisons across contexts (with a similar data source or similar study population) will be particularly important in determining a more comprehensive understanding of multimorbidity where it exists: in primary health care, hospitals and in the community. For example, the picture of multimorbidity from a clinical population sampled from a primary health care context will be much different than the picture of multimorbidity from a hospital-based population sampled from a hospital context (that is, the multimorbidity prevalence will be high in primary health care, and even higher in hospitals). Although this can be assumed in cross-national studies, this comparison has yet to be confirmed. Likewise, the outcomes of this multimorbidity burden have not been consistently explored across data sources and contexts. Comparing studies that have the first four criteria in common, but differ on the final criteria, will demonstrate how large this different population effect size is and how the pictures of multimorbidity differ.

10. **What should be the strategic response of both national and international research funders and agencies are to multimorbidity?**

The authors advocate for three strategic responses of national and international research funders to appropriately respond to the challenge of multimorbidity. Ultimately, this response should acknowledge both the methodological groundwork that is required to define and measure multimorbidity, as well as the need to allow for pragmatic, patient-centred, innovative and adaptable approaches to multimorbidity. This will not only move the research field forward, but a comprehensive understanding of what causes (and almost more importantly, prevents) multimorbidity is essential to advancing the care for this growing population. The strategic response must happen swiftly, and efficiently, to create solutions as soon as possible.

1. **More uniform operationalization of multimorbidity across study contexts.** As stated in this submission, a measure of multimorbidity that is comprehensive, valid and
associated with relevant outcomes should be selected by experts in multimorbidity care and research, with input from the patient perspective. This will help to facilitate common ground between the (multidisciplinary) clinical and research community, as well as the incorporation of the patient voice and achieving a patient-centred measurement of multimorbidity. Once selected, this measure should be consistently compared across national and international research agencies. The national and international research funders can support a more uniform operationalization of multimorbidity (with adaptations to study context as needed) that will assist in creating more comparable estimates of multimorbidity prevalence in the literature. This will also lead to a more comparable understanding of the impact and outcomes of multimorbidity. Indeed, this is the first step to fully characterizing this global health issue.

2. **Longitudinal and holistic data collection from participants and patients across the life course.** Increasingly, research is indicating that multimorbidity is not only a concern for the oldest old. In fact, multimorbidity prevalence is increasing (and often more dominant) among those who are 65 years of age and younger. The national and international research funders can facilitate the creation of cross-national, longitudinal cohorts in the primary health care, hospital and community-based populations. To do so, communication must occur among key and global research teams. This concerted effort must be facilitated by national and international research funders, and would be a key step forward into an exciting and united era of research. Importantly, a longitudinal and holistic data collection process should be conducted to determine how individuals accumulate multiple conditions or diseases, in varying contexts and considering all elements of life (that is, the burden and determinants described in the previous response). While this information will first be used to understand the incidence of multimorbidity, this fully comprehensive dataset can also be used to understand the prevention of multimorbidity and to help individuals maintain health as they age, globally.

3. **Determine the relation between multimorbidity and patient-relevant outcomes.** Ultimately, the study of multimorbidity should be conducted to improve the quality of life of those who are living with multimorbidity. Moving beyond understanding the prevalence of multimorbidity, research must then specifically understand what living with multimorbidity means for patients to inform the current efforts. Currently, there is a lack of
a multimorbidity-adapted patient-reported outcomes measure. This leads to a high heterogeneity in methodology and measurement in intervention research, creating a gap in the evidence to support clinical application. As such, determining the relation between multimorbidity and patient-relevant outcomes is necessary and again, this would require multimorbidity stakeholders to agree on a core set of outcome types and instruments. Moreover, because of the wide range of potential diseases considered in the pragmatic definition of multimorbidity, efforts must be focused on proposing a way to adapt outcomes that are not only clinically and methodologically relevant, but patient-relevant as well.

**Key References**


