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POSTER EXTRACTS

Report on the Joint Workshop on the Relations between Health Inequalities, Ageing and Multimorbidity, Iceland, May 3–4, 2023

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Abstract: This paper is a summary of key presentations from a workshop in Iceland on May 3–4, 2023 arranged by Aarhus University and with participation of the below-mentioned scientists.

Below you will find the key messages from the presentations made by:

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- Professor, Chair Henrik Toft Sørensen, Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Denmark
- Professor David H. Rehkopf, Director, the Stanford Center for Population Health Sciences, Stanford University, CA., US
- Professor Jaimie Gradus, Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, US
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1. Advancing Research to Tackle the Relations between Health Inequalities, Ageing and Multimorbidity

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Longer human lives have led to a global burden of late life disease.[1] Therefore more and more people across the globe are suffering from multiple long-term conditions - also called multimorbidity - making this an important clinical challenge for patients and health care providers. While the risk of multimorbidity increases with age, multimorbidity

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is also a common concern in children and younger adults. Decades of research has demonstrated that both chronic and communicable diseases affect low-income populations disproportionally.[2] It is well-known that health is unevenly distributed within society. Health inequality is associated with socio-economic inequalities: people in lower socio-economic positions live shorter lives, and within those shorter lives, they spend more years with disability and other health problems.[2] Thus, it is likely that people from lower socio-economic classes develop multimorbidity earlier in life.

The co-existence of several chronic diseases leads to major clinical challenges, lack of evidence-based therapy, polypharmacy and iatrogenic harm. Clearly, future research and treatment will not be optimal if focusing only on individual diseases, individual treatment or illness episodes.[3] Moreover, health inequalities have not disappeared with the build-up of the welfare state or free health care.[2] We need to understand how early life health inequalities lead much later in life to differences in morbidity, multi-morbidity in particular.

Infectious diseases are one area in which this layered effect might be very important. From times immemorial, infectious diseases have most often stricken the poorer part of the population – that was the case with ancient Cholera epidemics, and other pestilences. We have witnessed this again during the COVID-19 epidemic: it became clear that several co-morbidities like obesity, diabetes, hypertension, cardiovascular disease, were important determinants of COVID-19 severity and mortality. All of these are linked to health inequalities, and social and economic inequalities.

Denmark has some of the best existing data sources worldwide to identify disease clusters and understand risk and prognostic factors underlying multimorbidity, but there is a need for better definitions, standards, and research methodologies to facilitate multimorbidity research. We need to have a better understanding of the chains of causation. We furthermore need to examine how to analyze key multimorbidity questions and to build up new health data sources and science capabilities.

We need to discuss what exactly is meant by multimorbidity, and how health inequalities are measured and compared. As a first approximation, at younger ages (say, young middle age), multimorbidity is measured by just counting the different diagnosed diseases. However, at older ages, it is not the number of diagnoses anymore that counts, but the overall impact of the several diseases, as measured by a functional score (e.g., capacity to care for oneself). Health inequalities can be measured on a relative and an absolute scale – in terms of increase and decrease of inequalities, the question remains which scale is the most relevant for research and for action. For example, during the COVID-19 discussion it was pointed out in some countries that the increase in mortality was 'proportionally similar' for several socio-economic classes and/or income categories. A proportional increase looks like a maintenance of the 'status quo'. The discussion whether this presents a stronger absolute increase amongst the lower categories quickly can become 'ideological' as it would necessitate extra measures geared towards the lower socioeconomic categories, of which economists might say that the economic yield might be non-optimal.

The aim of the workshop was to discuss these challenges and to provide input for future research direction (See Appendix). In the following the key points from the meeting are presented.

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2. Heterogeneity Approaches applied to Health Inequities and Multimorbidity

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The phenomena of "lumping versus splitting" is a core issue underlying many of the difficult conceptual and analytic decisions that clinical and epidemiological researchers need to make. For a particular situation, the decisions come down to this - is it best to study a phenomenon with broader categories that may be a bit more internally heterogenous, or split into narrower categories that are as homogenous as possible. The dilemma applies to many problems in epidemiology and population health and has been fundamental to science since Linnaeus' classifications of animals and plants.[1]

While a common dilemma, it has become notably vexing for the problems that we are addressing here, health inequities and multimorbidity. In the examination of social inequalities in health, there has been increasing recognition that by lumping together all folks of a certain social class or race, we are missing the ability to truly capture the meaningfulness of that attribute for that person's lived experience in ways that matter for health. While epidemiologists have long examined this sort of issue through effect modification, it has in many cases been an afterthought, and in virtually all cases has not been well powered. Further, it has traditionally been only by one further characteristic, thus not capturing much beyond, say, social class differences by race (missing the important factors of at least gender and age, for example). From a theory driven perspective, recent attention to intersectionality has brought this to the forefront, and epidemiologists have begun to try to put this in to practice, despite some confusion over whether a method could be intersectional (it cannot be, just as methods themselves cannot be causal, they can only contribute to intersectional understanding).[2] But so far, there are few arguments against the need for more prominent intersectional considerations in public health.[3–5] With multimorbidity, the challenges are also clear. There are hundreds of unique clinical conditions, and many individuals have greater than three or four, resulting in incredible potential dimensionality of types of morbidity. Is the best way to characterize this by something lumpy like three latent factors,[6] or something much more complex and specific and splitty.

These are not new questions at all, they have been around since the beginning of epidemiology, but it seems that these questions are beginning to emerge as more important given theoretical and empirical work in intersectionality and the increasing prevalence of comorbid conditions associated with aging populations. There are two developments that should be explored that give us the possibility of understanding what level of lumping or splitting is optimal for improving health equity and population health.

The first is the opportunity to do analyses on large samples of data. This revolutionized genetic analyses,[7] and it could do the same for health equity and multimorbidity. Prior work, for example, regarding intersectionality between race and class, showed very few interactions across a systematic search, even in a large population based set of data.[8] It is perhaps only through large national registers, such as those that exist in Denmark, or through large initiatives to harmonize EHR datasets,[9] or from clinical care registries,[10] that we actually can find clusters of characteristics that are not primarily due to noise, whether those clusters are capturing power differentials in society, or characterizing chronic disease.

Secondly, there has been tremendous advances in data driven methods to identify subgroups of characteristics relevant to predicting a particular outcome. While developed primarily in computer science, political science and economics,[11] these methods are now reaching into epidemiology,[12] with applications to exposures related to health equity in particular.[13] Fundamentally this is not a different concept than effect modification, the main difference is that this new suite of methods are meant to search across a large number of potential effect modifiers to find the ones that matter most for predicting an outcome. A second difference with most typical epidemiologic approaches to effect modification is that the data driven methods in some cases allow and test for higher order interactions of 3 or more factors. These methods are primarily applied in descriptive approaches, but can be used for causal inference if used with an appropriate study design.[14] Like all data driven approaches, choice of both the method and the potential heterogeneity variables involves theory and investigator choice, driven by the research question. While often characterized pejoratively as a fishing expedition, one must choose what body of water to fish in, whether to fish from shore or from a boat, and what kind of lure or bait to use, decisions that will ultimately have an impact on what type of fish one will catch.

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3. Exploring the complexities of health inequities, multimorbidity, and aging

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As the world's population ages, clinicians, researchers, and policymakers are faced with addressing new and expanding combinations of diseases and disorders (i.e., multimorbidity) that accumulate with age. According to the World Health Organization (WHO), countries across the globe are already and will continue to face major challenges in the effort to accommodate this shift in population demographics.[1] In addition to expanding knowledge about the complex healthcare needs of an aging population, and the clinical capacity to accommodate such needs, there is also a need to address global social disparities that impact healthy aging.[2] The WHO estimates that by 2050 80% of the world's older population will live in low- to middle-income countries.[1]

The changing age demographics of the world population is already underway, with the rate of aging increasing in compared to the past.[1] It is expected that the proportion of the global population that is over 60 years old will double between the years 2015 and 2050.[1] And while research on aging has also expanding in recent years,[3] the demand for additional high-quality research aimed at understanding aging has been described in the literature as "huge" and includes a better understanding of public health prevention, clinical care, and best practices to address the complex multimorbidity that can occur in later life.[4] There is an urgent need to better understand aging, multimorbidity, and the effects of health inequities on both, to align with the population changes that are already underway.

While numerous types of research are likely needed to fully address these issues (e.g., randomized clinical trials of new treatments for comorbid conditions, research on policies that may improve healthcare access for older persons), one way to inform understanding efficiently and rapidly is through epidemiologic research that uses existing healthcare registries based on electronic medical record data. Several such registries exist in various countries throughout the world, including Medicare data and various sources specific to health insurance companies (e.g., Kaiser Permanente) in the United States. The Scandinavian countries are also known for their extensive healthcare record keeping systems, that have resulted in registries containing decades of population-level data that can be used for health research. In particular, the Danish national healthcare and social registries have been called "An Epidemiologist's Dream"[5] because healthcare and social data can be used for research from residents of the whole country and the country can be considered a single research cohort.[6] Importantly, while healthcare registries like those found in the United States and Scandinavia confer an

ability to examine health inequalities within those countries, comparable registries in lower- or middle-income countries that would allow for an ability to examine global health inequities are less common, highlighting an important disparity in existing research resources that form the basis of knowledge. Efforts are underway to address this disparity, however, with the WHO estimating in the last decade that 114 countries were working on implementing national electronic medical record systems, with many lower- and middle-income countries included.[7]

The benefits of using such registries for epidemiologic research on aging, multimorbidity, and health inequalities can be broadly described as two-fold. The existence of population-wide healthcare and social registry data over decades allows for the efficient examination of existing theories about aging processes, the development of disease and multimorbidity, and how social inequities impact both. In addition, such rich data provide for the ability to discover new information on these topics, particularly through the use of data-driven statistical methods such has machine learning, which has been widely adopted across areas of health research in recent years.[8]

By way of example, our team at Aarhus University in Denmark, and Boston University School of Public Health in the United States, has conducted numerous studies that highlight the ability to use existing Danish national health and social registry data specifically for data-driven explorations of multimorbidity and studies of health inequities. We have published data-derived combinations of health and social risk factors that predict death from suicide[9] and non-fatal suicide attempt,[10] data-derived combinations of diagnoses that are most likely to occur in the years following traumatic experiences,[11] data-derived combinations of pre-trauma social and health factors that predict poor outcomes following trauma,[12] and examinations of the differential risk of psychopathology following trauma among immigrants to Denmark as compared with native-born Danes.[13] These examples represent only a very small portion of the true potential for these data sources to contribute epidemiologic knowledge to our understanding of multimorbidity. Further research that applies data-driven methods to data sources such as these, and purposefully includes examinations of health inequities and aging, is warranted. The expansion of registries such as these to other lower- and middle-income countries through the development of electronic medical records systems will also be a crucial improvement to the landscape of research and knowledge in these areas.

In sum, as the world's population ages, there is a need for research to rapidly address multimorbidity and the impact of health inequities among older persons. Within epidemiologic research specifically, there is an opportunity to use existing and developing healthcare and social registry data to efficiently examine current theories, and to apply data-driven approaches to discover new knowledge and augment existing theories about aging, multimorbidity, and disparities.

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4. Reflections on Multimorbidity and Social Inequality

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Any discussion on the relationship between multimorbidity and social inequality should begin with a clarification of what we mean by these two terms. For both, there has been a lot of discussion in the international scientific literature, and my impression is that there is more consensus on how social inequality should be conceptualized and measured, than on how multimorbidity is to be conceptualized and measured. In a rapid exploration of the literature on multimorbidity I encountered many unresolved issues.[1] One possibility is to define multimorbidity as the co-existence of two active health problems in the same individual – or should it be more than two, counting active health problems in different body systems only? Many studies take a pragmatic approach, using a predetermined list of conditions to count, and the differences between these lists clearly illustrate the lack of consensus on how to measure multimorbidity.[2]

Despite these problems, there is a clear consensus in the literature that the prevalence of multimorbidity is higher in lower than in higher socioeconomic groups, with socioeconomic position measured in a variety of ways, e.g., as one's level of education or income, or as level of deprivation of one's neighborhood.[3] Beyond this general conclusion, however, a lot is still unclear. How large are these inequalities? Are they found everywhere and to the same extent? Are there particular combinations of conditions that are found more frequently in lower socioeconomic groups, or is this a generalized and diffuse phenomenon?

The fact that there is more multimorbidity in lower socioeconomic groups is not very surprising, because it is easy to see that there are four mechanisms causing another health problem to occur in a person who has already developed one, and all four work together to produce more multimorbidity among people with a lower socioeconomic position. These four mechanisms are: (1) Random co-occurrence of health problems, (2) One health problem causing another health problem (as in the case of diabetes causing heart disease), (3) Several health problems sharing the same risk factor (as in the case of lung cancer and COPD occurring together because of a common link to smoking), (4) Several risk factors sharing the same social background (as in the case of smoking and psychosocial stress occurring together because of a common link to low income).[4] To which extent each of these four mechanisms plays a role has, however, not yet been established.

Although the higher prevalence of multimorbidity in lower socioeconomic groups is perhaps unsurprising from a scientific point of view, it is potentially relevant from a practical point of view, because it may have important consequences. It may lead to two problems: (1) Because patients from lower socioeconomic groups have more multimorbidity than patients from higher socioeconomic groups, they have greater care needs, and probably have worse medical prognosis in terms of recovery and risks of lasting disability or even case fatality. It is well-known that the medical prognosis of patients from lower socioeconomic groups is usually worse than that of patients from higher socioeconomic groups, and multimorbidity is likely to be one of the explanations.[5] (2) Because patients from lower socioeconomic groups have more multimorbidity than patients from higher socioeconomic groups, they may also have worse 'social prognosis' in terms of, e.g., educational achievement and likelihood of losing their job. This will then strengthen the negative feedback loop from social disadvantage to health problems to social disadvantage.[6] As far as I can see, neither of these two consequences of more multimorbidity in lower socioeconomic groups has been studied in any depth.

This brings me to my four priorities for research on the relationship between multimorbidity and social inequality:

1. More descriptive studies of socioeconomic inequalities in the occurrence of multimorbidity, aiming at more precise quantification and at establishing whether there are any variations, e.g., between countries in the magnitude of the problem.

2. Studies measuring the consequences of the higher prevalence of multimorbidity in lower socioeconomic groups, both in medical terms (e.g., assessing the quantitative contribution of multimorbidity for higher case fatality in lower socioeconomic groups) and in social terms (e.g., assessing the quantitative contribution of multimorbidity for higher risks of job loss in lower socioeconomic groups).
3. Studies aiming at finding entry-points for prevention of multimorbidity in lower socioeconomic groups. Which of the four mechanisms play a role, and can one identify 'actionable nodes' which produce a lot of multimorbidity and can be addressed with prevention programs?
4. Studies aiming at finding entry-points for improving medical and social outcomes of multimorbidity in lower socioeconomic groups. Can better medical treatments and social programs be developed, and does the implementation of those improvements lead to better outcomes?

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5. The Relevance of Multimorbidity for Research on Social Inequalities in Healthy Aging

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Multimorbidity can be considered as either an outcome or an exposure of interest in health equity research. As an outcome, multimorbidity may be useful for health equity research as a simple approach to characterize the extensive and diverse health consequences of social disadvantage. The tradition of focusing on specific diseases or organ systems has long been considered a barrier to recognizing the importance of social determinants of health. Considering individual outcomes one-by-one systematically understates the total health impact of social determinants. A central premise of social epidemiology is that social resources are flexibly deployed to address whatever health challenge arises for an individual.[1,2] As a result, any particular social resource is often associated with numerous health outcomes. In fact, it is an unusual health outcome that does not manifest a social gradient. The COVID-19 pandemic illustrated how quickly social advantages become relevant to protect against novel emerging threats to health: within months of the first documented cases, major social inequalities in COVID-19 mortality had already emerged.[3,4] These inequalities persisted through subsequent years even as we learned more about the disease and developed effective preventive and treatment approaches.

Because social factors predict so many conditions, they will certainly also predict multimorbidity. Consider two completely unrelated conditions which each occur in 5% of high socioeconomic status individuals but 10% of low socioeconomic status individuals, so for both conditions the risk ratio associated with low socioeconomic status is 2. Even if the two conditions were completely independent, the conditions would co-occur in 0.25% of high socioeconomic individuals and 1% of low socioeconomic status individuals, resulting in a risk ratio for co-occurrence of 4 associated with low socioeconomic status. Thus, relative inequalities in multimorbidity would oftenbe much larger than inequalities

in single conditions. There is some hope that elevating multimorbidity as an outcome may help achieve a correct accounting of the scope and magnitude of the influence of social determinants on health. A more comprehensive tally of the total impact of social determinants of health across multiple disease outcomes might help motivate greater attention to alleviating social risk factors.

This approach, if pursued, faces several conceptual challenges, however. First, a nuanced characterization of multimorbidity and consensus on optimal measurements is needed. A recent review of 566 studies measuring multimorbidity noted that over a third of studies offered no reference definition of multimorbidity and the number of conditions considered ranged from 2 to 285, with a median of 17.[5] Only eight conditions (diabetes, stroke, cancer, chronic obstructive pulmonary disease, hypertension, coronary heart disease, chronic renal disease, and heart disease) were included in more than half of the studies. Variations in the number of conditions included lead to major differences in prevalence. An evaluation of English primary care data defining multimorbidity as more than 1 condition found a prevalence of under 5% when considering only the 2 most common conditions, 35% considering the 20 most common, and 41% when considering the 80 most common conditions.[6] Comparisons across definitions of multimorbidity demonstrated that the degree of socioeconomic inequality varies based on the number of conditions required to meet the criteria.[7]

Roughly two-thirds of prior studies of multimorbidity used a simple count of conditions to measure multimorbidity.[5] All diseases are not equal, however, and a reasonable characterization of multimorbidity would requires a thoughtful weighting across conditions and possibly multiple distinct clusters of comorbid conditions. Many multimorbidity measures now adopt weights, often estimated from regression coefficients for each morbidity predicting some validation outcome. Although in theory weights are likely to vary across populations, empirical work comparing weights derived from different US samples deliver strongly correlated multimorbidity measures.[8] The theoretical justification for using regression coefficients as weights is unclear however and thus the preferred regression specification is also unclear. Prior work shows that socioeconomic disparities in multimorbidity were evident among UK 1946 birth cohort study participants by age 35 and grew with time.[9] Typical measures of multimorbidity do not account for the sequencing of disease accumulation across the lifecourse, however. Developing hypertension at age 30 may have entirely different long-term health consequences than developing hypertension at age 60. Social factors not only influence cumulative lifetime risk of developing a disease, but frequently lead to earlier age-of-onset. Most multimorbidity definitions do not accommodate these nuances and instead provide cross-sectional snapshots of current diagnoses.

Further, typical operationalizations of multimorbidity do not recognize the influence of one condition on another (hypertension increasing risk of stroke, for example) or even the sequencing of occurrence. Understanding the sequencing of events is critical to establish the causal mechanisms and therefore to outline potential interventions. For example, depression and stroke commonly co-occur. This co-occurrence would increase a typical multimorbidity score by two points. However, those two points may represent myriad substantively distinct clinical scenarios. Depression may have contributed to the incidence of stroke via for example chronic disease management or changes in smoking patterns. Alternatively, the stroke and subsequent disability may have caused depression. Finally, cerebrovascular pathology may have led to both depression and stroke.[10] Disentangling the sequencing of depression and stroke would have critical implications for appropriate responses for both an individual patient and population health initiatives. By blurring the sequencing, typical multimorbidity measures obscure critical causal processes.

These limitations of multimorbidity measures for epidemiologic research could be overcome, for example incorporating detailed weights into contributing conditions and developing clusters of comorbidities based on physiologic links and sequencing. Research moving in this direction is being published and major administrative data sets such as Danish health registry have already proven invaluable for such efforts.[11] Approaches considering how conditions occur in clusters and over time, and approaches such as outcome-wide-association studies[12] may prove more promising than simple multimorbidity measures for capturing the widespread health consequences of socioeconomic disadvantage.

The concept of multimorbidity may be of more immediate practical use when conceptualized as an exposure or modifier of other exposures' influence on disability, quality of life, or mortality. The prevalence of multimorbidity is relevant for not only the organization of clinical care but for strategies to improve population health and health equity. For example, multimorbidity may render care strategies focused on a single condition ineffective for improving overall

health. Disability and mortality may be overdetermined by the co-occurrence of multiple conditions, each of which would be sufficient alone to cause disability or death. Because multimorbidity is especially common among people from socially disadvantaged groups, ignoring the importance of multimorbidity may further exacerbate health disparities. Both therapeutic and preventive strategies may be more successful when considering multiple domains of health or potential diseases.

For this research agenda, large health care registries with comprehensive follow-up across the lifecourse will be extremely valuable. A key question with such registries is the extent to which they can offer insight into processes of inequality and strategies to improve health equity. Many such large databases arise for populations with overall excellent quality and continuity of care – including Northern European health care data and large comprehensive care organizations in the United States. Health inequalities are remarkably pervasive: even in relatively well-resourced settings, inequities emerge.[13,14] Further, access to medical care is not the key driver of health inequality. These observations provide reason to think that studies of such large data resources may offer important and generalizable insights. Indeed, intriguing research on inequalities has emerged from Danish registry linkages.[15] However, all countries have distinctive cultural and social phenomena that may diverge from international patterns. An evidence base evaluating the ways in which Denmark is a microcosm of the world versus a place apart – with entirely different processes driving population health patterns – would lay the groundwork for a host of informative inequality-focused research projects in Danish registry data. Such evidence might take advantage of harmonized cross-national studies, for example the Study of Health, Ageing, and Retirement in Europe (SHARE), which has harmonized socioeconomic and health measures selected to facilitate comparisons with the US Health and Retirement Study and a network of international studies in many other low, middle, and high-income countries.[16] Because Denmark is represented in SHARE, it provides a simple platform to crosswalk from the Danish setting to patterns in numerous other countries.

Measuring multimorbidity may be useful for understanding the scope of socioeconomic health inequalities and identifying opportunities to eliminate such inequalities in older adults. Research attention should focus on opportunities for new insights about disease prevention or mechanisms that might be gained from multimorbidity studies, rather than documenting epidemiologic patterns that are inevitable consequences of very well-established social patterning of individual diagnoses. Very large administrative data sets that allow more detailed exploration of the timing, clustering, and social patterning of multiple health conditions may allow such new insights. As a foundation for this research, we need careful cross-national comparisons to establish the boundaries of generalizability of research from such administrative data and enriched theoretical and statistical approaches to characterizing multimorbidity.

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6. The Central Role of Social Determinants in Determining Health Inequities and Multimorbidity across the Lifecourse

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Understanding the intersection of health inequities, multimorbidity, and aging can be helped by clarity in our thinking around the foundational role played by social determinants over the lifecourse in the production of health.

Data about health inequities worldwide are incontrovertible. There are substantial differences in health achievement across countries and within countries.[1] While there is little question that some health variation is the product of unavoidable biological and genetic factors, there is broad academic consensus that health gaps are driven primarily by exogenous factors that produce health at multiple stages throughout the lifecourse.[2] These factors, often referred to as the "social determinants of health" represent the set of circumstances that shape our lived experience. These include, for example, the characteristics of places where we live, the quality of the food we eat, whether we have enough wealth and income to afford health-producing resources, whether we are exposed to risk of violence, the quality of the air around us, and the presence of structural racism.[3] The recognition that features of the world around us produce health points to an explicit link between our exposure to these determinants and health inequities. Persons with more access to positive determinants are healthier and live longer than those persons with less access to these positive determinants. This observation, while obvious at one level, also has profound implications for how we think about the production of health inequities. Once we understand that differential access to wealth, for example, is associated with differential health achievement,[4] it becomes clear that it is the remit of health scholarship to also understand wealth, and that not doing so will limit how far we can improve health and narrow health gaps. The radical proposition becomes that we cannot successfully remove health gaps unless we also remove gaps in access to the positive determinants of health, making the work of population health scientists expansive in scope. Therefore, an understanding of the social determinants of health, as summarized in any number of conceptual frameworks,[5] becomes central to our understanding of the production of health and must be part of thinking about health inequities and multi-morbidity over the lifecourse.

Thinking about the lifecourse is perhaps the second most important perspective that we can bring to a full understanding of the production of health.[6] When viewed through a curative medical lens, health often presents as disease at a particular point in time. A 60-year-old presents with an occluded left anterior descending coronary artery which results in a cardiac arrest. That presentation suggests a biomedical cause—arterial occlusion—that is present, and needs cure, in the moment. While that lens is an essential element of the work of health—and the foundational role of clinical medicine—it obscures the foundational causes of the disease in the 60-year-old, and those foundational causes, with few exceptions, are in the person's exposure to the social determinants throughout their life. Therefore, the 60-year-old with the coronary artery occlusion arrived there through early childhood limited education, subsequent inadequate income, poor dietary choices, limited opportunity for exercise, all of which contributed to their eventual cardiac arrest. This suggests that the role of social determinants is best understood across the lifecourse, wherein careful analysis can illustrate at which stages of life persons are exposed to adverse social factors that eventually become poor health. This combination of a social determinants and a lifecourse perspective both explains aggregate health as well as health inequities. Just as the risk of coronary artery disease in the 60-year-old discussed here can be traced to their exposure to

social factors at different life stages, the absence of the same disease in another 60-year-old can be largely traced to their exposure to more salutary social factors. Hence, health inequities at age 60 are a product of differential exposure to social determinants at multiple stages during the lifecourse. This suggests that it is difficult, and perhaps counterproductive, to consider the role of aging without seeing aging as one particular time period in the full lifecourse. We know that diseases typically associated with aging—e.g., cardiovascular, pulmonary, neurological—are associated with earlier-in-life factors.[7–11] The patterning of exposure to those factors is then socially determined, making an understanding of inequities in health in the latter part of the lifecourse (i.e., in aging populations) as much a product of differential access to salutary social factors as is our understanding of health inequities at any other part of the lifecourse.

Multi-morbidity, or the co-occurrence of symptoms and diseases across established diagnostic criteria, is a particularly apposite area of scholarship for social determinants and lifecourse production lenses of understanding. Foundational social determinants of health seldom affect single diseases. For example, limited access to wealth that narrows dietary choices, resulting in poorer diets, leads to cardiovascular disease, respiratory disease, and in time, increases risk of dementias.[12–14] Similarly, exposure to traumas and violence has been linked to post-traumatic psychiatric disorders, and also to diabetes, hypertension, and immune dysregulation. Therefore, understanding social determinants offers a unifying lens on the co-occurrence of disease at all stages of the lifecourse, including during aging. This explains the prevalence of, and importance of, multi-morbidity in the study of health inequities. Persons who are exposed to adverse social circumstances throughout the lifecourse are more likely to manifest a broad range of poor health conditions, with co-occurring pathologies and multi-morbidity, compared to persons who have access to positive social determinants. This underscores that we cannot understand inequities in multi-morbidities without also understanding the inequitable distribution of the foundational exposures that result in these inequities. In many ways it is "far too late" to start this consideration through the lens of aging. The production of these inequities happens throughout life and must be considered as such. This can lead to etiologic insights that can point to interventions, with the hope that this can lead to longer lives, and healthier aging.

Considered this way, the study of social determinants, lifecourse production of health, and multimorbidity are central to our understanding of health inequities. This suggests that scholarship at the interstices of these areas may be productive and a priority for scholars interested in a consequential population health science.

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7. Multimorbidity, Health Inequalities, and Dementia

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Multimorbidity refers to co-occurring conditions in the same person of more-or-less equal importance,[1] and dementia is perhaps the paradigmatic multimorbid disorder. The related concept of comorbidity is also germane to dementia, wherein a co-occurring condition modifies the impact of a primary condition.[1]

Dementia represents the loss of memory or other mental ability severe enough to interfere with independence in everyday activities. It is an age-related disorder, whose prevalence and incidence double about every five to six years after age 60 years, at least until the tenth decade of life. It is a leading cause of disability. The global prevalence of dementia, estimated at about 57 million people in 2019, is projected to exceed 150 million by 2050.[2] Worldwide, Alzheimer's disease and other dementias are the second leading cause of neurological death after stroke[3] and the seventh leading cause of death overall.[4]

Alzheimer's disease is the most common cause of dementia.[5] At the microscopic level, it is characterized by neuritic plaques and neurofibrillary tangles in vulnerable regions of the brain, and at the biochemical level by the accumulation of two abnormal proteins: amyloid-beta and hyperphosphorylated tau.[6] Other causes of dementia have different, distinct microscopic and biochemical features. Clinical manifestations can differ as well.

In early-onset disease, i.e., when dementia symptoms appear before age 60 years, the plaque and tangle pathology of Alzheimer's disease can occur in isolation, but in later life multiple neurodegenerative and vascular pathologies are the rule rather than the exception.[7] These other pathologies include Lewy bodies (found in Parkinson's disease and dementia with Lewy bodies), TAR DNA-binding protein-43 inclusions (associated with hippocampal sclerosis and a form of frontotemporal dementia), and pathologies linked to vascular disease in the brain. In a US autopsy study of more than 500 older people (mean age 90 years) with and without dementia, 69% of brains met criteria for the pathological diagnosis of Alzheimer's disease, but stroke, other forms of vascular disease, hippocampal sclerosis or TAR DNA-binding protein-43 pathology, and Lewy body pathology were also common.[8] Alzheimer pathology was nearly 12 times more likely to be accompanied by at least one of these pathologies than to occur alone.

The clear inference is that late-onset dementia is a multimorbid disorder in which the pathology of Alzheimer's disease may predominate but infrequently occurs in isolation. Each dementia morbidity on its own has the potential to impair cognition, and each is characterized by a unique profile of predisposing genetic and non-genetic factors. Although there is some controversy, the effect of multiple pathologies on cognitive impairment is usually interpreted as additive rather than synergistic.

Comorbidity in dementia

Many medical and psychiatric disorders are linked to risks of Alzheimer's disease or all-cause dementia. Examples of common comorbid conditions include diabetes, heart failure, visual impairment, kidney disease, depression, and stress disorders.[9–14] In most instances, it is not known whether the effect of a particular comorbid condition is in causal pathways that culminate in a dementia pathology, e.g., the abnormal accumulation of amyloid and tau proteins.

Other factors linked to dementia

Socioeconomic status, environmental exposures, and lifestyle practices are associated with dementia risk. Socioeconomic status —reflected by educational attainment, wealth and income, housing, occupation, and avocational activities — is related to a variety of health outcomes, including dementia.[15] Environmental exposures such as air pollution may play roles,[16] as might lifestyle practices such as sedentary behavior, unhealthy dietary choices, heavy alcohol use, smoking, and poor sleep hygiene.[17,18] The impact of these exposures over the life course is difficult to quantify, but there are potential effects on the initiation and progression of dementia pathologies and on resilience in the setting of these pathologies. Further, socioeconomic status affects the detection and diagnosis of dementia and the access to treatment and supportive services.[19,20]

Social gradient

Each of these factors – socioeconomic, environmental, and behavioral — has a social gradient. Gradients are manifest in comorbidity burden and perhaps in dementia pathologies themselves. They often find greater expression in minority or minoritized populations.[21] For example, neighborhood disadvantage, defined by a paucity of economic and social resources and by unhealthy environmental exposures, is associated with postmortem amyloid plaque and neurofibrillary tangle burden.[22]

Perspective

Multimorbidity is a common feature of chronic conditions of old age, and late-onset dementia is almost always a multimorbid disorder. Alzheimer's disease is important and common, but the cognitive impairment of plaque and tangle pathology usually emerges in the presence of other dementia pathologies. To varying extents, comorbid disease, socioeconomic factors, environmental exposures, and lifestyle practices may contribute to disease pathogenesis, clinical manifestations, and disease progression. These risk factors affect populations differently, with burdens weighing most heavily on disadvantaged groups. Effective approaches to treatment and prevention will need to consider the unequal distribution of these factors over the life course and the disadvantaged populations most affected. In future research, it will also be important to continue the search for new factors that impart risk and benefit and to devise interventions to reduce adverse exposures and mitigate harmful effects. Effective strategies will be those that address the multimorbid nature of dementia and take into consideration health inequalities and inequities that add to risk, delay diagnosis, and diminish treatment effectiveness.

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