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Understanding Multimorbidities

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Understanding Multimorbidities

Abstract

The prevalence of multimorbidities has and will continue to increase as both the population ages and the number of those who have not died prematurely due to a chronic condition increases. This is indicative of the heterogeneity of the population experiencing an individual condition. The complexity of multimorbidities and the lack of consensus as to how to define and measure them, contribute to the challenges underlying multimorbidity research and treatment. As its prevalence increases, the impact of multimorbidities on the individuals affected and society as a whole, through outcomes such as mortality, disability, frailty, functional decline, and health care costs, need further assessment. This paper focuses on development of an understanding of the underlying concepts involved and its implications on mortality and health care.

Section 1: Understanding Multimorbidities

1.1 WHAT ARE MULTIMORBIDITIES

A significant health concern for those in later life is the simultaneous existence of multiple adverse health conditions (usually at least two such conditions, although some studies have focused on at least three or more conditions). This situation has been referred to as "multimorbidities" or "comorbidities"[1]. This paper focuses on issues associated with multimorbidities.

Conditions in this context are often long-term chronic health conditions that may require ongoing care, with potentially significant adverse impacts on quality of life, reduced physical functioning, increased healthcare need complexity, increased health care costs, and ultimately, death.

Multimorbidities, particularly among older adults, have become more prevalent as mortality rates have decreased and case fatality rates of major chronic conditions have declined, with the consequence of population aging. The various studies referenced in this paper illustrate that the existence of multimorbidities can increase the probability of death compared with having only one condition. Both physical and psychological/mental conditions can be considered, although in many cases in the literature, co-existence of chronic physical conditions have been the focus.

There are many possible conditions that could be separately recognized, resulting in a broad range of morbidities included in the determination of multimorbidities, usually from three to almost 50. Clearly the more morbidity categories are used, the greater the likelihood that two or more of them will be identified for an individual.

The population of the world is ageing rapidly, with a global shift (except in cases of relatively rare pandemics) from communicable, maternal, neonatal and direct nutritional causes of morbidity and mortality toward noncommunicable ones. Ageing is a heterogeneous process[2], with individuals ageing in different ways and rates, depending on their genetic background, behaviors, environmental exposures, and other factors. These factors can lead to various chronic diseases in different ways. In some instances, diseases become more common in older populations, with malignancies such as lung or prostate cancer being examples. In other instances, the disease may have been present for some time but manifests itself with age because of the general senescence of cells in multiple organ systems. An example of this is arthritis and its complications.

With increasing survival into old age, the likelihood of developing multiple chronic diseases naturally increases. A person with a single chronic illness who survives may be more likely in turn to develop additional chronic illnesses, and so on. In addition, certain chronic diseases cluster with others, either because of common risk factors, complications of a primary disease or condition, or other factors such as an increased state of inflammation.

Adverse outcomes related to multimorbidity can occur in addition to what would be expected from the effect of any of the individual conditions and, in some cases, in excess of the summed effect of single conditions, as many chronic diseases interact with and in some cases exacerbate each other, mutually enhancing their adverse effects. In some cases, they ultimately lead to new clinical phenotypes, as well as being at risk for low functional status, fragmentation of care, poor adherence to medical protocol/recommendations due to the risk of interactions,

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[1] *Comorbidity:* the presence of co-existing or additional diseases or conditions with reference to an initial diagnosis or to an index condition that is the subject of study, such as a primary diagnosis of cardiovascular disease, with attendant hypertension and high cholesterol risk factors.
Multimorbidity: the co-occurrence of multiple diseases or adverse medical conditions or body organs within one person, with none of the diseases (or medical conditions or body organs) considered as the index disease.

[2] Some view aging itself as a disease. In this and other papers on multimorbidities, aging is not included as a condition per se.

incompatibility of different treatments, and other negative side-effects. Moreover, multimorbidity mirrors an accelerated global susceptibility and a loss of resilience, both of which are hallmarks of aging.

Three somewhat related concepts need to be kept in mind in defining the extent of ill-health: multimorbidity, frailty, and functional capacity / dependence. These partly overlap, but represent distinct concepts, as illustrated in Figure 1. Which concept is more appropriate to use to assess the level of health of an individual, community or group may depend upon the purpose or anticipated use of data and the availability of data. A brief discussion of these concepts follows:

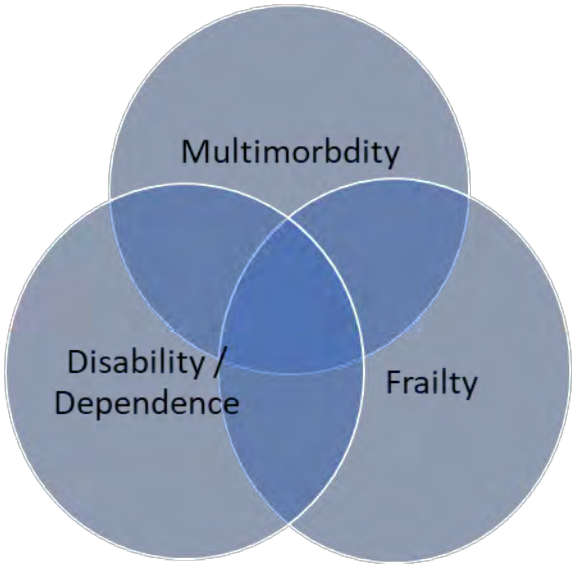
- Multimorbidities. The existence of more than one adverse health condition or disease. They are normally of a long-term chronic nature, and are either physically or mentally based.

- Frailty. A characterization of frailty often has multiple causes and can consist of at least three of the five following elements: weakness (lowest quintile of grip strength), lack of endurance (slowest quintile for slow walking speed), unintentional weight loss (at least ten pounds in one year), self-reported exhaustion, and lowest quintile for physical activity[3]. A pre-frail condition is considered as having one or two of these elements. Frailty and multimorbidity largely overlap – multimorbidity might be considered as the accumulation of clinically relevant biological abnormalities that lead to disease diagnoses. Frailty is often seen as both a predictor and outcome of multimorbidity. The accumulation of chronic diseases may accelerate the development of frailty and vice versa.

- Dependence. The degree of dependence or disability is often characterized by the extent a person cannot perform one or more activities, either relating to daily living or job performance if assessed for an occupational-related purpose. The former characterization is often used to assess the need for long-term care services, while the latter is often used to assess income-related benefits when not able to adequately perform job-related functions.

[3] These are the often-used Cardiovascular Health Study criteria. Alternative definitions of frailty include (1) an increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic reserve and resiliency and (2) a state of high vulnerability for adverse health outcomes.

Figure 1
CORE APPROACHES TO LOOKING AT ILL-HEALTH



Although in general multimorbidities are of greater concern for the elderly, because the general population will always consist of more people who are younger than age 65, there may be more people who suffer from multimorbidities who are younger than age 65. So, medical and other concerns regarding multimorbidities should not solely address the elderly population. Indeed, an increase in multimorbidity prevalence can serve as an early warning tool to identify an overall increase in or susceptibility to future medical issues.

Multiple concurrent conditions or diseases can emerge in an individual for several reasons, including:

- random chance, especially where two diseases are common in a population;
- two diseases that are part of the same disease continuum;
- two diseases that share a common risk factor;
- where the presence of one disease increases the risk of a second disease; and
- two diseases where one disease causes the second disease.

For example, both advanced age and multimorbidity contribute to frailty that in turn confers a higher risk of several complications and poor outcomes such as falls, disability, and hospitalization, leading to dependency, and ultimately, mortality.

As medical science and practice has enhanced the ability of individuals to avoid or delay death, longevity has increased. However, the longer one lives, the more likely one is to incur further chronic disease(s). In addition, while many chronic diseases are ultimately lethal, there may be a long period between onset and consequential death. As a result, a larger share of the population has "recovered from" or "are on their way to" other morbid conditions. Thus, those who live with one or more conditions may have an increased likelihood of living with multiple diseases or conditions that, although not immediately lethal, can lead to increased multimorbidity, either with respect to the number of conditions or their severity. In addition, those with one adverse behavior or condition (e.g., obesity, smoking, lack of physical exercise, hypertension, …) are more likely to be susceptible to other, either related or unrelated conditions. This may be due to a weakened immune system or increased sensitivity to other mortality drivers, such as frailty, lack of mobility, and visual impairment.

In sum, people living with a long-term condition often have multiple, rather than a single condition. Patients with multimorbidity are at higher risk of safety issues for many reasons, including:

- complex disease management regimens;
- demanding self-management regimens and competing priorities;
- polypharmacy, which may lead to poor medication adherence or adverse drug-related events;
- more frequent and complex interactions with health care services, leading to greater susceptibility to failures of effective coordination of care delivery;
- lack of clear communication and patient-centered care due to complex needs;
- greater vulnerability to additional diseases and less resistance to acute health threats (for example, higher susceptibility to infections);
- an increased likelihood of use of or referrals between different care providers, which can increase costs and lead to more fragmented care, possibly compromising patient safety through poor integration of care, and poor coordination; and
- greater vulnerability to safety issues due to poor health, advanced age, cognitive impairment, limited health literacy, and depression or anxiety.

Disease clusters and novel pathobiology mechanisms often occur, a knowledge of which can lead to a better understanding and, possibly, to more effective integrated management. Coexistence of multiple diseases or chronic conditions may not be the result of chance. There is also a need to identify and develop effective management of specific clusters of conditions among individuals with multimorbidity for better overall treatment.

1.2 PREVALENCE

Significant hurdles involved in studying multimorbidities include (1) inconsistent categorization of conditions and diseases included and (2) a dearth of studies covering the effects of particular sets of multimorbidities.

In particular, the number of separate conditions is an important factor; for instance, with the inclusion of obesity as an adverse health category, the percentage of those suffering from multimorbidity significantly increased in many countries. Naturally, the fewer the number of conditions, the lower is the prevalence of multimorbidities. The lack of consensus regarding the number or types of conditions used have resulted in inconsistent reporting across studies.

There is no universally accepted method for its categorization. In addition, some of the measures used that involve the assignment of severity or impact can be ambiguous with categorization being somewhat subjective. Key factors used have included the number and severity of the conditions, partly dependent on the data available. Both the number and severity used may be relevant to the recognition of the expected relative health and ultimately the mortality of those with multimorbidities. A discussion of some of the approaches that have been used is given in the Appendix.

In various studies, three factors have repeatedly been associated with the extent and effects of multimorbidity: age, sex, and socioeconomic status. The importance of these factors can differ depending on the conditions involved, e.g., obesity and cancer. Evidence suggests that the prevalence of multimorbidity will increase over the next several birth cohorts. In addition to age and sex, a number of other significant risk factors are associated with the development of chronic diseases. These include such factors as tobacco smoking and alcohol intake, type and quantity of nutrition, inactivity, level of income and occupational exposures. These factors can contribute to the onset and continuance of multiple diseases.

As morbidities accumulate with age, the number of them with multimorbidities is increasing. For example, in the United States, about eighty percent of Medicare funds are spent on patients with four or more chronic conditions And in the United Kingdom, the population of cancer survivors is growing at a rate of almost 2% per year. [Office of Cancer Survivorship. National Cancer Institute 2011]

As shown in Table 1, the prevalence curve in the Netherlands increases sharply by age. In addition, the number of chronic conditions per person, especially at older ages, is often quite high. Uijen and van de Lisdonk (2008) conducted an observational study using data from the Continuous Morbidity Registration (CMR) Nijmegen in the Netherlands, in which about 13,500 patients participated. To study the distribution of multimorbidity by age, sex, and socioeconomic class, all patients enlisted in the CMR in 2005 were analyzed, the prevalence of multimorbidity from 1985 to 2005 was observed. Those who were at higher ages, females, and low socioeconomic class were associated with an increasing number with multimorbidity. The prevalence of those with chronic diseases doubled between 1985 and 2005. The proportion of patients with four or more chronic diseases almost tripled (2.6% to 7.5%) – in 2005 there was 55% for those aged 75 and older. In contrast, the proportion of patients with one or two chronic diseases was relatively stable over this 20-year time period.

Table 1

PROPORTION OF DUTCH MALES HAVING AT LEAST A GIVEN NUMBER OF CHRONIC CONDITIONS BY AGE CATEGORIES

Ages	At least 3 chronic conditions	At least 4 chronic conditions
45-64	16%	7%
65-74	47	30
75+	73	55

Source: Uijen and van de Lisdonk (2008)

In a study by van Oostrom et al. (2015) of the Dutch population in which overall multimorbidity prevalence rates increased from 34.9% to 41.8% from 2001 to 2011 and from 41.0% to 46.6% from 2004 to 2011, aging explained only part of the increase in multimorbidity. This implies that other factors, such as health care, society-related developments, better detection, and increased self-reporting of conditions may have contributed to the increase in the proportion of diagnosed cases. Age groups over 55 years of age showed the largest increase.

Other studies have shown that multimorbidities can arise at any time during a person's life-course, although the importance of various combinations of conditions differs by age. An example is Canada, where the corresponding proportions of the population having at least four chronic conditions are shown in Table 2.

Table 2

PROPORTION OF THE CANADIAN POPULATION HAVING AT LEAST A GIVEN FOUR CHRONIC CONDITIONS BY AGE CATEGORIES

Ages	Males	Females
18-44	38%	30%
45-64	52	66
65+	83	91

Source: Fontin et al. (2005)

A study of 4,980 from Alberta in Canada (Agborsangaya et al., 2012) found an overall age-adjusted prevalence rate for adults (18+) of 19% (19.2% females and 15.6% males; 7.0% two, 4.3% three, 3.0% four and 3.8% five or more conditions). On an age-sex adjusted basis, this was broken down to 2.4% of those aged 18-24, 9.3% aged 25-44, 25.5% aged 45-64, and 35.8% aged 65+. For those with a household income of less than or equal to C$30,000 prevalence was 28.5%, C$30,000-C$59,000 was 19.4%, and C$60,000-C$99,000 was 11.8%. In this study, the most important predictors of multimorbidity prevalence were age, household income and family structure (not living with children). The most common combinations for three conditions were depression/anxiety, arthritis, and chronic pain; for four conditions were hypertension, depression/anxiety, arthritis, and chronic pain; for five and more conditions were diabetes, hypertension, high cholesterol, arthritis, and chronic pain. Educational attainment was not a strong predictor after adjusting for these other factors.

Prefayo et al. (2015), in a study of the entire Ontario population (using 16 conditions) as shown in Table 3, found that, in the aggregate, multimorbidity prevalence was 17.4% in 2003 and 24.3% in 2009, with similar increases in all age groups. There was no dominant co-occurring condition pattern, with the most common conditions being, in order of commonality, arthritis, hypertension, asthma, depression, diabetes, cancer, and chronic coronary syndrome. Contributing factors included tobacco use, physical inactivity, harmful use of alcohol, and unhealthy diet.

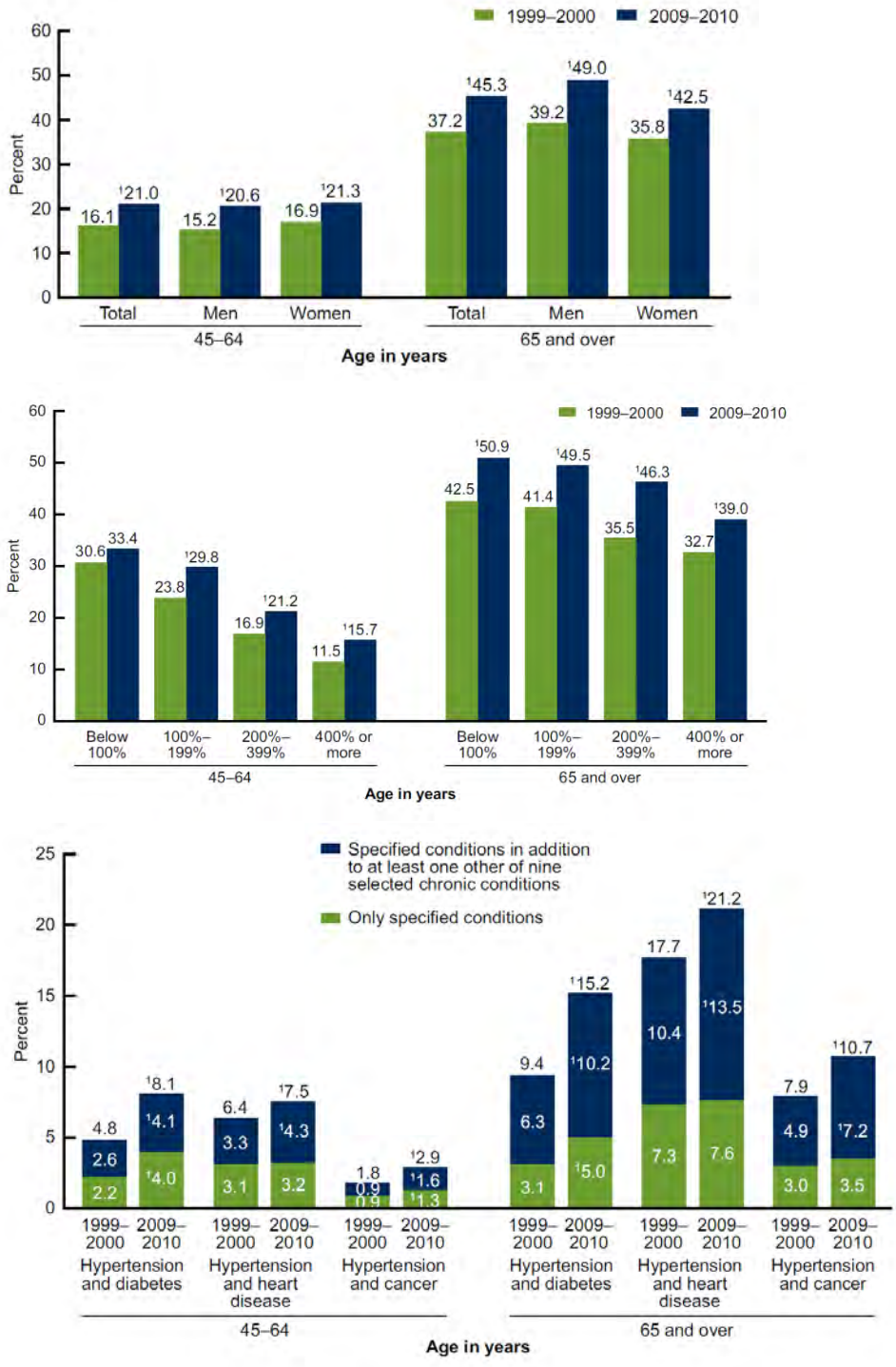
Table 3
MULTIMORBIDITY PREVALENCE RATES IN ONTARIO CANADA IN 2003 AND 2009

Age categories	2+ conditions		5+ conditions	
	2003	2009	2003	2009
0-17	1.4%	2.2%	0.0%	0.0%
18-44	7.4	10.6	0.05	0.1
45-54	20.4	27.4	0.5	1.0
55-64	35.3	46.6	1.8	3.5
65-74	53.6	66.4	5.1	9.2
75-89	68.3	80.9	11.0	20.9
90+	74.6	83.2	14.8	27.8

Source: Prefayo et al. (2015As shown in Figure 2, increases in the prevalence of multimorbidities (with 9 morbidity categories) also were reported in the United States between the 1999-2000 and 2009-2010 periods. According to Fried et al. (2012), the percentage of adults aged 65 and over with both hypertension and diabetes increased over this period from 9% to 15%, with increases from both hypertension and heart disease of 18% to 21% and increases from hypertension and cancer of 8% to 11%. Prevalence rates increased for each racial/ethnic group and income level.

Figure 2

MULTIMORBIDITY PREVALENCE IN THE UNITED STATES BY AGE AND SEX (A) AND BY PERCENTAGE OF POVERTY LEVEL AND PRINCIPLE MULTIMORBIDITY COMBINATIONS



Source: CDC/NCHS. National Health Interview Survey

[1]significantly different from 1999-2000, with $p < 0.05$

Orueto et al. (2013), in a study using four years of clinical data of those at least age 65 in the Basque country in Spain who used 47 chronic conditions, found that, overall, 66% suffered from multimorbidities. They found that the presence of multiple physical diseases was more common in those with mental disease than those without (75% versus 58%). By age group, 54% of those 65-69 had multimorbidities, 64% of those 70-74, 72% of those 75-79, 76% of those 80-84 and 71% of those 85+ years old. 70.0% were in the most deprived category, in contrast with 60.2% of those better-off. The leading chronic conditions involved in multimorbidities were hypertension (54%), diabetes (17%), degenerative joint disease (12%), treated dyspepsia (12%), anxiety/other neurotic disorders (11%), atrial fibrillation (9%) depression (8%), malignancies (8%), osteoporosis (8%), cerebrovascular disease (7%), prostatic hypertrophy (7%), emphysema, chronic bronchitis (7%), ischemic heart disease (7%), and chronic heart disease (7%).

Results similar to Orueto et al. were found in McLean et al. (2014) in the United Kingdom: at ages 25-34 (8.1%), 35-44 (13.9%), 45-54 (23.0%), 55-64 (38.9%), 65-74 (59.0%), and 75+ (76.1%). A reduced difference was observed between those most and least deprived at ages 75 and older than at earlier ages.

Staimez et al. (2017) examined data from adults aged 18–79 years who participated in the U.S. National Health and Nutrition Examination Survey (NHANES) 2007–2012. Multimorbidity was defined as at least two co-occurring diseases across four common cardiometabolic and chronic pulmonary disease groups. Among 16,676 adults, the age-standardized prevalence of multimorbidity was 9.3%, increasing by age from 1.5% to 5.9%, 15.0%, and 34.8% for adults aged 18–39, 40–54, 55–64 and 65–79 years, respectively. Multimorbidity was greatest among the poorest and among African-Americans. Multimorbidity was also greater in adults with obesity, hypertension, and low HDL cholesterol. The largest modifiable risk factors for multimorbidity was hypertension (38.8%) and obesity (19.3%).

High levels of non-communicable multimorbidity are also found in many low- and middle-income countries (LMICs). Agrawal and Agrawal (2016) reported that multimorbidity was strongly associated with obesity in those countries. Its prevalence in LMICs is one and half times greater in those who are obese (according to Body Mass Index, BMI, measures) than individuals of normal weight. Older adults in the LMICs are gradually approaching the multimorbidity levels in developed countries. Prevalence of multimorbidity in older adults ranged from 45.1% to 71.9% in the nine countries studied by Garin et al. (2016). Garin et al. also found, for seven countries, as shown in Table 4, that obesity was an important independent predictor of the occurrence of multimorbidity in these population. The prevalence of multimorbidity was 37% among those who were obese and 27% among those overweight in the pooled countries. The odds ratio of being obese, 5.78, was associated with a significantly higher likelihood of having multimorbidity as compared to those of normal weight.

Table 4
CHARACTERISTICS AMONG DIFFERENT COUNTRIES RELATING TO MULTIFORMITY AND OBESITY IN OLDER ADULTS

	China	India	Mexico	Russia	South Africa	Ghana	Total
Obese	5.5%	3.1%	32.5%	32.9%	42.5%	10.0%	13.4%
Daily smoking	74.9	85.6	31.5	56.1	64.1	38.2	69.5
Multimorbidity prevalence	22	24	27	50	32	23	23
Prevalence of multimorbidity among obese	36.4	30.1	31.1	58.7	28.0	27.7	37.1

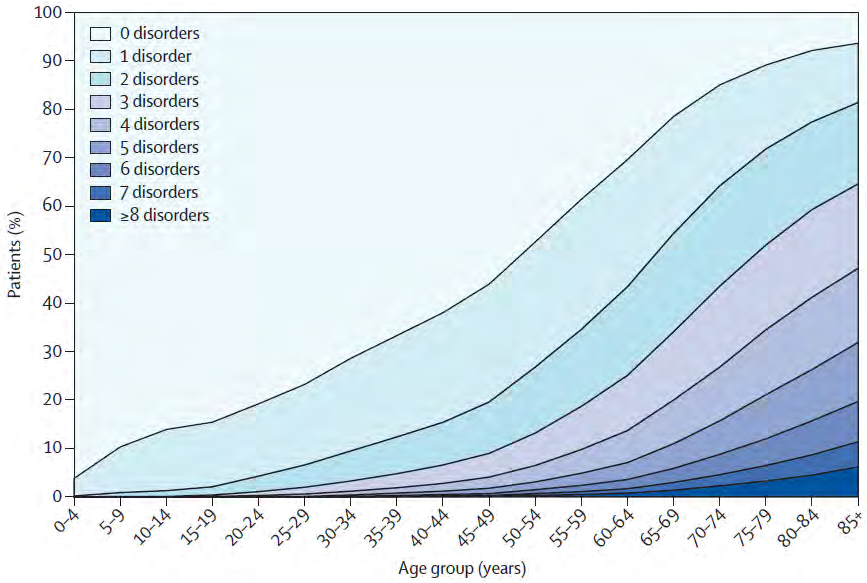
Source: Garin et al. (2016). Multimorbidity conditions consisted of angina pectoris, arthritis, asthma, low visual acuity, diabetes.

Barnett, et al. (2012) found that, in a large nationally representative primary care study (about 1.75 million participants) in Scotland, 42.2% of all patients had one or more morbidities, while 23.2% were multimorbid. Results from this study are shown in Figures 3 and 4. Although the prevalence of both physical and mental health multimorbidity conditions were substantially more common in older people (by age 65, half of the population had at least 2 disorders) than in younger people and more than half of those aged 65 and older had multimorbidity; in many countries nearly two-thirds of those with physical/mental health multimorbidity were younger than age 65.

According to Barnett et al., on average, the onset of multimorbidity occurred 10 to 15 years earlier in people living in the most deprived areas compared with the most affluent areas, with socioeconomic deprivation particularly associated with multimorbidity that included mental health disorders (prevalence of both physical and mental health disorder was 11.0% in the most deprived area compared with 5.9% in the least deprived area). The likelihood of a mental health disorder increased as the number of physical morbidities increased (odds ratio of 6.74 for five or more disorders compared with 1.95 for one disorder). Whether this relationship is a result of a concentration of one or more common causes or risk factors, such as smoking that may be amenable to preventive intervention, or an accumulation of disparate causes that may be harder to prevent, is a function of the morbidities and circumstances involved. In addition, multimorbidity was greater in females than in males; mental health disorders, particularly depression, were more prevalent in those with increasing numbers of physical disorders.

Figure 3

PREVALENCE OF NUMBER OF DISORDERS BY AGE, 1.75M, SCOTLAND - 2007

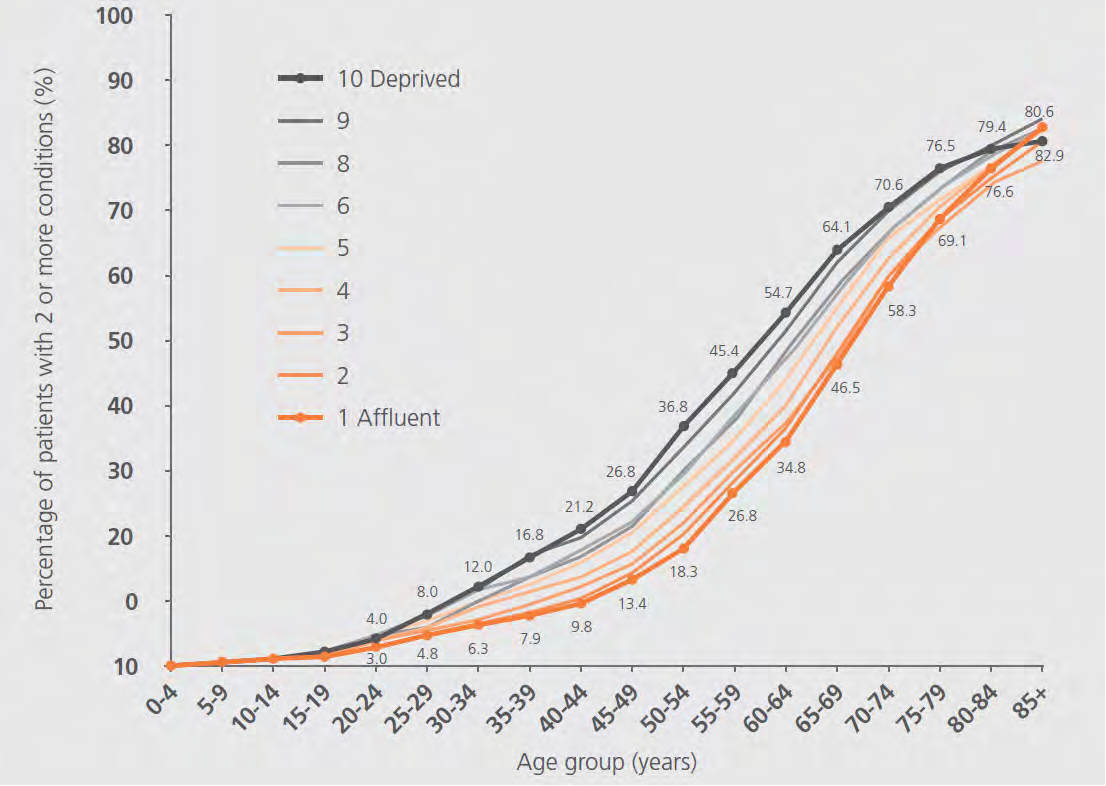


Source: Barnett et al. (2012)

As shown in Figure 4, the prevalence of multimorbidity tends to depend upon socioeconomic status. From age 20 to age 85, an individual at a lower socioeconomic status is more likely to have multiple medical conditions compared to an individual at a higher socioeconomic status. For example, for those in age group 50-54, about 18% of the most affluent Scottish patients have multiple health problems, while the most deprived has twice this percentage.

Figure 4 also shows that multimorbidity differences are more pronounced by socioeconomic level for ages 60 to 80 than for those at more advanced ages (after about age 80). Thus, while it may be appropriate for actuaries dealing with post-retirement health insurance to take such differences into account, for long-term care actuaries these differences may not be as important. These differences are most pronounced for ages 20 to 80, significantly affecting both life and health actuaries.

Figure 4
PREVALENCE OF MULTIMORBIDITY BY AGE AND SOCIOECONOMIC STATUS, SCOTLAND



Source: Barnett et al. (2012)

A study by Fortin et al. (2014) of 1,196 of those at least 45 years old found that unhealthy lifestyle factors are associated with multimorbidity. This study used fourteen chronic diseases and five lifestyle characteristics. It suggests that some individual lifestyle factors, as well as their combined effect, are associated with the likelihood of the simultaneous presence of three or more chronic conditions in the same person. Considering lifestyle factors individually, smoking habits and BMI were associated with a higher likelihood of multimorbidity, but greater physical activity was not. When lifestyle factors were aggregated, starting from a threshold of two lifestyle factors in females and four or five in men, accumulating unhealthy lifestyle factors progressively increased the likelihood of multimorbidity.

For those aged 65 and older in the National Health and Nutrition Examination Surveys (U.S.), nationally representative surveys conducted between 2005 and 2012 reported in Jindai et al. (2016), there was a significant positive association between multimorbidity and the number of functional limitations. A significant interaction was found with age, stronger among females and those age 75 and older. Overall, 67% of survey participants (64% of those between 65 and 74 and 71% of ages 75 and older) had multimorbidities (using 8 conditions), while 64% of participants had at least one functional limitation (out of 19 functional limitations (including activities of daily living, instrumental activities of daily living, leisure and social activities, lower extremity mobility, and general physical activities). Each additional chronic condition was associated with 1.35 times the number of functional limitations for males age 65-74 and 1.62 for females. For males age 75 and older the corresponding multiple was 1.71 for ages 65-74 and 2.06 for females for each additional chronic condition.

Increasing multimorbidity prevalence by age appears to be a global phenomenon. In a study of 28 countries, Afshar et al. (2015) found a positive but non–linear relationship between national GDP and multimorbidity prevalence. Trend analysis of multimorbidity by educational attainment suggests that there are intergenerational (or at least

birth cohort) differences, with a more inverse education gradient for younger adults compared to older adults. Higher educational attainment (possibly a proxy to socioeconomic status that may reflect a proliferation of several key risk factors, including unhealthy behaviors) was significantly associated with a decreased risk of multimorbidity in the study's all-region analyses. Afshar et al. noted a greater prevalence in multimorbidity in females than in males, which is also common in morbidity studies, often attributed to greater use of health services and disease diagnosis.

1.3 CONSEQUENCES

Multimorbidity can affect a person's quality of life, ability to work and employability, disability, and mortality. It is especially important when the causes and consequences of multiple conditions are interrelated with possible exacerbation of adverse health or living consequences. Especially in the case of elderly adults, it can be relevant to clinical and public health, especially because many health care systems are still structurally geared around acute care conditions, rather than single or multiple long-term chronic care conditions. The complexities and support needs of multiple adverse health conditions can also contribute to poorer overall health outcomes.

The epidemiology of multiple chronic conditions remains unevenly and generally poorly understood, since the majority of studies have assessed single diseases or comorbid pairs in association with a single index disease. Despite the rigor that goes into pre-testing the effects of new pharmaceuticals, the effects of a medication or treatment regimen for a given condition might differ when observed, for example, in an individual with only that disease compared to a frail individual who also has other conditions. Inadequate research conducted regarding the effects of pharmaceuticals used in patients with multiple conditions might result in adverse outcomes.

The study of the relation between multimorbidities and mortality has in some cases reported inconsistent results, with an increasing number of diseases or conditions found to increase the risk of death in some studies, but not in others. A proper comparison with other or previous studies can be difficult because of limited duration of follow-up, the set of diseases chosen, and the age range studied. Often, studies have been limited to patients in primary care settings, having a specific index disease, or who are elderly.

A meta-analysis conducted by Nunes et al. (2016) of the relationship between multimorbidity prevalence and the mortality of older adults included twenty-six studies through January 2015 – overall, a positive association was found, with a hazard ratio of 1.44. The number of morbidities was positively related to risk of death [HR: 1.20]. Compared to individuals without multimorbidity, the risk of death was 1.73 and 2.72 for people with 2 or more and 3 or more morbidities, respectively. Heterogeneity between studies was high (96.5%). However, adjustment for demographic socioeconomic and behavior variable tempered these relationships. The existence of disability also appeared to mediate the effect of multimorbidity on mortality. Nevertheless, it was found that the existence of multimorbidity increased the risk of death regardless of its characterization.

Specific combinations of conditions in a multimorbidity situation are associated with mortality in the oldest old population segment. Ferrar et al. (2017), for example, using 16 conditions, found that, among 328 people who were age 85 in a community-based cohort followed for three years in Barcelona, the mortality hazard ratio of individual disease conditions was chronic obstructive pulmonary disease (COPD) (2.47), atrial fibrillation (2.41), and cancer (1.90) and through five years was dementia (2.04), cancer (1.84) and COPD (1.77). Mortality hazard ratios were greatest through three years for the combination of atrial fibrillation, chronic kidney disease, and visual impairment (4.19) and hypertension, chronic kidney disease and visual impairment (3.24) through five years. This suggests that for these octogenarians, chronic kidney disease, although not a significant individual predictor of mortality, was important in combination with other impairments. Ferrar et al. indicated that the interactions between morbidities may accelerate functional limitations, disease, and death.

Usually, reported deaths are attributed to a single cause of death, even though there may be several contributing factors involved. Similarly, in projecting the future trajectory of mortality, it is common to estimate future mortality using estimates of individual causes of death – few estimates reflect the effects of multimorbidities. However, if the effect of one mortality driver is reduced or eliminated, survivors may be more susceptible to other existing or future

conditions, whether as a result of an impaired immune system, increased susceptibility to other diseases or accidents, or the cumulative adverse effects of previous or current conditions.

In a study of 2,087 randomly selected Australians (1992-2006) who were at least age 65, Caughey et al. (2008) studied the association between the number of chronic diseases and mortality over a 14-year follow-up period. After adjusting for age, sex, and residential status (in a community or institution), participants with three/four, or at least five diseases had a 25% and 80% increased risk of mortality, respectively, in comparison with those with no chronic disease. When cardiovascular disease, a mental health condition, or diabetes were comorbid with arthritis, there was a trend towards increased survival (range 8.2–9.5 years) in comparison with those with cardiovascular disease, mental health condition, or diabetes alone (survival 5.8–6.9 years). However, this increase in survival with arthritis as a comorbidity was negated when cardiovascular disease and mental health conditions or cardiovascular disease and diabetes were also present. This study shows that, although older people with at least three chronic diseases have increased risk of mortality, discordant effects on survival can depend on the specific disease combination involved. Caughey et al. also indicated that those with an increased likelihood of opportunity for care may be more likely to have comorbid diseases that are detected, which allows for more effective management.

In a study of the relationship between educational attainment, multimorbidity and mortality, Jensen et al. (2017) analyzed the Danish National Health Survey, which covered about 240,000 people between ages 25 and 89 with a 3.8 year follow-up period, using 39 disease categories based upon prescription drug information. The relative risk of overall and premature mortality for people with low educational attainment (less than or equal 10 years) compared with those with high educational attainment (greater or equal 15 years) decreased with increasing number of underlying chronic conditions. The mortality hazard ratio, adjusted for lifestyle factors, for those of low education to high education was 2.31 for those with 0 or 1 long-term disease, 1.57 for those with 2 or 3 diseases, and 1.40 for 4+ diseases. This indicates that both educational attainment and the extent of multimorbidities were significant indicators of mortality. In addition, the relative effect of multimorbidities was strongest for those with lower educational attainment than those with higher educational attainment.

Another study of the impact of educational attainment, by Nagel et al. (2008), was analyzed on both an age-adjusted and a more fully-adjusted basis. As shown in Table 5, 13,781 German adults who were participants in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC), were 50–75 years at the end of the follow-up period. Information on diet and lifestyle was collected at participant recruitment (1994–1998), with a median follow-up period of 8.7 years. The prevalence rate of multimorbidity, using fifteen conditions, was 67.3% and was significantly associated with the level of educational attainment. Compared to the highest educational category, the lowest was significantly associated with increased odds of multimorbidity in males (odds ratio of 1.43) and females (odds ratio of 1.33). After adjustment, the positive associations were attenuated (for males the odds ratio was 1.28; for females the odds ratio was 1.16). BMI was a stronger intermediate factor than smoking status in the association between education and multimorbidity. However, even the fully adjusted model, i.e., also considering other risk factors for chronic diseases, could not entirely explain socioeconomic inequalities in multimorbidity. A stronger association between educational attainment and multimorbidity was found among participants aged 50 to 60 years than among those older than 60, which can at least partly be explained by premature mortality in relatively low socioeconomic groups.

Table 5

EFFECT OF EDUCATIONAL ATTAINMENT, MULTIMORBIDITY AND MORTALITY – GERMANY

Sex	Males		Females	
Educational level	Medium : High	Low : High	Medium : High	Low : High
Multimorbidity				
Age-adjusted	1.32	1.43	1.13	1.33
Fully adjusted*	1.21	1.28	1.06	1.16
All-cause mortality:				
Age-adjusted	1.38	1.90	1.04	1.30
Fully adjusted*	1.26	1.60	1.32	1.49

Source: Nagel et al. (2008). *Fully adjusted on a multivariate basis for smoking status, BMI, fruit intake, vegetable intake, alcohol consumption, age, combined total physical activity index.

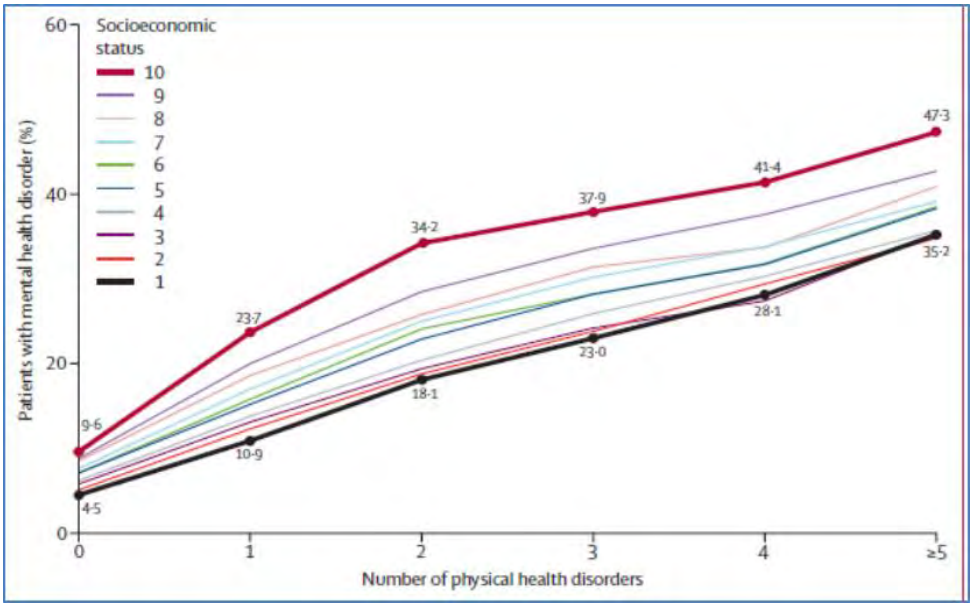
People often have both adverse physical and mental health issues simultaneously. Based on a systematic review of 86 studies by Panagioti (2015), those with both mental and physical multimorbidities had the highest risk of active patient safety incidents and precursors of safety incidents. One study found that for those over the age of 55, multimorbidity most likely consisted of people with multiple physical health conditions, while for those in younger age groups, multimorbidity most likely involved both physical and mental health conditions. This was two to three times more common in the most deprived compared with the least deprived groups. Depression and pain were included in the top five conditions across all age groups.

In a manner similar to Figure 3, Figure 5 illustrates that people in the most deprived areas in Scotland are much more likely than others to have mental health conditions in addition to physical ones.

Figure 5

PHYSICAL AND MENTAL HEALTH MULTIMORBIDITY AND THE ASSOCIATION WITH SOCIOECONOMIC STATUS, SCOTLAND

ON SOCIOECONOMIC STATUS SCALE, 1=MOST AFFLUENT AND 10=MOST DEPRIVED.



Source: Barnett et al. (2012)

As found in Lynch et al. (2014) that was based on a national cohort of 625,903 veterans with type 2 diabetes with a mean age of about 65 from 2002 through 2006, physical morbidities exerted the greatest influence on mortality and

had significantly stronger effects on mortality compared to psychiatric (mental) morbidities. Mortality rates for those with increasing physical morbidity remained high across each level of mental morbidity.

Lynch et al. also found that hypertension (78%) and depression (13%) were the most prevalent physical and mental morbidities, respectively. 23% had at least three physical multimorbidities and 3% had at least two mental multimorbidities. Among physical multimorbidities, the mortality risk was greatest in those with congestive heart failure (hazard ratio 1.92), lung disease (hazard ratio of 1.42) and cerebrovascular disease (hazard ratio of 1.39). Among mental multimorbidities, the mortality risk was highest for those with substance abuse (hazard ratio of 1.50), psychoses (hazard ratio of 1.16) and depression (hazard ratio of 1.05). There was an interaction between physical and mental multimorbidities, with hazard ratios for at least three physical multimorbidities (hazard ratio of 2.63) remaining high across the number of mental multimorbidities. Hazard ratios for the mortality of at least two mental multimorbidities (hazard ratios of 1.69, 1.63, 1.42, 1.38) declined across levels of physical multimorbidity (0, 1, 2, 3+), respectively. For example, those with alcohol or drug abuse/dependence experienced a 22% higher mortality. In sum, several of both physical and mental multimorbidities are significant predictors of mortality.

Between 2001 and 2008 Bayliss et al. (2012) studied a cohort of 6,500 adults with an initial cancer diagnosis and a range of cardiovascular conditions. During the five years of the study, 15.3% died from cancer, 5.1% from serious cardiovascular events, and 8.3% from other causes. Although those with a cancer prognosis experienced the greatest mortality, cardiovascular and other conditions independently increased the risk of mortality. In multimorbid oncology populations, mortality estimates derived from models that examine cancer or cardiovascular outcomes separately may be not be relevant for multimorbid individuals because the effect of other adverse health conditions can be misestimated by the models. At the same time, the study suggested that cancer may affect the risk of adverse cardiovascular outcomes and other-cause mortality.

Wei and Mukami (2017) reported on the Nurses' Health Study, the Nurses' Health Study II and the Health Professional Follow-up Study conducted between 2000/01 and 2010. These studies cumulatively had about 220,000 participants. They were, on average age 55, with 2.7 diseases at baseline. They used three types of multimorbidity categorizations: a simple condition count, a multimorbidity weighted index (MMI) and a Charlson Comorbidity Index (CCI) – see the Appendix for a description of these methods. In a comparison of the mortality of the highest to lowest quartile using each method, the resulting hazard ratios were 6.04 using the MMI, 4.86 using condition counts, and 3.26 for the CCI. A conclusion was that, no matter which type of index was used, multimorbidities play an important role in mortality and future physical functionality.

Multimorbidity is not only an issue for mortality, but also for long-term care needs. As indicated above, multimorbidity is particularly common among the oldest-old, with respect to both physical and mental conditions. For example, many studies have found, even during the late-life period, that cardiovascular health and its risk factors are associated with deterioration of the cerebral function in later life. Thus, better control of all cardiovascular risk factors may lead to a lower incidence and trajectory of neurological diseases, such as Parkinson's or dementia. For example, the prevalence of comorbid conditions in people with dementia is high, especially diabetes, stroke and visual impairment.

In a study of mortality and nursing home admissions of 4,414 elderly individuals (average age 76.4, all from Reykjavik Iceland with a study period of 5.94 years for nursing home admissions and 7.76 years for mortality), Aarts et al. (2015) found that both multimorbidities (using 11 conditions) and disability (needing assistance with at least two out of five activities of daily living) played a significant role for those who were frail. As shown in Table 6, the rate of nursing home admissions was especially affected by the existence of multimorbidities, while mortality was affected by both multimorbidities and extent of disability.

Table 6

HAZARD RATIOS FOR ELDERLY TO EXPERIENCE OF NON-FRAIL INDIVIDUALS -- ICELAND

	Mortality		Nursing home admissions	
	Age/Sex adjusted	Further adjusted*	Age/Sex adjusted	Further adjusted*
Frail only	1.13	1.01	1.24	1.40
Frail plus disability	2.80	2.00	1.14	1.20
Frail plus multimorbidities	2.10	1.47	2.10	1.47
Frail plus disability and multimorbidities	2.65	1.45	2.37	1.42

Source: Aarts et al. (2015). *Adjusted for age, sex, educational level, smoking, alcohol, living arrangements, disability and depression symptoms

Some studies emphasize that other factors, such as functional decline, frailty, or disability can have a greater effect than multimorbidity. For example, Woo and Leung (2014), studied mortality over nine years and physical function decline, depression, and polypharmacy over four years of about 4,000 people over age 65 in Hong Kong, beginning between 2001 and 2003. Although multimorbidity was not associated with excess mortality (in fact, it was found to be preventive), using at least four types of medication was more important than the level of dependence and frailty. Multimorbidity was also, along with frailty, associated with an increase in physical limitations over a four-year period. Mortality in this study was associated with the degree of frailty.

Hanlon et al. (2018) studied the effect of frailty and multimorbidity on about 500,000 people aged 37-73 in the United Kingdom (U.K. Biobank) beginning between 2006 and 2010. They found that, over a 7 year follow-up period, the rate of mortality increased by more than two times for those who were frail (for males 37 and older and females 44 and older), as shown in Table 7. Adjusted for sociodemographic and lifestyle behaviors, this relationship was consistent across age and sex categories, independent of the mortality risk associated with multimorbidity. The percentage of the U.K. population that exhibited frailty and pre-frailty characteristics was 3% and 38%, respectively. The effect of frailty on mortality was strongly associated with socioeconomic deprivation, obesity, smoking, and multimorbidity. Mortality rates were also significantly increased by level of multimorbidity. In addition, those who exhibited frailty and pre-frailty were strongly associated with multimorbidity. The top five long-term conditions associated with frailty were multiple sclerosis, chronic fatigue syndrome, COPD, connective tissue disease, and diabetes.

Table 7

FRAILTY/MULTIMORBIDITY IN RELATION TO MORTALITY – UNITED KINGDOM

Number of chronic conditions	Pre-frail to non-frail	Frail to non-frail
0	1.00	1.00
1	1.32	2.27
2	1.72	5.12
3	2.25	10.40
4+	3.31	27.10

	Compared to non-pre-frail and non-frail			
	Pre-frail		Frail	
Ages / sex	Males	Females	Males	Females
37-45	1.36	0.87	2.70	1.42
45-55	1.51	1.28	2.41	2.38
55-65	1.40	1.37	2.52	2.20
65-73	1.45	1.50	2.42	2.53

Source: Hanlon et al. (2018)

Jani et al. (2019), in a further study of this same U.K. Biobank cohort, found a strong association between both the number of conditions and cardiometabolic multimorbidity (also see below “Cardiometabolic Multimorbidity”) with all-cause, cancer, and vascular mortality, while non-cardiometabolic multimorbidity was associated with all-cause

and vascular mortality. 43 conditions, plus cancer and cardiometabolic conditions were used in this study. For those with at least:

- four long-term conditions – all-cause mortality was 2.79 times (hazard ratio) compared with those with no long-term conditions;
- four cardiometabolic conditions – all-cause mortality was 3.20 times higher; and
- four non-cardiometabolic conditions (excluding cancer) – all-cause mortality was 1.50 times greater.

Morbidity combinations with the greatest impact on all-cause mortality included cardiometabolic conditions, chronic kidney disease, cancer, epilepsy, chronic obstructive pulmonary disease, depression, osteoporosis, and connective tissue disorders. While socioeconomic status was a significant predictor of all-cause mortality, mortality risk with an increasing number of conditions remained constant across socioeconomic gradients. The type, rather than the number of conditions, may have an important role in the relationship between multimorbidity and mortality. The relative importance of the type and number of conditions can differ by the conditions involved. Multimorbidity had a greater relative impact on all-cause mortality in those who are middle-aged, rather than older populations, particularly among males. In addition, the relationship between multimorbidity and mortality risk was consistent across all categories of socioeconomic status. In sum, Jani et al.'s study indicates that multimorbidity is associated with higher all-cause, cancer, and vascular mortality.

Another study (Marengoni et al., 2008) suggested that higher mortality, especially that of the oldest-old, is associated with disability (needing assistance with at least one activity of daily living), rather than multimorbidity. Marengoni found, in a Swedish population between 1987 and 2000, that multimorbidity contributed to increased loss of functionality, but not additional mortality. They did however find that disability and multimorbidity were related.

Based on the experience of about 300,000 people, Kingston et al. (2018) estimated that, between 2015 and 2035, multimorbidity prevalence in the United Kingdom will significantly increase. They projected that (1) the proportion of those with at least four diseases will almost double (2015: 9.8%; 2035: 17.0%), (2) two-thirds of those with at least four diseases will suffer from a mental health condition (dementia, depression, or cognitive impairment with no dementia), and (3) multimorbidity prevalence in incoming cohorts aged 65–74 years will rise (2015: 45.7%; 2035: 52.8%). The gain in years lived with two or more conditions will almost equally be a result of longer survival with and increased prevalence of multimorbidity, while most of the life expectancy gains (males 3.6 years; females 2.9 years) will be spent with at least four diseases (males: 2.4 years, 65.9%; females: 2.5 years, 85.2%). Thus, they project that people will live longer with multimorbidity. Kingston et al. indicated that this will partly be due to younger cohorts who will have a higher prevalence of obesity than those a generation earlier, which has also contributed to increased multimorbidity. Leading diseases in 2015 and projected in 2035 were arthritis (48.6% and 62.6%), hypertension (49.0% and 55.9%), respiratory disease (18.6% and 24.4%), cancer (12.6% and 23.7%), diabetes (14.7% and 21.6%), cardiovascular heart disease (18.3% and 15.0%), a hearing disease (12.4% and 12.5%), and dementia (6.8% and 8.5%).

1.4 CARDIOMETABOLIC MULTIMORBIDITIES

A set of multimorbidities of particular interest is referred to as cardiometabolic, especially in view of the tremendous progress that has been achieved over the last several decades in the reduction of premature deaths due to cardiovascular causes. Multimorbidity for a set of these conditions, usually consisting of at least two of the following: type 2 diabetes, coronary heart disease, and stroke. Any combination of these conditions has been associated with a multiplicative additional mortality risk.

Kivimäki et al. (2017) studied the risk of cardiometabolic multimorbidity incidence in adults who are overweight and obese compared with that in those of a healthy weight. Sixteen pooled prospective cohort studies from the United States and Europe were studied, covering 120,813 adults with 1,627 cases of multimorbidity with a mean follow-up of 10.7 years. After adjusting for sociodemographic and lifestyle factors, the risk of developing cardiometabolic multimorbidity by those who were overweight was twice as high, about 4.5 times for individuals with class I obesity,

and about 14.5 times higher for those with class II or III obesity combined. Those with class II or III obesity were 2.2 times more likely to experience vascular disease only (coronary heart disease or stroke), 12.0 times for vascular disease followed by diabetes, 18.6 times for diabetes only, and 29.8 times for diabetes followed by vascular disease. These associations held for both males and females, white and non-white, younger and older individuals, and were not attributable to lifestyle risk factors, such as physical activity, smoking, or alcohol consumption. This strongly suggests that the primary method of addressing multimorbidities should be to reduce the number or effect of possible cardiometabolic risk factors.

Socioeconomic, behavioral (e.g., physical activity, alcohol consumption, diet, and smoking) and clinical (hypertension, overweight and obesity, high cholesterol, and family history of diabetes or cardiovascular disease) risk factors have been shown to be significant causes and effects of multimorbidities. In the Whitehall II study (U.K.) of these factors of 8,270 participants at age 50 followed over a mean of 23.7 years for cardiometabolic disease incidence, cardiometabolic multimorbidity, and mortality. Based on this study, Singh-Manoux et al. (2018) assessed three stages of the trajectory of cardiometabolic disease:

1. To an initial cardiometabolic disease. An adverse clinical profile was the strongest predictor (with a 3.7 hazard ratio of the least compared with the most favorable profile) but played a more modest role in progression from a single disease to cardiometabolic multimorbidity or risk of mortality in those with cardiometabolic multimorbidity.
2. To multimorbidity from a cardiometabolic disease. Midlife socioeconomic (1.54 hazard ratio) and behavioral (2.00 hazard ratio) factors were found to be important predictors.
3. To death from a single cardiometabolic disease (2.12 hazard ratio) or from multimorbidity (3.47 hazard ratio). In midlife, behavioral factors were important predictors.

These findings demonstrate that a focus on one stage of health trajectories may overlook the changing role of risk factors in the development, progression, and outcome of cardiometabolic (or, indeed, other) multimorbidities. For example, being overweight or obese had the strongest association with the development of a first cardiometabolic disease, while smoking had the strongest association with both cardiometabolic multimorbidity and mortality. When looking at behavioral and clinical risk factors, only smoking was significantly associated with all the transitions. The treatment and study of each type or combination of risk factors are thus important for each trajectory. Such findings strongly suggest the need for further efforts to promote lower body weight, blood pressure, and total cholesterol, as well as secession of smoking.

Di Angelantonio et al., reporting on behalf of the Emerging Risk Factors Collaboration (2015), studied about 690,000 U.K. participants recruited between 1960 through 2007, with a 23.7-year follow-up period through 2007. As mortality associated with cardiovascular disease has plummeted over the last several decades, the prevalence of those living with cardiometabolic multimorbidity has increased rapidly. Eight mutually exclusive baseline disease groups were covered: (1) diabetes, (2) stroke, (3) myocardial infarction (MI), (4) diabetes and MI, (5) diabetes and stroke, (6) stroke and MI, (7) diabetes, stroke, and myocardial infarction, and (8) none of these (the reference group). Compared with the reference group, the age- and sex-adjusted hazard ratios for mortality were 1.9 for participants with diabetes, 2.1 in those with stroke, 2.0 in those with MI, 3.7 for those with both diabetes and MI, 3.8 for those with both diabetes and stroke, 3.5 in those with both stroke and MI, and 6.9 in those with diabetes, stroke, and MI. The hazard ratios for those with a history of two or more conditions were generally consistent with having a multiplicative effect, with the exception of the hazard ratio for those with a history of both stroke and MI. The hazard ratios attenuated slightly, but were not eliminated after adjustment for total and high-density lipoprotein cholesterol, systolic blood pressure, and BMI. For participants with all three conditions at baseline, the age- and sex-adjusted hazard ratios were 11.8 for cardiovascular mortality, 2.1 for cancer mortality, and 7.9 for the aggregate of nonvascular and noncancer deaths. The hazard ratios were stronger among females than males. These findings indicate that cardiovascular conditions have a multiplicative effect – a mortality hazard ratio of about 2 for those with one condition and a mortality hazard ratio of about 4 for those with any two conditions; and for those with all three conditions the hazard ratio was about 8. Di Angelantonio et al. concluded that the coexistence of multiple conditions was associated with a risk of death substantially greater than that for an individual disease and

that studying the effects of one cardiovascular disease may underestimate the mortality of a population with cardiometabolic multimorbidities.

A variation of cardiometabolic multimorbidity was used by Zhang et al. (2019), using the combination of cardiovascular disease (including coronary heart and cerebrovascular diseases), diabetes, and hypertension. In this study (Chinese Electronic Health Records (EHR) research in Yinzhou), Zhang et al. studied the mortality of more than a million Chinese over the age of 18 from 2010 to 2016. The prevalence of cardiometabolic multimorbidity more than doubled over a mean follow-up period of five years. 12.2% of the participants had at least one of these cardiometabolic conditions, while nearly 3% had cardiometabolic multimorbidity. The initial cardiometabolic disease prevalence of 10.1% changed during the follow-up period – the prevalence of cardiometabolic multimorbidity increased from 2.41% to 5.94% of the participants. A mortality hazard ratio of 1.37 for those with one disease, 1.71 for those with two diseases and 2.22 for those with three diseases, all compared to the mortality of those with no cardiometabolic disease at baseline. The highest hazard ratios were observed for cardiovascular disease only (3.31) and the combination of diabetes and cardiovascular disease (3.12). Those with hypertension had the lowest hazard ratio (1.26). Longitudinal data showed the hazard ratios in patients with one, two and three diseases were 1.36, 2.03 and 2.16, respectively. Although these results may suggest that associations between mortality and hypertension, diabetes, and cardiovascular disease were additive, Zhang et al. indicated that there was a significant degree of heterogeneity within each disease combination.

1.5 HEALTH CARE SERVICES

Most of the above consequences of multimorbidity relate to mortality, with some mention of functional limitations of those needing long-term care. This section describes the effects on the provision of health care services as reported in a few studies. Overall, the existence of multimorbidities increases health care utilization and costs. The growing numbers of the very old with multimorbidities will dramatically increase the overall health and social care burden. Partly because of this increase, current healthcare systems may not be designed to effectively deal with today's medical and social reality that multimorbidity represents.

Based on a study between 2005 and 2008 of about 100,000 U.K. adults (Salisbury et al. 2011), the 16% of participants who had more than one chronic condition included in the Quality and Outcomes Framework (QOS) accounted for 32% of all consultations. Using the wider Adjusted Clinical Groups (ACG) list of conditions (see Appendix for a short description of QOS and ACG), the 58% of those with multimorbidity accounted for 78% of consultations. This represented 9.35 consultations per year for those with multimorbidities, compared with 3.75 of those without. Salisbury et al. indicated that age and degree of deprivation were strongly associated with multimorbidity.

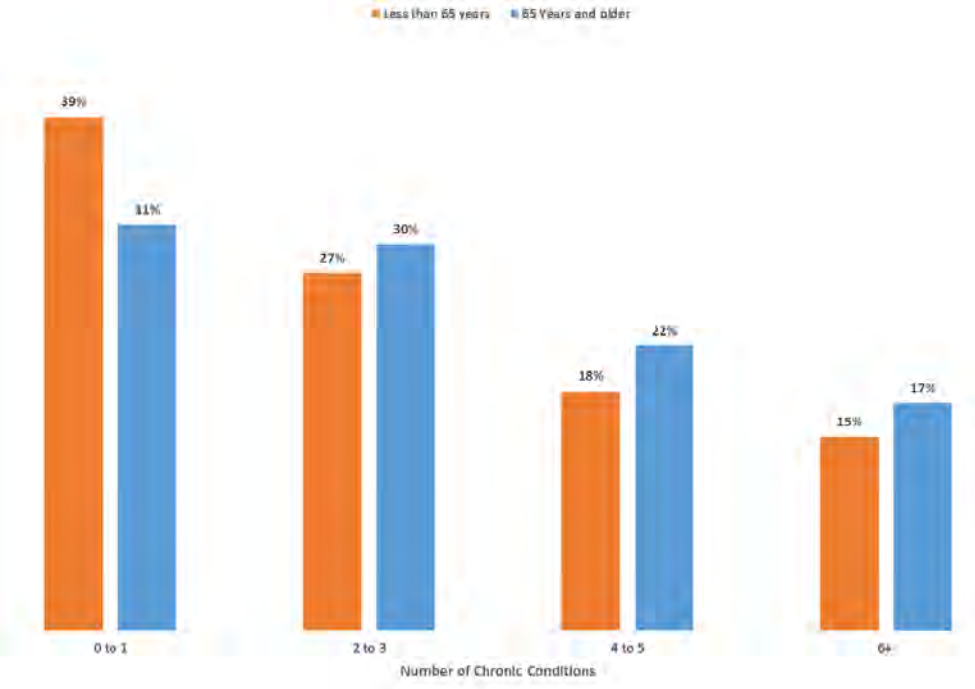
The percentage of health care costs associated with those with multimorbidities is significantly larger than the prevalence of these conditions. For example, Yoon et al. (2014) indicated that, utilizing a 28 condition system, about a third of the 5.2 million adults under age 65 who utilized health care services at the U.S. Department of Veterans Affairs' health care facilities in 2010 had at least three chronic long-term conditions and accounted for about two-thirds of total health care costs. About 80% had at least two chronic long-term conditions. The most common conditions of those with at least three conditions were diabetes, hyperlipidemia, and hypertension. Of the costliest triads (those with three conditions) were spinal cord injury, heart failure, renal failure, ischemic heart disease, peripheral vascular disease, stroke, and depression. Although those with these conditions experienced three times greater than average health care costs among those with more than three conditions, they only constituted a 0.1% to 0.4% overall prevalence rate.

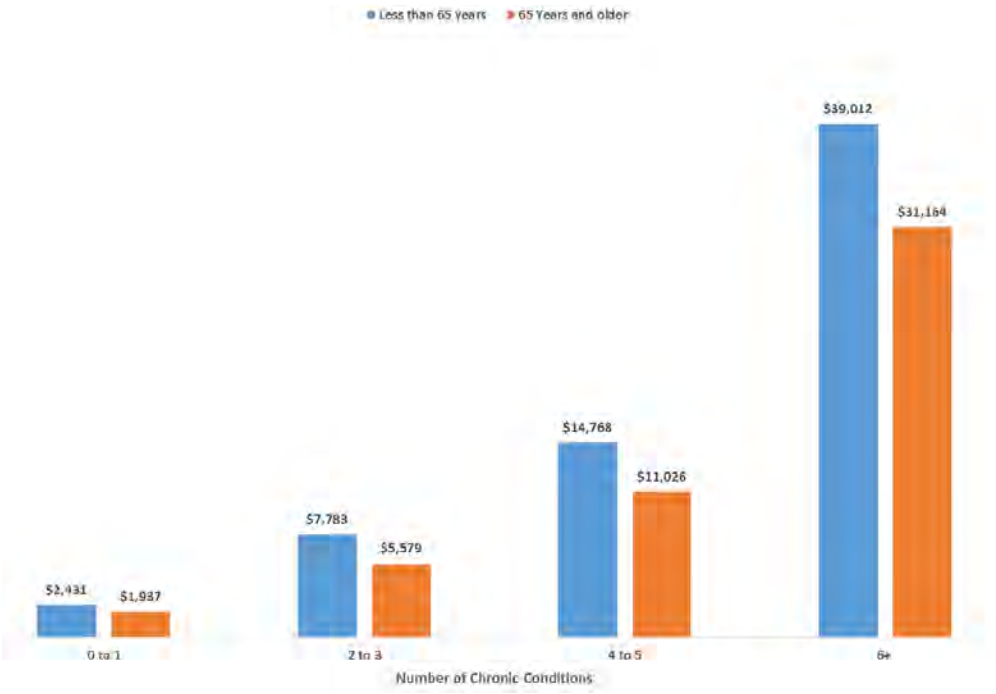
In the U.S. Medicare system (those who are disabled or are at least age 65), the relative prevalence and cost of multimorbidities is shown in Figure 6. Note that prevalence of multimorbidity in those under 65 included in Part A are greater than that of the rest of the population because these beneficiaries are receiving permanent disability benefits.

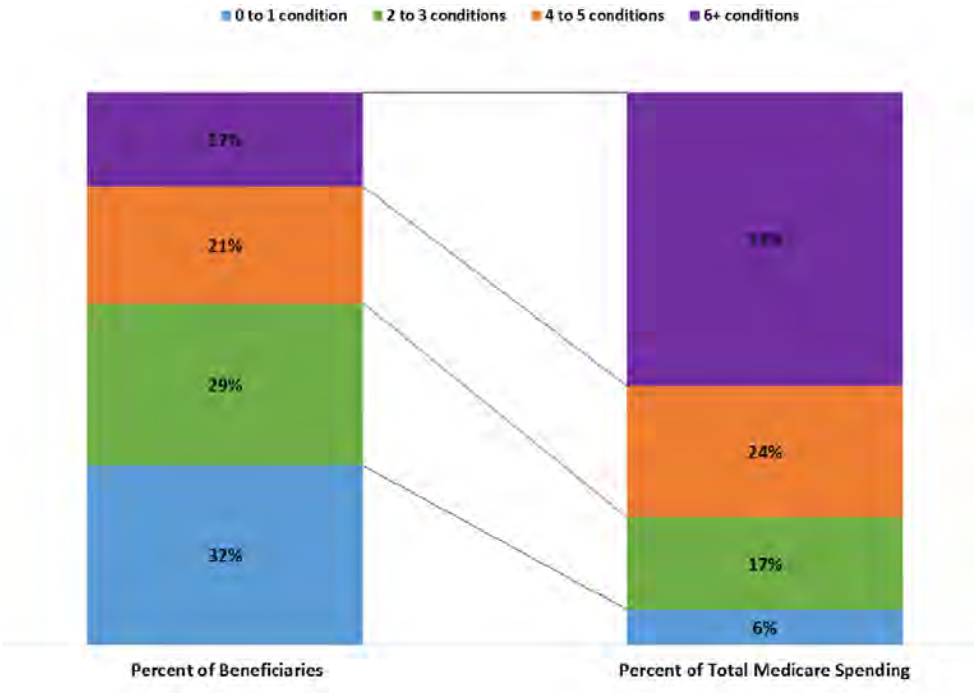
Although the 1994 Medicare Expenditure Panel Survey is relatively old, costs for inpatient care and medications for older adults with two or more chronic conditions and a disability were five times greater than for those with disability alone, and over two times greater than for those with multimorbidity alone. Studies of health care costs in other countries demonstrate similar increases with an increasing number of medical conditions (e.g., in Germany, Nagl, et al., 2012).

Figure 6

FEE-FOR-SERVICE BENEFICIARIES, 2017. A: PREVALENCE OF MULTIPLE CHRONIC CONDITIONS; B: PER CAPITA MEDICARE SPENDING BY AGE; C: DISTRIBUTION OF BENEFICIARIES AND MEDICARE SPENDING BY NUMBER OF CHRONIC CONDITIONS







Source: Medicare Conditions website: cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Maps_Charts.html.

As another example, in a 2006-2008 Dutch study (van Oostrom et al. 2014) of general practitioners with patients at least 55 years old, there were 6.1 contacts (face-to-face, phone or home visits) per person per year for those with non-chronic diseases, 11.7 contacts for those with one chronic disease and 18.3 contacts for those with more than one chronic disease. With each additional disease, the number of contacts per person decreased (a diminishing

number of contacts for each additional condition). In addition, there was more prescriptions and more referrals to specialized care for those with multimorbidities.

1.6 CONCLUSIONS AND NEED FOR FURTHER RESEARCH

Enhanced understanding, recognition and treatment of multimorbidities and combinations of health diseases/conditions has become increasingly important. Those with multimorbidities can have poorer functional status, quality of life, and health outcomes. They use more ambulatory and inpatient care and will ultimately have long-term support needs.

Measured consistently over time, trends in the prevalence, composition, and consequences of multimorbidities can serve as useful early warning indicators of future mortality and health care needs. This information can be effectively used to enhance the understanding of the heterogeneity of population segments that experience several simultaneous health risk factors.

Those experiencing multiple adverse chronic conditions represent a heterogeneous overall population segment. An example is that one quartile of a group of females age 80 may have a life expectancy of more than fourteen years, while another group of females age 80 may have a life expectancy of less than five years. The use of information regarding multimorbidity (or the comorbidities of the disease/condition at issue) can help identify the upcoming health risks of an individual, as well as for the estimation by actuaries of mortality and morbidity experience of a specific population segment .

As society achieves a degree of success against certain health conditions – first among infectious disease and more recently cardiovascular diseases, other adverse conditions have tended to become more important to overall health and effective prevention and health care treatment. Those successfully treated for a single condition may become subject to more adverse health compared with those who had not experienced that condition. The inter-relationships among conditions implies a dynamic mortality and morbidity process, especially among those at older ages. A greater emphasis will be needed on improvement of healthy life expectancy and aging, encompassing successful healthy living considering the multiple conditions that will affect all of us. Treatment of the whole person may likely be emphasized, rather than treatment of a health care condition.

Multimorbidity is relevant to the effective treatment of many individuals. Its high prevalence, particularly in those at older ages, points to some of the problems of current medicine and organization-of-care, as pointed out by Lefèvr et al. (2014). It is particularly important in generalist settings, such as primary care, where family practitioners act as the first point of contact for those suffering from multiple conditions and who frequently manage patients with multiple coexisting conditions and polypharmacy (with the risk of adverse combination of medications). These medical professionals need to recognize and be able to treat disease combinations/clusters. As the number of health professionals involved in a patient's care increases, conflicting instructions and care pathways, and fragmented medical care might arise. This can make it more challenging for the patient to understand and adhere to these instructions, in turn reducing their effective participation in their own care. Compounding these issues is an increasing tendency of many to seek out their own care by means of web-based information.

Multimorbidity can generate uncertainty at different levels during the care process, from care planning to goal definition and therapeutic strategies. It is a major contributor to the heterogeneity of the causes and consequences of those suffering from a specific condition. The existence of multimorbidities indicates the need for greater and more personalized assistance and support will further emerge. This is especially the case in the presence of frailty, disability, and social and environmental disadvantages.

Many medical studies are conducted to study the effect of a single condition, even though they look at all-cause mortality. In fact, those that have a disease/condition other than the one specifically being studied may be excluded from a study to avoid risk-confounding. However, this can also lead to an underestimation of the effect of that condition as it might also exacerbate the effects of other conditions. For example, in attempting to isolate the effect

of obesity on mortality, it is common to eliminate from study those at baseline measurement who suffer from a cardiovascular condition or cancer to avoid confounding. This approach however, may have the effect of underestimating the total effect of obesity. A study of just those individuals with multiple characteristics could reveal more useful results of the interplay of a combination of obesity and cardiovascular diseases. By carefully studying effects of multiple simultaneous conditions, our knowledge will be enhanced.

In addition, not all comorbidities are adverse. For example, the obesity paradox suggests that some conditions can be preventive against certain risks associated with certain adverse health conditions, e.g., post-heart disease and certain cancers. Can such associations be taken advantage of?

Further research is needed, with much siloed research broadened, where practical, to address the health care, costs, and mortality due to multimorbidity issues. Some of the open question include the following, as discussed in the Academy of Medical Science (2018, UK):

- Quantification of the primary behavioral, environmental, sociodemographic, and biological factors involved in the causation of multimorbidities and mitigation of their effects;
- Identification and more effective treatment of the most common clusters of conditions, such as cardiometabolic multimorbidities, that create conditions and alternative treatments than would be the case if individual conditions were treated separately;
- How to embed multimorbidity in medical education for and treatment protocols used by health care professionals; and
- Enhanced multimorbidity measurement standardization to enable more comparable estimates, which remains an impediment to better understanding of the relationships and patterns involved.

Appendix: Commonly Used Measures of Multimorbidity

Commonly used measures (based upon Huntley et al. 2012) include:

- Age;
- Disease counts. These range from 3 to almost 50 different conditions or diseases, which can use combinations of diagnosis codes from the International Classification of Diseases (ICD, currently using version 10) or some other pre-defined set;
- Quality and Outcomes Framework (QOS). This consists of 17 diseases that have been classified as chronic in previous research;
- Chronic Disease Score (CDS) / RxRisk. This uses automated pharmacy usage data during a 1-year period, with medications utilized as proxies for disease conditions, using weights for health utilization and costs derived empirically, although alternatively a count of drugs used could alternatively be used;
- Adjusted Clinical Groups (ACG) System. This uses age, sex, and diagnosis adjustments, derived from medical records, insurance claims, or expected resource use for each diagnosis using ACG System software;
- Charlson Comorbidity Index. This uses 17 to 22 weighted disease categories, reflecting age, with weights based on the observed strength of association with mortality;
- Cumulative Index Illness Rating Scale (CIRS). This uses a rating scale that consists of 14 body system categories, derived by trained assessors, or from medical records, using severity-weights for each domain;
- Elixhauser Comorbidity index. This index is based on ICD diagnosis codes, using a set of about 30 indicators, originally proposed in 1998 in an article by Elixhauser; and
- Duke Severity of Illness Checklist (DUSOI). A severity of illness checklist for measuring the severity of each of a person's illness, using four parameters for each diagnosis: symptoms, complications, prognosis without treatment, and treatment potential.

Other than the first two, the others differentially weight a range of conditions or diseases, with weights based on mortality, severity, or likely resource utilization for the conditions and diseases. Variations of each have been applied, often designed to measure the need for medical resources, with some requiring professional input that may be subjectively determined, especially when severity of a condition is an input. Most have some available software support, and several depending upon the applicable version of ICD codes. However, all suffer because of the different number of conditions included, which makes it difficult to compare research that includes observational findings. In any event, it is important to reflect the most significant and relevant conditions (e.g., relating to cost or mortality) and recognize their possible effects.

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