The Era of Geriatric Medical Challenges: Multimorbidity among Older Patients

Masafumi Kuzuya, M.D., Ph.D.

Department of Community Healthcare & Geriatrics,
Nagoya University Graduate School of Medicine,
Institutes of Innovation for Future Society, Nagoya University
65 Tsuruma-cho, Showa-ku, Nagoya 466-8550,
TEL.: +81-52-744-2369; FAX: +81-52-744-2371
Email: kuzuya@med.nagoya-u.ac.jp

Short running title: Challenges of multimorbidity

Abstract

The number of older adults is increasing worldwide, including in Asian countries. Various problems associated with medical care for older adults are being highlighted in aging societies. As the number of chronic diseases increases with age, older adults are more likely to have multiple chronic diseases simultaneously (multimorbidity). Multimorbidity results in poor health-related outcomes, leading to increased use and cost of healthcare. Above all, it leads to deterioration in older adults' quality of life. However, it is unclear whether any medical interventions are effective for multimorbidity, which means medical practitioners currently offer medical care "in the dark." It is therefore necessary for researchers and medical professionals involved in geriatric medicine to establish ways to manage multimorbidity among older adults. This means that development of research in this field is essential.

Keywords: multimorbidity, older adults, chronic diseases, guidelines, evidence-based

Introduction

Developed countries have experienced increases in the older adult population as well as in life expectancy. The prevalence of various chronic diseases increases with age, and the number of older adults who simultaneously have multiple chronic diseases (multimorbidity) is increasing[1-4]. In older adults, functional decline is observed in most organs, including the cardiac, respiratory, and renal functions. This age-related functional decline occurs even without organ-specific diseases. For example, cognitive function gradually declines with aging even without pathological cognitive decline (i.e., dementia). Aging also affects the bones and muscles that support the human skeleton, resulting in osteoporosis (bones) and sarcopenia (skeletal muscles).

Publications related to multimorbidity have increased in recent years. Fig. 1 shows the number of articles published between 2006 and 2018 retrieved in a search of PubMed using the search term "multimorbidity." The number of relevant papers has increased rapidly since 2010. A literature search conducted on May 15, 2019 found that 311 articles on this topic had already been published in 2019. It can therefore be inferred that the total number of articles on multimorbidity in 2019 will exceed those published in 2018. This rapid increase in the number of articles indicates that this is an era in which many chronic diseases can be observed in one person, and the medical problems associated with multimorbidity have become widely recognized. Multimorbidity causes more medical problems than the issue of simply overlapping diseases. Furthermore, it should be noted that we are still not able to provide medical care for multimorbidity based on sufficient evidence. This review article describes the epidemiology of multimorbidity, its impact on healthcare, and the associated medical problems we are currently facing.

Definition of multimorbidity

Although there is no clear definition of multimorbidity, many articles refer to multimorbidity as a person having two or more chronic diseases at the same time. Some studies also include conditions that are not limited to chronic diseases. In 2016, the World Health Organization defined "multimorbidity" as meaning people with multiple health conditions[5]. In a 2018 report by the Academy of Medical Science, multimorbidity was defined as follows[6].

- The co-existence of two or more chronic conditions, each of which is either a physical non-communicable disease of long duration (e.g., cardiovascular disease) or cancer.
- A mental health condition of long duration, such as a mood disorder or dementia.
- An infectious disease of long duration, such as HIV or hepatitis C.

This broad definition of multimorbidity includes concepts such as mental illness and persistent infections.

Epidemiology of multimorbidity

Because definitions of multimorbidity are inconsistent, the prevalence of multimorbidity varies among reports; however, a common finding is that the prevalence of multimorbidity increases with age. For example, a report from Scotland based on a database of 1,751,841 people aged 0–85 years showed 23.2% of people had two or more chronic diseases, and this percentage increased with age (64.9% in those aged 65–84 years and 81.5% in those aged ≥85 years)[1]. The US National Health and Nutrition Examination Survey 2013–2014 found that among 5541 people aged ≥20 years, the prevalence of multimorbidity (two or more chronic diseases) was 59.6% overall, 37.5% in those aged 20–44 years, 70.6% in those aged 45–64 years, and 91.5% in those aged ≥65

years[2]. In addition, the proportion with four or more chronic diseases was 6.0%, 26.4%, and 55.6% for those aged 0–44 years, 45–64 years, and ≥65 years, respectively. According to a survey of 3737 people aged ≥45 years in China, the prevalence of multimorbidity (two or more chronic diseases) was 34.9% in those aged 45–59 years, 54.9% in those aged 60–69 years, and 60.6% in those aged ≥70 years[3].

A meta-analysis of 39 studies on multimorbidity (two or more chronic diseases) was reported that included a total of 70,057,611 patients in 12 countries[4]. That analysis showed that although the prevalence of multimorbidity was largely dependent on the age of the person surveyed, age and multimorbidity prevalence had a significant positive relationship in all 14 studies that considered this relationship. With regard to patterns of multimorbidity, hypertension and osteoarthritis were the most frequent combination, followed by different combinations of cardiovascular conditions[4].

Impact of multimorbidity on older patients (Fig. 2)

High risk for polypharmacy

The definition of polypharmacy is not always clear, but often refers to the use of 5–6 (or more) drugs. In addition, excessive polypharmacy generally refers to using more than 10 types of drugs. There is a clear link between multimorbidity and polypharmacy, and patients with more chronic diseases tend to use more medications with a greater dosage frequency[7]. Associations between polypharmacy and specific diseases and disease groups have also been reported[8]. A major concern is that polypharmacy increases adverse drug reactions[9], and additional medications may be added to these address adverse reactions.

Relationship with frailty

Definitions of frailty are not consistent, but may be roughly divided into phenotype and deficit accumulation models. For example, in an analysis of a database of 490,000 people in a UK biobank, multimorbidity was more common in frail participants (phenotype model) compared with non-frail participants: odds ratio (OR) 5.14, 95% confidence interval (CI): 4.82–5.49 for two long-term conditions; OR 10.4, 95% CI: 9.7–11.2 for three long-term conditions, and OR 27.1, 95% CI: 25.3–29.1 for four long-term conditions[10]. Although a meta-analysis of nine studies (14,704 people in total) showed the combination of multimorbidity (two or more diseases) and frailty (phenotype model) was about 6%, a pooled analysis of eight cross-sectional studies demonstrated that a diagnosis of frailty was significantly associated with multimorbidity (two or more chronic diseases) compared with those without frailty (OR 2.27, 95% CI: 1.97–2.62)[11]. Although research from longitudinal studies is limited, it has been reported that the presence of multimorbidity (three or more chronic diseases) was a risk factor for developing new frailty (deficit accumulation model) (adjusted OR 6.24) in 1 year[12]. Conversely, a prospective study of patients with HIV showed the risk for incident multimorbidity increased as the frailty index (range 0–1.0) rose by 0.1 (adjusted relative risk 1.98, 95% CI: 1.65–2.35)[13].

Physical function

A systematic review of articles involving primary care outpatients or community dwelling adults that investigated multimorbidity (two or more chronic diseases) and physical function decline (using physical function items included in the 36-item Short Form Health Survey) was conducted in 2015[14]. That review analyzed 37 studies (28

cross-sectional studies and nine cohort studies) with 1–6 years of observation. Most cross-sectional surveys (n = 24/28) found multimorbidity was associated with physical dysfunction, and five cohort studies found multimorbidity was a predictor of incident disability[14].

Several recent cross-sectional and prospective studies have been reported that investigated the effects of multimorbidity on activities of daily living (ADL) decline. A cross-sectional Canadian community-based cohort study involving 1751 older adults reported that an increase in the number of chronic diseases strengthened the association with ADL disorders (adjusted OR 1.35, 95% CI: 1.29–1.42)[15]. In a 5-year prospective report of 1028 older adults from the same study, the risk for ADL decline increased with each additional chronic disease (adjusted OR 1.15, 95% CI: 1.09–1.24). Recently, several prospective studies demonstrated that the combination of chronic disease and mental illness was a strong risk factor for ADL decline in older adults[16].

Cognitive function

Although few studies have focused on the relationship between multimorbidity and cognitive function, many reports have noted that patients with dementia simultaneously possess multiple chronic diseases. For example, 95% of patients with dementia have at least one other chronic disease, 82% have two or more chronic diseases, and 64% have three or more chronic diseases[3]. The Baltimore Longitudinal Study of Aging was a prospective follow-up (mean of 3 years) of 756 people aged 65 years and older without dementia or mild cognitive impairment[17]. As part of that study, a cross-sectional survey at enrollment demonstrated that participants with two or more chronic diseases had significantly worse scores for Digit Symbol Substitution Text and Trail-

Making Test Part B compared with those with one or no chronic disease. However, the significant differences disappeared after adjustment for sex, age, and educational history[17].

A prospective longitudinal survey (mean of 3 years) was conducted with the same participants[17]. Older adults that had an increased number of chronic diseases during the observation period showed significant deterioration in category and letter fluency in the Verbal Fluency Test compared with participants without an increased number of chronic diseases, even after adjustment for confounding factors[17]. That report indicated Trail-Making Test Parts A and B scores also decreased, but there was no significant difference. However, there was no decline in verbal memory or visual memory during the observational period, even among those with an increased number of chronic diseases[17]. These results suggest that the accumulation of chronic diseases may be accompanied by deterioration of certain cognitive functions in older adults, even without the presence of dementia.

Quality of life (QOL) and mental health

Many cross-sectional studies have shown that health-related QOL is reduced in multimorbidity[18-20]. In a 2-year longitudinal study of people aged over 60 years, multimorbidity (two or more chronic diseases) was shown to reduce general health, body function, self-care ability, emotion, and social adaptability domains of health-related QOL, but not memory function[21].

A meta-analysis examined the relationship between multimorbidity and mental health (depression)[22]. That meta-analysis included 43 studies (total of 1,095,93 participants) from low- and middle-income countries, and showed that depression was

significantly associated with multimorbidity (pooled OR 3.26, 95% CI: 2.98–3.57)[22]. In another meta-analysis including 40 studies (total of 381,527 participants), the relative risk for depression was twice as great for participants with multimorbidity compared with those without multimorbidity (risk ratio 2.13, 95% CI: 1.62–2.80), and three times greater for those with multimorbidity compared with those without any chronic diseases (risk ratio 2.97, 95% CI: 2.06–4.27)[23]. In addition, as the number of chronic diseases increased, the OR increased by 45% (OR 1.45, 95% CI: 1.28–1.64) compared with participants who did not have any chronic diseases. These results suggested that multimorbidity was associated with depressive disorder, although the causal relationship was not clear.

Mortality

A relationship between multimorbidity and mortality was highlighted in a meta-analysis conducted in 2016 that analyzed 26 studies[24]. That analysis showed mortality risk increased as the number of diseases increased (hazard ratio [HR] 1.20, 95% CI: 1.10–1.30); the presence of two or more and three or more chronic diseases significantly increased the risk for death compared with non-multimorbidity (HR 1.73, 95% CI: 1.41–2.13 and HR 2.71, 95% CI: 1.81–4.08, respectively)[24]. In an 11-year observational study (1099 participants) over age 78 years, older patients with multimorbidity (two or more chronic diseases) accounted for 70.4% of the total sample, and 70% of all deaths in the 11-year observation period[25]. Those with multimorbidity were also at a significantly higher risk for death (adjusted HR 5.1, 95% CI: 2.6–9.6)[25].

Healthcare utilization and costs

Many studies have demonstrated that multimorbidity increased primary care and specialist visits, as well as hospitalization frequency and length of hospitalization. Furthermore, the more chronic diseases a person possessed, the greater the risk for outpatient visits and hospitalization. A survey of more than 229,493 people in Switzerland aged over 65 years showed patients with multimorbidity (two or more chronic diseases; 76.6% of the sample) were more likely to have had consultations with primary care physicians and specialists and more likely to be hospitalized compared with those without multimorbidity[26]. Specifically, the average number of consultations for patients with multimorbidity was 15.7 times per year compared with 4.4 times for those without multimorbidity, and the cost was 5.5 times higher for patients with multimorbidity. When the number of chronic diseases increased by one, the number of consultations increased by 3.2 times per year and medical expenses increased by 33%. In addition, patients with multimorbidity had a 5.5-fold increased risk for hospitalization compared with those without multimorbidity[26].

A survey of 3737 people in China showed the number of outpatient visits in the past month increased as the number of chronic diseases increased compared with people without chronic diseases[27]. In addition, compared with those without chronic diseases, the adjusted OR (95% CI) for outpatient service use among those with two, three, four, and five or more chronic diseases were 2.9 (1.8–4.7), 4.3 (3.0–6.1), 5.7 (3.4–9.6), and 8.5 (5.6–12.9), respectively; those for inpatient service use were 3.4 (2.1–5.5), 4.0 (2.3–7.1), 4.9 (2.6–9.2), and 7.6 (4.4–13.0), respectively[27].

A 2018 systematic review of 26 papers on the effects of multimorbidity on medical costs conducted by Wang et al. found large variances in each report[28]. However, they noted that compared with non-multimorbidity, multimorbidity with two or more

diseases and three or more diseases was associated with 2–16 times and 2–10 times higher costs, respectively.

Limitations of disease-oriented guidelines

A large number of clinical practice guidelines are currently available worldwide. These guidelines set relevant clinical questions and provide guidance on evidence-based diagnosis and treatment based on systematic reviews of relevant articles. Most current medical care diagnoses and treatments are based on these guidelines. However, it is important to note that most guidelines assume that one patient has a single illness, and do not consider patients that have multiple diseases at the same time. This has implications for medications as well as for other non-drug therapies, such as diet and exercise.

A 2005 study by Boyd et al. reported that available practice guidelines for chronic diseases rarely mentioned older patients with multiple comorbidities, and no guidelines mentioned the burden on patients/carers associated with the complex treatment of multiple diseases[29]. They discussed a hypothetical female patient aged 79 years with a number of chronic diseases (e.g., high blood pressure, diabetes, osteoarthritis, osteoporosis, chronic obstructive pulmonary disease [COPD]). If this hypothetical patient was treated according to the guidelines for each disease, she would have to take 12 drugs frequently. Furthermore, in compliance with each guideline, 14 non-drug therapies also had to be performed. They concluded that it is impossible to carry out such guideline-based actions every day[29].

In 2013, Hughes et al. examined five guidelines published in the UK for type 2 diabetes mellitus, secondary prevention in people with previous myocardial infarction,

osteoarthritis, COPD, and depression[30]. None of these guidelines sufficiently addressed the response to older people aged over 75 years, comorbidity, patient choice and preferences, and adherence in the recommendations[30].

In Japan, a joint committee of the Japan Diabetes Society and the Japan Geriatrics Society for improving treatment of older adults with diabetes proposed "glycemic control targets for elderly diabetes" in 2016[31]. In this proposal, older patients were classified by ADL, cognitive dysfunctions, and comorbidity. Treatment targets were set to prevent hypoglycemia and provide patient-centered and individualized treatment. Furthermore, these societies jointly published the "Aging Diabetes Practice Guideline 2017" and "Aging Diabetes Treatment Guide 2018," which refer to the coexistence of diseases other than diabetes in older patients and various disorders that they may have. Since then, the Japan Geriatrics Society has issued guidelines on various diseases of older patients in collaboration with other agencies including the Japan Hypertension Society, the Japan Atherosclerosis Society, and the Japan Society for the Study of Obesity[32-34]. There is no doubt that these guidelines are extremely important for a super-aged society. However, sufficient concrete guidelines that cover management goals and optimal treatments for each comorbidity have not yet been proposed, as there may not be sufficient research and evidence for such recommendations.

Dietary therapy

In 2018, the European Society for Clinical Nutrition and Metabolism reported new guidelines on nutritional support for polymorbid internal medicine patients[35]. They set 12 clinical questions, conducted systematic reviews, and made recommendations. However, the resulting guideline does not consider nutritional therapy for the

coexistence of specific chronic diseases, but only provides general recommendations. In other words, this guideline does not recommend specific nutrition treatment for certain combinations of chronic diseases. For example, what kind of nutrition treatment should be given to patients with diabetes in addition to other chronic diseases? What kind of nutritional therapy should be given to frail patients with chronic kidney disease?

Pharmacotherapy

Pharmacotherapy for multiple chronic conditions is an important issue. Multimorbidity increases the complexity of therapeutic management for healthcare providers and patients, and impacts on health outcomes. As described above, polypharmacy is not uncommon when drug therapy is performed according to the guidelines for each disease in older patients with multimorbidity. However, in the context of multimorbidity, it is necessary to re-evaluate medications, review prescriptions, and consider alternative treatments to drug treatment. However, there are currently no specific indicators, such as how to prioritize prescriptions.

Exercise programs and rehabilitation

Exercise therapy and rehabilitation are described in many medical practice guidelines; however, only intervention methods for single diseases are described, and existing guidelines do not consider the presence of comorbidity. To our knowledge, there are no well-established exercise or rehabilitation programs for multimorbidity.

Guideline on multimorbidity

For relatively young patients, multiple interventions tailored to the description

of each guideline that emphasize the target value of each guideline for multiple diseases may increase the therapeutic effect. For example, the J-DOIT3 study conducted in Japan was an intervention study that aimed to clarify whether multifactorial interventions for control of glucose, blood pressure, and lipids could reduce macrovascular complications and mortality in patients with type 2 diabetes. The results suggested that cerebrovascular events (stroke, carotid endarterectomy, percutaneous transluminal cerebral angioplasty, and carotid artery stenting) were significantly less frequent in the intensive therapy group (HR 0.42, 95% CI: 0.24–0.74)[36]. However, only a limited number of patients can perform combined treatment consistent with such practice guidelines. In particular, older patients have more chronic diseases and may have many complex problems including psychological and physical disorders, various organ dysfunctions, decline in physiological reserves, sensory disorders, frailty, and malnutrition.

Older adults have various background factors that differ from younger adults. For example, they may have a short life expectancy, living arrangement problems (living alone and older adult households), emphasis on QOL, priorities for medical care, and differences in life values (Fig. 3). Given these differing backgrounds, it may not be possible to follow guidelines for specific diseases that were targeted to younger adults. Therefore, with regard to the multimorbidity of older adults, it is not sufficient to integrate individual guidelines. In addition, there are many combinations of chronic diseases, and it is currently not possible to create complex medical evidence-based guidelines based on a single disease. Multimorbidity research remains insufficient, and it is necessary to advance research on multimorbidity to build as much evidence as possible.

For older adults with multimorbidity, healthcare providers should emphasize

person-centered care rather than disease-oriented treatment, and focus on care that incorporates personal health goals and wishes. A 2016 Cochrane review reported a meta-analysis of 18 intervention studies in primary care and community settings for patients with multimorbidity[37]. Twelve of those studies examined intervention effects of the healthcare delivery system, such as strengthening case management or multidisciplinary team work. The other six studies were patient-oriented interventions; for example, educational or self-management support-type interventions delivered directly to participants. Although some studies in the meta-analysis reported improvement effects on mental health outcomes and physical function, the results were inconsistent, and it was concluded that the intervention effect was not clear overall[37].

Recently, a guideline on multimorbidity has been issued[38]. This guideline is intended to provide guidance on the optimum management of people with multimorbidity who need an approach to care that considers their multimorbidity. Although the recommendations in this guideline are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness, most recommendations were based on weak evidence and lacked specific treatment guidelines for the chronic diseases.

More recently, a cluster-randomized trial of general practices in England and Scotland was conducted for 1546 patients with multimorbidity. The intervention group received a 6-month patient-centered three-dimensional approach[39]. This was a multi-dimensional holistic approach, built from nurse, pharmacist, and physician reviews, where the three professions intervened through a review of the patient's condition from their respective perspectives. The results showed no significant intervention effect on QOL as a primary outcome and no significant difference in hospitalization and death

between the control and intervention groups. Although this article also conducted a meta-analysis of intervention trials for multimorbidity published since the 2016 Cochrane review, the effect of interventions on the QOL of patients with multimorbidity could not be recognized. Therefore, it should be highlighted that we have not yet been able to establish effective interventions for multimorbidity.

Conclusion

It is expected that the number of older patients with multimorbidity will continue to increase in coming years. We need an effective intervention method to manage this issue and support older adults to remain independent and maintain their QOL. However, as described above, effective intervention methods for older patients with multimorbidity remain unclear. Although there are innumerable combinations of chronic disease patterns, recent factor analysis has reported combinations that are easy to merge, and it is important to develop separate intervention methods for these specific chronic disease combinations. Another direction for further research is the development of comprehensive, patient-centered guidelines that can be adapted to the majority of older adult patients with multimorbidity. These guidelines may need to incorporate a comprehensive geriatric assessment-based assessment of the physical and mental functions of older patients. It is important that any such guidelines are evidence-based.

Recent studies on multimorbidity have increased, but there are still few reports from Asian countries. We look forward to future research from Asia that contributes to the evidence of multimorbidity among older patients. The Japan Geriatrics Society, in collaboration with other organizations, has published guidance on the diverse and complex medical care of older patients who have multimorbidity, different clinical

symptoms of diseases, increased risk of adverse drug reactions, and varying social, physical backgrounds[40]. This guidance statement is aimed at helping care providers understand the basic concepts of geriatric medicine and provide proper medical care for older patients. The Japan Geriatrics Society is expected to develop this guidance through further research and to contribute to the further advancement of medical care for older patients with multimorbidity.

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Figure legends

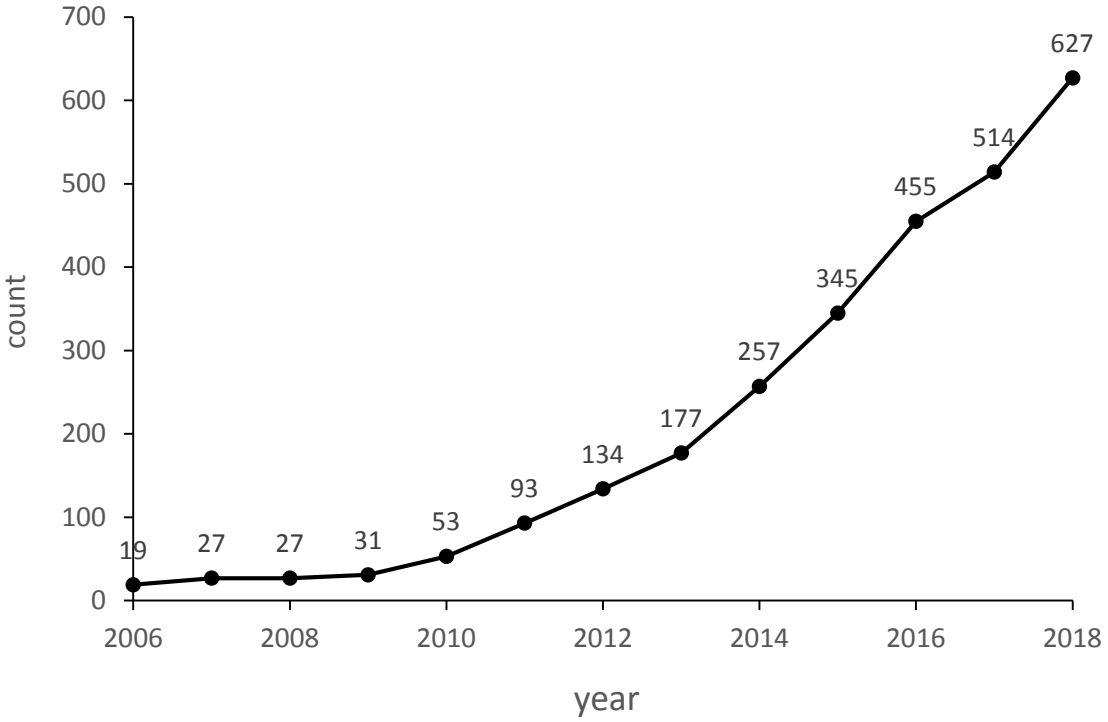
Fig.1 Trends in the number of articles published in PubMed searched by multimorbidity

Fig. 2 Poor health outcomes related with multimorbidity

Fig.3 Older patients with multimorbidity have many complex problems as well as various background factors.

CHD: coronary heart disease; CKD: chronic kidney disease; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; CLD: chronic liver disease.

Fig.1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year

Fig.2

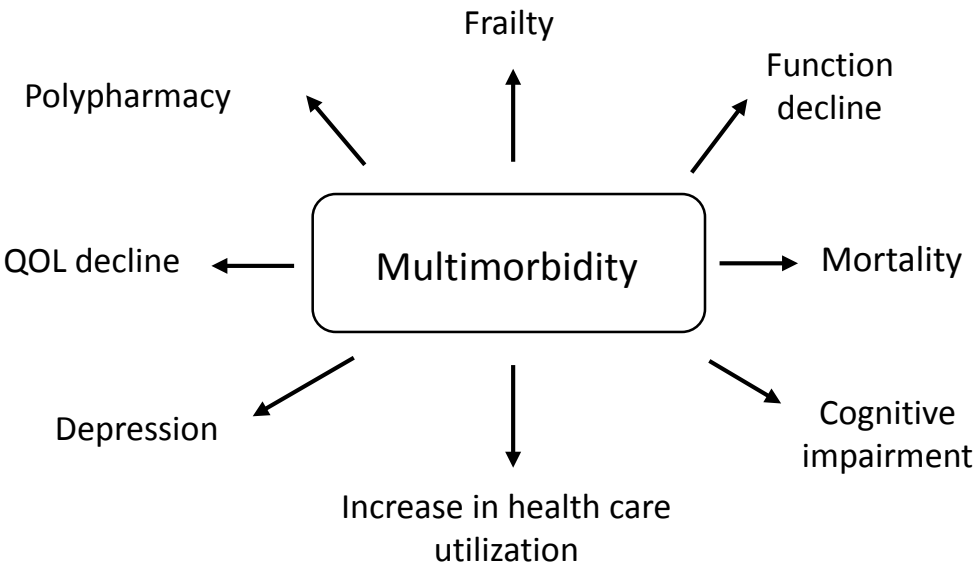
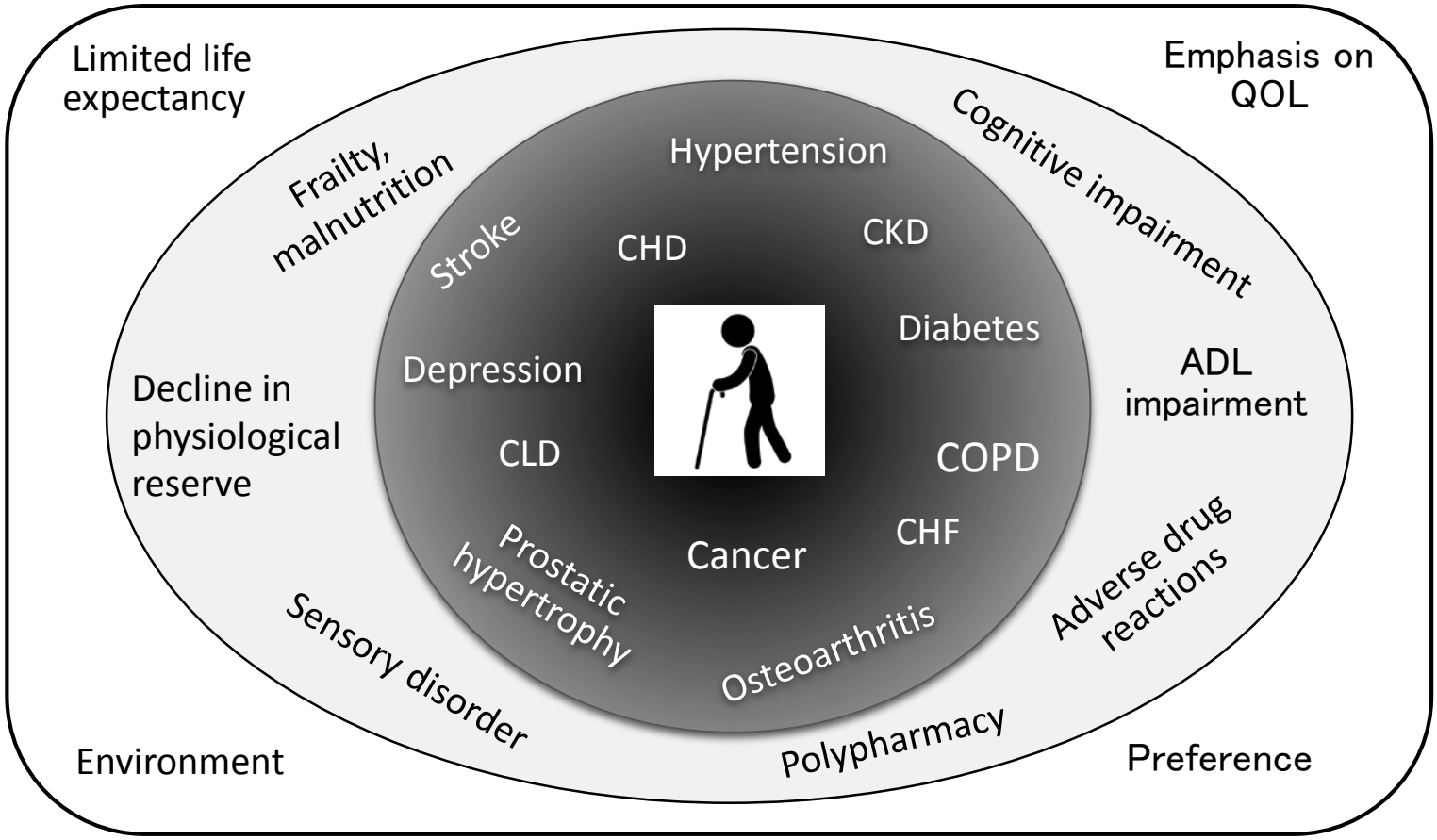

Frailty
Polypharmacy
Function decline
QOL decline
Multimorbidity
Mortality
Depression
Cognitive impairment
Increase in health care utilization

Fig.3


Limited life expectancy
Emphasis on QOL
Frailty, malnutrition
Cognitive impairment
Hypertension
Stroke
CHD
CKD
Diabetes
Depression
Decline in physiological reserve
ADL impairment
CLD
COPD
CHF
Cancer
Prostatic hypertrophy
Adverse drug reactions
Sensory disorder
Osteoarthritis
Environment
Polypharmacy
Preference