Epidemiology of Sarcopenia and Frailty in CKD

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Abstract

Chronic kidney disease (CKD) is very common in the elderly. CKD-related metabolic derangements increase the risk of skeletal muscle wasting, so the prevalence of sarcopenia and frailty are substantially higher in CKD patients compared to the general population. Sarcopenia is defined according to the Asian Working Group for Sarcopenia (AWGS), while frailty according to the Japanese version of the Cardiovascular Health Study (J-CHS) in Japan. Sarcopenia and frailty are closely associated with protein-energy wasting. Frailty is also more prevalent in female than in male in CKD patients.

Sarcopenia and frailty are both related to survival prognosis and accelerated progression to end-stage kidney disease in patients with non-dialysis-dependent CKD. In dialysis patients, low muscle strength rather than muscle mass volume is more strongly associated with physical inactivity, inflammation, and total mortality. Frailty is also an independent predictor of cognitive impairment, hospitalization, and mortality in the dialysis population.

Given the convincing relationship between sarcopenia, frailty, and adverse clinical outcomes, we should be more aware of the concept of sarcopenia and frailty and prevent their progressions especially in older patients with advanced CKD.

Keywords

CKD prevalence · Definition · Protein-energy wasting · Renal outcome · Mortality

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1.1 Introduction

Sarcopenia is a progressive and generalized "skeletal muscle disease" that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality. In contrast, frailty is "a geriatric syndrome" that is observed as the decline over a lifetime in multiple physiological systems, resulting in negative consequences to physical, cognitive, and social dimensions.

In this chapter, demonstrating after the current trends of CKD epidemiology, I review the epidemiology of sarcopenia and frailty in patients with non-dialysis and dialysis-dependent CKD.

1.2 Current trends in CKD epidemiology

1.2.1 Renal Replacement Therapy (RRT)

More than 2 million people worldwide are being treated for end-stage renal disease (ESRD). The global incidence of dialysis more than doubled from 44 incidents per million people (pmp) in 1990 to 93 pmp in 2010 [1]. The global prevalence of maintenance dialysis has also increased 1.7 times, from 165 pmp in 1990 to 284 pmp in 2010. A systematic review [2] also estimates that 2.6 million people received RRT worldwide in 2010, whereas the number of patients requiring RRT is between 4.9 and 9.7 million. This review also points out that, with rising global incomes, worldwide use of RRT will be more than double to 5.4 million people in 2030, with the most growth in Asia (1.0 million to a projected 2.2 million) and most rapid relative increase projected in Latin America (from 0.37 million in 2010 to 0.90 million by 2030).

In contrast, in already developed nations that provide universal access to maintenance dialysis, there has been a plateauing in rates of ESRD, with recent declines in incidence. In the USA, ESRD incidence adjusted for age, sex, and race/ethnicity was 386 pmp in 2003, but decreased to 356, 352, and 351 pmp in 2011, 2012, and 2013, respectively [3]. In Japan, the actual number of new dialysis patients with diabetic nephropathy has almost been unchanged for the recent few years [4].

1.2.2 Non-dialysis CKD

A meta-analysis of 44 country prevalence studies [5] have demonstrated that the worldwide prevalence of CKD at 13.4% in 2010 (95% confidence interval [95% CI], 11.7–15.1%). A survey of 33 prevalence studies [6] also estimates worldwide prevalence of CKD at 10.4% in men (95%CI, 9.3–11.9%) and at 11.8% in women (95%CI, 11.2–12.6%), with a 15% higher prevalence in low- and middle-income countries compared with high-income countries. The Global Burden of Disease study [7] predicts that there were 21 million incident case of CKD

per year, 276 million prevalent cases, and nearly 1.2 million death and 35 million years of healthy life lost due to CKD in 2016.

The prevalence of CKD is especially high in the elderly. Analyses of recent data from the US National Health and Nutrition Examination Survey (NHANES) demonstrated that the crude prevalence of CKD at stages G3 (eGFR from 30 to 59 ml/min/1.73 m^2) and G4 (eGFR from 15 to 29 ml/min/1.73 m^2) were 4.1% in subjects aged 20–39 years and 10.8% in those aged 40–64 years, while it reached 31.5% in those aged 65–79 years and 65.0% in those over 80 years [8]. Similarly, in Japan, prevalence rates of stage G3 and G4 CKD have been estimated at 43.1% in males and 44.5% in females aged over 80 years old [9].

1.2.3 Clinical Outcomes of CKD

In addition to being a precursor to ESRD, CKD is a potent risk factor for other adverse outcomes, such as acute kidney injury, cardiovascular disease, and mortality. The risk of ESRD, or death related to CKD comorbidities prior to dialysis initiation, varies by age. Analyses of data from a cohort of US veterans [10] demonstrated that younger patients (18–44 years old) were at risk of reaching ESRD before death at eGFR <45 ml/min/1.73 m^2, whereas for older patients (65–84 years old), the risk of ESRD first exceeded death at an eGFR of <15 ml/min/1.73 m^2. It was also demonstrated that the risk of death always exceeded the risk of ESRD among those 85 years or older. Among patients with CKD stage G4 who were referred to nephrologists, the rate of death without requiring RRT increased from the age of 50 years onwards, and exceeded that of RRT in incident patients aged ≥80 years old [11]. Specifically, older patients with low-grade proteinuria were more likely to die before requiring RRT [11]. A retrospective review of CKD in stage G3 to G5 patients also demonstrated that younger individuals are at higher risk of ESRD, whereas older individuals are more likely to die prior to developing ESRD [12]. The review found that the risk of death prior to ESRD relative to the onset of ESRD was about threefold higher for CKD stage G3, while equal for stage G4, and lower for stage G5, after adjusting for age and other cofounders [12]. It follows from these studies, therefore, that the oldest CKD patients almost died before the initiation of RRT.

In Japan, a cohort study in 461 referred CKD patients (mean age: 67.0 years) demonstrated that the incidence of death before RRT was 2.8/100 patient-years and none had ESRD among CKD stage 3 patients older than 65 years without overt proteinuria during median follow-up was 3.2 years [13]. Newly visiting CKD patients with normal-range proteinuria also did not exhibit a decline of kidney function even in advanced CKD stages 4–5 under specialized nephrology care [14]. The observations suggest that elderly CKD patients with normal-range proteinuria may not exhibit CKD progression even in advanced CKD stage. Therefore, elongation of a healthy life expectancy is more complicated than simply slowing eGFR decline in the elderly with CKD stage G3 and G4.

1.3 Epidemiology of Sarcopenia in CKD

1.3.1 Definition of Sarcopenia

Sarcopenia originally refers to the age-related reduction of appendicular skeletal muscle mass volume. However, in recognition that loss of strength or physical function often accompanies loss of muscle mass, it has been defined to include both low muscle mass and compromised functionality, such as reduced handgrip strength and/or slower gait speed.

Recently, the European Working Group on Sarcopenia in Older People (EWGSOP2) [15] updates the original definition in order to reflect scientific and clinical evidence that has built over the last decade. The working group recognizes sarcopenia, i.e., muscle failure, as "a muscle disease" rooted in adverse muscle changes across a lifetime that may be acute or chronic. Sarcopenia is defined by low levels of measures for three parameters in numerical order: (1) muscle strength, (2) muscle quantity/quality, and (3) physical performance as an indicator of severity (Table 1.1). They also recommend an algorithm for case-finding, diagnosis, and severity determination for systematic and consistent identification of people with sarcopenia or its risk.

In Asia, the Asian Working Group for Sarcopenia (AWGS) [16] defined the cutoff values for muscle mass measurements (7.0 kg/m^2 for men and 5.4 kg/m^2 for women by using dual X-ray absorptiometry, and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women by using bioimpedance analysis), handgrip strength (<26 kg for men and <18 kg for women), and usual gait speed (<0.8 m/s) for the elderly. A revised consensus paper of AWGS (AWGS2019) has been recently published (Chen LK, et al. J Am Med Dir Assoc, in press). In this revision, calf circumference (<34 cm for men and <33cm for women) is available for the screening of sarcopenia. In addition, the cutoff of handgrip strength for men is elevated to <28 kg. Low physical perfomance can be diagnosed by either usual gait speed (<1.0 m/s), 5 sit to stand test (> or = 12 sec), or short physical perfprmance battery (< or = 9 points).

Table 1.1 EWGSOP2 sarcopenia cutoff points

Test	Cutoff points for men	Cutoff points for women
Low strength by chair stand and grip strength		
Grip strength	<27 kg	<16 kg
Chair stand	>15 s for five rises	
Low muscle quantity		
ASM	<20 kg	<15 kg
ASM/height^2	<7.0 kg/m^2	5.5 kg/m^2
Low performance		
Gait speed	≤0.8 m/s	
SPPB	≤8 point score	
TUG	≥20 s	
400 m walk test	Non-completion or ≥6 min for completion	

ASM appendicular skeletal muscle mass, *SPBB* short physical performance battery, *TUG* timed-up-and-go test

1.3.2 Sarcopenia in Non-dialysis CKD

The prevalence of sarcopenia is higher among adult patients with non-dialysis-dependent CKD compared to the general population, ranging from 5.9 to 50.0% [17–21] (Table 1.2). Sarcopenia is more prevalent in men than in women [19, 20]. An increased risk of sarcopenia is associated with age, body mass index, diabetes mellitus, and loop diuretic use [20].

Sarcopenia is related to survival prognosis [17] and GFR decline [19]. A lower bilateral psoas mass area at CT slice is an independent predictor of major adverse cardiovascular events in CKD patients [22].

1.3.3 Sarcopenia in Dialysis Patients

Dialysis patients exhibit more functionally muscle wasting than patient with CKD stage G4 [23]. The prevalence of sarcopenia is substantially high among hemodialysis (HD) patients, ranging from 9.5 to 37.1% (Table 1.3) [24–29]. The prevalence of sarcopenia was 8.4% in Japanese peritoneal dialysis (PD) patients using the AWGS criteria [30].

Low muscle strength rather than muscle mass volume was more strongly associated with physical inactivity, inflammation, and mortality than low muscle mass in incident dialysis patients [24]. Physical performance measures, including slow gait speed and weak grip strength, were also associated with mortality even after adjustment for

Table 1.2 Prevalence of sarcopenia in CKD patients not yet on dialysis

N	Age (years)	Mean eGFR (ml/min/1.73 m^2)	Definition	Prevalence of sarcopenia (%)	Reference
287	59.9 ± 10.5 (Brazil)	25.0 ± 15.8	Handgrip (<30th percentile of a reference population adjusted for sex and age) ASM/height^2 (BIA) (Male <10.76, Female <6.76 kg/m^2)	5.9	[17]
100	73.6 ± 9.2 (Brazil)	36.0 ± 16.0	EWGSOP FNIH	11.9 28.7	[18]
148	66 [19–87] (Sweden)	22.5 ± 8.2	EWGSOP	13.5	[19]
260	79 [69–80] (Japan)	31.5 ± 12.9	AWGS	25.0	[20]
80	73.7 ± 7.2 (Italy)	28.3 ± 9.8	EWGSOP	12.5 (60–74 years) 50.0 (≥75 years)	[21]

ASM appendicular skeletal muscle mass, *EWGOP* European Working Group on Sarcopenia in Older people, *FNIH* Foundation for the National Institutes of Health, *AWGS* Asian Working Group for Sarcopenia, *BIA* bioelectrical impedance analysis

Table 1.3 Prevalence of sarcopenia in dialysis patients

N	Age (years) (country) [reference]	Sample characteristics	Cutoff values		Prevalence of sarcopenia (%)
			Appendicular SMI (kg BW/height m^2)	Handgrip (kg)	
330	53 ± 13 (Sweden) [24]	Incident (HD 100%)	DEX Male <7.3 Female <5.5	Male <30 Female <20	20.6
95	64 ± 10 (South Korea) [25]	Prevalent (HD 57%)	BIA (2SDs below the sex-specific mean of young adults)		9.5
102	71 ± 7 (Brazil) [26]	Prevalent (HD 73.5%)	1. DEX 2. BIA (2SDs below the sex-specific mean of young adults)		1. 30.6 2. 12.7
111	77.5 (71–85) (France) [27]	Prevalent (HD 100%)	BIA Male <8.87 Female <6.42		31.5
645	56.7 ± 14.5 (USA) [28]	Prevalent (HD 100%)	BIS-derived total-body muscle mass to $height^2$, BW, BSA, and BMI (2SDs below the sex-specific mean of young adults)	Male <26 Female <16	$Height^2$: 3.9 BW: 11.4 BSA: 15.9 BMI: 14.0
170	70 ± 7 (Brazil) [29]	Prevalent (HD 100%)	DEX (2SDs below the sex-specific mean of young adults)	Male <30 Female <20	37.1

HD hemodialysis, *SMI* skeletal muscle mass index, *DXA* dual energy X-ray absorptiometry, *BIA* bioelectrical impedance analysis, *BIS* bioelectrical impedance spectroscopy, *BSA* body surface area, *BW* body weight, *BMI* body mass index

muscle size and other confounders in prevalent HD patients [28]. Low muscle strength was associated with worse quality of life (QOL) domains [29]. So, functional limitations (in strength or speed) are mainly associated with mortality, whereas muscle size appeared to be less important with regard to survival among dialysis patients.

Sarcopenia is also related to accelerated changes of arteriosclerosis. Reduced thigh muscle mass area is independently related to arteriosclerotic parameters such as carotid artery intima-medial thickness, brachial-ankle pulse wave velocity, and ankle-brachial pressure index, indicating that thigh sarcopenia is closely associated with systemic changes of arteriosclerosis in HD patients [31].

1.4 Epidemiology of Frailty in CKD

1.4.1 Definition of Frailty

Frailty is "a multidimensional geriatric syndrome" that is characterized by cumulative decline in multiple body systems or functions. Frailty increases

vulnerability to poor health outcomes such as disability, hospital admission, reduced QOL, and even death.

There are two approaches to assessing frailty: one is phenotype model [32] and the other is accumulated deficit model [33]. The physical phenotype of frailty, originally described by Fried and co-workers [32], is characterized by the phenotype according to limitations in three or more of the following five conditions based on Cardiovascular Health Study (CHS): slow gait speed, weakness, exhaustion, low activity, and weight loss. This criteria overlaps with sarcopenia; low grip strength and slow gait speed are characteristic of both.

In contrast, frailty index, a typical accumulated deficit model, is to count deficits in health (which can be symptoms, signs, diseases, disabilities or laboratory, radiographic or electrocardiographic abnormalities) on the grounds that the more deficits a person has, the more likely that person is to be frail. This index is often expressed as a ratio of deficits present to the total number of deficits considered [34].

To date, fundamental differences in the conceptualization of frailty among these approaches result in long-standing hurdles to uniform agreement on a single definition that can be used for identifying those who are at high risk and in need of comprehensive care.

1.4.2 Modified Definition of Frailty in Japan

The Kihon Check List (LCL), which consists of 25 questions to screen participants who require care prevention, is used as a screening tool to assess frailty in Japan [35]. KCL is divided into the eight domains: instrumental activities of daily living (ADL), social ADL, exercise, falling, nutrition, oral function, cognitive function, and depression. Participants are asked to respond either "negative" (score: 1) or "positive" (score: 0), for a total score of 25. Frailty is evaluated by the total points as follows: frail, 8–25 points; pre-frail, 4–7 points; and robust, 0–3 points [35].

Frailty can be also diagnosed by the Japanese version of the Cardiovascular Health Study (J-CHS) [36]. Slow gait speed is established based on a cutoff of <1.0 m/s. Weakness is defined using maximum grip strength and was established according to a sex-specific cutoff (<26 kg for men and <18 kg for women), identical to AWGS criteria [16]. Exhaustion is considered present if a participant responded "yes" to the following question included in the KCL: "In the last 2 weeks, have you felt tired without a reason?" Physical activity is evaluated by asking the following questions about the time spent engaged in exercise: "Do you engage in low levels of physical exercise aimed at health?" If participants answered "no" to the questions, we classified them to the low activity category. Weight loss was assessed by a response of "yes" to the question, "Have you lost 2 kg or more in the past 6 months?". Participants who do not have any of these components are considered as non-frail (robust), and those with one or two components were considered as pre-frail.

1.4.3 Frailty in Non-dialysis CKD

The prevalence of frailty defined by the Fried phenotype [32] ranges from 7 to 20.9% in pre-dialysis patients [37]. Frailty phenotypes such as body weight loss, low physical activity, and slow gait speed are independently associated with CKD progression and/or total mortality in CKD stages G1 to G4 patients [38]. Physical function such as gait speed and handgrip decreases in ambulant patients with CKD stage 4 or 5 than those with CKD stage 2 or 3 [39].

In community-dwelling Japanese older adults, participants with CKD stage 4 or 5 were more frail (odds ratio [OR] 1.90, 95% confidence interval [CI] 1.01–3.59). In addition, the individuals with a history of diabetes (OR 2.76, 95% CI 1.21–8.24), hypertension (OR 2.53, 95% CI 1.45–5.12), or both (OR 3.67, 95% CI 1.13–14.1) showed a significantly higher risk of frailty [40]. In addition, reduced kidney function (CKD stage 4–5) was associated with a higher risk of weight loss, low physical activity, and slowness [41].

The frailty phenotype was associated with an estimated 2.5 (95% CI, 1.4–4.4)-fold greater risk of death or incident dialysis therapy [42]. Frailty is independently linked to adverse outcomes such as lower physical and metal QOL [43], and limited activity of daily life (ADL) [44].

1.4.4 Frailty in Dialysis Patients

The prevalence of frailty is high in the dialysis populations, ranging from 24 to 78% [37]. However, since several studies have made modification to the frailty phenotype originally proposed, reported prevalence changes depending on the method of frailty assessment [37]. The prevalence of pre-frailty and frailty based on J-CHS criteria [36] was 52.6 and 21.4% in prevalent 413 Japanese HD patients (mean age 67.2 ± 11.9 years old). The 56.6% of the patients were categorized as pre-frailty and 32.7% as frailty among those aged over 75 years old ($n = 113$) [45]. The prevalence of frailty is reported as 10.9% when diagnosed using the Clinical Frailty Scale [30] in Japanese PD patients.

Frailty is an independent predictor of mortality and hospitalization in maintenance dialysis patients [46]. All five phenotype components are associated with higher mortality, and gait speed was the strongest individual predictor. The number of frailty components met was associated with mortality in a gradient that ranged from a hazard ratio of 2.73 for one component to 10.07 for five components met [47], indicating that measurement of all components was exclusively essential for optimal mortality prediction.

Frailty is also associated with impaired cognitive function using the Modified Mini-Mental State test and Trail Making Tests A and B among patients new to HD [48].

Table 1.4 Criteria for the clinical diagnosis of PEW in CKD

Serum chemistry
Serum albumin<3.8 g/dL (Bromocresol green assay)
Serum transthyretin <30 mg/dL (for maintenance dialysis patients only)
Serum cholesterol<100 mg/dL
Body mass
Body mass index (BMI) <23 kg/m^2
Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
Total body fat percentage <10%
Muscle mass
Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population)
Creatinine appearance
Dietary intake
Unintentional low daily protein intake <0.80 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients with CKD stages 2–5
Unintentional low daily energy intake <25 kcal/kg/day for at least 2 months

Incident dialysis patients self-reporting frailty experienced nearly twice the risk of medically urgent falls or fractures compared to those who did not report frailty [49].

1.5 Association of Protein-Energy Wasting with Sarcopenia, and Frailty Phenotype

Protein-energy wasting (PEW) is defined by an expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) in 2008 as the loss of somatic and circulating body protein and energy reserves [50]. PEW develops as the consequence of a combination of insufficient, uremic toxins, systematic inflammation, and superimposed catabolism. PEW can be diagnosed if at least 3 of the 4 listed categories (and at least one test in each of the selected category) are satisfied (Table 1.4).

A systematic review [51] reported that PEW prevalence ranges 11–54% in patients with CKD stages G3 to G5, and 28–54% in dialysis patients. About 15.3–17.1% of Japanese HD patients have PEW based on the ISRNM criteria [52, 53]. Since the hazard ratio for mortality became maximal at BMI <20 kg/m^2 in Japanese HD patients, a lower BMI may be more suitable to diagnose the presence of PEW in the Asia population.

Decreased muscle mass is the same category in sarcopenia and PEW, while anthropometric measurements are different. Unintentional loss of body weight is also applied in the phenotype of frailty and PEW (Fig. 1.1).

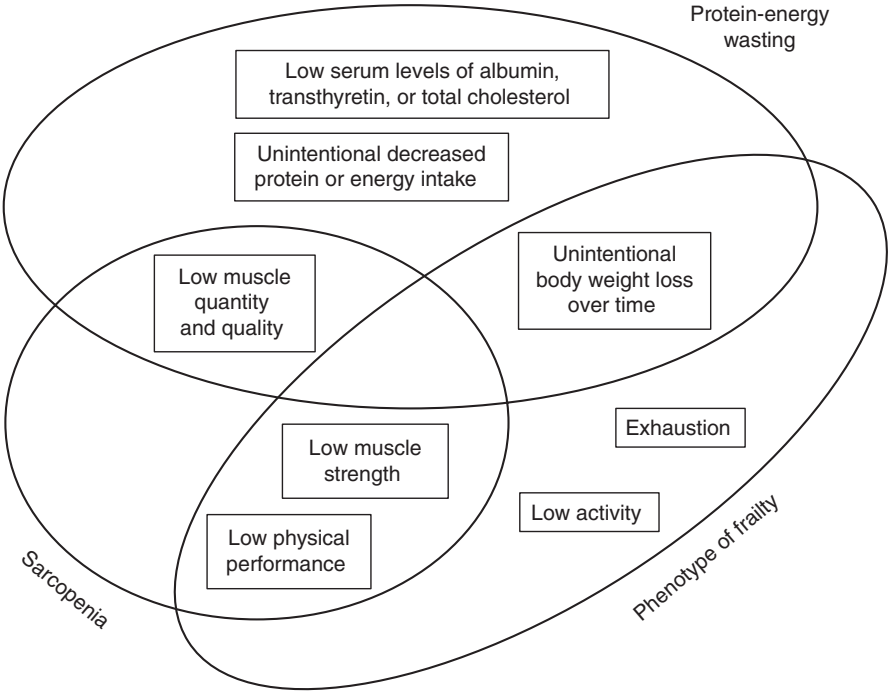

Fig. 1.1 Comparison of protein-energy wasting, sarcopenia, and phenotype of frailty

1.6 Conclusion

Currently, over 850 million people have been suffering from some form of kidney disease in the world. CKD is a potent risk for fatal cardiovascular events. Annual costs per one patient for HD are expensive, thereby imposing a heavy financial burden on healthcare budgets.

CKD is a predominant disease of the elderly. So, we need to consider the influence of aging, lifestyle, and social factors on renal and overall health, as well as CKD-related comorbidities and complications (Fig. 1.2). Especially, sarcopenia and frailty are very common. Given the convincing relationship between sarcopenia, frailty, and adverse clinical outcomes, we should be more aware of the concept of sarcopenia and frailty in older patients with advanced CKD.

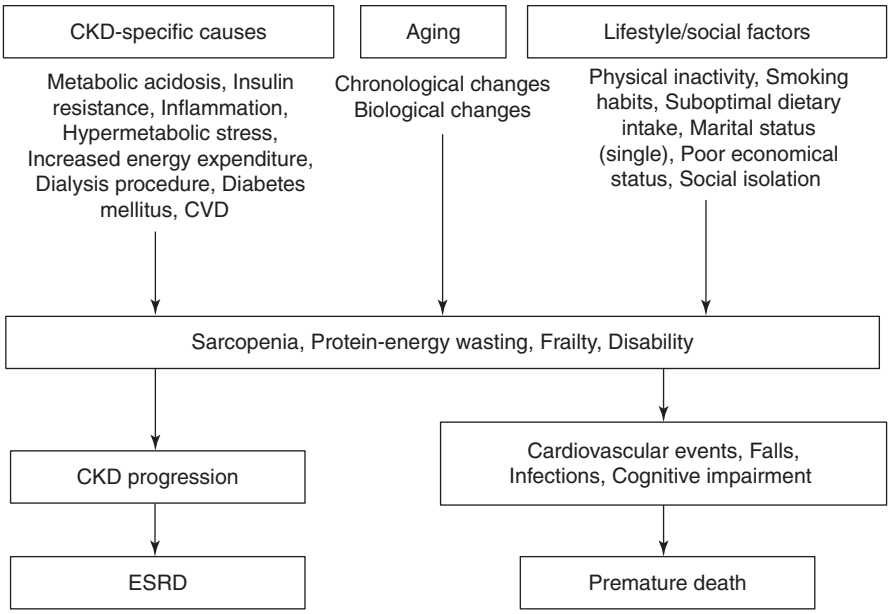

Fig. 1.2 Association of chronic kidney disease-related causes, aging, and lifestyle/social-related factors with clinical outcomes. *CKD* chronic kidney disease, *CVD* cardiovascular disease, and *ESRD* end-stage renal disease

Disclosures I declare that I have no competing interests.

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