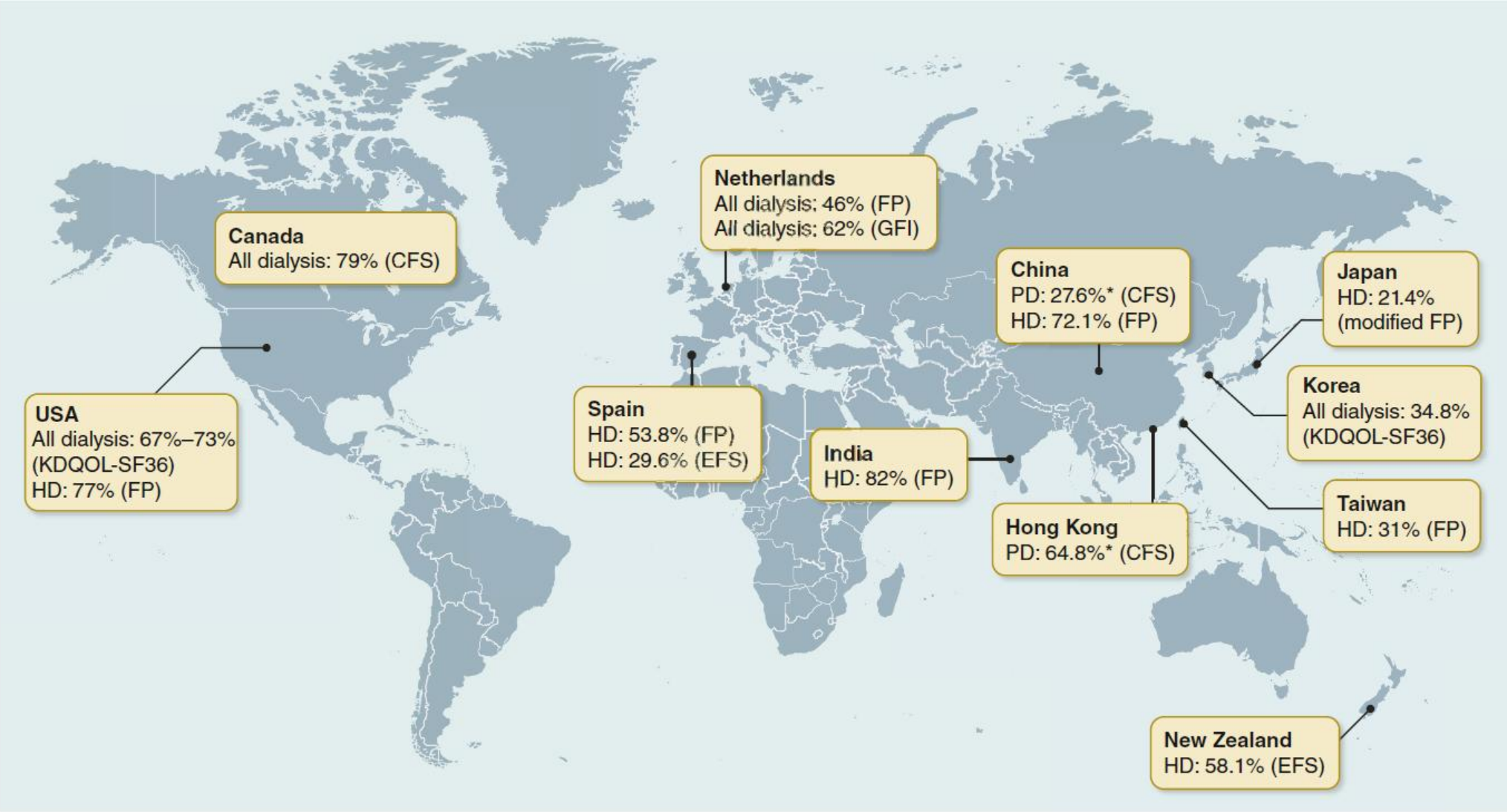
Sex Differences of Frailty in Dialysis Patients

Ting-Yun Lin, MD

Division of Nephrology, Taipei Tzu Chi Hospital

Prevalence of frailty in ESKD



Chan GC et al. Kidney Int 106:35–49, 2024

Associations and outcomes with frailty in dialysis patients

Associations	Outcomes
Morbidities	Lower bone mass[17]
	Higher rate of fall and fracture[5,15,17]
	Anxiety and depression[10,18]
	Cognitive impairment[2]
	Disease symptom[18]
	Disability and institutionalization[7,10]
Hospitalization	Higher rate of emergency room attendance[5]
	Shorter time to first hospitalization[14]
	Higher rate of hospitalization[4,5,7,11,19]
	Longer duration of hospitalization[4,19]
	Higher hospitalization expenditure[20]
Cardiovascular	Higher rate of cardiovascular event[19,21]
Infection	Higher rate of infection-related hospitalization[4]
Transplant-related	Less likely to be waitlisted[4]
	Higher chance of being delisted[4]
	Higher rate of waitlist mortality[4,22]
	Higher rate of delayed graft function[23]
	Longer duration of postoperative hospitalization[23]
Dialysis-specific	Slower rate of vascular access (arteriovenous fistula and graft) maturation[24]
	Higher rate of vascular access thrombosis[12,25]
	More frequent vascular access revision and/or intervention[24]
	Increased peritoneal dialysis–associated peritonitis rate[2]
Survival	Higher rate of mortality[1,7,11]

Chan GC et al. Kidney Int 106:35–49, 2024

Predictors of frailty among incident dialysis patients

The Comprehensive Dialysis Study (CDS)

- ✓ 1576 incident patients receiving hemodialysis
- ✓ A modified version of Fried's criteria—comprising slowness/weakness, exhaustion, and low physical activity—was applied.
- ✓ Frailty was defined as a score of two or higher.

	Frail	
Variable	**OR (95% CI)**	***P* Value**
Age, per 10 y	1.00 (0.90-1.11)	.98
Male sex	0.49 (0.39-0.62)	<.001
White race	1.25 (0.96-1.62)	.10
Medicaid, vs other payers	1.70 (1.22-2.36)	.002
Current smoker	1.27 (0.76-2.13)	.36
eGFR, per 5 mL/min/1.73 m^2 increase	1.44 (1.23-1.68)	<.001
Albumin quartiles/missing		.37 for trend
Group 1: ≤2.5 g/dL	0.98 (0.66-1.46)	.92
Group 2: >2.5-3.0 g/dL	1.12 (0.78-1.61)	.55
Group 3: missing	1.11 (0.80-1.54)	.53
Group 4: >3.0-3.5 g/dL	1 [Reference]	
Group 5: >3.5 g/dL	0.85 (0.61-1.20)	.35
Hemoglobin quartiles/missing		.07 for trend
Group 1: ≤9 g/dL	1 [Reference]	
Group 2: >9-10 g/dL	1.07 (0.76-1.51)	.69
Group 3: missing	0.99 (0.63-1.57)	.97
Group 4: >10-12 g/dL	1.04 (0.77-1.42)	.80
Group 5: >12 g/dL	1.61 (1.02-2.53)	.04
Hemodialysis	1.04 (0.71-1.53)	.84
Comorbidity		
Diabetes mellitus	1.52 (1.18-1.96)	.001
Congestive heart failure	1.27 (0.94-1.70)	.11
Atherosclerotic heart disease	0.96 (0.68-1.34)	.80
CVA/TIA	1.85 (1.04-3.28)	.04
Peripheral vascular disease	1.67 (1.16-2.41)	.006
COPD	1.77 (0.96-3.25)	.07
Cancer	1.19 (0.70-2.03)	.52

Bao Y et al. Arch Intern Med 172:1071–1077, 2012

Factors associated with frailty

A prospective Taiwanese cohort study

- ✓ 761 prevalent patients receiving hemodialysis
- ✓ Performance-based frailty was defined as 3 of the following: unintentional weight loss, weakness, exhaustion, low physical activity, and slow gait speed.

Variable	Univariable OR (95% CI)	*P*	Multivariable[a] OR (95% CI)	*P*
Demographic Factors				
Age				
<65 y	1.00 (reference)	—	1.00 (reference)	—
65-75 y	2.80 (1.86-4.20)	<0.001	1.90 (1.22-2.95)	0.004
>75 y	5.55 (3.78-8.16)	<0.001	4.13 (2.72-6.29)	<0.001
Female sex	1.86 (1.37-2.54)	<0.001	1.62 (1.15-2.31)	0.006
BMI				
<18.5 kg/m^2	1.00 (reference)		1.00 (reference)	
18.5-24 kg/m^2	0.40 (0.25-0.65)	<0.001	0.37 (0.22-0.65)	<0.001
24-27 kg/m^2	0.38 (0.22-0.66)	0.001	0.35 (0.19-0.66)	0.001
>27 kg/m^2	0.32 (0.17-0.59)	<0.001	0.37 (0.19-0.74)	0.005
Socioeconomic Factors				
Education >6 y	0.52 (0.38-0.72)	<0.001		
Employed	0.24 (0.16-0.37)	<0.001		
ADL disability	6.97 (4.96-9.81)	<0.001		
Comorbidities				
Diabetes	1.75 (1.29-2.40)	<0.001	1.65 (1.15-2.37)	0.01
CAD	1.42 (1.02-1.97)	0.04		
PAD	2.03 (1.34-3.07)	0.001		
CVA	2.33 (1.38-3.92)	<0.001	2.09 (1.16-3.76)	0.02
Vascular diseases	1.79 (1.31-2.45)	<0.001		
Comorbidity index >4	1.11 (1.00-1.24)	0.05		
Dialysis				
AVG	1.88 (1.28-2.76)	0.001		
Albumin, per 1-g/dL greater	0.21 (0.13-0.34)	<0.001	0.38 (0.22-0.66)	0.001
Hemoglobin, per 1-g/dL greater	0.81 (0.72-0.91)	<0.001		

Luo CM et al. Am J Kidney Dis 80:353–363.e1, 2022

Risk factors for frailty in hemodialysis patients

A systematic review and meta-analysis

Risk Factors	No. of Studies	No. of Participants	OR/SMD	95% CI	I^2 (%)	*p*-Value	Egger's Test p
Demographic characteristics							
Age (years)	6	1787	0.43 *	0.24–0.61	72	0.003	0.018
Sex (female)	7	2604	1.89	1.33 –2.67	71	0.002	0.395
Smoking, yes	3	721	1.39	0.58–3.32	80	0.005	0.186
Comorbidities							
Diabetes mellitus, yes	7	2604	2.42	1.68–3.49	73	0.001	0.108
Hypertension, yes	3	721	2.16	0.46–10.04	82	0.003	0.472
CAD, yes	3	1249	0.96	0.63–1.46	57	0.098	0.668
PVD, yes	5	1600	1.87	0.81–4.29	68	<0.001	0.240
HF, yes	4	1483	1.35	0.92–2.00	57	0.070	0.588
CVA or TIA, yes	4	1454	1.96	0.93–4.17	73	0.011	0.161
COPD, yes	3	633	1.43	0.98–2.09	0	0.835	0.532
Cancer, yes	2	516	1.35	0.48–3.84	68	0.077	NA

Note. * SMD = standardized mean difference; OR = odds ratio; CI = confidence interval; CAD = coronary artery disease; PVD = peripheral vascular disease; HF = heart failure; CVA = cerebral vascular disease; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease.

Lee HJ et al. Int J Environ Res Public Health 18:3471, 2021

Sex-specific associations in frailty

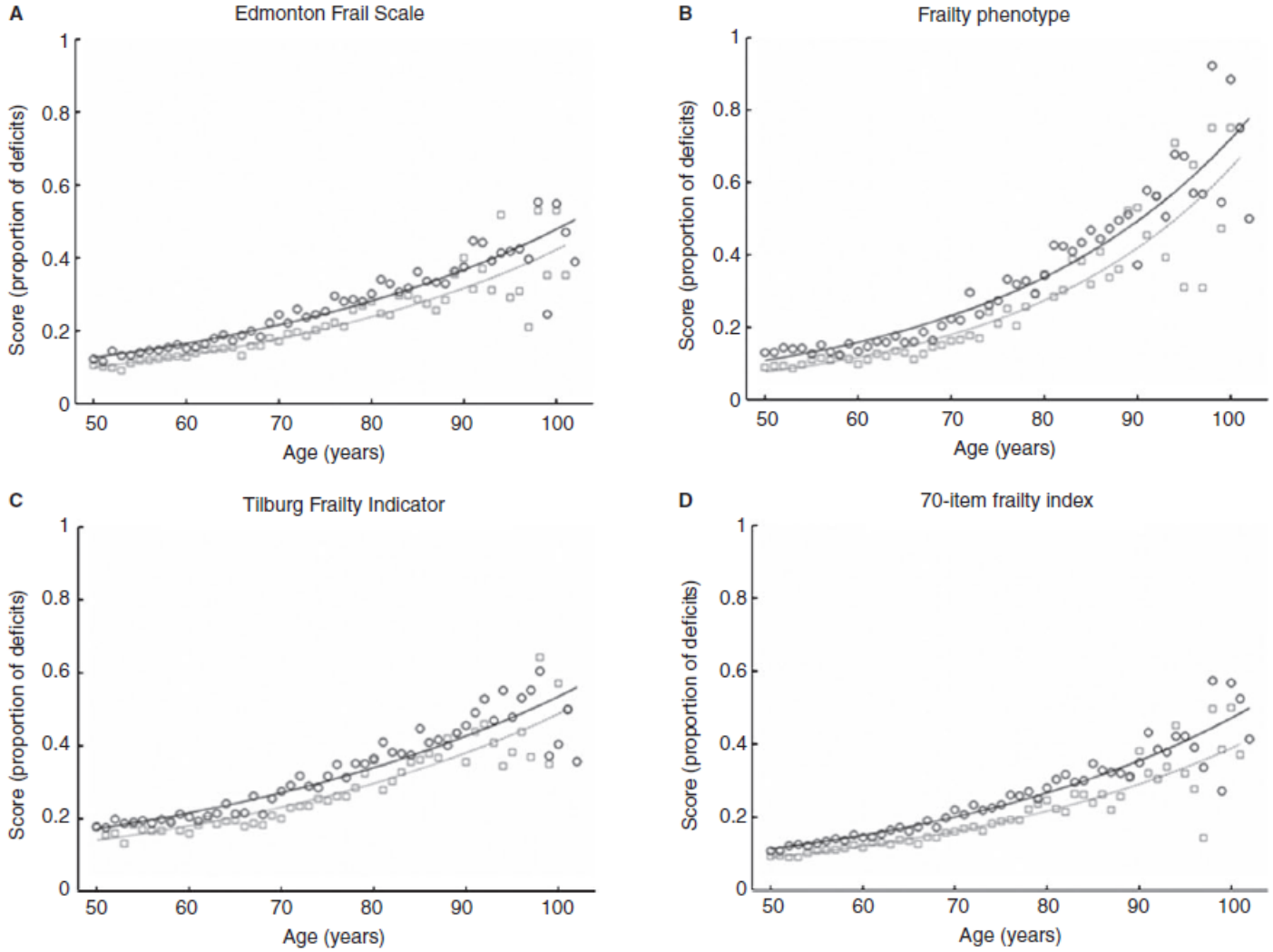
Clinical studies in the elderly

	Finding	Reference
Pre-frailty Prevalence	Women: 39.0% (95% CI, 38.1-39.9%) Men: 37.3% (95% CI, 36.6-38.0%; v2 = 8,629, df = 1, *P* = 0.003)	Systematic Review (Collard et al. 2012)
	Women: 15% (95% CI, 14-17%; n = 143, I2 = 99%; *P* < 0.005) Men: 11% (95% CI, 10-12%; n = 145, I2 = 97%; *P* < 0.005)	Meta-analysis (O'Caoimh et al. 2020)
Frailty Prevalence	Women: 9.6% (95% CI, 9.2-10%) Men: 5.2% (95% CI, 4.9-5.5%; *P* < 0.001)	Systematic Review (Collard et al. 2012)
	Women: 49% (95% CI, 14-17%; *P* < 0.005) Men: 45% (95% CI, 44-47%; n = 119, I2 = 97%; *P* < 0.005)	Meta-analysis (O'Caoimh et al. 2020)

Park C et al. Clin Geriatr Med 37:625–638, 2021

Average frailty scores at each age, stratified according to sex

- Design: Secondary analysis of the Survey of Health, Ageing, and Retirement in Europe (SHARE).
- Participants: Community-dwelling adults (N = 27,527; mean age 65.3 ± 10.5, 55% female).



Women: black circles and solid lines

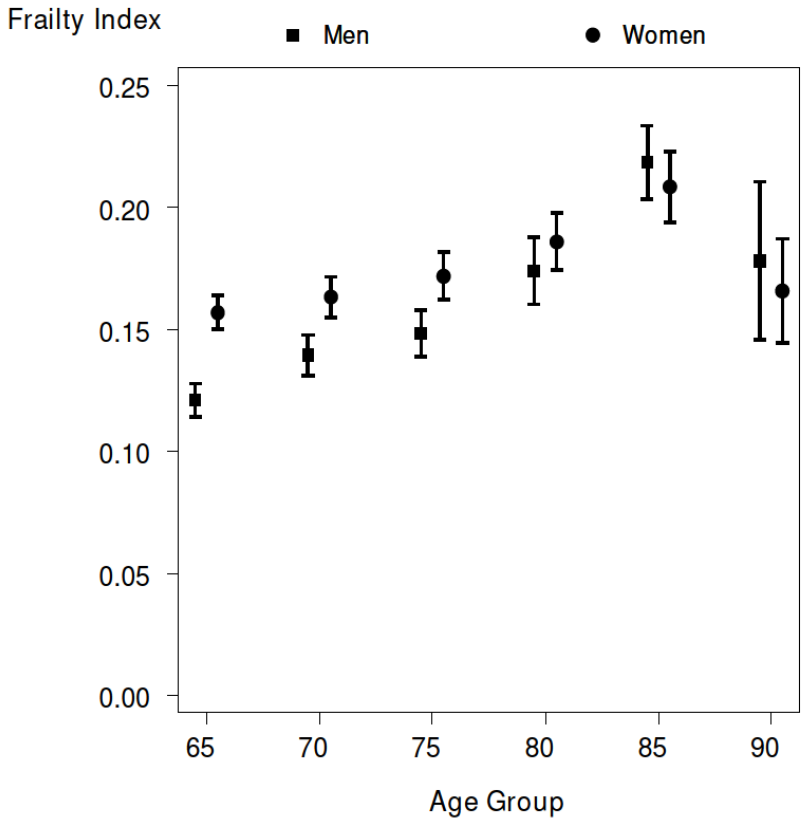
Men: gray boxes and dashed lines

Theou O et al. J Am Geriatr Soc 62:901–6, 2014

The “sex-frailty paradox” in the elderly

The Mexican Health and Aging Study (MHAS)

Frailty index by age and gender



Mortality hazard ratios

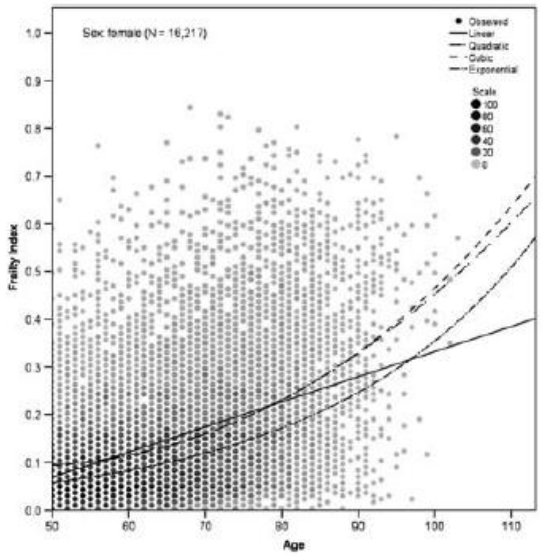
	All (n = 4082)	Men (n = 1932)	Women (n = 2150)
Frailty index			
.00-.07	1	1	1
.07-.14	**0.93** (0.58-1.50)	**0.99** (0.56-1.76)	**0.83** (0.35-1.95)
.14-.21	**1.56** (1.00-2.44)	**1.30** (0.73-2.32)	**1.84** (0.85-3.96)
.21-.35	**2.20** (1.42-3.41)	**2.69** (1.59-4.57)	**1.73** (0.80-3.77)
.35-.65	**6.45** (4.10-10.14)	**5.96** (3.32-10.72)	**6.63** (3.07-14.35)
Age (years)	**1.05** (1.04-1.07)	**1.05** (1.02-1.07)	**1.06** (1.04-1.09)
Gender			
Men	1		
Women	**0.66** (0.52-0.84)		

García-González JJ et al. BMC Geriatr 9:47, 2009

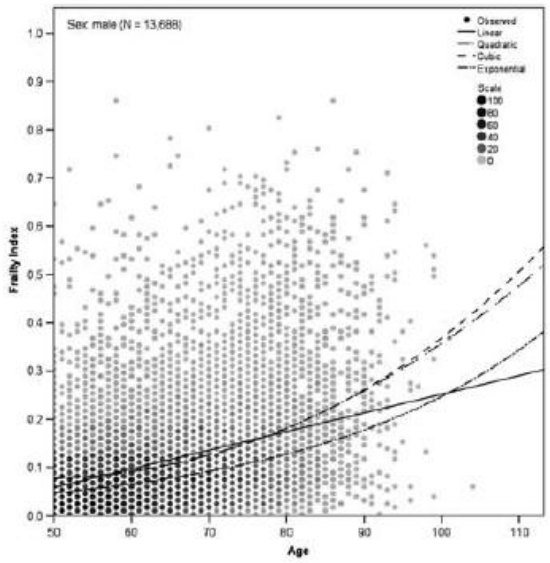
The “sex-frailty paradox” in the elderly

The Survey of Health, Ageing and Retirement in Europe (SHARE)

Women



Men



FI-associated mortality

Age Group	FI-age-adj. OR (95% CI, P)	
	Female	Male
All	100.5 (46.3–218.2) P<0.001	221.1 (106.7–458.4) P<0.001
50s	302.6 (14.2–6446.7.2) P<0.001	565.6 (74.1–4315.2) P<0.001
60s	140.9 (19.1–1038.6) P<0.001	463.7 (89.7–2396.5) P<0.001
70s	55.5 (14.6–210.9) P<0.001	267.6 (85.1–841.5) P<0.001
80s	137.0 (34.2–548.3) P<0.001	84.7 (20.1–357.1) P<0.001
90+	71.0 (7.7–650.5) P<0.001	24.7 (0.8–733.0) P=0.064

Romero-Ortuno R et al. Age Ageing 41:684–689, 2012

The “sex-frailty paradox”

- This phenomenon—where women exhibit a higher prevalence and greater severity of frailty, yet men experience higher mortality—is known as the sex-frailty paradox.
- This is consistent with the long-recognized observation that women have longer lifespan than men despite having higher chronic disease burden and disability.

Park C et al. Clin Geriatr Med 37:625–638, 2021

The “sex-frailty paradox”?
In the kidney transplant candidates

Background & Methods

Understanding sex-based differences in frailty perception and its impact on outcomes is essential to prevent disparities in transplant assessments.

A prospective longitudinal cohort of 767 KT candidates in Canada

- ✓ Men: 65%
- ✓ White race 82%
- ✓ Mean age: 54 ± 14 y/o
- ✓ **75% on RRT**

Frailty assessments

- ✓ Frailty Phenotype
- ✓ Frailty Index
- ✓ Clinical Frailty Scale

Results

- ✓ The prevalence of frailty for women was not significantly higher by the FP (16% vs 13%, *p*=0.15) or the FI (48% vs 46%, *p*=0.38), but was **by the CFS (15% vs 12%, *p*=0.04)**.
- ✓ **Frailty by the CFS was significantly associated with death/withdrawal from the waitlist for men (HR 2.59, 95% CI 1.16–6.79) but not women (HR 1.41, 95% CI 0.48–4.18).**

Worthen GL et al. ASN Kidney Week, 2021

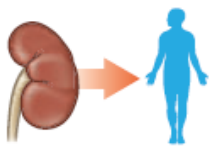
Clinical Kidney Journal

Frailty among chronic kidney disease patients on the kidney transplant waiting list: the sex–frailty paradox

Frailty prevalence in CKD patients who are kidney transplant (KT) candidates is high, and its presence is associated with a higher rate of complications and death after transplant

Aim and methods

Barcelona, Spain

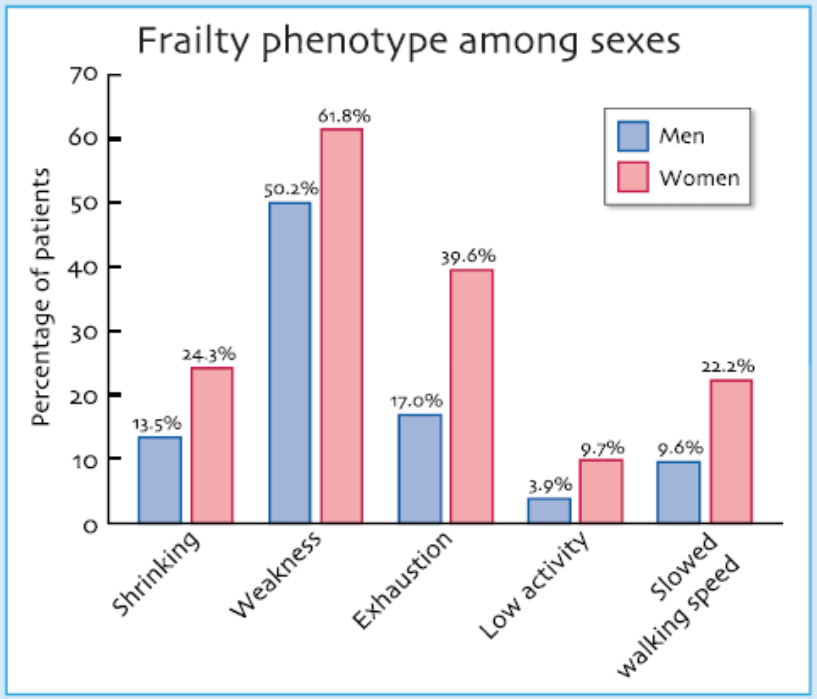


Prospective longitudinal study of **455 KT** candidates evaluated for frailty

✓ **80.9% on RRT**

Physical frailty phenotype:
- Pre-frailty = 2 criteria
- Frailty ≥ 3 criteria

Results



	Pre-frail	Frail
Total	20.0%	10.3%
M : F	Male 22.5% Female 47.2%	

Characteristics:

- Poor family/social support
- Comorbidities
- Disabilities

Conclusion: Frailty is twice as frequent in women with advanced CKD than in men. Criteria distribution and phenotype seem also to differ among sexes.

Pérez-Sáez et al.
Clinical Kidney Journal (2021)
@CKJsocial

The “sex-frailty paradox”?

In the kidney transplant candidates

Factor associated with frailty in men

	OR (95% CI)	P-value
Deficient family support	3.35 (1.37–8.23)	0.008
Instrumental activities disability	5.32 (1.86–15.15)	0.002
Haemodialysis as RRT (yes)	2.51 (1.13–5.57)	0.024
Cerebral vasculopathy	3.28 (1.01–10.62)	0.047
Heart failure	3.35 (0.95–11.92)	0.061
Peripheral vasculopathy	1.72 (0.58–5.02)	0.324
Basic activities disability	1.35 (0.38–4.77)	0.641

Factor associated with frailty in women

	OR (95% CI)	P-value
Medical treatment adherence (no)	2.75 (1.1–7.47)	0.046
Basic activities disability	8.80 (1.00–77.21)	0.050
Haemodialysis as RRT (yes)	2.22 (0.91–5.42)	0.079
Instrumental activities disability	1.91 (0.82–4.46)	0.132
Lean mass (kg/m^2)	0.86 (0.7–1.06)	0.166

Pérez-Sáez MJ et al. Clin Kidney J 15:109–118, 2021

The “sex-frailty paradox”?
In the hemodialysis patients

Study Design

A prospective cohort of 206 patients requiring maintenance hemodialysis in a single center

- ✓ Women: 49.5%
- ✓ Mean age: 66.9 ± 12.5 y/o
- ✓ Dialysis vintage: 7.8 (3.3–12.5) years
- ✓ Diabetes: 54.4%
- ✓ CVD: 27.7%

follow-up period of 3.2 (1.3) yrs

Primary outcome

- ✓ All-cause mortality

Frailty assessments

- ✓ Fried Frailty Phenotype
- ✓ Clinical Frailty Scale

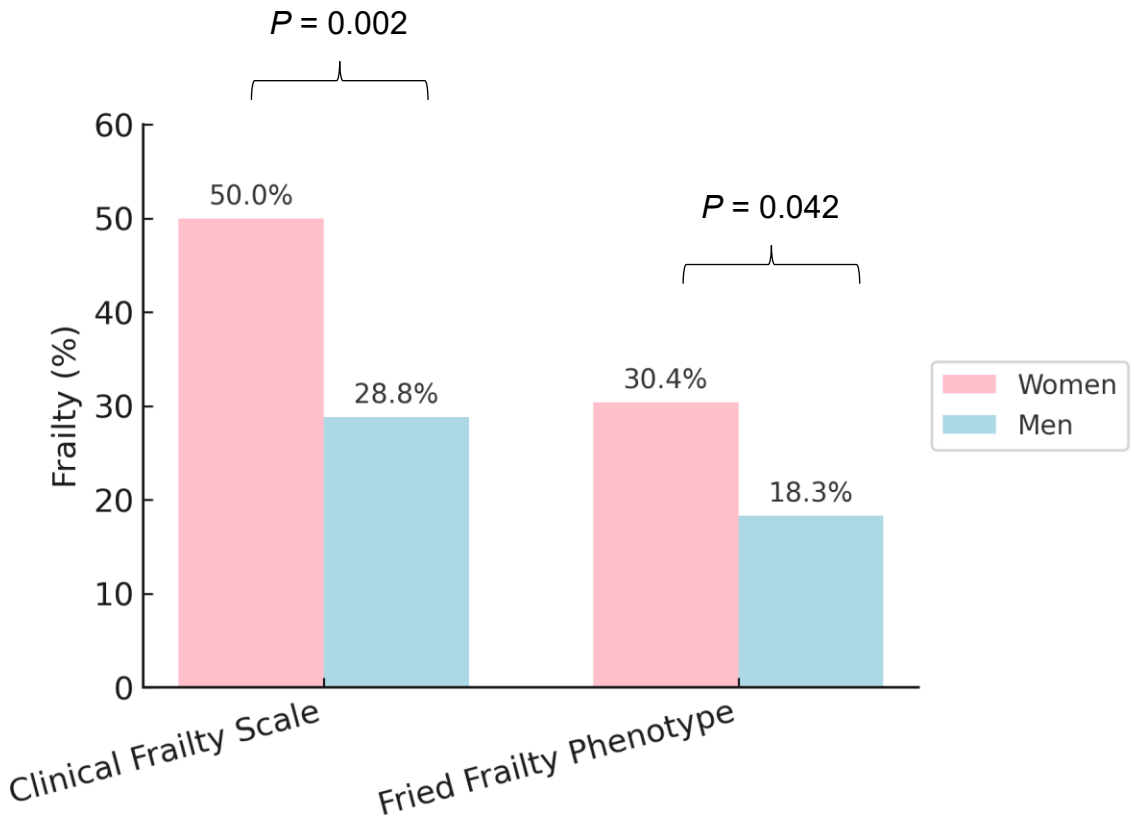
Baseline characteristics

Variables	Women (n=102)	Men (n=104)	*P*
Age (yr)	68.8 ± 11.2	65.1 ± 13.5	0.034
Smoking history, n (%)	4 (3.9%)	35 (33.7%)	<0.001
Dialysis vintage (yr)	7.1 (3.1–12.0)	8.1 (3.7–13.0)	0.263
nPCR (g/kg/day)	1.10 ± 0.25	1.08 ± 0.23	0.524
Body mass index (kg/m^2)	23.2 ± 3.7	23.7 ± 3.9	0.368
Diabetes mellitus, n (%)	54 (52.9%)	58 (55.8%)	0.684
Hypertension, n (%)	95 (93.1%)	91 (87.5%)	0.172
CVD, n (%)	19 (18.6%)	38 (36.5%)	0.004
Stroke, n (%)	4 (3.9%)	4 (3.8%)	0.978

Baseline characteristics

Variables	Women (n=102)	Men (n=104)	*P*
Creatinine (mg/dL)	8.4 ± 1.6	10.1 ± 2.1	<0.001
Albumin (g/dL)	3.7 ± 0.3	3.9 ± 0.3	<0.001
Fasting glucose (mg/dL)	145 (114–191)	140 (116–198)	0.916
Total cholesterol (mg/dL)	169 (142–196)	137 (113–165)	<0.001
Triglycerides (mg/dL)	144 (94–197)	133 (96–197)	0.311
LDL-C (mg/dL)	85 (68–103)	72 (55–97)	0.004
Hemoglobin (g/dL)	10.4 (9.5–11.0)	10.4 (9.5–11.1)	0.704
Calcium (mg/dL)	9.4 (8.9–10.1)	9.4 (8.8–10.0)	0.483
Phosphate (mg/dL)	4.2 (3.5–5.3)	4.5 (3.7–5.3)	0.288

Prevalence and severity of frailty



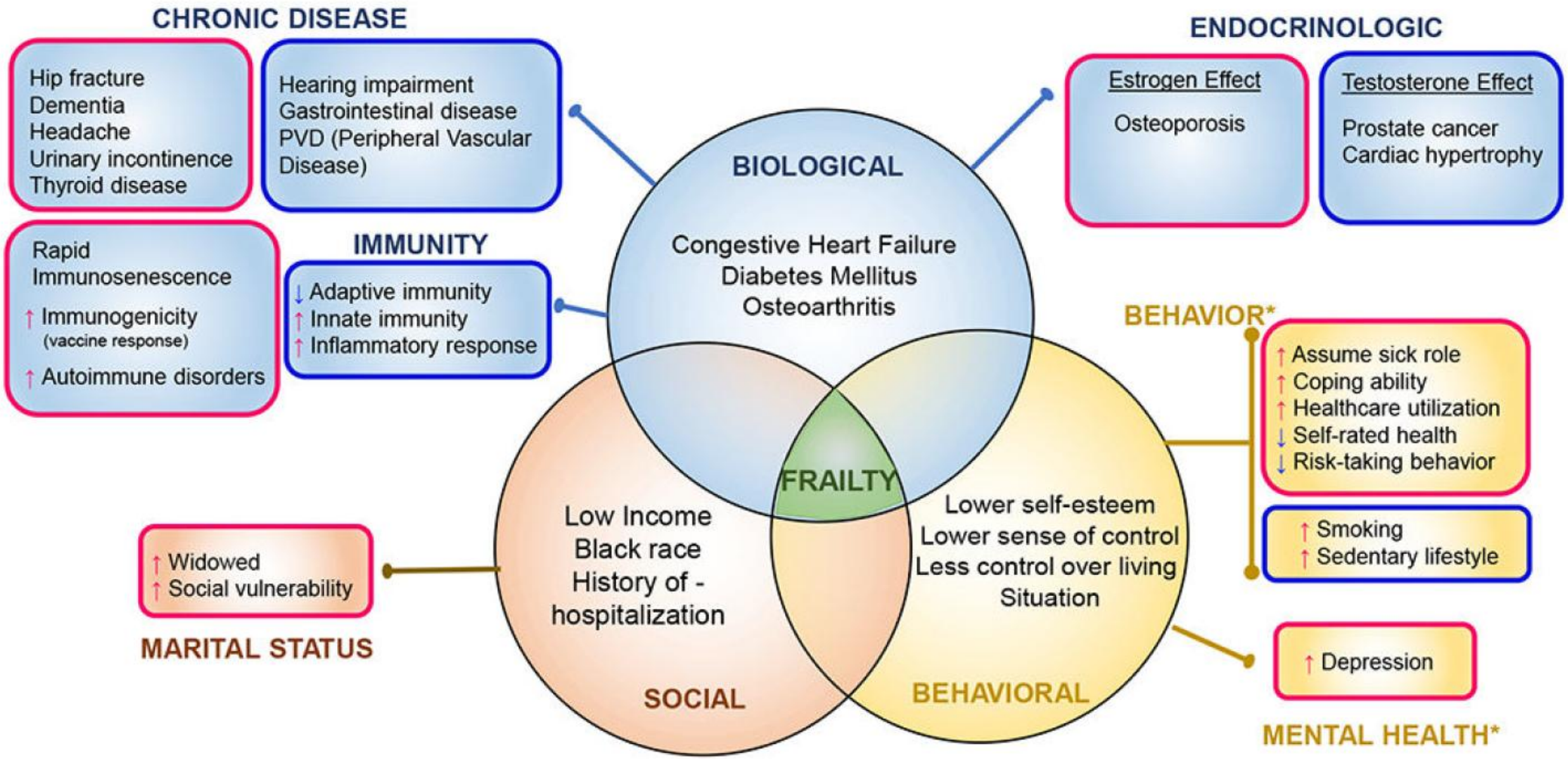
	Women (n=102)	Men (n=104)	*P*
Clinical Frailty Scale	4.5 (3.0–6.0)	3.0 (3.0–5.0)	0.003
Fried frailty phenotype	1.0 (0.0–3.0)	1.0 (0.0–2.0)	0.035

Association of frailty with mortality according to sex

	Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Women				
Frailty accoridng to CFS	1.72 (0.69–4.30)	0.245	0.89 (0.31–2.55)	0.833
Frailty according to Fried phenotype	4.61 (1.05–10.37)	<0.001	2.40 (0.90–6.36)	0.079
Men				
Frailty accoridng to CFS	2.90 (1.27–6.59)	0.011	2.30 (1.01–5.27)	0.048
Frailty according to Fried phenotype	7.93 (3.64–17.29)	<0.001	6.10 (2.60–14.28)	<0.001

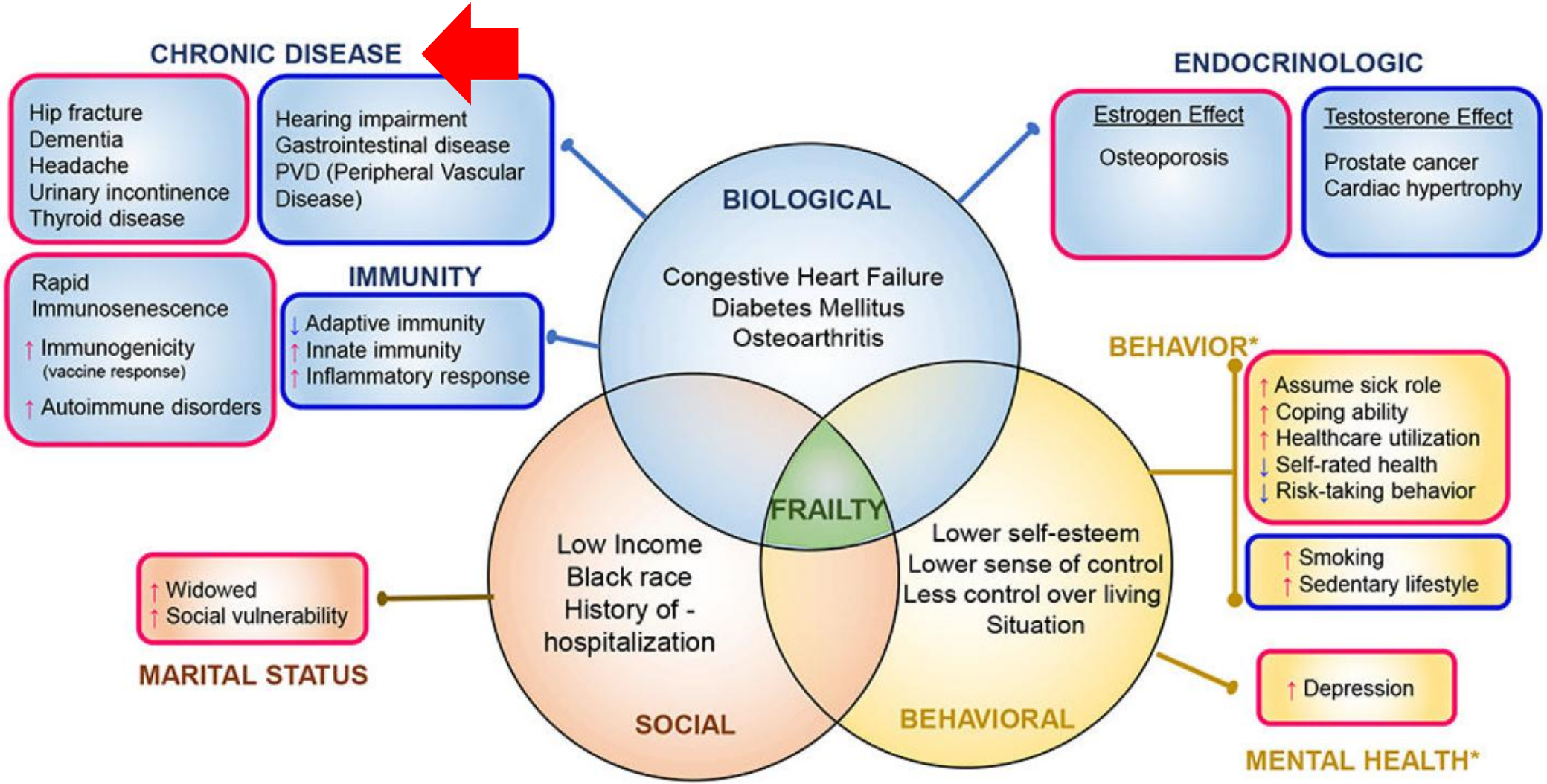
Model 1 is adjusted for age.
Model 2 is adjusted for age, diabetes, cardiovascular disease, and serum albumin.

Contributory domains and factors for frailty and sex-specific associations



Park C et al. Clin Geriatr Med 37:625–638, 2021

Contributory domains and factors for frailty and sex-specific associations



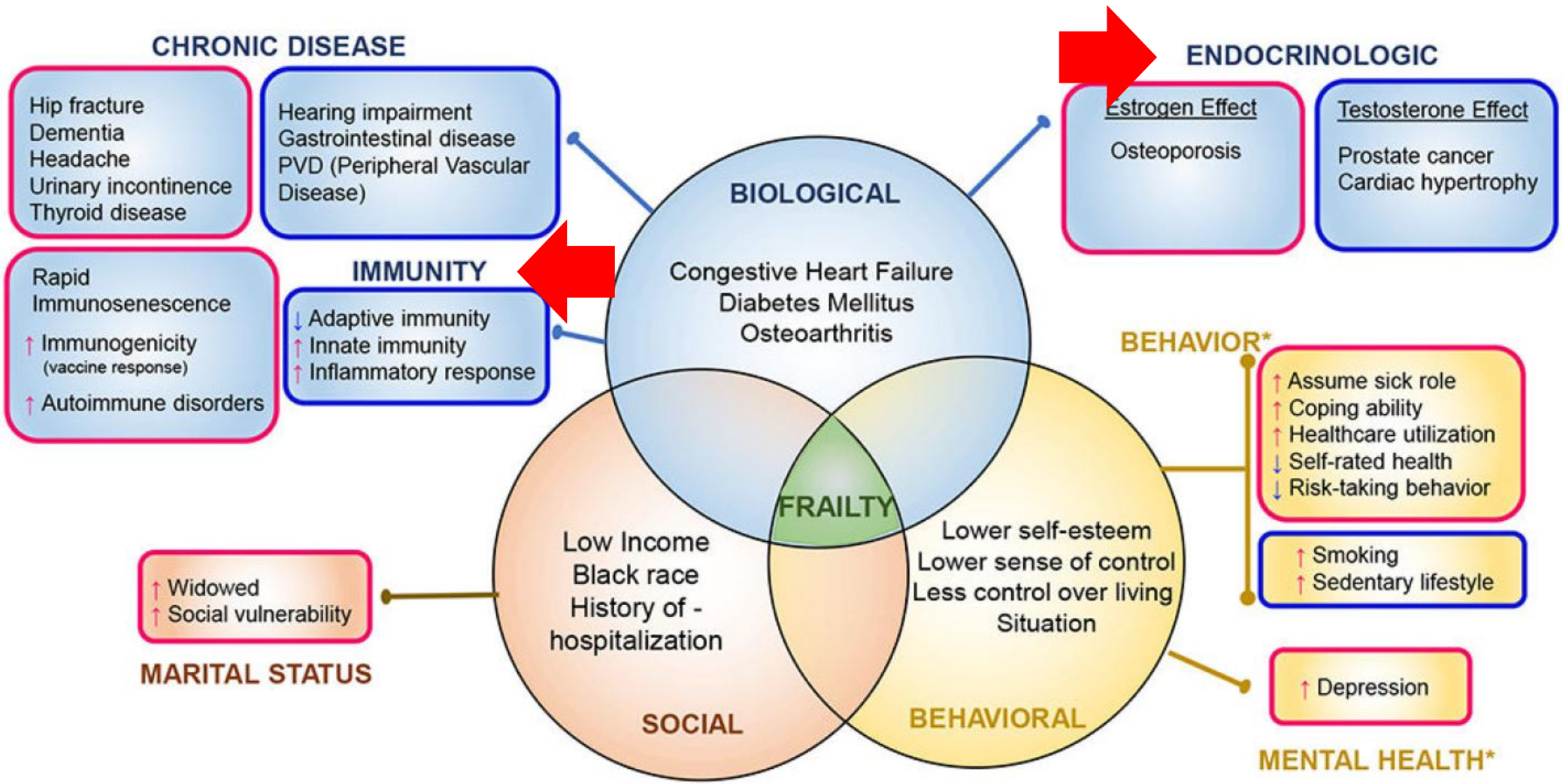
Park C et al. Clin Geriatr Med 37:625–638, 2021

Comorbidities in hospitalized ESRD patients in the prior year

	Male patients			Female patients		
	2020	2021	2022	2020	2021	2022
Cardiovascular disease	19,104(80.0%)	18,814(78.6%)	18,731(76.4%)	16,625(77.3%)	16,033(75.7%)	15,566(73.7%)
Arrhythmia	6,573(27.5%)	6,095(25.5%)	5,596(22.8%)	6,188(28.8%)	5,651(26.7%)	5,053(23.9%)
Stroke	7,351(30.8%)	6,887(28.8%)	6,444(26.3%)	6,327(29.4%)	5,826(27.5%)	5,176(24.5%)
Diabetes	11,624(48.7%)	11,452(47.9%)	11,413(46.6%)	9,552(44.4%)	9,365(44.2%)	8,921(42.3%)
COPD	5,284(22.1%)	4,791(20.0%)	4,359(17.8%)	4,043(18.8%)	3,585(16.9%)	3,203(15.2%)
Peptic ulcer disease	9,729(40.7%)	9,038(37.8%)	8,306(33.9%)	9,328(43.0%)	8,544(40.3%)	7,728(36.6%)
Malignancy	5,550(23.2%)	5,470(22.9%)	5,104(20.8%)	5,194(24.2%)	4,997(23.6%)	4,646(22.0%)
Hypertension	22,733(95.2%)	22,734(95.0%)	23,131(94.3%)	20,180(93.9%)	19,877(93.8%)	19,662(93.2%)
Dyslipidemia	9,040(37.9%)	8,888(37.1%)	9,043(36.9%)	8,878(41.3%)	8,562(40.4%)	8,480(40.2%)
Polycystic kidney disease	838(3.5%)	857(3.6%)	855(3.5%)	521(2.4%)	511(2.4%)	530(2.5%)
Peripheral vascular disease	2,138(9.0%)	1,952(8.2%)	1,774(7.2%)	1,953(9.1%)	1,766(8.3%)	1,591(7.5%)

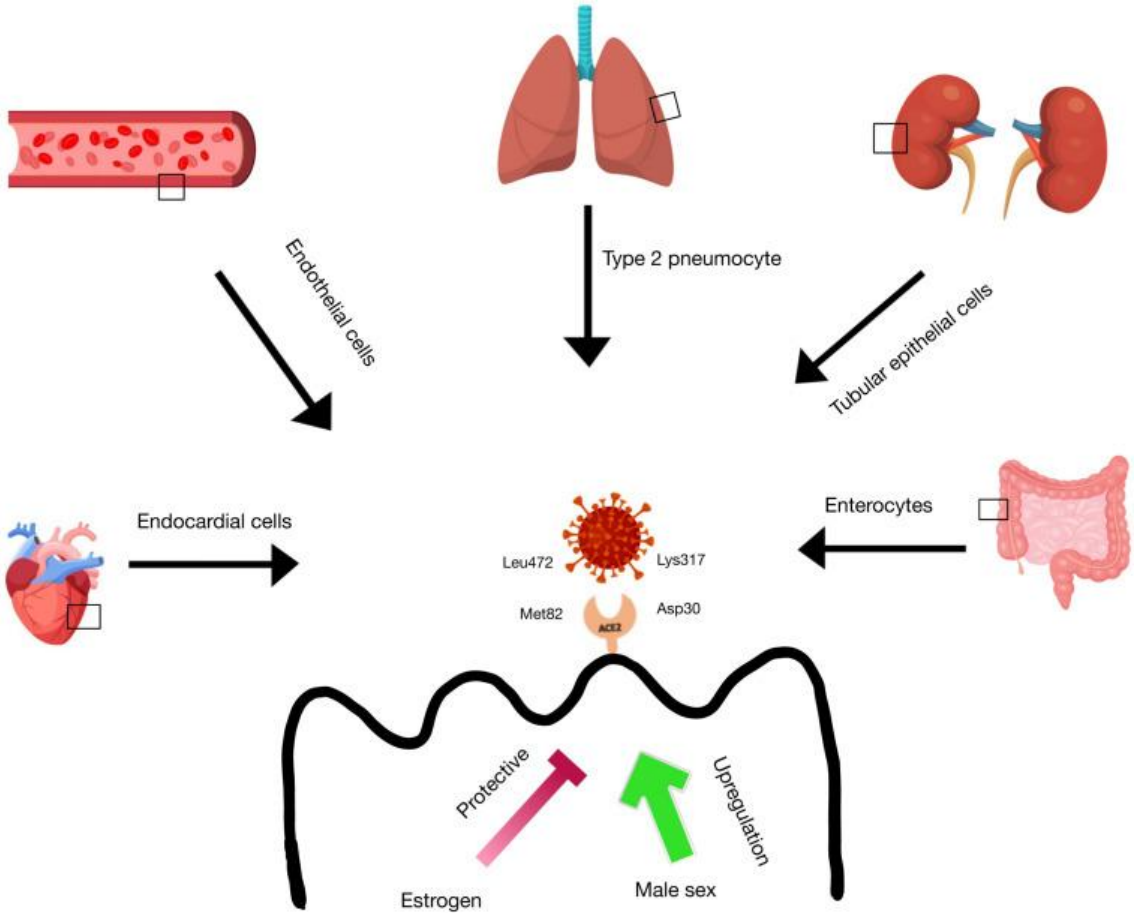
Data sourced from the Annual Report on Kidney Disease in Taiwan, 2020–2022

Contributory domains and factors for frailty and sex-specific associations



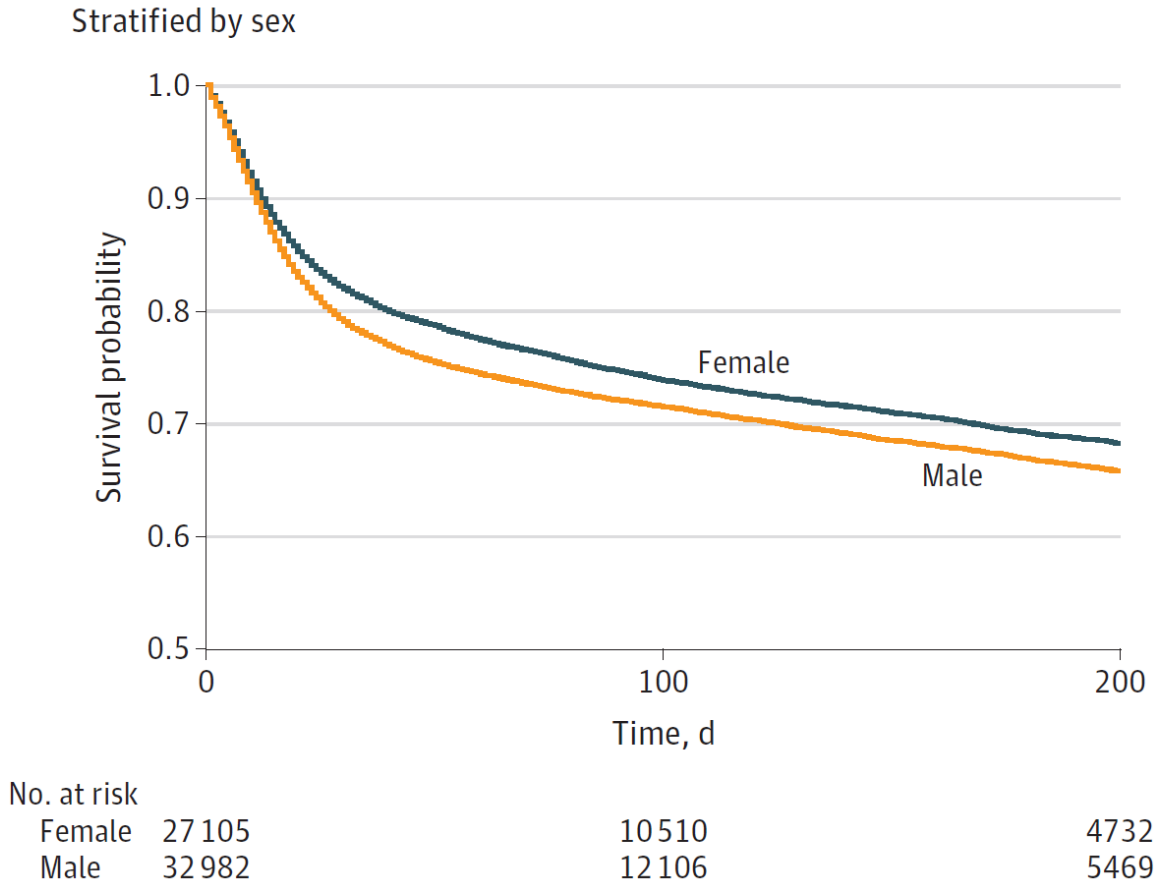
Park C et al. Clin Geriatr Med 37:625–638, 2021

Sex hormones and ACE-2 receptor



Gadi N et al. Front Immunol. 11:2147, 2020

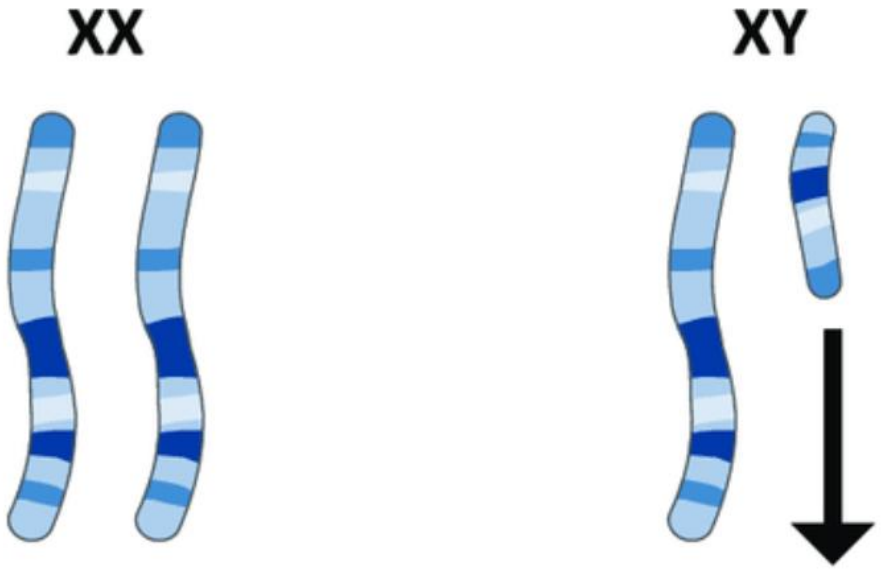
COVID-19 mortality outcomes among Medicare patients receiving long-term dialysis



Men versus women: adjusted HR (HR, 1.20; 95 %CI, 1.16-1.24)

Salerno S et al. JAMA Netw Open. 4:e2135379, 2021

Immune-related genes implicated in the sex-based differences in the immune response



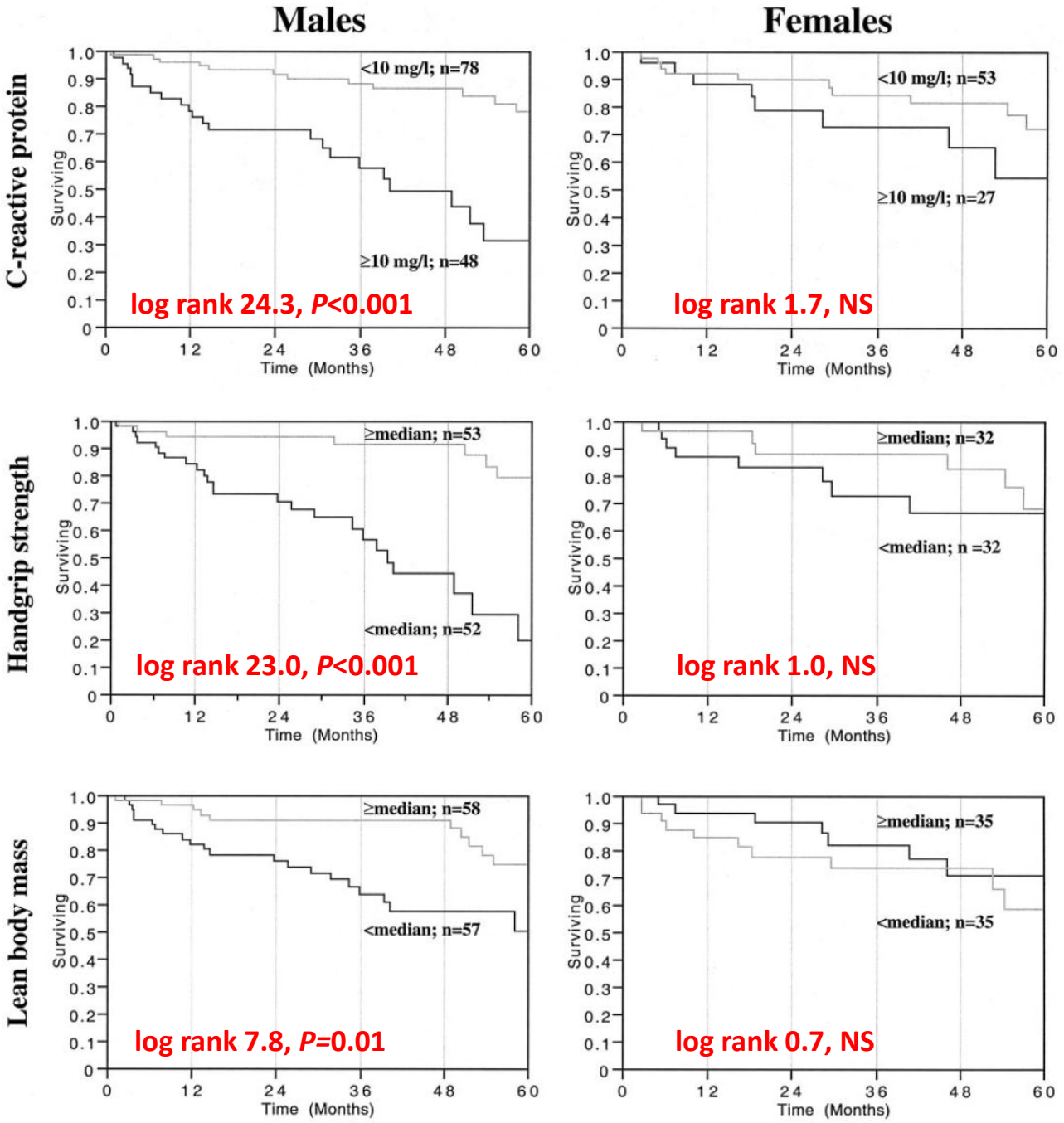
X chromosome: genes for Toll-like receptors, cytokine receptors, and other genes important for T- and B-cell function

Y chromosome: genes for certain inflammatory pathways

Park C et al. Clin Geriatr Med 37:625–638, 2021

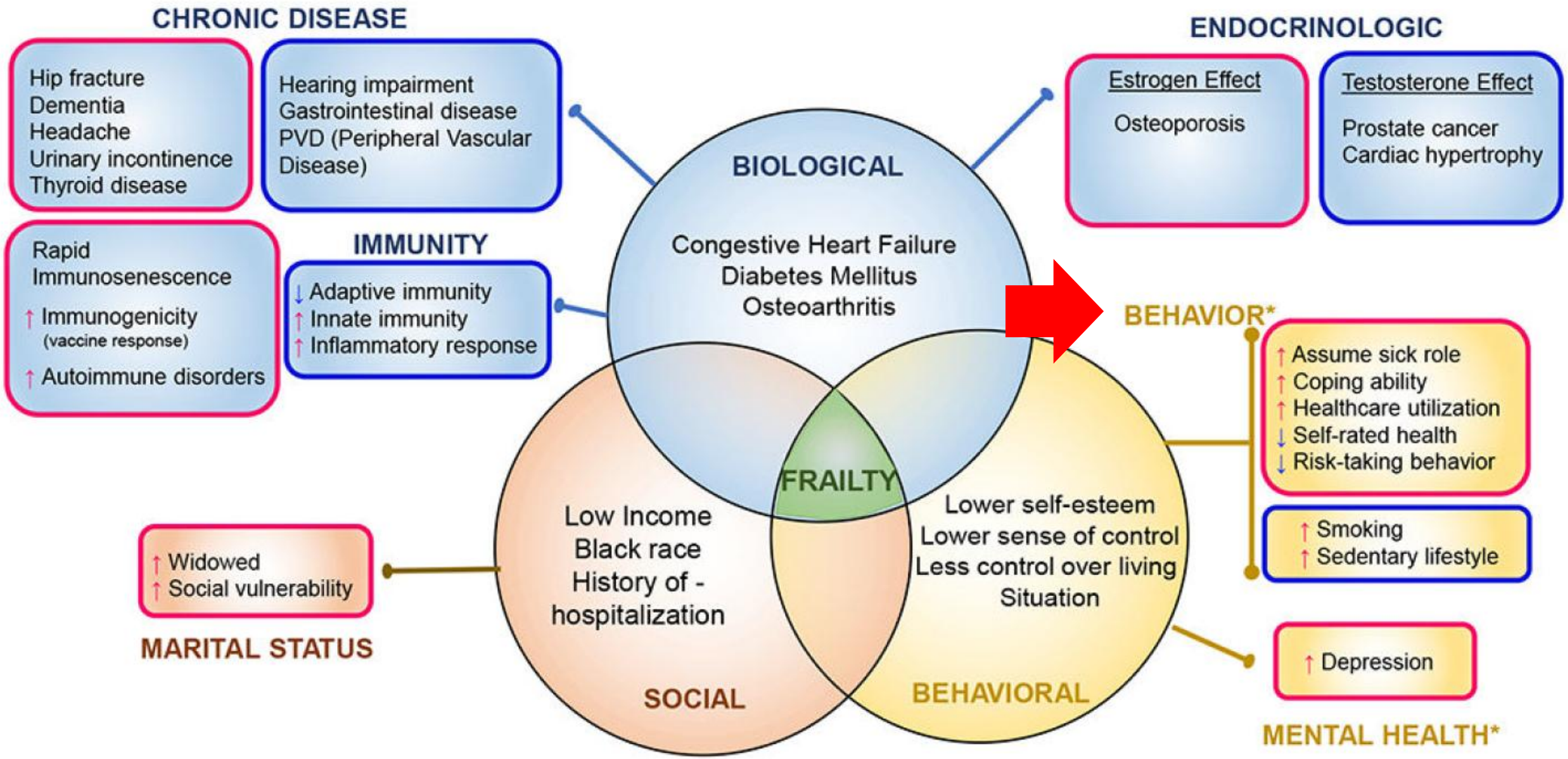
A comparative analysis of nutritional parameters as predictors of outcome in male and female ESKD patients

- 206 ESKD patients (126 males) with a mean age 52+/-1 years



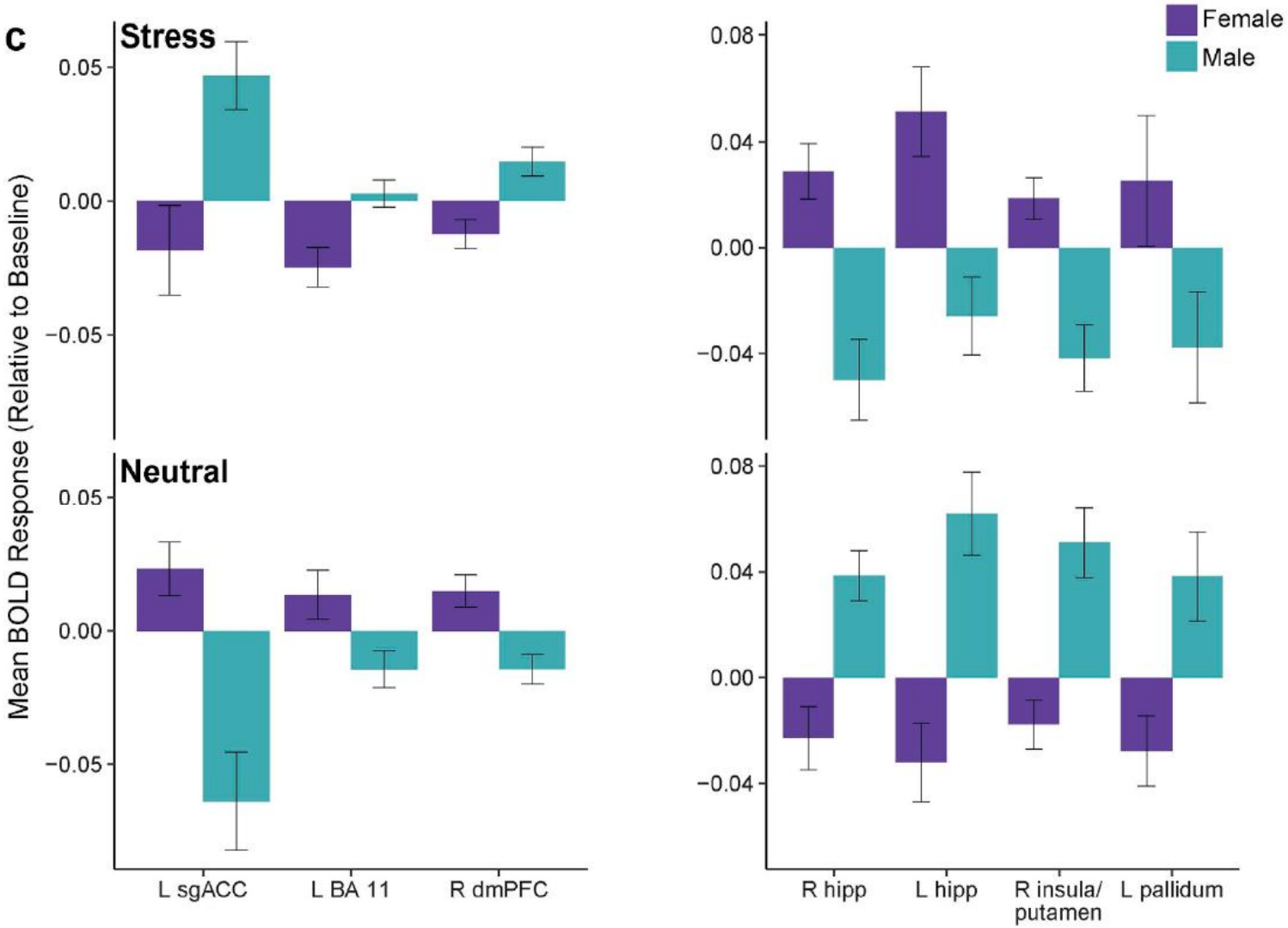
Stenvinkel P et al. Nephrol Dial Transplant 17:1266–1274, 2002

Contributory domains and factors for frailty and sex-specific associations



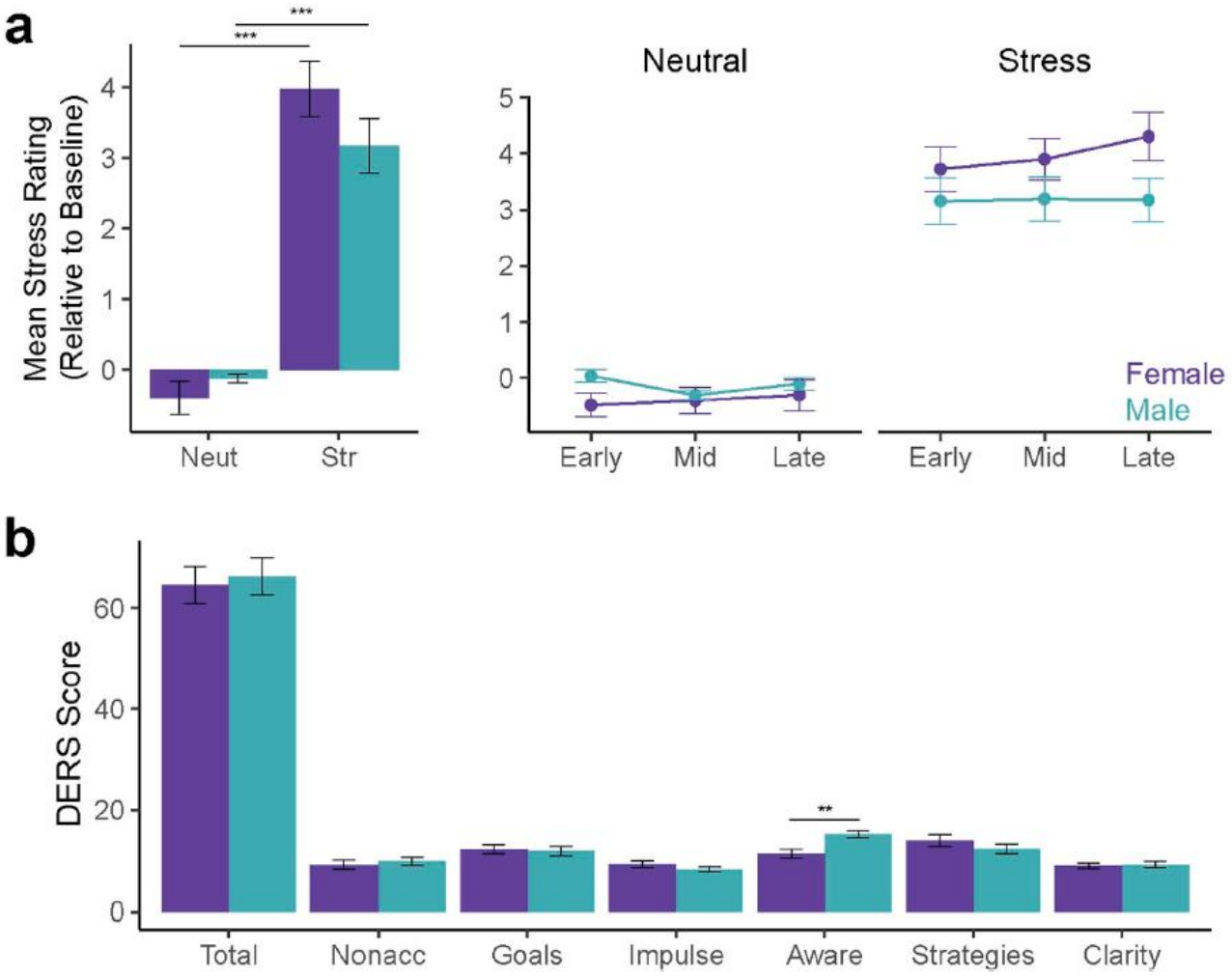
Park C et al. Clin Geriatr Med 37:625–638, 2021

Sex differences in neural stress responses and correlation with subjective stress and stress regulation



Goldfarb EV et al. Neurobiol Stress 11:100177, 2019

Sex differences in neural stress responses and correlation with subjective stress and stress regulation

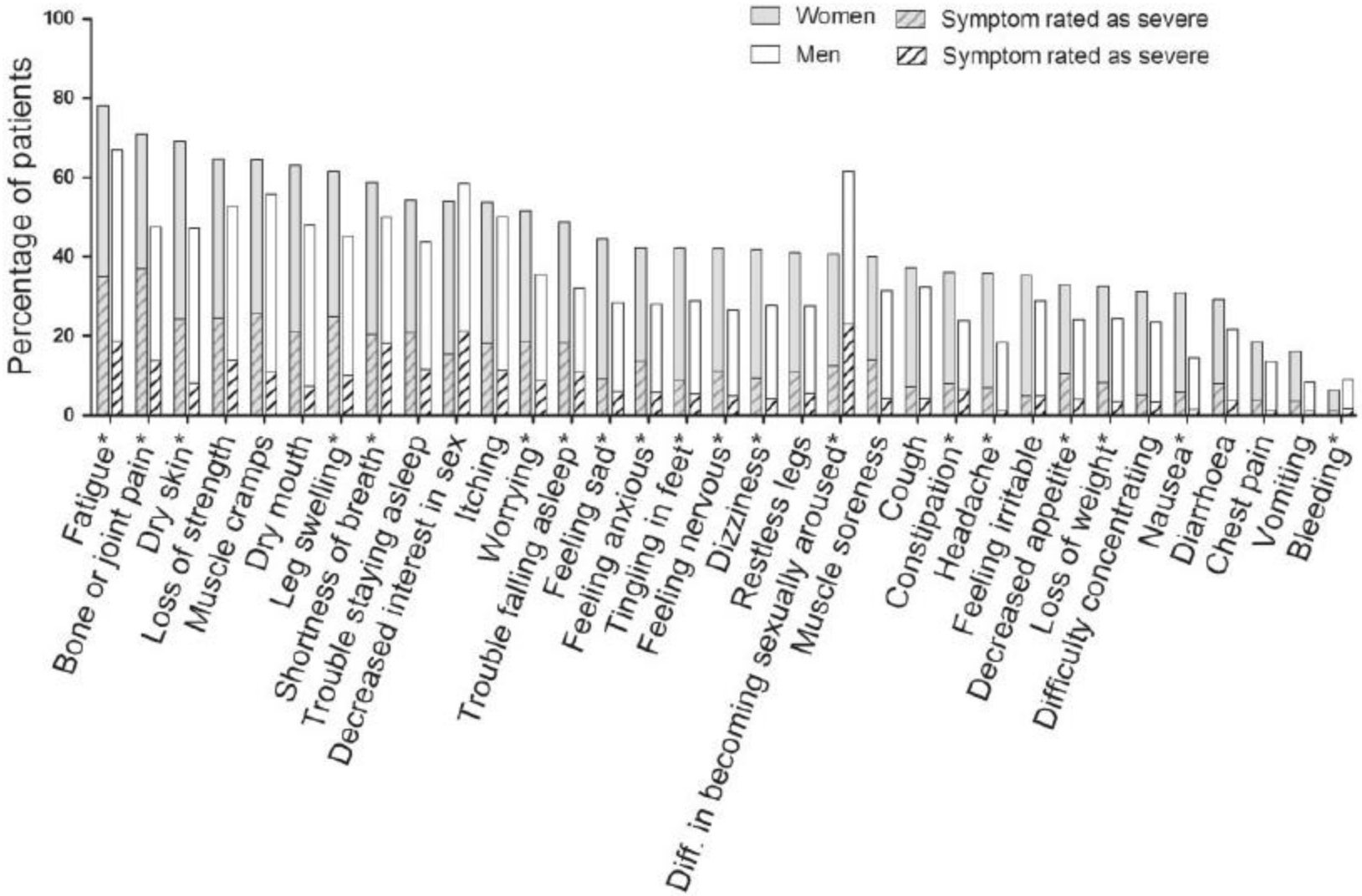


These sex-specific differences in stress perception may partly explain variations in women's health-related behaviors, including illness perception, self-rated health, and healthcare utilization.

Goldfarb EV et al. Neurobiol Stress 11:100177, 2019

Uremic symptom burden and clinical condition in women and men of ≥65 years of age with advanced CKD

- The European QUALity study on treatment in advanced chronic kidney disease (EQUAL)
- six European countries of ≥65 years of age years whose eGFR ≤20mL/min/1.73m^2



van de Luijtgaarden MWM et al. Nephrol Dial Transplant 34:1189–1196, 2019

Conclusions

- Being a woman is a risk factor for frailty among dialysis patients, whereas men with frailty exhibited higher mortality.
- The so-called “sex–frailty paradox” exists not only in the elderly but also among patients undergoing dialysis.
- This paradox highlights the importance of addressing not only frailty itself but also its underlying determinants.
- A substantial knowledge gap remains in this area, underscoring the need for further clinical research.