

Frailty Index as a Measure of Biological Age in a Chinese Population

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Background. The concept of a frailty index, developed in Canadian elderly populations as an indicator of biological age as opposed to chronological age, was tested in an elderly Chinese population to determine whether it is applicable in a different ethnic and cultural setting.

Methods. A data set including 62 physical, psychological, and socioeconomic variables from a cohort of 2032 persons 70 years and older (999 men, 1033 women) was used. The distribution of the index was evaluated using the Cramer-von Mises goodness-of-fit test, and multiple linear regression was used to assess its relationship with age and sex. A biological age for each participant was calculated based on an inverse regression of age on mean frailty index and sex. The Cox proportional hazards regression model was used to assess the ability of biological age to predict death.

Results. The distribution of the frailty index most closely resembled a Weibull distribution. The frailty index increased with age until the mid-80s, when it leveled off, and was higher in women than men for each age group. The distribution of biological age is wider than that for chronological age, and it strongly predicted death. Women had an estimated 20% lesser chance of dying at a given time than did men of the same chronological age and degree of frailty.

Conclusions. The study confirms the robustness of the concept and method of calculating the frailty index developed in elderly Canadian populations. It also suggests that the sex difference in life expectancy may have an underlying genetic basis independent of frailty.

FRAILITY is a characteristic of aging, such that geriatric health care is essentially care for frail elderly persons, whereas its prevention or delay in onset has implications for the public health care system (1,2). It may be regarded as a dynamic state of balance between assets and deficits covering physical, functional, psychological, nutritional, and social domains, with frailty resulting when deficits exceed assets (1,3,4). Its validity as a concept has been shown in its ability to predict death, health status, functional decline, and use of health services (5–8). The underlying pathogenesis includes neuroendocrine and immune function changes predisposing persons to the development of diseases and to sarcopenia as a result of an increase in the catabolic process and loss of anabolic signals (9–12).

The public health implications of frailty have been noted as a significant but modifiable economic burden on health care services (13), and various precursor conditions and sarcopenia may be amenable to public health interventions (10,14). In this regard, the goal of improving healthy life expectancy is to prevent or delay the onset of frailty. Therefore, measurement of frailty would be an important public health indicator. The frailty index (15) is an example of such a measure. Derived from measurement of many items in a cohort of elderly Canadians, the composite index represents general “system damage.” This model has been further developed so that biological age versus chronological age may be estimated depending on the frailty index (16). The development of such a numeric value representing frailty is important both as a tool in monitoring the health of populations and enabling heterogeneity in frailty to be considered in the calculation of life tables predicting life expectancy (17).

However, this concept has not been tested in other populations, in other ethnic or cultural groups, in societies with different health care systems, or using different types and numbers of health survey variables. In the current study, we tested this concept using the data from a health survey of a population of elderly Chinese persons living in Hong Kong aged 70 years and older by calculating the frailty index and analyzing its distribution, the relation between biological and chronological age, and the relation with death. We compared the findings with those from the Canadian population.

METHODS

In 1990 and 1991, a health survey of elderly persons was conducted in Hong Kong, and the cohort was followed for 10 years. We used the data from that survey for the current analysis. A cohort of 2032 persons aged 70 years and older was gathered by stratified random sampling of the population, for which physical, psychological, and socioeconomic variables were obtained. Territory-wide stratified random sampling from a registered list of all recipients of old age and disability allowances was used to recruit 999 men and 1033 women. The old age allowance list covers more than 90% of the population 70 years and older, because eligibility is based on age alone, independent of income. The remaining 10% of the elderly persons would be the very wealthy, who may not elect to claim the allowance. The disability allowance list covers those who are receiving additional social welfare support. The recipients were stratified by age and sex so that there would be 300 in the 70–74 and 75–79 age groups for each sex and 150 in the

80–84, 85–89, and 90+ age groups for each sex. Letters were sent to these persons to recruit the required number in each group. Approximately 60% of men and women agreed to be interviewed: this comprised 62% of men aged 70–79 years, 66% of men aged 80+ years, 53% of women aged 70–79 years, and 61% of women aged 80+ years. A higher proportion of women aged 70–79 years refused to participate, whereas more men and more women aged 80+ years agreed. Details of the sampling method and survey population have been reported elsewhere (18).

Interviewers administered a questionnaire consisting of information on social, functional, physical, and mental health status, and place of residence. Functional status was assessed using the Barthel Index (19), mental function using the information/orientation part of the Clifton Assessment Procedure for the Elderly (20), and depressive symptoms using the Geriatric Depression Scale (21). The questionnaire was successfully administered by interviewing the participants in person in 86% of the total sample, by proxy (formal or informal caregivers) in 3%, and by a combination of participant and proxy in 11%. Those who were cognitively impaired, based on a cutoff score of ≤ 7 on the information/orientation part of the Clifton Assessment Procedure for the Elderly, were excluded from the Geriatric Depression Scale assessment (421 of 2032 for the whole sample).

The maximum score for the Barthel Index is 20, representing independence in all activities of daily living. The information/orientation subsection of the Clifton Assessment Procedure for the Elderly has a maximum score of 12, when all questions are answered correctly. When compared with more detailed tests of cognitive function with a clinical assessment component (such as CAMDEX) (22) or clinical diagnosis, the Clifton Assessment Procedure for the Elderly has been reported to have sensitivity and specificity rates of 80% and 99% (23), and 87% and 97% (24), using a cutoff point of 7–8, which is similar to the Mini-Mental State Examination (25) as a screening test (24). In the current survey, we used a score of ≤ 7 to indicate the presence of cognitive impairment. Using this criterion, the prevalence of cognitive impairment for men (5%) and women (22%) (25) was similar to that from a local survey using the Mini-Mental State Examination: 6% for men and 15% for women (26). The maximum score for the Geriatric Depression Scale is 15, with high scores indicating increased likelihood of depression. The scale had been validated in the Chinese population, with depression indicated by a cutoff value greater than 8 (27).

The participants were followed for 10 years, with face-to-face interviews conducted at 3, 5, and 10 years and telephone contacts at 18-month intervals. For those lost to follow-up, we searched the Death Registry to determine the number who had died.

We created a list of 62 variables covering cognitive, psychological, and physical health, with a score of 1 representing a deficit for each variable, with the exception of a score of 2 for those taking 5 drugs or more, and those who have fallen three times or more in the past year (Appendix 1). The maximum score is 62, and the frailty index was calculated by dividing the total score for each participant by

62. Participants were considered fit if they had fewer deficits and frail if they had more deficits. Therefore, participants may have equal numbers of deficits but be of different ages. As described by Mitnitski and colleagues (15), a person's age may be compared with the average age of the population with the same number (proportion) of deficits. This age may be considered an estimate of a person's biological age (16).

Statistical Methods

We performed all analyses using SPSS version 12.0 (Chicago, IL) for Windows or SAS version 8.2 (Cary, NC). We used the Cramer-von Mises goodness-of-fit test to test the hypotheses that the distribution of the frailty index followed a normal, gamma, Weibull, or lognormal distribution. We evaluated the relationship of the frailty index to age first by separating participants into the following age groups: 70–72 years, 73–75 years, 76–78 years, 79–81 years, 82–84 years, 85–87 years, 88–90 years, 91–93 years, and 94+ years, and calculating the mean and 95% confidence interval of the index for each age group and sex. We conducted multivariate analyses by first calculating the mean frailty index for each age (not grouped) and sex. We used multiple linear regression to assess the relationship between age (not grouped) and mean frailty while controlling for sex (coded as 0 = men, 1 = women). We used square root transformations of both the mean frailty index and age to improve the fit of the model. We used an inverse regression of the square root of age on the square root of the mean frailty and sex to calculate a biological age corresponding to a particular sex and frailty index value. We used the Cox (28) proportional hazards regression model to assess the ability of this biological age to predict death while controlling for chronological age and sex. We estimated crude relative risks using univariate Cox models, and we estimated adjusted relative risks using multivariate Cox models.

RESULTS

The mean and median ages of the participants at baseline were 79.7 and 77.0 years, respectively. The youngest participants were 70 years old, and the oldest were 107 years old. There were slightly more women ($n = 1033$; 50.8%) than men ($n = 999$; 40.2%). The mean ages for men and women were similar, at 79.3 and 80.1 years, respectively, but 72.6% of the 73 participants who were 94 years or older were women. Sixteen of the participants had frailty indexes of 0, and the frailest participant had an index of .532. The mean and median of the index were .142 and .129, respectively, and the distribution was right skewed. The standard deviation was .081 and the middle 50% of the observations was between .08 and .19. Figure 1 is a histogram of the frailty index with estimated gamma, Weibull, and lognormal density curves, and Figure 2 is a histogram of the index for participants aged 77 years. The Cramer-Von Mises goodness-of-fit test rejected the hypotheses that the frailty index followed a normal ($p < .0001$), gamma ($p = .001$), lognormal ($p = .005$), or Weibull ($p = .01$) distribution. Figure 1 indicates that of the three distributions, the Weibull appears to be the closest fit.

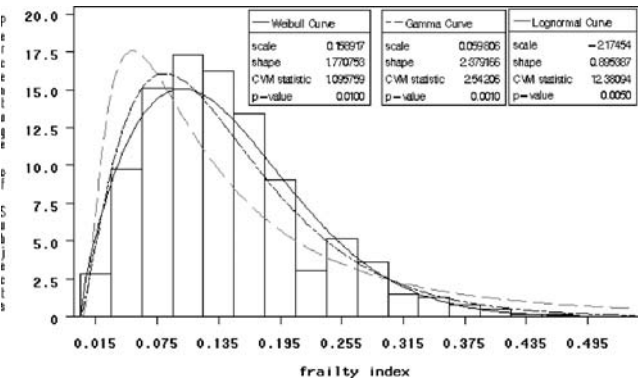


Figure 1. Distribution of the Frailty Index.

Overall, the mean frailty index for each age group increased in a fairly linear pattern until it leveled off at the mid-80s (Table 1). For each age group, the frailty index value for women was greater than that for men, and the index appears to stabilize at a younger age for men than for women (Table 1). Fitting a multiple linear regression equation with the square root of the mean frailty index as the outcome variable and sex and the square root of age as covariates resulted in the equation

$$\sqrt{\text{frailty}} = 0.021 + 0.038 * \sqrt{\text{age}} + 0.034 * \text{sex}$$

Both the age and sex parameters were significant ($p < .001$), but the constant term was not significantly different from 0 ($p = .73$). The inverse regression of the square root of age on sex and the square root of mean frailty resulted in the following model:

$$\sqrt{\text{age}} = 6.06 + 8.14 * \sqrt{\text{frailty}} - 0.23 * \text{sex}$$

which was then used to produce the equation

$$BA = [6.06 + 8.14 * \sqrt{\text{frailty}} - 0.23 * \text{sex}]^2$$

for calculating a biological age for each participant.

As noted by Mitnitski and colleagues (16), participants'

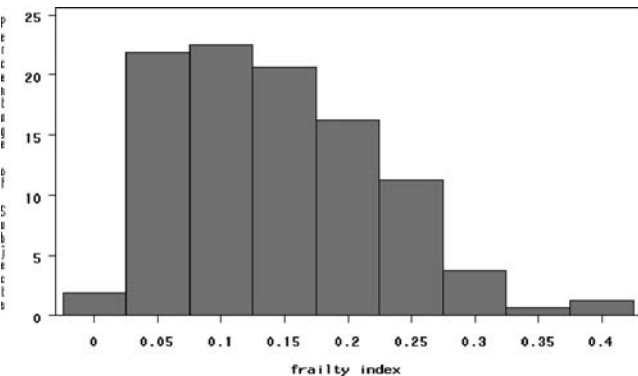


Figure 2. Distribution of the Frailty Index for 77 year olds.

Table 1. Descriptive Statistics of Frailty Index by Age Group and Sex

Age Group, y	Overall		Men		Women	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
70–72	337	.121 (.113–.128)	159	.109 (.099–.119)	178	.131 (.121–.142)
73–75	354	.128 (.120–.136)	190	.115 (.105–.126)	164	.143 (.132–.154)
76–78	411	.136 (.129–.143)	209	.125 (.114–.135)	202	.148 (.137–.158)
79–81	230	.141 (.131–.152)	118	.126 (.112–.140)	112	.158 (.143–.172)
82–84	148	.159 (.145–.174)	70	.151 (.130–.172)	78	.167 (.147–.187)
85–87	191	.172 (.159–.186)	94	.146 (.131–.160)	97	.198 (.176–.219)
88–90	131	.152 (.138–.166)	68	.150 (.132–.169)	63	.154 (.133–.175)
91–93	157	.171 (.157–.185)	71	.149 (.129–.168)	86	.189 (.170–.208)
94+	73	.158 (.138–.179)	20	.129 (.090–.168)	53	.170 (.146–.193)

Note: CI = confidence interval.

biological age, calculated in this manner, reflects their fitness, or absence of frailty, compared with other participants of the same age. Participants whose frailty index is average for their age and sex will have a biological age equal to their chronological age. Participants who are frailer than the average for their age and sex will have a biological age greater than their chronological age, and participants less frail than the relevant average will have a biological age that is less than their chronological age. Overall, the observed biological ages in our data set ranged from 34 to 138 years, which is wider than the range of chronological ages. This is due in part to the fact that participants with the highest frailty index values were considerably frailer than the average for any age group, and those with the lowest frailties were much less frail than the average for any of the age groups in the sample. However, approximately 90% of biological ages in our data set were between 45 and 100 years.

Table 2 shows the outcomes of the cohort. We found no difference in frailty index between those lost to follow-up and those contacted. Figures 3 and 4 show Kaplan-Meier survival curves comparing the proportions of surviving participants grouped by chronological and biological ages

Table 2. Frailty Index by Sex and Outcome

Outcome	Men (N = 999)		Women (N = 1033)	
	N	Mean Index Value ± SD	N	Mean Index Value ± SD
3-Year follow-up				
Alive	559	0.116 ± 0.066*	612	0.142 ± 0.074*
Lost to follow-up	168	0.118 ± 0.076	174	0.143 ± 0.077
Died	272	0.159 ± 0.085	247	0.200 ± 0.094
p value (by analysis of variance)		<.001		<.001
10-Year follow-up				
Alive	151	0.104 ± 0.054*	148	0.120 ± 0.064*
Lost to follow-up	290	0.107 ± 0.069	360	0.135 ± 0.070
Died	558	0.145 ± 0.079	525	0.181 ± 0.089
p value (by analysis of variance)		<.001		<.001

Note: SD = standard deviation.

* $p < .05$ by Multiple Range Test compared with those who died.

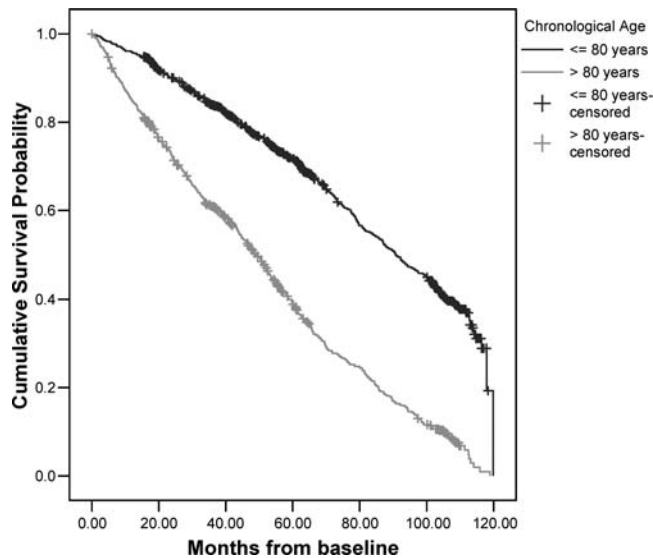


Figure 3. Kaplan-Meier survival probability by chronological age group.

(80 years or younger and older than 80 years). Table 3 shows the results for the Cox proportional hazards model with sex, chronological age, and biological age as predictors of death. The results indicate that higher biological age is a highly significant predictor of death even after controlling for sex and chronological age. However, chronological age was a stronger predictor of death than biological age, as can be seen from a comparison of their respective Wald statistics. Sex was not a significant predictor of death in the univariate model because the women in the sample tended to be older and frailer. However, the results of the multivariate model indicate that, on average, women had an estimated 20% lesser chance of dying at a given time compared with men of the same chronological age and frailty.

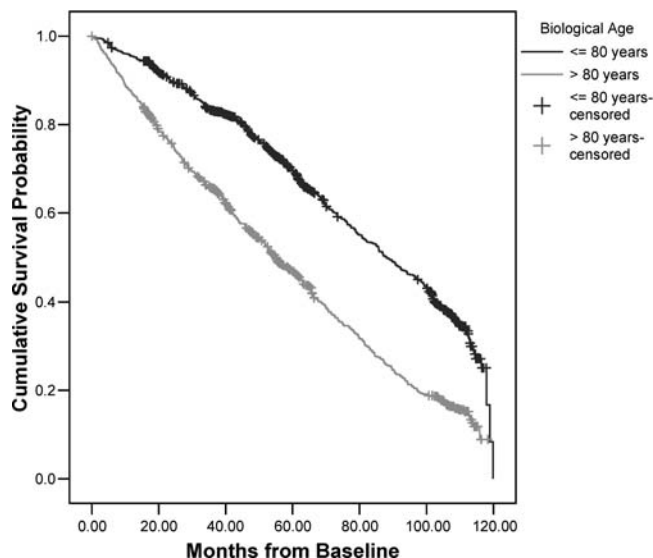


Figure 4. Kaplan-Meier survival probability by biological age group.

Table 3. Results of Fitting the Cox Proportional Hazards Model for Death

Covariate	Univariate RR (95% CI)	Wald χ^2	p Value	Adjusted RR (95% CI)	Wald χ^2	p Value
Chronological						
age*	2.16 (2.00–2.25)	365.6	<.0005	2.04 (1.88–2.22)	294.6	<.0005
Biological age*	1.36 (1.29–1.41)	214.3	<.0005	1.28 (1.23–1.33)	144.4	<.0005
Sex†	0.94 (0.84–1.06)	1.02	.31	0.80 (0.71–0.90)	13.5	<.0005

Note: RR = relative risk; CI = confidence interval.

*RRs calculated based on 10-year increments.

†Women = 1; men = 0 (without points).

DISCUSSION

The distribution of the frailty index in this population is similar compared with that for elderly Canadians (15) with similar median values. However, instead of having a gamma distribution, a Weibull distribution provided a better fit in our population. The biological implications of this are unclear.

The leveling off of the frailty index in the mid-80s age group is unlikely to be accounted for by recruitment characteristics of those oldest persons who participated in the study, because this was a territory-wide stratified random sampling, covering persons living in the community and those living in institutions, and therefore is likely to represent a survival effect. As in the previous study (16), the frailty index strongly predicts death. The distribution of biological age at 77 years is similar to that for elderly Canadians (16,29), except that there is a wider spread of biological age in our population. This may indicate greater heterogeneity in frailty, perhaps reflecting on a wider economic disparity in our population (if one accepts that poor economic status is associated with frailty). The groups of variables in the frailty index cover physical health, objective disease burden and use of drugs, cognitive functioning, mobility difficulties, dependency in activities of daily living, self-esteem, depression, malnutrition, and body mass index, all of which have been reported to be predictors of death among older white persons (30–36). They also include blood pressure, body mass index, lifestyle factors, and physical performance measures that have also been shown to predict death among elderly Chinese in Hong Kong (37–39). Therefore, the frailty index would be expected to be a predictor of death.

However, in this study, biological age did not appear to be superior to chronological age in predicting death, contrary to previous findings. This may be due to the different characteristics of the current cohort compared with the Canadian cohort, as well as the variables used. The data from the Canadian cohort form part of a cross-sectional and longitudinal study of the risks and burden of dementia in elderly persons, and the database consisted of 92 items covering physical symptoms and signs relating to psychiatric/neurologic diseases, disabilities, and the findings of physical examinations (25 variables), blood tests (15 variables), and psychological examinations (5 variables). The major difference between the current study variables and those of the Canadian study is that physical examination and blood tests were not performed, nor were psychological

assessments. Although the theoretical maximum biological age from our formula is rather high, at 201, the actual range in our data set is fairly reasonable. Given the distributions of frailty indexes in our study and in the Canadian studies (15,16), frailty index values close to 1, which would produce unrealistic biological ages for our model, seem unlikely. Despite the likely differences in characteristics between the Chinese and Canadian cohorts, and the difference in the list of variables used, the similarity of the findings supports the robustness of the concept of frailty index calculated from a summation of deficits covering many domains. It also supports the concept that which deficits were used was not critical (29).

If the frailty index were used merely to predict death, our study shows that it would be no better than chronological age, raising the question of the value of measuring biological age using so many variables. However, the value of the frailty index or biological age would be greater from a public health perspective, as an indicator reflecting the health burden of aging populations and as an outcome indicator monitoring interventions aimed to compress morbidity with increasing life expectancy, rather than being just a tool for predicting life expectancy.

An interesting finding is the confirmation that the sex difference in life expectancy is not entirely due to sex difference in frailty, because men with the same chronological age and frailty index have a higher risk for death compared with women. There may be an underlying genetic basis, in that reaching a very old age may be a byproduct of longevity-enabling genes that maximize the time when women bear children, a process that allows women to age as slowly as possible (40).

Our study does have limitations. Data were not available for all the variables selected for all the participants. For example, participants with cognitive impairment were not evaluated using the Geriatric Depression Scale. For this latter group, symptoms may be underreported. For those lost to follow-up, some may have moved away from Hong Kong and died elsewhere, so that the number of deaths may have been greater. The choice of variables used to calculate the frailty index is based on a review of the literature, of factors that may be a feature of frailty. The greater weight placed on the use of 5 or more drugs, and the number of falls of 3 or more in the past 12 months, is arbitrary, and there may be other variables that should also carry different weightings. Furthermore, no investigations (blood tests, radiographs, electrocardiograms) have been included. Although the Canadian Study included many blood results, it is uncertain whether they are necessary, because the index may be regarded as a "macroscopic variable" reflecting general system damage rather than any particular organ abnormality.

Further analyses that could be conducted include evaluation of the effect of using different numbers or combinations of variables on the calculation of the frailty index, and factors associated with frailty such as lifestyle, socioeconomic factors, and social support. Such information would be important in assessing the public health implications of ameliorating frailty. The frailty index may be used as an indicator of population health for older persons and to assess the effectiveness of efforts to promote successful aging.

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12. PMH1 Past medical history: cerebrovascular diseases
13. PMH2 Past medical history: Parkinson diseases
14. PMH3 Past medical history: cardiac diseases
15. PMH4 Past medical history: hypertension
16. PMH5 Past medical history: chronic bronchitis
17. PMH6 Past medical history: asthma
18. PMH7 Past medical history: tuberculosis
19. PMH8 Past medical history: peptic ulcer
20. PMH9 Past medical history: diabetes mellitus
21. PMH10 Past medical history: arthritis
22. PMH11 Past medical history: old fracture
23. PMH12 Past medical history: dementia
24. PMH13 Past medical history: psychiatric problems
25. PMH14 Past medical history: malignancy
26. PMH15 Past medical history: other diseases
27. SYMPTOM1 Headache in the past month
28. SYMPTOM2 Dizziness in the past month
29. SYMPTOM3 Heart palpitation in the past month
30. SYMPTOM4 Worsening of memory in the past month
31. SYMPTOM5 Constipation in the past month
32. SYMPTOM6 Stomach pain in the past month
33. SKEL Have joint pain
34. FALL Falls in the past year: 1 or 2 times
35. FALL Falls in the past year: 3+ times
36. CHESTPN2 Have chest pain while walking uphill or briskly
37. CHESTPN3 Have chest pain while walking on level ground
38. BREATH3 Cannot walk for 1 mile
39. BREATH4 Cannot walk for 100 yards
40. BREATH6 Feel breathlessness while lying flat in bed
41. SWELL Swelling in leg in the past month
42. COUGHBLD Cough blood in the past month
43. WHEEZE1 Wheezing or whistling in chest in the past year
44. WHEEZE2 Woken with a feeling of tightness in chest in the past year
45. BREATH8 Breathless when not doing anything strenuous
46. BREATH9 Woken at night by attack of breathless
47. PHLEGM1 Bring up phlegm in the morning
48. PHLEGM2 Cough up phlegm for 3 consecutive months for 2 years
49. ADL1 Dependent in feeding
50. ADL3 Dependent in personal grooming
51. ADL7 Dependent in chair/bed shifting
52. ADL9 Dependent in walking
53. ADL11 Dependent in walking up and down stairs
54. ADL13 Dependent in using toilet
55. ADL15 Dependent in bathing
56. ADL17 Urinary incontinence
57. ADL19 Bowel incontinence
58. BP1 Systolic blood pressure >140 mmHg
59. BP2 Diastolic blood pressure >90 mmHg
60. BMI Body mass index <18.5 kg/m²
61. GAIT1 Need a walking aid usually
62. GAIT5 Walking unsteadily or staggering

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APPENDIX

List of Variables

1. MSCORE Mental Score <7
2. DEPSOR Geriatric Depression Score 8+
3. HEALTH Self-perceived physical health not quite good or poor
4. GP Doctor consultation in the past year 3+ times
5. HOSPITAL Hospital admission in the past year 2+ times
6. DRUGNO Number of drugs used 1–4
7. DRUGNO Number of drugs used 5+
8. HEARING Difficulties with hearing
9. VISION Difficulties with vision
10. CHEWING Difficulties with chewing
11. WGT1 Weight loss ≥ 5 pounds in past year