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Inflammation, Coagulation, and the Pathway to Frailty

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Abstract

There are inevitable physiologic changes associated with advancing age, yet for some people these changes are exaggerated, and as a result a phenotype emerges recognized as “frailty.” Why some people become frail and others do not remains incompletely understood. Although chronic illnesses are common among frail elderly persons, some will develop all of the phenotypic features without a diagnosed underlying disease. It has been recognized that certain proinflammatory cytokines and coagulation factors are elevated to a greater extent in those who are frail than in age-matched nonfrail individuals. In this review, we provide an overview of current research in the biology of frailty with particular emphasis on the role of inflammatory pathways and disordered coagulation in its pathogenesis.

Keywords

Coagulation; Cytokines; D-dimer; Frailty; Inflammation; Interleukin-6; Sarcopenia; Tumor necrosis factor- α

As the world population ages, it has become increasingly important to understand the physiologic consequences of aging and quickly identify those changes that are likely to result in progression to “frailty.” Frailty, to distinguish it from normal aging, usually implies a state of heightened vulnerability to acute and chronic stressors as a consequence of significant reduction in physiologic reserve. It is usually associated with decline in function across multiple systems that in composite contribute to geriatric syndromes, including falls, osteoporotic fractures, incontinence, cognitive decline, anemia, malnutrition, and muscle wasting. When exposed to stress, frail, compared with nonfrail, elderly persons have worse clinical outcomes and are at increased risk for hospitalization, nursing home placement,¹ and death.² Hospitalization in frail older patients can lead to further functional decline and new development of dependence in activities of daily living.^{3,4} Caregivers of frail elderly in the community also undergo physical, psychologic, and economic hardships, the latter of which may include loss of employment.⁵ Thus, clinicians should become familiar with the diagnosis of frailty and aware of its protean manifestations, including an increased risk for hospitalization, nursing home placement, and death. Current research has focused on the

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pathophysiologic underpinnings of frailty, and attention has been drawn to the fundamental role for dysregulation of inflammatory pathways.⁶ Yet, no single process or consensus pathway can be credited for the entirety of the changes observed.

THE “FRAILTY” PHENOTYPE

With the aging of our population and the reduction in early deaths from acute illness and initial infection, but more recently from myocardial infarction and cerebrovascular accidents, more people are living longer and with chronic illness.^{7,8} The term “frailty” has become synonymous with an apparent global decline, presumably on the basis of advancing age and the presence of disease. However, it is clear that not all old people are frail and that not all frail people have disease. Although it is true that frailty is associated with increased comorbid illness^{5,9,10} and functional limitations, including basic deficiencies in activities of daily living, it also is true that frailty may occur in the absence of known comorbidity and that some who meet criteria for frailty (see below) may be able to maintain functional capacity, at least for activities of daily living. For example, in the Cardiovascular Health Study, only 6% of those identified as “frail” had difficulty in activities of daily living, 46% had comorbid illness, and 27% had neither disability nor comorbid illness.² For the purposes of clinical investigation, several operational definitions have been proposed, and most include some assessment of functional impairment, muscle strength, and body composition.^{2,11} With a more objective definition applied, current research has led to the identification of common pathways to frailty, and these include alterations in immune, inflammatory, neuroendocrine, metabolic, and vascular physiologies. Each of these affect the complex coagulation pathway, and it should come as no surprise that evidence indicates an association of frailty with activation of this system.

A commonly used definition of frailty has been formulated into a “Frailty Index” by Fried and colleagues² (Table 1) and validated in the Cardiovascular Health Study¹² and the Women’s Health and Aging Study.^{13,14} By this index, frailty is defined as meeting 3 or more of established criteria for weight loss, grip strength, endurance, walking speed, and physical activity (Table 1).

The Women’s Health Initiative, a prospective study conducted on 40,657 women aged 65 to 79 years, used the above instrument with slight adjustments for the measure of muscle weakness and walking speed and the incorporation of the RAND 36-item scale (self-reported physical function on 10 items) for assessment of exhaustion.¹⁵

Other tools to define frailty include the “Clinical Frailty Scale,” which consists of 7 variables from very fit to complete functional dependence,¹⁶ the “Frailty Index-Comprehensive Geriatric Assessment,” a frailty index that incorporates a comprehensive geriatric assessment,¹⁷ and the Canadian Study of Health and Aging frailty index, which includes a count of 70 clinical deficits elicited by thorough clinical assessment.¹¹ Each of these instruments correlates with functional decline, increased risk of institutionalization, and mortality. Of note, each also defines a “pre-frail” level, a feature that implies the progression from a state of robust to pre-frail to frail.^{18–21} It is the ultimate goal of several

research programs to identify modifiable antecedents of frailty and to intervene early enough to prevent or slow the progression to more advanced stages.

PREVALENCE OF FRAILITY

In the Cardiovascular Health Study approximately 7% of the population aged more than 65 years met criteria for frailty² (Table 2). A similar prevalence also was reported by Chin et al,²² who used only inactivity and weight loss more than 5 kg over 4 years to define frailty in a study of approximately 1000 independently living elderly persons participating in the Survey in Europe on Nutrition and the Elderly, a Concerted Action. From the Cardiovascular Health Study analysis, it was apparent that frailty also was more prevalent among African Americans,²³ and from the Longitudinal Aging Study of Amsterdam, frailty was more prevalent in women.²¹ In the Women's Health Initiative 16.3% were frail and 28.3% pre-frail.¹⁵

Risk Factors for Frailty

Comorbidities increase the risk for frailty. Among these, congestive heart failure, history of myocardial infarction, arthritis, peripheral vascular disease, diabetes, hypertension, chronic obstructive lung disease, and depression are most prevalent.^{9,24} In an analysis of participants in the Cardiovascular Health Study, subclinical atherosclerotic disease, as manifested by significant carotid stenosis, low ankle-brachial index, and silent infarcts in the brain, was associated with increased prevalence of frailty.²⁴

Factors other than these recognized and distinct medical illnesses contribute to the risk of developing frailty. For example, in a study of 575 adults aged 65 to 102 years, excessive drinking, smoking cigarettes, depression, low physical activity, and self-perceived poor or fair physical health were each found to be significantly more likely in the 25% of subjects who met criteria for frailty.²⁵ In addition, from the Women's Health Initiative, a body mass index < 18.5 or > 25.0, activities of daily living limitations, and the presence of depression were additional factors associated with frailty.¹⁵ Furthermore, undernutrition and loss of muscle mass (sarcopenia) are important precursors in the progression from pre-frail to frail, and the presence of obesity,^{26–29} particularly in those with sarcopenia, heightens the risk of functional decline.

It is likely that in many, if not the majority, underlying chronic medical illness will lead to changes recognized in these epidemiologic surveys as risk factors for frailty. Yet, not all older people with these conditions become frail, and not all who meet the criteria for frailty have a recognizable underlying medical condition.

Whereas no specific cause for frailty has been identified, there has been considerable attention paid to metabolic and inflammatory pathways. For example, lower levels of insulinlike growth factor-1³⁰ and testosterone³¹ are seen in individuals with "sarcopenic obesity" and weight loss.³² However, the data are not consistent, and some studies show no significant association between these variables and frailty.³³ Low levels of vitamin D, vitamin E,³⁴ and carotenoids^{35,36} increase the frailty risk. Similarly, elevated inflammatory

cytokines and prothrombotic factors are associated with frailty, and there has been considerable emphasis placed on these variables with regard to its pathogenesis.

Inflammation and Frailty

Inflammation has long been considered as one of the most important physiologic correlates of the frailty syndrome⁶ (Table 3). Hallmarks of inflammation, such as C-reactive protein, leukocytosis, interleukin (IL)-6, and tumor necrosis factor- α also are associated with normal aging and late-life disease (including atherosclerosis, Alzheimer's disease, osteoporosis, anemia, diabetes, and frailty).^{6,37-45} High levels of IL-6 also are associated with loss of mobility and development of disability in older adults,⁴⁶ whereas tumor necrosis factor- α levels correlate with increased mortality among older individuals.⁴⁷ The Longitudinal Aging Study of Amsterdam included an evaluation of the effect of inflammatory markers on frailty and demonstrated that high C-reactive protein levels (but not IL-6) were related to both baseline and incident frailty.⁴⁸ In the Cardiovascular Health Study, nonfrail participants at baseline were assessed for the development of frailty after 5 and 9 years. It was found that total white blood cell count, C-reactive protein, and IL-6 levels were each associated with increased risk of frailty. Of these, however, only C-reactive protein remained significant after adjusting for confounders.⁴⁹ Also of demonstrable risk in the Cardiovascular Health Study cohort were those found to have insulin resistance. Finally, in the Women's Health and Aging Study, higher white blood counts and IL-6 levels were independently associated with prevalent frailty.¹⁴

Sarcopenia and Inflammation

As mentioned previously, sarcopenia or loss of muscle mass occurs with aging and is an important component of the phenotype of frailty. In fact, it is common. For example, in a study of 337 men and women aged 62 to 93 years, the prevalence of sarcopenia was as high as 50% in men older than 80 years.³¹

Mediators of inflammation contribute to the pathogenesis of sarcopenia. Although direct evidence is not yet available in humans; in certain animal models, it is apparent that activated inflammatory pathways contribute to muscle loss after chemical toxin or neuronal injury. In animals in which inflammatory pathways were generally inhibited, muscle loss was significantly less and post-injury regeneration was enhanced.⁵⁰

Although direct evidence of a causal relationship of dysregulated inflammation and sarcopenia is lacking in humans, there is abundant epidemiologic data that would support such a hypothesis. For example, in the Health Aging and Body Composition study, IL-6 and tumor necrosis factor- α levels in individuals aged 70 to 79 years were inversely associated with muscle mass as determined by computed tomography imaging and formal strength testing.⁵¹ This association was present even after adjusting for anti-inflammatory drug use and the presence or absence of inflammatory-associated conditions. Similarly, in the "Invecchiare in Chianti" study of 1020 participants aged 65 years and older living in the Chianti area of Italy, high levels of IL-6, IL-1RA, and C-reactive protein were significantly associated with poor overall physical performance and reduced muscle strength.⁵²

Another important aspect of sarcopenia in the elderly is that its occurrence is often accompanied by an increase in fat mass, a condition now termed “sarcopenic obesity.”^{53–55} Sarcopenic obesity is particularly ominous, having been associated in a number of studies with worse functional outcomes and disability.^{56,57} Evaluation of baseline data from 3075 men and women aged 70 to 79 years in the Health ABC study showed that lower leg muscle mass (as assessed by computed tomography estimation of mid-thigh cross-sectional area and muscle fat infiltration) was associated with poor performance on the 6-m walk tests, chair stand tests, and mobility disability.^{58,59} The “Invecchiare in Chianti” study also demonstrated high IL-6 levels correlated with the presence of central obesity.⁵² Similar results were reported from the Framingham Heart Study, in which higher IL-6 levels predicted a greater degree of sarcopenia, most notably in women.³⁰

Aging as a Prothrombotic State

Activation of the coagulation system and increase in procoagulant markers have been associated with the pathogenesis of atherosclerosis.^{60,61} However, procoagulant markers, most notably D-dimer,⁶² fibrinogen, and factor VIII⁶³ also increase with advancing age and may, in fact, correlate better with aging than with cardiovascular disease.^{60,61} Pieper and colleagues,⁶⁴ examining 1729 participants 70 years and older in the Established Populations for the Epidemiological Study of the Elderly cohort, clearly demonstrated that increasing age was associated with high D-dimer levels. For example, 23% of the participants aged 90 to 99 years had high D-dimer levels (>600 µg/L) compared with 13% in the age group 80 to 89 years and 7% in the age group 70 to 79 years.⁶⁴ French investigators measured fibrinogen concentrations in healthy subjects aged 19 to 96 years and found levels to be significantly higher in participants aged more than 60 years when compared with younger subjects.⁶⁵ Hager et al.,⁶⁶ in Germany, examining healthy individuals across the life span, found that fibrinogen levels increased by 25 mg/dL per decade of life and that levels as high as 320 mg/dL were found in more than 80% of people aged more than 65 years.⁶⁶ Other markers of activated coagulation, such as plasminogen activating inhibitor (PAI)-1 and factor VIII, have been shown to be increased with age.^{67–69} Thus, it is now apparent that aging is associated with markers of activated coagulation. In this context, it is notable that the incidence of venous thrombosis and pulmonary emboli increases dramatically in geriatric populations.^{70,71}

Coagulation and Functional Decline

From the Established Populations for the Epidemiological Study of the Elderly mentioned above, it was demonstrated that increases in D-dimer and IL-6 were related to increases in both morbidity and mortality.⁶⁴ The correlation for adverse outcomes was stronger with D-dimer than IL-6.⁷² In this, and other studies,^{73–75} D-dimer and other markers of activated coagulation were associated with limitation in a wide variety of functional domains, including independent activities of daily living, lower-extremity function, and performance on cognitive testing. The age-associated changes in coagulation markers occur earlier than other aging biomarkers, and thus it has been argued that they could be early predictors of those elderly at increased risk for functional decline.⁷⁶

This age-associated prominence of coagulation factors also has been reproduced in animals. For example, when stress associated with physical restraint was compared in aged versus young C57BL/6J mice, there was a significantly increased expression of m-RNA for PAI-1 in almost all the tissues in older mice.⁷⁷ Similar results were seen for expression of tissue factor mRNA in aged mice.⁷⁸ In both these experimental models, there was an increase in microthrombi distributed through multiple organ systems in the older mice.

In humans, depression and psychologic stress are associated with increased coagulation^{79–81} and decreased fibrinolytic activity.⁸² In elderly subjects without cardiovascular disease, physical exhaustion, a characteristic frequently used to distinguish frail from nonfrail individuals, was associated with significant increase in both inflammatory and coagulation factors as estimated by fibrinogen, C-reactive protein, and white blood cell levels.⁷⁹ As mentioned earlier, frail and pre-frail subjects from the Cardiovascular Health Study had significantly higher levels of fibrinogen, factor VIII, and D-dimer levels compared with the nonfrail group. The association with frailty persisted even after adjusting for the presence of cardiovascular disease and diabetes.⁸³ Frailty also is associated with increased risk of venous thromboembolism when compared with nonfrail individuals of the same age, especially in association with increased factor VIII levels.⁸⁴

Interaction between Inflammatory and Coagulation Markers

Thus, it has become apparent that both inflammatory and coagulation pathways are increasingly active with advancing age and to a greater extent in those who meet criteria for frailty. The coexistence of these factors suggests an interaction of inflammation and coagulation in the pathophysiology of frailty. It is known that inflammatory cytokines stimulate release of procoagulant factors in a wide range of cell types, and that the age-associated increase in these cytokines may thereby account for the associated activation of coagulation. However, it should be recalled that adipose tissue expression of both prothrombotic factors and proinflammatory cytokines is high.⁷⁷ Thus, the relative increase in adiposity with advancing age, and particularly with frailty, may offer some explanation for the inflammatory and procoagulant profiles observed.

Within adipocytes, these processes are tightly linked. For example, tumor necrosis factor- α is a powerful stimulant of adipocyte production of PAI-1, and antibody to tumor necrosis factor- α inhibits endogenous PAI-1 adipocyte secretion.^{85,86} Human pre-adipocyte cells in suspension increase production of PAI-1 in response to tumor necrosis factor- α ⁸⁷ and IL-6.⁸⁸ It is now apparent that IL-6 also plays a major role in synthesis and release of fibrinogen, tissue factor, Factor VIII, and platelets from multiple tissues.^{89–91} When IL-6 was added to hepatocyte cultures, Factor VIII mRNA rapidly increased, reaching maximal levels at 12 hours.

Thrombopoietin, a 353 amino acid polypeptide synthesized by liver and kidney, enhances bone marrow megakaryocyte proliferation and maturation and is the major regulator of platelet production.^{92,93} IL-6 increases thrombopoietin transcription and rapidly increases platelet production.⁹⁴ Thus, under inflammatory circumstances, platelet numbers increase. It remains to be determined whether age-associated changes in IL-6 relate to increased platelet

numbers, and whether such would contribute to yet another stimulus for the activation of the coagulation cascade.

The inflammatory/coagulation pathways have the potential to spiral into a self-perpetuating cycle, as several of the key factors feed back in a positive manner. For example, D-dimers are known to stimulate the synthesis and release of proinflammatory cytokines, including IL-6, and from peripheral blood monocytes and mouse hepatic cells in vitro, as noted above.^{95,96} IL-6 in turn, perpetuates the cycle by enhancing coagulation factor and platelet synthesis. Microthrombi, in turn, result in endothelial cell damage and further stimulate both inflammatory and coagulation pathways. Thus, an increase in generalized thrombotic tendency seen in late life could be the result of the commonly acknowledged inflammatory dysregulation of aging. (Figure).

CONCLUSIONS

There is now a robust literature describing both inflammatory and coagulation alterations with age and the interaction of these 2 pathways in the pathogenesis of frailty. It remains to be determined to what extent these pathways are activated by underlying disease processes,⁹⁷ a reflection of age-associated changes in body composition,⁵⁵ or merely the result of an age-associated dysregulation of inflammatory pathways.⁹⁸ Whatever the explanation, it is now clear that with age, and to a greater extent with frailty, there are both inflammatory and coagulation proteins evident in the circulation and within the tissue microenvironment that are not present, or present to a much lesser extent, in midlife or younger. It now seems likely that the inappropriate activation of these systems produces a catabolic cascade from which the phenotype of frailty evolves (Figure 1). These observations will assume greater importance if interventions aimed at regulating inflammatory or coagulation pathways result in clinically important improvements, such as in physical or cognitive function.

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CLINICAL SIGNIFICANCE

- Frailty is a distinct syndrome associated with functional decline, loss of independence, and mortality.
- Features include sarcopenia, osteoporosis, anemia, and immune deficiency.
- Risks include number of comorbidities, depression, obesity, and race, but some individuals will become frail without identifiable risk factors.
- A common feature of frailty is a demonstrable activation of inflammatory and coagulation pathways, and these are currently the target of interventional trials.

Figure.

Pathway to frailty. Proinflammatory signals, including IL-6 and TNF- α , increase with age, as do markers of activated coagulation, including D-dimer, fibrinogen, PAI, and Factor VIII. To the extent that these are primary processes, they may contribute to a cycle of physiologic changes that, in composite, are described as “frailty.”

Table 1

Frailty Index

Criteria Used to Define Frailty²

- * Weight Loss: "In the last year, have you lost more than 10 lbs unintentionally (ie, not due to dieting or exercise)?" If yes, then frail or weight loss criterion. At follow-up, weight loss was calculated as: (weight in previous year – current measured weight)/(weight in previous year) = K. If K is ≥ 0.05 and the subject does not report that he/she was trying to lose weight (ie, unintentional weight loss of at least 5% of previous body weight), then frail for weight loss = Yes.
- * Exhaustion: Using the CES-D, the following statements are read. (a) I felt that everything that I did was an effort; (b) I could not get going. The question is asked, "How often in the last week did you feel this way?" 0 = rarely, 1 = some or a little of the time (1–2 days), 2 = a moderate amount of time (3–4 days), or 3 most of the time. Subjects answering 2 or 3 to either of these questions score positively for this criterion.
- * Physical Activity: Based on the short version to the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercising, cycling, dancing, bowling, golf, singles tennis, racquetball, calisthenics, swimming. Kilocalories per week expended are calculated using standardized algorithm. This variable is by gender.

Men: Those with kcal per week < 383 are frail.

Women: Those with kcal per week < 270 are frail.

- * Walk time: stratified by gender and height (gender-specific cutoff a medium height)

Cutoff for Time to Walk 15 ft Criterion for Frailty

Men	
Height 173 cm	7 sec
Height > 173 cm	6 sec
Women	
Height 159 cm	7 sec
Height > 159 cm	6 sec

*Grip strength, stratified by gender and BMI quartiles:

Cutoff for Grip Strength (kg) Criterion for Frailty

Men	
BMI 24	29
BMI 24.1–26	30
BMI 26.1–28	30
BMI > 28	32
Women	
BMI 23	17
BMI 23.1–26	17.3
BMI 26.1–29	18
BMI > 29	21

CES-D = Center for Epidemiologic Studies Depression Scale; BMI = body mass index.

Table 2

Prevalence of Frailty

Population	Study-Specific Frailty Criteria	Percent Frail
CHS, n = 5317 men and women aged 65 y, community dwelling ^{2,23}	Three or more of the following criteria: unintentional weight loss (10 lbs in past year) self-reported exhaustion weakness (grip strength) slow walking speed low physical activity	Overall, 7% White men, 4.6% White women, 6.8% Black men, 8.7% Black women, 15.0%
Canadian Study of Health and Aging, n = 9008 men and women, 65+, community dwelling ^{1,5,11,16}	Used "Frailty Scale," ⁹⁹ which considers: mobility ADL bladder and bowel continence cognition	Prevalence of frailty: 7.0% 65–74 y 17.5% 75–84 y 36.6% 85+ y
Survey in Europe on Nutrition and the Elderly, a Concerted Action, n = 849, aged 75–80 y ²²	Low physical activity weight loss of 5 kg/4 y	Low physical activity 24% Weight loss 6.3% Both 3.2%
Longitudinal Aging Study of Amsterdam, n = 2257 men and women, mean age 72 y ²¹	Three or more of the following criteria: body weight peak expiratory flow cognition vision and hearing problems incontinence sense of mastery depressive symptoms physical activity	Male 17% Female 18.3%
WHI, n = 40,657 women, community dwelling, age 65–79 y ¹⁵	Three or more of the following criteria: unintentional weight loss (10 lbs in past year) self-reported exhaustion weakness (grip strength) slow walking speed low physical activity.	Baseline, 16.3% Incident, at 3 y, 14.8%
WHAS I and II. n = 1002, community dwelling, ages 65–79 y ¹³	Three or more of the following criteria: unintentional weight loss (10 lbs in past year) self-reported exhaustion weakness (grip strength) slow walking speed low physical activity	Women 11.6%

CHS = Cardiovascular Health Study; WHI = Women's Health Initiative; WHAS = Women's Health and Aging Study; ADL = activities of daily living.

Table 3

Aging and Frailty Cohorts

Study	Sample (No., Sex, Age)	Findings/Added Value
CHS ^{2,23,70}	5317 men and women, 65+ community dwelling	First use of Frailty Index in a large cohort Found approximately 6% met criteria for frailty, and of these ~46% had comorbidities and 27% had neither ADL deficiency or diagnosed illness Identified frailty to be more common among African Americans Catalogued the likelihood of various comorbidities to be associated with frailty Identified age-associated coagulation factors with risk for cardiovascular disease
SENECA ²²	849 men and women, aged 75–80 y	Used a simple assessment tool to identify frailty
LASA ²¹	2257 men and women, mean aged 72 ± 8 y (SD)	Identified frailty to be more common among women Identified high levels of CRP to be a risk factor for frailty
Alameda County Study ²⁵	574 men and women aged 65–102 y, community dwelling	Established social, psychologic factors associated with frailty, including smoking, excessive alcohol consumption, depression, self-perceived poor, or fair physical health
WHI ¹⁵	40,657 women, aged 65–79	Established BMI (either high or low) as a frailty risk factor
WHAS ¹³	1002 women, aged 65–79 y, community dwelling	Validated the effectiveness of the Frailty Index Identified obesity as risk factor Found white blood count and IL-6 levels to be higher in frail vs nonfrail
Health ABC ^{51,58}	3075 men and women aged 70–79 y	Found elevated levels of IL-6 and TNF- α to be inversely associated with muscle mass and strength
CSHA ^{1,5,11,16}	9008 men and women, community dwelling	Assessed and validated methods for determining frailty Found an increased risk of institutionalization among frail and a greater sense of social isolation
Beaver Dam Eye Study ⁹	2962 men and women, community dwelling	Longitudinal cohort demonstrating frailty to be associated with cardiovascular disease and hypertension. When controlled for sex, age, cardiovascular disease, hypertension, and diabetes, the presence of frailty remained an independent predictor of mortality.
EPESE ^{46,64,72}	1729 men and women, 70+ y	Demonstrated age-associated increase in IL-6, D-dimer, factor VIII, and fibrinogen and that IL-6 and D-dimer levels were predictive of mortality
InCHIANTI ⁵²	1020 men and women, 65 y	Found that high levels of IL-6, IL-1RA, and CRP were significantly associated with poor overall physical performance, reduced muscle strength, and central obesity

CHS = Cardiovascular Health Study; SENECA = Survey in Europe on Nutrition and the Elderly; LASA = Longitudinal Aging Study of Amsterdam; WHI = Women's Health Initiative; WHAS = Women's Health and Aging Study; Health ABC = Health Aging and Body Composition; CSHA = Canadian Study of Health and Aging; EPESE = Established Populations for Epidemiological Study of the Elderly; InCHIANTI = Invecchiare in Chianti; ADL = activities of daily living; CRP = C-reactive protein; IL = interleukin; BMI = body mass index; TNF = tumor necrosis factor; SD = standard deviation.