# Insulin Resistance and Inflammation as Precursors of Frailty

## *The Cardiovascular Health Study*

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**Background:** Our research group has previously shown that the geriatric syndrome of frailty is associated with features of the metabolic syndrome (MetS) on cross-sectional analysis.

**Methods:** To test whether MetS and its physiologic determinants—insulin resistance as measured by homeostasis model assessment score (IR-HOMA), increased inflammation and coagulation factor levels, and elevated blood pressure—are associated with incident frailty, we studied a subcohort of participants from the Cardiovascular Health Study observed from 1989/1990 through 1998/1999: 3141 community-dwelling adults, aged 69 to 74 years, without frailty and illnesses that increase inflammation markers or mimic frailty. The association of baseline MetS, IR-HOMA, levels of inflammation and coagulation factors, and systolic blood pressure (SBP) with time to onset of frailty was adjusted for demographic and psychosocial factors and incident events. Our main outcome measure was incident frailty.

**Results:** Metabolic syndrome was not significantly associated with incident frailty (hazard ratio, 1.16 (95% confidence interval [CI], 0.85-1.57). On the other hand, IR-HOMA and C-reactive protein levels were associated with incident frailty: for every standard deviation increment the hazard ratio for frailty was 1.15 (95% CI, 1.02-1.31) and 1.16 (95% CI, 1.02-1.32), respectively. The white blood cell count and factor VIIIc levels had a borderline association. Elevated systolic blood pressure had no association. Similar trends were found for incident prefrailty, a condition that precedes frailty.

**Conclusions:** Two physiologic components of MetS—IR-HOMA and inflammation—are associated with incident frailty. Based on these results, IR-HOMA can be considered part of a larger process that leads to generalized decline.

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THE GERIATRIC SYNDROME OF frailty is characterized by decreased reserve in multiple physiologic systems.[1] It predicts adverse health outcomes independent of advancing age, chronic disease, and functional limitations, thereby suggesting that it is a distinct condition.[2-4] Using data from the Cardiovascular Health Study (CHS)[5] and the Women's Heath and Aging Studies,[6]



our research group tested and validated the hypothesis that frailty could be defined as a syndrome consisting of involuntary weight loss, exhaustion, low physical activity, slowness, and weakness. Subsequently, a physiologic basis for this phenotype was explored.[7] On cross-sectional analysis, frailty was associated with adiposity, altered markers of carbohydrate metabolism, hypertension, and elevated markers of inflammation and coagulation. All of these findings are characteristics of the metabolic syndrome (MetS).[8]

As noted by Kahn et al,[9] several studies using factor analysis have identified 3 "principal factors" that underlie MetS. These include (1) a metabolic factor with positive loadings of insulin resistance (IR), elevated glucose levels, and obesity; (2) an inflammation factor with positive loadings of inflammation and coagulation factors; and (3) a blood pressure factor, with positive loadings of systolic and diastolic blood pressure. Given our cross-sectional findings, we hypothesized that a prospective association might exist between MetS and its physiologic determinants with frailty. In the present study, we test this hypothesis by examining a cohort from the CHS,[10] a study of older adults observed prospectively for the development of cardiovascular disease and frailty.

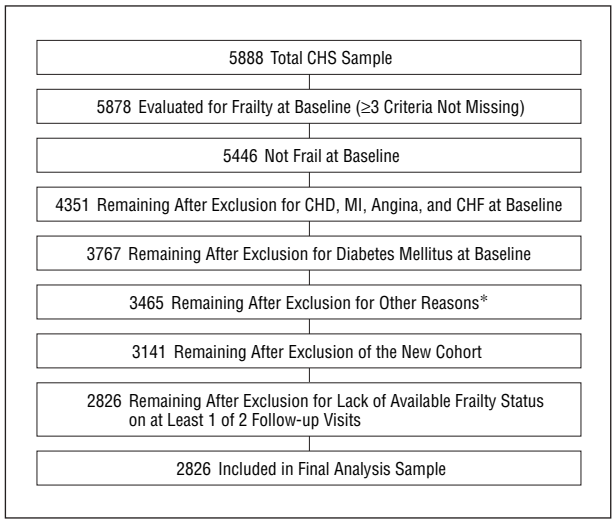


**Figure.** Creation of the subcohort from the Cardiovascular Health Study[10] (CHS) that was analyzed for incident frailty. CHD indicates coronary heart disease; CHF, congestive heart failure; MI, myocardial infarction. *Baseline antidepressant use, Parkinson disease, stroke, and/or Mini-Mental State Examination score lower than 18.

## METHODS

Recruitment methods for the CHS have been published.[10] In brief, an age- and sex-stratified random sample of individuals 65 years or older (oversampling for those older than 85 years) was drawn from Medicare eligibility lists. Such individuals and eligible household members were invited to participate at 4 US field centers. Potential participants were excluded if they (1) had cancer under active treatment, (2) would have been unable to attend a field center for examination, or (3) did not expect to remain in their area of residence for more than 3 years. Of those who were contacted, 9.6% were ineligible, and 34.9% refused participation. A total of 5201 participants were recruited in the 1989-1990 period (*original cohort*), and 687 in 1992-1993 (*new cohort*). The new cohort included additional representation of African Americans. All participants gave informed consent at study entry. Institutional review board approval was received at all 4 clinical sites.

At the time of baseline examination, data on standardized laboratory tests, caloric intake, alcohol consumption, and energy expenditure were obtained.[11,12] Information on clinical cardiovascular disease and socioeconomic status was also obtained.[13]

### LABORATORY STUDIES

At each CHS field center, baseline blood samples were drawn after an overnight fast, processed for storage, and shipped to a central laboratory at the University of Vermont following standardized protocols. Methods of phlebotomy sample handing and quality assurance have been described previously.[14] White blood cell counts and levels of hemoglobin and hematocrit were evaluated at local laboratories. Levels of glucose, insulin, albumin, fibrinogen, factor VIIc, factor VIIIc, and plasma lipids were measured at the central laboratory. A 75-g oral glucose tolerance test was performed on all subjects without diabetes mellitus (DM), and fasting and 2-hour glucose and insulin levels were measured. Coagulation factors were measured with the Coag-A-Mate X2 instrument (Organon Teknika Corp, Durham, NC) using immunodeficient plasma (Baxter Dade AG, Dudingen, Switzerland) and human placental thromboplastin (Thromborel S; Dade Behring Inc, Deerfield, Ill) for factor VIIc and a partial thromboplastin reagent for factor VIIIc (Organon Teknika Corp). Values were reported as a percentage of normal plasma pool, and standardization was performed by assaying reference plasma from the World Health Organization.

The mean monthly coefficients of variation for the factor VIIc and VIIIc assays were 5.31% and 9.67%, respectively. Plasma fibrinogen levels were measured using a semiautomated modified clot-rate method with a BBL Fibrometer (Becton Dickinson and Company, Bedford, Mass) and reported in milligrams per deciliter. The mean monthly coefficient of variation for the fibrinogen assay was 3.09%. Albumin was assessed using the Kodak Ektachem 700 analyzer (Eastman Kodak, Rochester, NY) as part of the standard clinical chemical assays.[14] White blood cell counts were performed at each of the 4 local CHS laboratories using automated counters (Coulter Stack S cell counter; Beckman Coulter Inc, Fullerton, Calif; or the SysmexNE8000 counter; Toa Electronics Inc, South San Francisco, Calif).[10] C-reactive protein (CRP) was assessed with a high-sensitivity enzyme-linked immunosorbent assay using purified protein and polyclonal anticlonal anti-CRP antibodies.[15] The interassay coefficient of variation was 5.50%. Interleukin 6 levels were measured by ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, Minn). The analytical coefficient of variation for this assay was 6.3%.

### SUBJECT COHORT

There were 5888 participants in the original and the new CHS cohorts combined (**Figure**). Of these, 5878 had data available to evaluate frailty status at baseline; 5446 of these were not frail at baseline. The original cohort was assessed for frailty characteristics at baseline and follow-up was conducted at years 5 and 9. The new cohort was assessed for frailty at baseline and year 5. Owing to the small number of participants available for assessment of frailty in the new cohort at year 5 (n=246) and the small number who became frail (n=28), only the original cohort was examined in these analyses.

Participants excluded from the original cohort were those with any of the following at baseline: frailty, DM, coronary heart disease, myocardial infarction, angina, congestive heart failure, stroke, transient ischemic attack, peripheral arterial disease requiring intervention, antidepressant use, Parkinson disease, and/or a Mini-Mental State Examination score lower than 18. This left 3141 original cohort participants available for analysis at baseline. These exclusions were chosen to ascertain the association of IR and inflammation and coagulation factors with the development of frailty, independent of other confounding factors. Participants with DM, heart disease, and/or stroke were excluded because these conditions increase IR and inflammation and coagulation factors. The other excluded conditions can manifest as frailty characteristics specific to the single disease. Finally, participants had to be alive and assessed for frailty on at least 1 available follow-up visit.

### DEFINITIONS

*Frailty* was defined as the presence of 3 or more of the following criteria: weight loss, exhaustion, low physical activity, slowness, weakness (**Table 1**).[6,7] Those with fewer than 1 or 2 of these criteria were considered *prefrail*, an intermediate syndrome with increased risk for the development of frailty.

Insulin resistance was measured using the homeostasis model assessment score (hereinafter IR-HOMA), based on the HOMA Calculator version 2.2 computer program. The IR-HOMA assesses insulin sensitivity based on insulin and glucose levels

**Table 1. Measurable Physical Characteristics of Frailty From the Cardiovascular Health Study Data[3]**

| Frailty Characteristic | Measure |
|---|---|
| Weight loss (unintentional) | Baseline: >4.54 kg lost unintentionally in prior year (reported); follow-up: unintentional loss of ≥5% of body weight in prior year (measured) |
| Weakness | Grip strength: lowest 20% by sex and BMI (eg, for women: grip strength ≤17 kg, BMI ≤23) |
| Exhaustion | Self-report: answer "moderate or most of the time" to (1) "I felt everything I did was an effort" or (2) "I could not get going" |
| Slowness | Walking time per 15 ft: slowest 20% by sex and height |
| Low activity and/or low exercise tolerance | Kilocalories per week: lowest 20% for men, <383 kcal/wk; women, <270 kcal/wk (based on the short version of the Minnesota Leisure Time Activity Questionnaire[16]) |

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

in the fasting state using nonlinear modeling based on assumptions regarding the function of various organs involved in glucose regulation. The IR-HOMA has been validated as a measure of insulin sensitivity against precise measures of insulin sensitivity or resistance.[17]

The MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria.[8] These criteria include 3 or more of the following findings: triglycerides level of 150 mg/dL or higher (≥1.7 mmol/L); high-density lipoprotein cholesterol level lower than 40 mg/dL in men (<1.0 mmol/L) or lower than 50 mg/dL in women (<1.3 mmol/L); blood pressure of 130/85 mm Hg or higher or treated hypertension; fasting glucose level of 110 mg/dL or higher (≥6.1 mmol/L); and waist girth greater than 102 cm in men or greater than 88 cm in women. For these analyses, those with fasting glucose levels between 110 and 125 mg/dL alone (6.1-6.9 mmol/L) were not automatically considered to have MetS at baseline or follow-up.

## STATISTICAL ANALYSIS

Participants were categorized into 3 mutually exclusive frailty categories at the end of study follow-up: never frail, prefrail only, or frail (whether the participant was ever prefrail or not). Incidence data were grouped into 2 intervals defined by the 2 follow-up visits. Because of the discrete nature of these time-to-event data, multivariate discrete time proportional hazard models[18] were used to estimate the association between the independent variables of interest (MetS, IR-HOMA, inflammation and coagulation factors, and systolic blood pressure) and the likelihood of developing frailty during follow-up. Multivariate models were specified for incident prefrailty and for incident frailty (including baseline prefrailty as a covariate in all models for incident frailty).

In addition, separate models were specified for both dependent variables to include only 1 independent variable of interest at a time to evaluate each hypothesized component of MetS. Covariates were entered into the multivariate models in blocks to evaluate effects of different groups of covariates: model 1 was not adjusted for other covariates; model 2 was adjusted for time-independent and baseline covariates (age, sex, income, smoking status, marital status, education, depressive symptoms, cognitive function, arthritis, and body mass index [calculated as weight in kilograms divided by height in meters squared] [categorized by World Health Organization criteria[19]: <18.5, underweight; 25-29.9, overweight; >29.9, obese; vs normal weight 18.5-24.9]); and model 3 included all of the adjustments of model 2 plus adjustments for time-dependent variables such as incident chronic diseases (DM, coronary heart disease, stroke, and cancer). We also entered waist circumference and waist-hip ratio into model 2 in place of body mass index, but no differences in outcomes were found.

**Table 2. Distribution of Components of Frailty* Among CHS Participants Who Were Not Frail at Baseline and Who Became Frail at Either Year 5 or 9 of Follow-up**

| Frailty Component | Study Participants Who Developed Frailty, % |
|---|---|
| Baseline | |
| Diminished grip strength | 24.4 |
| Diminished walking speed | 22.8 |
| Weight loss >10% | 4.2 |
| Exhaustion | 20.5 |
| Low physical activity | 20.5 |
| Frail at year 5 (n = 113) | |
| Diminished grip strength | 54.9 |
| Diminished walking speed | 88.5 |
| Weight loss >10% | 7.1 |
| Exhaustion | 83.2 |
| Low physical activity | 76.1 |
| Frail at year 9 (n = 121) | |
| Diminished grip strength | 58.7 |
| Diminished walking speed | 84.3 |
| Weight loss >10% | 7.4 |
| Exhaustion | 58.7 |
| Low physical activity | 76.9 |
| Total frail (n = 234) | |
| Diminished grip strength | 58.5 |
| Diminished walking speed | 89.5 |
| Weight loss >10% | 15.5 |
| Exhaustion | 77.0 |
| Low physical activity | 79.0 |

Abbreviation: CHS, Cardiovascular Health Study.[5]
*Frailty is defined as having 3 or more of the 5 criteria listed in Table 1.

## RESULTS

Of the 2826 participants from the original CHS cohort without frailty at baseline, 738 (26%) did not develop prefrailty or frailty at either year 5 or 9 follow-up; 1854 (66%) remained prefrail or developed prefrailty at years 5 and/or 9; and 234 (8%) became frail at year 5 or 9. Components of frailty at baseline and at follow-up for those who became frail are listed in **Table 2**. The most common components were slow walking speed, weak grip strength, and low physical activity. Unintentional weight loss was the least common component.

Baseline characteristics and incident events of this cohort categorized by prefrailty and frailty incidence are summarized in **Table 3**. Those who became frail were

**Table 3. Baseline Characteristics and Incident Events of CHS Participants Categorized by Frailty Status Through 9 Years of Follow-up***

| Characteristic | Frailty Development | | |
|---|---|---|---|
| | Never (26%; n = 738) | Prefrailty Only (66%; n = 1854) | Frailty (With or Without Prefrailty) (8%; n = 234) |
| Demographics | | | |
| Race, % black | 2.6 | 3.7 | 6.0‡ |
| Age, y | 70.4 ± 4.0 | 72.1 ± 5.1† | 74.7 ± 5.8† |
| Sex, % male | 46.2 | 36.3† | 21.8† |
| Current smoker, % | 8.4 | 10.9 | 13.7 |
| Total alcohol consumption, drinks/wk | 3.2 ± 6.3 | 2.9 ± 7.1 | 1.8 ± 5.1‡ |
| Obesity and activity | | | |
| Weight, lb | 156.1 ± 28.3 | 156.5 ± 31.0 | 153.7 ± 33.7 |
| BMI | 25.5 ± 3.5 | 26.2 ± 4.4† | 26.8 ± 5.3† |
| Waist circumference, cm | 90.6 ± 11.5 | 92.7 ± 12.7† | 93.4 ± 13.9‡ |
| Hip circumference, cm | 99.9 ± 7.6 | 101.4 ± 9.5† | 102.5 ± 11.4† |
| Energy expended, kcal/d | 2753.2 ± 2312.2 | 1809.1 ± 2042.8† | 1471.0 ± 1760.9† |
| Psychosocial factors, % | | | |
| Low education (grade 8 or less) | 7.1 | 12.0† | 16.2† |
| Low income (<$12 000) | 10.4 | 20.3† | 25.6† |
| Married | 79.6 | 68.2† | 60.7† |
| Fair or poor self-rated health | 5.8 | 13.3† | 25.6† |
| MMSE score | 28.5 ± 1.6 | 28.2 ± 2.0 | 27.9 ± 2.2† |
| MMSE score range 18-23 | 1.4 | 3.6‡ | 7.3† |
| CES-D score | 2.7 ± 2.8 | 4.2 ± 4.1 | 5.3 ± 3.8† |
| CES-D score ≥10 | 2.2 | 7.4† | 11.1† |
| Medical factors | | | |
| Arthritis, % | 40.1 | 50.2† | 59.5† |
| COPD, % | 8.9 | 12.5 | 11.5 |
| Impaired fasting glucose level (ADA criteria[20]), % | 13.9 | 15.9 | 17.5 |
| Chronic diseases, No.§ | 1.8 ± 1.3 | 2.1 ± 1.4† | 2.5 ± 1.4† |
| Medications, No. | 1.2 ± 1.4 | 1.6 ± 1.7† | 2.0 ± 1.9† |
| SBP, mm Hg | 132.6 ± 20.7 | 134.3 ± 20.7 | 137.1 ± 20.3 |
| DBP, mm Hg | 70.6 ± 10.9 | 70.5 ± 10.8 | 69.6 ± 10.8 |
| Metabolic laboratory measure | | | |
| Cholesterol, mg/dL | 215.0 ± 37.4 | 213.5 ± 37.2 | 214.4 ± 37.5 |
| LDL cholesterol, mg/dL | 133.9 ± 34.2 | 130.3 ± 34.4 | 131.1 ± 33.8 |
| Triglycerides, mg/dL | 130.1 ± 61.8 | 134.0 ± 61.8 | 135.5 ± 69.5 |
| HDL cholesterol, mg/dL | 55.7 ± 15.4 | 56.7 ± 15.8 | 57.1 ± 17.1 |
| Fasting insulin level, log transformed | 2.5 ± 0.4 | 2.5 ± 0.4† | 2.6 ± 0.4† |
| Fasting insulin level, μIU/mL | 12.8 ± 6.3 | 13.5 ± 7.0 | 14.7 ± 7.4† |
| Fasting glucose level, mg/dL | 98.9 ± 9.3 | 99.9 ± 9.3 | 99.6 ± 10.3 |
| Inflammatory laboratory measure | | | |
| WBC count, $\times 10^3/\mu L$ | 5.9 ± 1.5 | 6.2 ± 2.0† | 6.4 ± 1.6† |
| CRP level, log transformed | 0.6 ± 0.9 | 0.8 ± 1.0† | 1.0 ± 0.9† |
| CRP level, mg/L | 3.0 ± 4.7 | 3.8 ± 6.0† | 4.2 ± 5.5† |
| Fibrinogen, mg/dL | 309.4 ± 58.9 | 314.1 ± 60.2 | 321.9 ± 61.4‡ |
| Factor VIIc, % activity | 121.2 ± 25.3 | 127.2 ± 29.1† | 128.7 ± 28.6† |
| Factor VIIIc, % activity | 114.7 ± 32.5 | 117.3 ± 35.2 | 124.5 ± 38.5† |
| Albumin, mg/dL | 4.0 ± 0.3 | 4.0 ± 0.3 | 4.0 ± 0.2 |
| Interleukin 6, pg/mL | 1.8 ± 2.2 | 2.0 ± 1.8‡ | 2.3 ± 1.7‡ |
| Interim health events, % | | | |
| Diabetes mellitus | 4.2 | 5.2 | 8.6† |
| CHD (MI, angina, PTCA, and/or CABG) | 12.5 | 11.9 | 14.1 |
| Stroke | 4.6 | 6.9 | 12.0† |
| Cancer | 12.5 | 10.9 | 11.1 |
| Metabolic syndrome and components, % | | | |
| Metabolic syndrome | 16.7 | 22.3‡ | 25.6‡ |
| Increased girth (waist ≥88 cm for women or ≥102 cm for men) | 31.7 | 46.1† | 51.7† |
| Low HDL level (≥50 mg/dL for women or ≥40 mg/dL for men) | 21.7 | 24.7 | 29.9 |
| High triglyceride level (≥150 mg/dL) | 25.9 | 29.5 | 27.4 |
| High fasting glucose level (≥110 mg/dL) | 13.8 | 15.8 | 17.5 |
| Hypertension (BP ≥130/85 mm Hg) | 34.3 | 38.0 | 43.2 |
| IR-HOMA score | 1.67 ± 0.82 | 1.77 ± 0.89 | 1.96 ± 0.98† |

Abbreviations: ADA, American Diabetes Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CABG, coronary artery bypass graft; CES-D, Center for Epidemiologic Studies–Depression; CHD, coronary heart disease; CHS, Cardiovascular Health Study[5]; COPD, chronic obstructive pulmonary disorder; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IR-HOMA, insulin resistance as measured by homeostasis model assessment; LDL, low-density lipoprotein; MI, myocardial infarction; MMSE, Mini-Mental State Examination; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; WBC, white blood cell.

SI conversion factors: To convert weight to kilograms, multiply by 0.45; glucose to millimoles per liter, multiply by 0.0555; any cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; insulin to picomoles per liter, multiply by 6.945; fibrinogen to micromoles per liter, multiply by 0.0294.

*Unless otherwise indicated, data are reported as mean ± SD values.

†$P<.001$.

‡$P<.01$ using $\chi^2$ tests and $t$ tests, with never frail as reference group.

§Chronic diseases include arthritis, COPD, cancer, hearing impairment, vision impairment, and hypertension.

**Table 4. Hazard Ratios as Determined by Discrete Time Proportional Hazard Models for Incident Prefrailty and Frailty**

| | Hazard Ratio (95% Confidence Interval) | | | | | |
|---|---|---|---|---|---|---|
| | Model 1† | | Model 2‡ | | Model 3§ | |
| Variable* | Prefrail | Frail | Prefrail | Frail | Prefrail | Frail |
| Metabolic syndrome (yes vs no) | 1.36 (1.15-1.60) | 1.10 (0.98-1.24) | 1.30 (1.09-1.54) | 1.07 (0.94-1.21) | 1.28 (1.07-1.53) | 1.05 (0.92-1.19) |
| White blood cell count | 1.08 (1.00-1.16) | 1.09 (0.99-1.20) | 1.06 (0.98-1.15) | 1.09 (0.98-1.21) | 1.06 (0.98-1.15) | 1.07 (0.96-1.20) |
| C-reactive protein | 1.10 (1.03-1.18) | 1.20 (1.06-1.36) | 1.07 (1.00-1.15) | 1.18 (1.04-1.34) | 1.07 (0.99-1.15) | 1.16 (1.02-1.32) |
| IL-6 (interleukin 6) | 0.99 (0.92-1.07) | 1.10 (1.01-1.21) | 0.96 (0.89-1.04) | 1.03 (0.94-1.13) | 0.96 (0.89-1.03) | 1.03 (0.94-1.13) |
| Factor VIIc | 1.19 (1.11-1.28) | 1.05 (0.92-1.21) | 1.14 (1.05-1.23) | 0.93 (0.80-1.08) | 1.14 (1.05-1.23) | 0.92 (0.78-1.06) |
| Factor VIIIc | 1.03 (0.95-1.11) | 1.29 (1.15-1.46) | 0.96 (0.89-1.04) | 1.11 (0.97-1.26) | 0.96 (0.88-1.04) | 1.11 (0.97-1.26) |
| Systolic blood pressure | 1.02 (0.94-1.10) | 1.16 (1.01-1.33) | 0.97 (0.90-1.05) | 1.02 (0.89-1.17) | 0.96 (0.89-1.04) | 1.01 (0.88-1.17) |
| IR-HOMA score | 1.07 (0.99-1.15) | 1.16 (1.04-1.29) | 1.06 (0.97-1.15) | 1.17 (1.03-1.31) | 1.06 (0.97-1.16) | 1.15 (1.02-1.31) |

Abbreviation: IR-HOMA, insulin resistance as measured by homeostasis model assessment.
*Hazard ratios for all variables except metabolic syndrome are per standard deviation unit difference in the predictor: white blood cell count, 1.86; C-reactive protein, 0.96; interleukin 6, 1.97; factor VIIc, 28.22; factor VIIIc, 34.90; systolic blood pressure, 20.55; and IR-HOMA score, 0.89.
†Model 1, unadjusted.
‡Model 2, adjusted for time invariant covariates and selected baseline conditions (age, sex, smoking status, education, income, marital status, body mass index, depression, and cognition).
§Model 3, adjusted for all factors in model 2 plus incident diabetes mellitus, heart disease, stroke, and cancer.

more likely to be African American, older, and female, and at baseline to be heavier, have more central obesity, and have lower self-assessed health status and Mini-Mental State Examination scores than those who did not become frail. They had fewer years of education, lower income, and were less likely to be married. Those who developed frailty were also more likely to have baseline depressive symptoms and arthritis and to use more medications. They also had higher white blood cell counts, higher IR-HOMA scores, and higher levels of fasting insulin, CRP, factors VIIc and VIIIc, and interleukin 6 at baseline than those who did not develop frailty. They were about 50% more likely to have MetS. The most common components of MetS were increased girth and increased IR-HOMA scores. Those who became frail did not differ significantly from those who did not become frail by blood pressure levels. Those who became frail were also more likely to develop DM and stroke. The same baseline characteristics were associated with incident prefrailty as with incident frailty, but the associations were generally weaker or the correlations intermediate.

The adjusted risk for developing prefrailty and frailty by MetS, IR-HOMA, inflammation and coagulation factors, and systolic blood pressure are summarized in **Table 4**. Metabolic syndrome and increasing systolic blood pressure at baseline were not independently associated with frailty, although MetS was associated with incident prefrailty. On the other hand, IR-HOMA score and CRP level were consistently associated with an increased risk of developing frailty. Every standard deviation unit increment in IR-HOMA score was associated with a hazard ratio of 1.15 (95% confidence interval, 1.02-1.31). Every standard deviation unit increment in CRP level was associated with a hazard ratio of 1.16 (95% confidence interval, 1.02-1.32). The white blood cell count and factor VIIIc levels had a borderline significant association. Similar trends were seen with prefrailty. In all models, increased age, current smoking, and prefrailty at baseline were independent risk factors for incident frailty (data not shown).

To validate our criteria for frailty, we examined the progression of those with baseline frailty (n=432). We found that 45% (n=198) had died and 15% (n=65) had been lost to follow-up by year 9. Of those who remained alive at year 9 (n=169), only 15 (3.5% of the cohort with baseline frailty) were neither frail nor prefrail.

## COMMENT

In the present study, we found that 2 principal components of the MetS—IR-HOMA score and increased CRP levels—were associated with increased risk for the development of frailty. On the other hand, the MetS itself was not prospectively associated with incident frailty.

The association of the IR-HOMA score with frailty was modest. Several reasons may account for this. First, the IR-HOMA score, while a validated measure of IR useful for population-based studies, moderately underestimates exact measures of insulin-mediated glucose disposal.[17] As such, the IR-HOMA score estimate of the association of IR with frailty may underestimate the true association between the 2 disorders. Second, we did not include individuals with DM, cardiovascular disease, and chronic illnesses in our analyses. This was done to examine the association of IR, as much as possible, independent of conditions that are associated with increased inflammation and coagulation factor levels. The effect of so doing was to examine a relatively healthy cohort with a low degree of IR. Finally, there is growing evidence that frailty may result from dysregulation of multiple physiologic systems,[2] so that the independent physiologic contribution of any 1 system may be relatively small.

How IR may be associated with frailty is uncertain. One possibility is that the 2 conditions are related to a primary defect in muscle metabolism.[21,22] For example, one study of elderly individuals with loss of sensitivity to the effect of insulin had impaired muscle protein breakdown.[23] Another study showed that hyperinsu-

linemia (an indirect marker of IR) was associated with less muscle protein production.[24] Impaired muscle quality, presenting initially with IR, may subsequently result in impaired energy regulation and performance, as seen in frailty. A recent study shows that people with DM—most of whom have IR—have low muscle strength and quality.[25] An alternate explanation may be that inflammation gives rise to IR and muscle dysfunction. Increased inflammation factors have been implicated in muscle weakness and age-related declines in physical function.[26]

Metabolic syndrome, without DM, was not associated with frailty in this study. The term *metabolic syndrome*, as construed from the National Cholesterol Education Program Adult Treatment Panel III criteria,[8] implies that the risk factors that cluster to make up this syndrome are interrelated through IR. Recent studies show, however, that the association of MetS with insulin-mediated glucose disposal is weak and that not all people with MetS are insulin resistant.[27,28] Then, too, the term *metabolic syndrome* is defined in several ways by different medical organizations.[9] As such, it is an inexact diagnosis. For these reasons, MetS may not have been associated with frailty in our study. We also found that hypertension—another principal component of MetS—was not associated with incident frailty. Univariate analyses showed no differences in prevalence of hypertension between those who did and those who did not become frail.

Several other findings from this study deserve mention. First, we report that prefrailty predicted frailty, consistent with prior findings,[7] but now with longer follow-up. Second, we report that the same factors that predicted frailty, in general, also predicted prefrailty. This provides support for the hypothesis that prefrailty and frailty represent degrees of severity within the same chronic, progressive process. Third, weight loss was the least common component of frailty. Weight loss is believed to be consonant with frailty. It follows that weight loss may be a late manifestation of frailty and/or may reflect an end stage of disease that is strongly associated with loss to mortality. Fourth, participants who developed incident frailty had more depression, chronic disease burden, and lower socioeconomic indicators than those who did not develop frailty. Whether these factors played a causal role in the development of frailty or were a consequence of other unidentified factors that lead to frailty deserves further exploration. Finally, people who developed frailty were more likely to develop DM. This suggests that the 2 disorders may have common pathogenic mechanisms. We have shown that CRP level predicts DM,[29] much as it predicted frailty. The IR-HOMA score, which predicted frailty, also predicts DM.

This study has several strengths. It examined many metabolic, inflammatory, socioeconomic, and medical conditions simultaneously for a broad understanding of the relationship of IR with frailty. It included time-dependent covariates to account for interim events from baseline that could have affected the incidence of frailty. We were careful to exclude individuals with conditions that could have mimicked frailty or increased inflammation factors.

Limitations should also be noted. The analysis focused primarily on healthy individuals, so its findings might not be generalizable to the entire elderly population. The number of African Americans was small, so analyses by race could not be done. Finally, given the age of the cohort, loss to follow-up was common. Assuming that individuals who died had more IR, our estimates of the association between IR and frailty are most probably conservative.

In conclusion, we believe that IR, a physiologic determinant of the MetS, should be viewed as part of a larger process that leads to declines in multiple physiologic systems, which, in the aggregate, lead to frailty. Such a framework may explain why older adults with MetS and consequent glucose disorders also have high rates of frailty and disability.

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