**Appendix A**. Cohort Assembly

| Framingham Offspring Cohort at Exam 8 (2005-2008) N= 3,021 | + | Omni 1 Cohort at Exam 3 (2007-2008) N= 298 |

→ <60 years (n=834)

→ Missing >1 item in the Fried index (n=122), or >4 items for the Rockwood Frailty Index (n=55), or both

Total lost:  n=130

Frailty Study Cohort
N= 2,355

→ Not seen at exam site or nursing home status (n=9)

Frailty Study Cohort
N=2346

→ Missing data for tonometry (n=151)

→ Missing data for: covariates: physical activity, mean arterial pressure, or smoking (n=24)
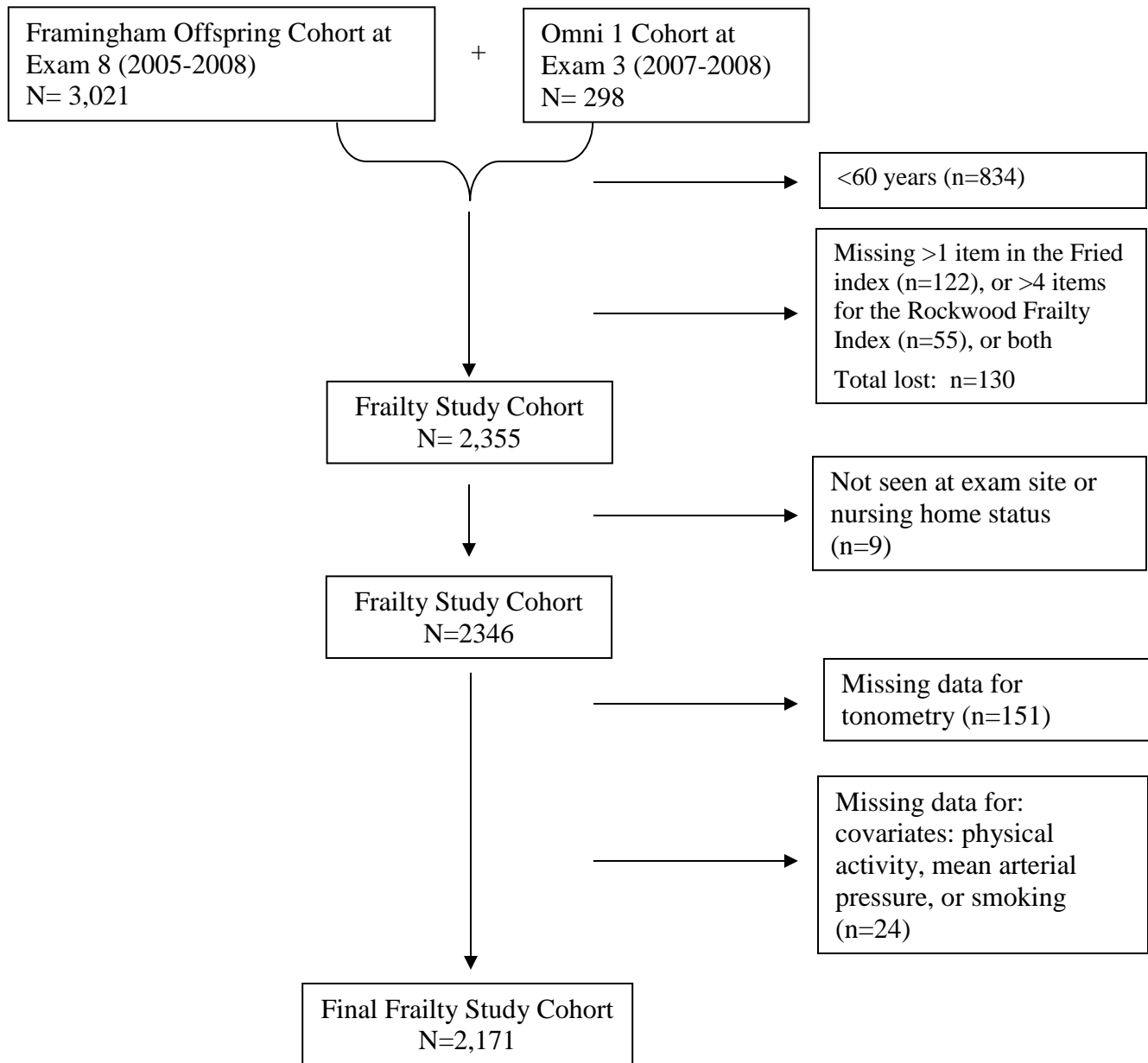
Final Frailty Study Cohort
N=2,171

**Appendix B.** Defining Frailty in the Framingham Heart Study

**1. Variables used to derive the Fried frailty phenotype as previously defined in the Framingham Offspring Study:[1]**

| Characteristics of frailty: | | |
|---|---|---|
| **Characteristic** | **Men** | **Women** |
| **Weight loss** | Unintentional weight loss >10 pounds in last year | |
| **Exhaustion** | Answer of 'Most or all of the time' to question of 'Could not get going' and/or 'I felt that everything I did was an effort' | |
| **Low physical activity** | Lowest 20% of Framingham physical activity index for men | Lowest 20% of Framingham physical activity index for women |
| **Slow: gait speed (m/s)** | Height ≤ 173 cm: ≤0.96<br>Height >173 cm: ≤1.04 | Height ≤ 159 cm: ≤0.90<br>Height >159 cm: ≤1.02 |
| **Weak: hand grip strength (kg)** | BMI ≤ 24.0: ≤ 29<br>BMI 24.1-26.0: ≤ 30<br>BMI 26.1-28.0: ≤ 30<br>BMI > 28.0: ≤ 32 | BMI ≤ 23.0: ≤ 17<br>BMI 23.1 to 26.0: ≤ 17.3<br>BMI 26.1 to 29.0: ≤ 18<br>BMI > 29.0: ≤ 21 |

Calculating frailty: Participants with ≥3 criteria are considered frail, those with 1-2 criteria are pre-frail while those with none are robust.

**2. Variables used to derive the Rockwood frailty index (FI)**

| Count | Variable | Coding for the Frailty Index |
|---|---|---|
| | *Function* | |
| 1 | Are you able to do heavy work around the house, like shoveling snow or washing windows, walls, or floors without help? | Yes = 0, No =1 |
| 2 | Are you able to walk half a mile without help? (About 4-6 blocks) | Yes = 0, No =1 |
| 3 | Are you able to walk up and down one flight of stairs without help? | Yes = 0, No =1 |
| *4*<br><br>*5* | 1. During the past week, I felt that everything I did was an effort<br>2. During the past week, I could not "get going" | Rarely=0,<br>Some or Occasionally = 0.5,<br>Most of the time =1 |
| *6*<br>*7*<br>*8*<br>*9* | *Katz ADL:* During the Course of a Normal Day, Can you do the following activities independently or do you need human assistance or use of a device?<br>    1.   Dressing<br>    2.   Bathing<br>    3.   Transferring<br>    4.   Toileting | 0 = 0 (independent)<br>1, 2 = 0.5 (any assistance)<br>3 = 1 (dependent) |
| | *Health Status and Function* | |
| | Does your health now limit you in these activities? If so, how much? | |
| 10 | Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | A lot =1, a little = 0.5, No = 0 |
| 11 | Climbing several flights of stairs? | A lot =1, a little = 0.5, No = 0 |

| | During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health? | |
|---|---|---|
| 12 | Accomplished less than you would like | Yes =1, No = 0 |
| 13 | Were limited in the kind of work or other activities | Yes = 1, No = 0 |
| 14 | Self-rating of health: "In general, would you say your health is: excellent, very good, good, fair, poor" | Poor =1, Fair =0.75, Good = 0.5, Very Good = 0.25, Excellent = 0 |
| | *Mood* | |
| | During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? | |
| 15 | Accomplished less than you would like | Yes = 1, No = 0 |
| 16 | Didn't do work or other activities as carefully as usual | Yes = 1, No = 0 |
| 17 | During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework) | Not at all = 0, a little = 0.25, Moderately = 0.5, Quite a bit = 0.75, Extremely = 1 |
| | How much of the time during the past 4 weeks… | |
| 18 | Have you felt calm and peaceful? | All or most of the time = 0, A good bit of the time =0.25, some of the time = 0.5, a little of the time = 0.75, none of the time = 1 |
| 19 | Did you have a lot of energy? | All or most of the time = 0, A good bit of the time =0.25, some of the time = 0.5, a little of the time = 0.75, none of the time = 1 |
| 20 | Have you felt downhearted and blue? | All or most of the time = 1, A good bit of the time =0.75, some of the time = 0.5, a little of the time = 0.25, none of the time = 0 |
| 21 | During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with social activities (like visiting friends, relatives, etc.)? | All of the time = 1, Most of the time =0.75, some of the time = 0.5, a little of the time = 0.25, none of the time = 0 |
| | *Comorbidities* | |
| 22 | Hypertension – measured or medication use | >140/90 or history or med use=1, <140/90 or no history or med use=0 |
| 23 | Lung comorbidity: asthma, chronic bronchitis, emphysema, COPD, or pulmonary fibrosis | If answered Yes to any = 1, If answered Maybe to any = 0.5, If all No then =0 |
| 24 | Diabetes – fasting blood glucose >125 mg/dl or use of oral hypoglycemic medications or insulin | Elevated blood glucose or med use=1, Normal blood glucose or no med use=0 |
| 25 | Coronary artery disease | Using validated events: Myocardial infarction or coronary insufficiency  = Yes = 1 Angina or possible coronary insufficiency = Maybe= 0.5 No events =0 |
| 26 | Chronic Kidney Disease | eGFR ≥60 (stage I and II) = 0 eGFR ≥30-60 (stage III) = 0.5 eGFR <30 (stage IV and V) = 1 |
| 27 | Any osteoporosis related fracture between exam 7-8 | Yes = 1, No =0 |
| 28 | CHF | Yes = 1, Maybe = 0.5, No =0 |
| 29 | Stroke or TIA | Yes = 1, Maybe = 0.5, No =0 |
| 30 | Cancer (excluding non-melanoma skin cancer) | Yes = 1, Maybe = 0.5, No =0 |

| 31 | Arthritis comorbidity: rheumatoid disease, degenerative joint disease, gout, or musculoskeletal/connective tissue disorder | If any are Yes = 1<br>If any are Maybe without Yes = 0.5<br>If all No then =0 |
|---|---|---|
| | *Cognition* | |
| 32 | Dementia by self-report, validated events or Mini-Mental Status Exam (MMSE)<br>- Self report: Have you been told by a doctor you have memory problems, dementia or Alzheimer's disease? | if ever diagnosed with dementia or if they report ever being told they have dementia, or MMSE <18 (consistent with significant cognitive impairment) =1,<br>self-report maybe or MMSE 18-23 (consistent with mild cognitive impairment diagnosis)=0.5,<br>else if both event and self-report are no and MMSE >/=24 =0. |
| | *Directly measured variables and performance measures* | |
| 33 | BMI | <18.5 or >30=1,<br>25-<30 = 0.5<br>18.5-<25 = 0 |
| 34 | Weight loss | >10 lbs in the last year =1, otherwise =0 |
| 35 | Grip strength (in kg)<br>- Participants were asked to squeeze a Jamar dynamometer (Lafayette Instrument Co, Lafayette, IN) as hard as possible with each hand, three times. The force generated was recorded in kilograms, and the highest value was used. | Men:<br>For BMI ≤24, GS≤29 =1<br>For BMI 24.1-28, GS≤30 =1<br>For BMI >28, GS ≤32 =1<br>Women:<br>For BMI ≤23, GS≤17 =1<br>For BMI 23.1-26, GS≤17.3 =1<br>For BMI 26.1-29, GS ≤18 =1<br>For BMI >29, GS≤21 =1<br>If unable to complete due to physical limitation =1 |
| 36 | Gait speed<br>- 4-meter measured walk | <0.8m/s =1<br>Unable to complete walk due to physical limitation=1 |
| | *Other* | |
| 37 | Have you been admitted to a nursing home (or skilled facility) in the past year? | Yes = 1, No =0 |

## 3. Distribution of Frailty according to the Fried Phenotype

**Physical Phenotype**
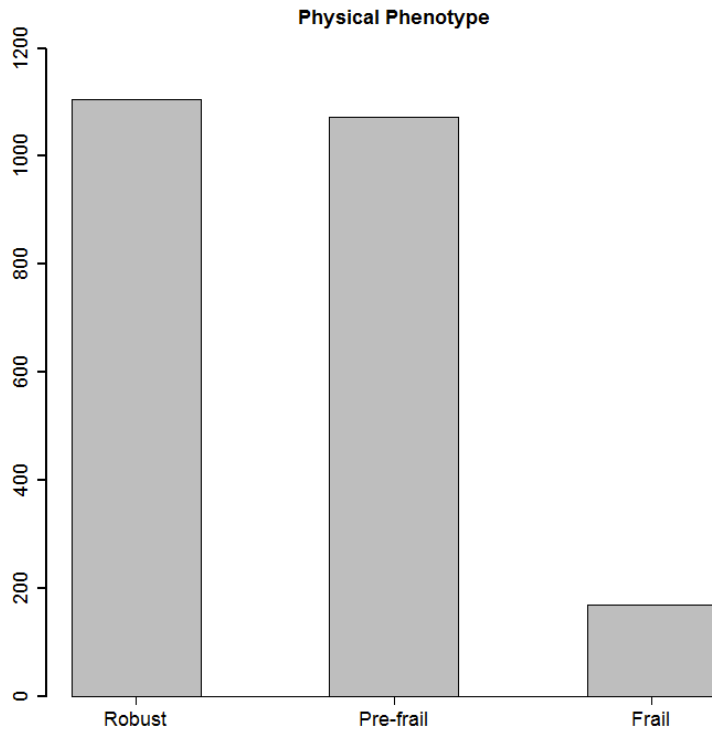


## 4. Distribution of Frailty according to the Rockwood Frailty Index

**Distribution of Frailty Index**
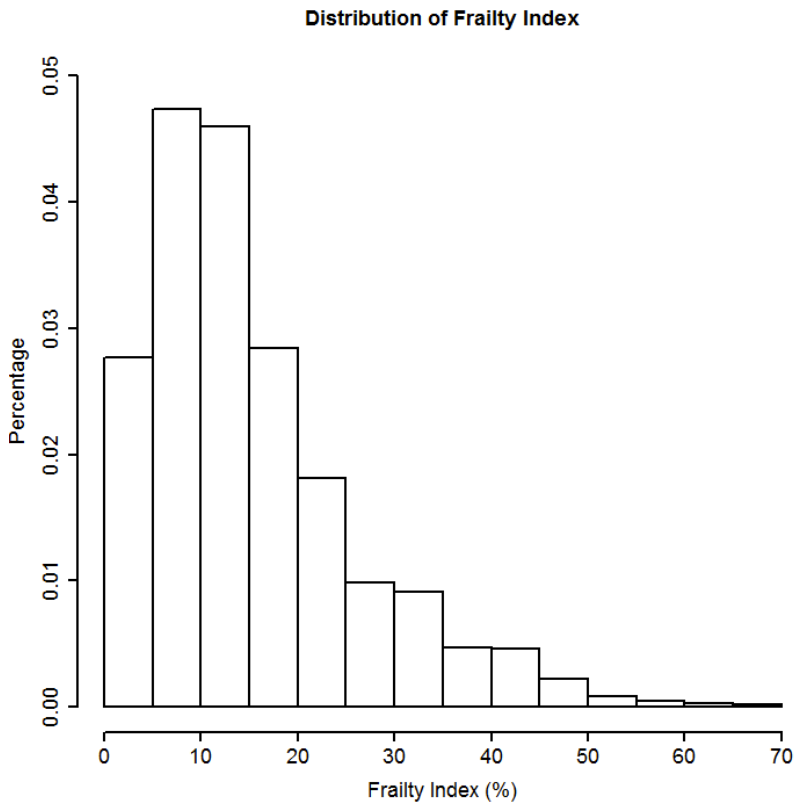
Reference:

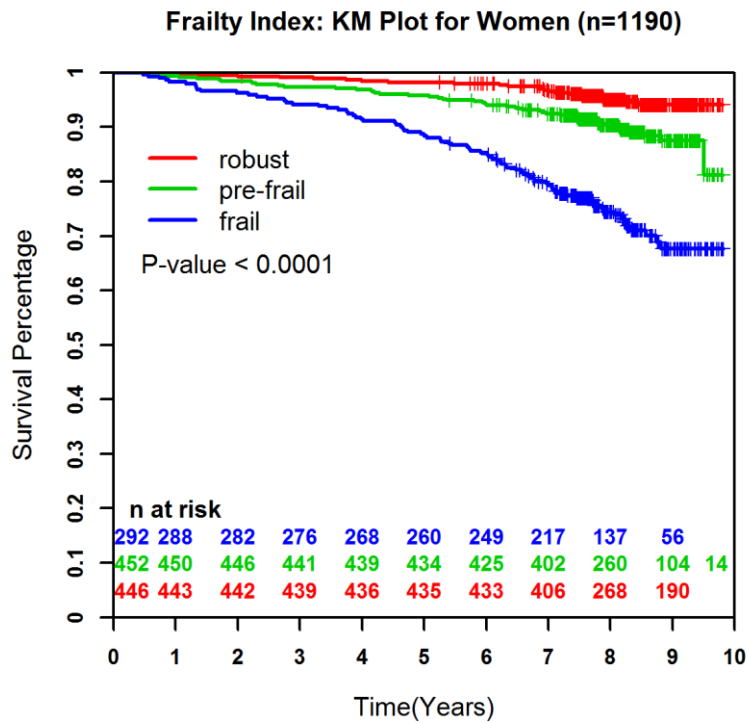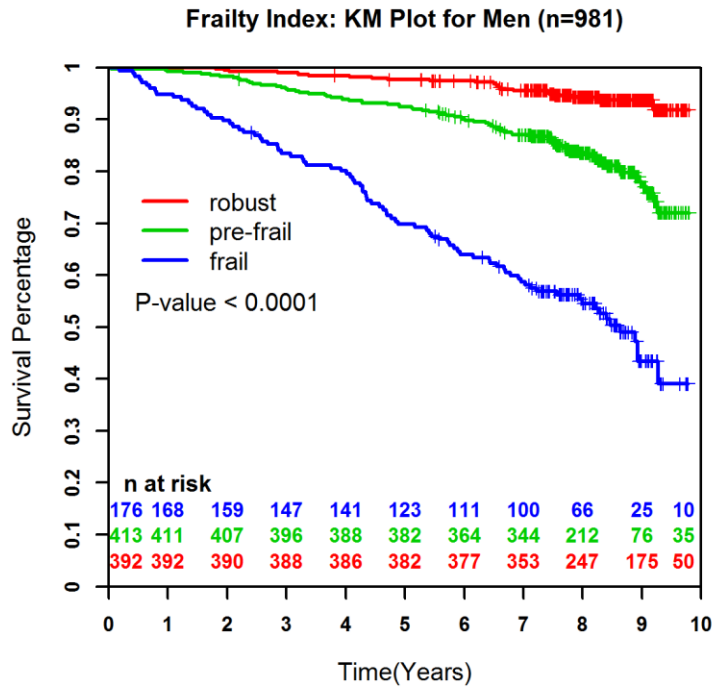1.      Liu CK, Lyass A, Larson MG, et al. Biomarkers of oxidative stress are associated with frailty: the Framingham Offspring Study. Age (Dordr) 2016;38:1.

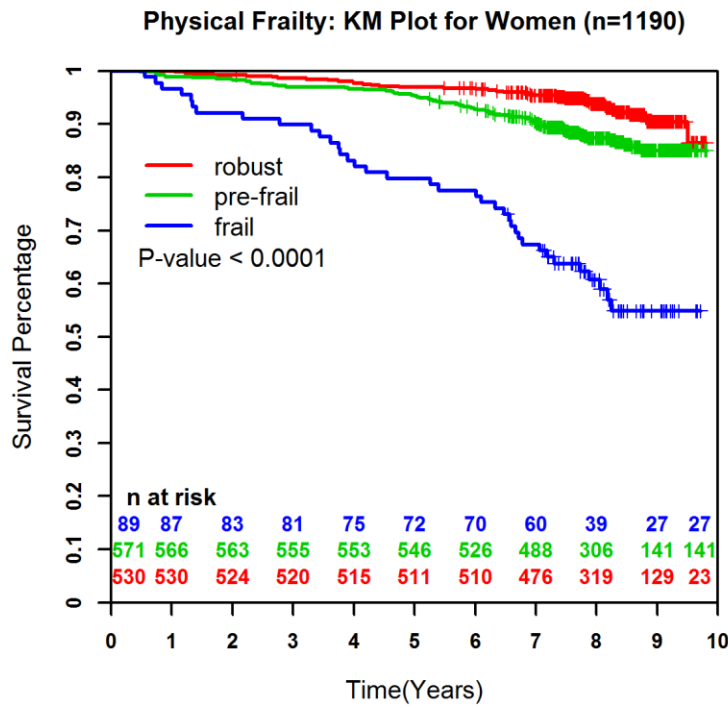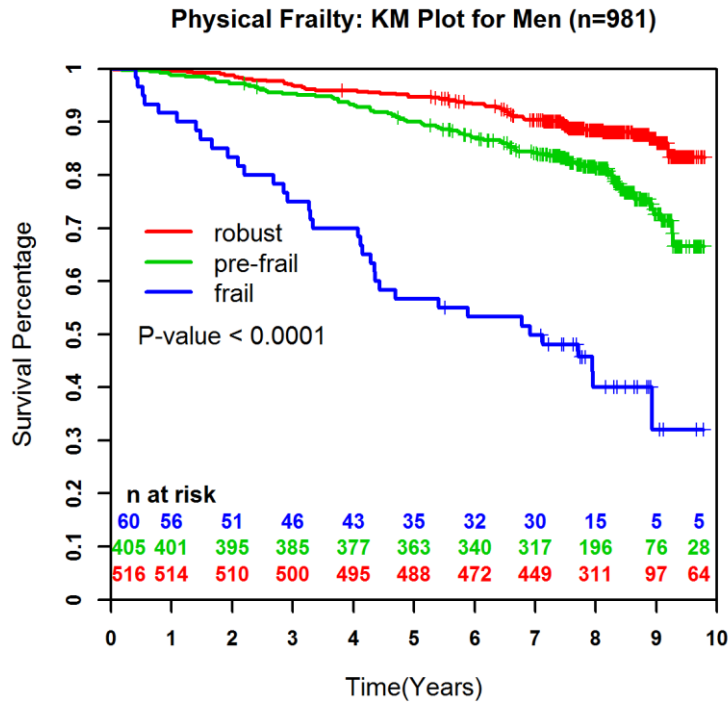# Appendix C: Characteristics of the Omni cohort (n=149), by frailty status

| | Fried Physical Phenotype | | | Rockwood Frailty Index | | |
|---|---|---|---|---|---|---|
| | non-frail | pre-frail | frail | non-frail | pre-frail | frail |
| N | 50 | 89 | 10 | 59 | 56 | 34 |
| Age, mean (SD) | 67.6 (5.8) | 68.1 (5.9) | 74.1 (9.9) | 66.3 (5.3) | 68.2 (5.3) | 71.9 (7.9) |
| Women (%) | 50 | 67 | 80 | 54 | 62 | 76 |
| Body Mass Index, mean(SD) | 27.4 (5.8) | 29.4 (6.2) | 28.8 (6.0) | 26.0 (4.7) | 29.5 (6.4) | 32 (6.0) |
| Systolic BP, mmHg, mean(SD)‡ | 133 (23) | 129 (16) | 142 (17) | 133 (22) | 128 (15) | 134 (18) |
| Diastolic BP, mmHg, mean(SD) ‡ | 74 (9) | 72 (8) | 75 (8) | 75 (7.5) | 72 (9) | 72 (8) |
| Mean Arterial Pressure, mm Hg, mean (SD)* | 97 (13) | 99 (10) | 103 (12) | 99 (12) | 96 (10) | 102 (11) |
| Heart Rate mean(SD) | 58 (9) | 61 (11) | 61 (10) | 58 (9) | 59 (10) | 64 (13) |
| Height (inches) mean(SD) | 65.0 (3.9) | 64.3 (3.5) | 61.8 (2.9) | 64.8 (3.7) | 64.4 (3.7) | 63.4 (3.5) |
| Smoking status(%) | | | | | | |
|   Current | 0 | 4.5 | 10.0 | 3.4 | 0 | 8.8 |
|   Former | 0 | 4.5 | 10.0 | 0 | 1.8 | 11.8 |
|   Never | 100 | 91.0 | 80.0 | 96.6 | 98.2 | 79.4 |
| Prevalent Coronary heart disease(%) | 6 | 9 | 10 | 5 | 5 | 18 |
| Prevalent Diabetes(%) | 24 | 34 | 20 | 8 | 38 | 53 |
| Prevalent Hyperlipidemia(%) | 80 | 73 | 70 | 78 | 73 | 74 |
| Prevalent Hypertension(%) | 57 | 68 | 100 | 52 | 75 | 79 |
| Physical Activity Index score, mean(SD) | 36.3 (5.2) | 33.8 (3.9) | 28.9 (2.2) | 35.8 (5.1) | 34.3 (4.0) | 31.7 (3.8) |
| Gait speed, m/s, mean(SD) | 1.24 (0.19) | 1.02 (0.23) | 0.79 (0.25) | 1.16 (0.22) | 1.1 (0.23) | 0.89 (0.26) |
| Hand grip strength(kg) | 34.7 (10.5) | 27.6 (9.1) | 18.8 (6.3) | 32.9 (9.8) | 28.5 (11.1) | 24.7 (7.9) |
| Frailty Index score, mean (SD) | 9.11 (5.85) | 16.6 (10.56) | 39.46 (12.2) | 6.23 (2.44) | 14.49 (3.25) | 33.78 (10) |
| Physical Frailty score, mean (SD) | 0 (0) | 1.3 (0.4) | 3.5 (0.7) | 0.5 (0.7) | 0.9 (0.7) | 1.9 (1.2) |
| Carotid-Femoral Pulse Wave Velocity, m/s, mean(SD) | 9.5 (2.3) | 10.2 (3.3) | 12.0 (4.6) | 9.7 (2.8) | 9.9 (3.2) | 11.0 (3.6) |

Appendix D.
Kaplan Meier Curves for Mortality Using Each Frailty Definition

1. Rockwood Frailty Index

**Frailty Index: KM Plot for Men (n=981)**



**Frailty Index: KM Plot for Women (n=1190)**

## 2. Fried Physical Phenotype

**Physical Frailty: KM Plot for Men (n=981)**



**Physical Frailty: KM Plot for Women (n=1190)**

**Appendix E:** Nested models demonstrating how the estimates and p-values change as covariates are added.

Results are shown using the negative inverse CFPWV as the outcome.

| Model | Variable | Fried Phenotype | | | Rockwood FI | | |
|---|---|---|---|---|---|---|---|
| | | b | Standard Error | p-value | b | Standard Error | p-value |
| **Unadjusted** | Intercept | -102.95 | 0.86 | < 2e-16 | -104.76 | 0.92 | < 2e-16 |
| | **Pre-frail** | **7.82** | **1.17** | **2.1e-11** | **7.36** | **1.28** | **< 2e-16** |
| | **Frail** | **17.08** | **2.52** | **1.2e-11** | **16.55** | **1.43** | **8.6e-9** |
| **Age only** | Intercept | -229.48 | 5.44 | <2e-16 | -226.52 | 5.56 | < 2e-16 |
| | Age | 1.86 | 0.08 | <2e-16 | 1.81 | 0.08 | <2e-16 |
| | **Pre-frail** | **3.17** | **1.04** | **0.002** | **2.30** | **1.15** | **0.045** |
| | **Frail** | **3.16** | **2.31** | **0.17** | **6.05** | **1.42** | **1.93E-05** |
| **Age and sex** | Intercept | -231.83 | 5.47 | < 2e-16 | -228.74 | 5.6 | <2e-16 |
| | Age | 1.85 | 0.08 | < 2e-16 | 1.80 | 0.08 | <2e-16 |
| | Male | 6.21 | 0.94 | 3.5e-11 | 6.26 | 0.93 | 1.77E-11 |
| | **Pre-frail** | **3.69** | **1.04** | **0.0004** | **2.27** | **1.13** | **0.045** |
| | **Frail** | **3.80** | **2.28** | **0.096** | **6.69** | **1.42** | **2.64E-06** |
| **Age, sex, cohort** | Intercept | -236.93 | 5.67 | < 2e-16 | -233.51 | 5.79 | <2e-16 |
| | Age | 1.83 | 0.08 | < 2e-16 | 1.78 | 0.08 | <2e-16 |
| | Male | 6.09 | 0.93 | 6.7e-11 | 6.13 | 0.93 | 3.62E-11 |
| | Cohort | 6.72 | 2.06 | 0.0011 | 6.19 | 2.07 | 0.003 |
| | **Pre-frail** | **4.01** | **1.04** | **0.0001** | **2.27** | **1.13** | **0.045** |
| | **Frail** | **4.06** | **2.28** | **0.076** | **6.77** | **1.42** | **1.9E-06** |
| **Age, sex, cohort, MAP, HR** | Intercept | -329.89 | 6.4 | < 2e-16 | -327.35 | 6.51 | < 2e-16 |
| | Age | 1.68 | 0.07 | < 2e-16 | 1.65 | 0.07 | < 2e-16 |
| | Male | 8.83 | 0.91 | < 2e-16 | 8.82 | 0.90 | < 2e-16 |
| | Cohort | 5.53 | 1.78 | 0.0019 | 5.13 | 1.79 | 0.004 |
| | MAP | 0.74 | 0.04 | < 2e-16 | 0.74 | 0.04 | < 2e-16 |
| | HR | 0.50 | 0.05 | < 2e-16 | 0.49 | 0.05 | < 2e-16 |
| | **Pre-frail** | **3.15** | **0.88** | **0.0004** | **1.90** | **0.95** | **0.046** |
| | **Frail** | **4.90** | **2.08** | **0.019** | **5.64** | **1.28** | **1.14E-05** |
| **Age, sex, cohort, MAP, HR smoking** | Intercept | -329.82 | 6.32 | < 2e-16 | -327.3 | 6.43 | < 2e-16 |
| | Age | 1.67 | 0.07 | < 2e-16 | 1.65 | 0.07 | < 2e-16 |
| | Male | 8.42 | 0.94 | < 2e-16 | 8.42 | 0.93 | < 2e-16 |
| | Cohort | 4.08 | 1.85 | 0.028 | 3.77 | 1.87 | 0.044 |
| | MAP | 0.74 | 0.04 | < 2e-16 | 0.74 | 0.04 | < 2e-16 |
| | HR | 0.51 | 0.05 | < 2e-16 | 0.50 | 0.05 | < 2e-16 |
| | Current Smoking | 0.81 | 1.68 | 0.63 | 0.56 | 1.65 | 0.735 |
| | Former Smoking | 2.77 | 0.98 | 0.005 | 2.59 | 0.98 | 0.008 |
| | **Pre-frail** | **3.21** | **0.88** | **0.0003** | **1.91** | **0.96** | **0.05** |
| | **Frail** | **4.85** | **2.08** | **0.020** | **5.57** | **1.28** | **1.30E-05** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Age, sex, cohort, heart rate, MAP, smoking, height,** | Intercept | -351.39 | 14.10 | < 2e-16 | -346.59 | 14.38 | < 2e-16 |
| | Age | 1.70 | 0.07 | < 2e-16 | 1.67 | 0.07 | < 2e-16 |
| | Male | 6.65 | 1.46 | 5.41E-06 | 6.84 | 1.46 | 2.93E-06 |
| | Cohort | 3.84 | 1.87 | 0.04 | 3.54 | 1.88 | 0.06 |
| | MAP | 0.74 | 0.04 | < 2e-16 | 0.74 | 0.04 | < 2e-16 |
| | HR | 0.50 | 0.05 | < 2e-16 | 0.50 | 0.05 | < 2e-16 |
| | Current Smoking | 0.84 | 1.69 | 0.62 | 0.60 | 1.66 | 0.72 |
| | Former Smoking | 2.76 | 0.98 | 0.005 | 2.58 | 0.98 | 0.0083 |
| | Height | 0.32 | 0.19 | 0.09 | 0.28 | 0.19 | 0.14 |
| | **Pre-frail** | **3.30** | **0.88** | **0.0002** | **1.94** | **0.96** | **0.04** |
| | **Frail** | **5.04** | **2.09** | **0.02** | **5.60** | **1.27** | **1.07E-05** |
| **Age, sex, cohort, heart rate, MAP, smoking, height, and PAI** | Intercept | -345.68 | 14.53 | < 2e-16 | -340.32 | 14.62 | < 2e-16 |
| | Age | 1.70 | 0.07 | < 2e-16 | 1.67 | 0.07 | < 2e-16 |
| | Male | 6.73 | 1.46 | 4.12E-06 | 6.92 | 1.46 | 2.17E-06 |
| | Cohort | 3.92 | 1.86 | 0.04 | 3.69 | 1.88 | 0.05 |
| | MAP | 0.74 | 0.04 | < 2e-16 | 0.74 | 0.04 | < 2e-16 |
| | HR | 0.50 | 0.05 | < 2e-16 | 0.49 | 0.05 | < 2e-16 |
| | Current Smoking | 0.81 | 1.69 | 0.63 | 0.53 | 1.67 | 0.75 |
| | Former Smoking | 2.758 | 0.983 | 0.005 | 2.58 | 0.98 | 0.008 |
| | Height | 0.31 | 0.19 | 0.10 | 0.28 | 0.19 | 0.14 |
| | PAI | -0.13 | 0.09 | 0.16 | -0.15 | 0.09 | 0.09 |
| | **Pre-frail** | **2.95** | **0.89** | **0.0009** | **1.81** | **0.96** | **0.06** |
| | **Frail** | **4.16** | **2.22** | **0.06** | **5.13** | **1.28** | **6.16E-05** |