## Supplemental Appendix


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**Supplemental Table 1. Framingham Heart Study criteria for HF diagnosis.**

| **Major Criteria** | **Minor Criteria** |
|---|---|
| Paroxysmal nocturnal dyspnea or orthopnea | Pleural effusion by X-ray |
| Distended neck veins | Pulmonary vascular engorgement by X-ray |
| Hepatojugular reflux | Heart rate > 120/minute |
| Rales | Hepatomegaly |
| S3 gallop | Ankle edema |
| Treatment-induced weight loss >10lbs/5 days | Decrease in vital capacity by 1/3rd |
| Increased venous pressure > 16 cm water | Dyspnea on ordinary exertion |
| Pulmonary edema, visceral congestion, or cardiomegaly on autopsy | Night cough |
| Enlarged heart by X-ray | |
| Acute pulmonary edema on chest X-ray | |

HF was diagnosed by the presence of 1 major criterion and 2 minor criteria, or 2 major criteria in the absence of an alternative explanation for findings.

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**Supplemental Table 2. Comparison of cumulative incidence of HF at age 50 years across the two epochs, adjusted for competing risk of death and according to risk factor strata: participants without antecedent myocardial infarction**

| | | Adjusted Cumulative incidence, % (95% CI), 1965-1989, Epoch 1 | | | Adjusted Cumulative incidence, % (95% CI), 1990-2014, Epoch 2 | | | RLR Rate ratio Epoch2/ Epoch 1, P |
|---|---|---|---|---|---|---|---|---|
| | | 30-year | 40-year | Lifetime (RLR) | 30-year | 40-year | Lifetime (RLR) | |
| **Overall** | N/ Pyr | 255/87687 | 354/94536 | 362/95087 | 210/100124 | 456/113722 | 542/116044 | |
| | ACI | 7.62 (6.71-8.53) | 13.41 (12.00-14.82) | **14.44** (12.88-16.01) | 6.18 (5.37-7.00) | 14.95 (13.67-16.22) | **18.36** (16.95-19.77) | 1.27 P<0.001 |
| **Sex** | | | | | | | | |
| Women | N/ Pyr | 139/52856 | 207/57753 | 214/58207 | 97/56899 | 250/66005 | 307/67762 | |
| | ACI | 6.96 (5.84-8.09) | 13.50 (11.65-15.36) | **14.99** (12.86-17.11) | 5.17 (4.16-6.18) | 14.38 (12.72-16.04) | **18.02** (16.18-19.85) | 1.20 P=0.035 |
| Men | N/ Pyr | 116/34831 | 147/36783 | 148/36880 | 113/43227 | 206/47720 | 235/48282 | |
| | ACI | 8.64 (7.12-10.17) | 13.30 (11.13-15.47) | **13.57** (11.35-15.80) | 7.42 (6.10-8.75) | 15.75 (13.74-17.77) | **19.07** (16.82-21.32) | 1.41 P=0.001 |
| P | | 0.08 | 0.89 | 0.37 | 0.008 | 0.30 | 0.48 | |
| **BMI Category** | | | | | | | | |
| Normal | N/ Pyr | 72/36016 | 95/38118 | 98/38211 | 48/35352 | 136/41747 | 175/42959 | |
| | ACI | 5.48 (4.23-6.74) | 10.22 (7.93-12.50) | **15.51** (9.75-21.28) | 3.89 (2.81-4.97) | 11.27 (9.49-13.06) | **14.81** (12.78-16.84) | 0.95 P=0.82 |
| Overweight | N/ Pyr | 91/31403 | 123/33507 | 125/33856 | 70/33112 | 159/37674 | 192/38425 | |
| | ACI | 7.77 (6.21-9.34) | 13.48 (11.00-15.96) | **14.37** (11.64-17.09) | 6.31 (4.87-7.75) | 15.58 (13.34-17.82) | **19.33** (16.86-21.80) | 1.35 P=0.008 |
| Obese | N/ Pyr | 41/10417 | 51/10948 | 52/10973 | 66/17312 | 110/18590 | 121/18777 | |
| | ACI | 9.94 (6.95-12.94) | 15.98 (11.39-20.58) | **17.53** (12.18-22.89) | 12.84 (9.86-15.82) | 25.83 (21.49-30.16) | **29.23** (24.68-33.78) | 1.67 P=0.001 |
| P Overweight vs. normal | | 0.025 | 0.06 | 0.73 | 0.008 | 0.003 | 0.006 | |
| P Obese vs. normal | | 0.007 | 0.028 | 0.61 | <0.001 | <0.001 | <0.001 | |
| **BP category** | | | | | | | | |
| Normal | N/ Pyr | 44/26458 | 57/27802 | 59/27860 | 40/41849 | 98/46851 | 135/47684 | |
| | ACI | 4.96 (3.48-6.43) | 10.11 (6.77-13.45) | **12.56** (7.93-17.18) | 3.29 (2.27-4.31) | 9.81 (7.93-11.69) | **14.60** (12.29-16.92) | 1.16 P=0.44 |
| Intermediate | N/ Pyr | 61/27992 | 78/29544 | 79/29609 | 67/23821 | 148/28378 | 172/29199 | |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ACI | 6.55 (4.91-8.19) | 10.98 (8.35-13.62) | **11.67** (8.74-14.61) | 7.28 (5.60-8.95) | 15.71 (13.38-18.03) | **18.44** (15.95-20.93) | 1.58 P=0.001 |
| Hypertension | N/ Pyr | 102/24290 | 139/26181 | 142/26256 | 77/20911 | 159/23732 | 181/24245 | |
| | ACI | 9.77 (7.96-11.59) | 15.97 (13.38-18.56) | **21.31** (15.95-26.67) | 9.90 (7.79-12.00) | 21.39 (18.43-24.34) | **24.40** (21.30-27.49) | 1.15 P=0.33 |
| P Intermediate vs. Normal | | 0.16 | 0.69 | 0.75 | <0.001 | <0.001 | 0.027 | |
| P Hypertension vs. Normal | | <0.001 | 0.007 | 0.015 | <0.001 | <0.001 | <0.001 | |
| **Diabetes Status** | | | | | | | | |
| Normal | N/ Pyr | 194/75708 | 253/80101 | 256/80235 | 171/83423 | 385/95370 | 468/97470 | |
| | ACI | 6.98 (6.01-7.95) | 12.38 (10.69-14.07) | **13.29** (11.33-15.25) | 6.15 (5.25-7.04) | 14.94 (13.56-16.33) | **18.64** (17.11-20.17) | 1.40 P<0.001 |
| Diabetes | N/ Pyr | 5/540 | - | - | 10/1918 | 12/1948 | 12/1953 | |
| | ACI | 22.15 (4.06-40.24) | - | - | 23.71 (9.38-38.04) | 37.59 (18.55-56.62) | **37.59** (18.55-56.62) | - |
| P Diabetes vs. Normal | | 0.10 | - | - | 0.016 | 0.020 | 0.05 | |
| **Cumulative Risk factor burden*** | | | | | | | | |
| Low* | N/PYrs | 59/35068 | 76/36834 | 77/36878 | 55/44218 | 131/50707 | 176/51860 | |
| | ACI | 5.17 (3.85-6.50) | 9.52 (6.93-12.12) | **10.44** (7.33-13.55) | 3.98 (2.94-5.02) | 10.50 (8.79-12.22) | **14.82** (12.78-16.86) | 1.42 P=0.021 |
| Intermediate* | N/PYrs | 109/34871 | 142/37146 | 144/37223 | 80/32113 | 196/36955 | 229/37811 | |
| | ACI | 8.03 (6.56-9.51) | 13.12 (10.90-15.33) | **14.10** (11.53-16.66) | 6.92 (5.45-8.38) | 17.60 (15.36-19.84) | **20.82** (18.41-23.22) | 1.48 P<0.001 |
| High* | N/PYrs | 28/5474 | 36/5786 | - | 46/8253 | 70/8770 | 75/8854 | |
| | ACI | 11.73 (7.58-15.88) | 19.08 (12.84-25.31) | - | 18.18 (13.28-23.09) | 32.46 (25.97-38.94) | **34.51** (28.00-41.02) | - |
| P Intermediate vs. Low | | 0.005 | 0.039 | 0.08 | 0.001 | <0.001 | <0.001 | |
| P high vs. Low | | 0.003 | 0.006 | - | <0.001 | <0.001 | <0.001 | |

ACI= adjusted cumulative incidence, %. N = number of HF events, Pyrs= person-years of observation. Lifetime risk was evaluated at 45 years except for the analyses of the stratum according to diabetes status, in which 30 years was used due to limited data.

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*participants received a score of 0-2 for the three BMI categories (0 for normal BMI, 1 for overweight, and 2 for obesity), a score of 0-2 for BP categories (0 for normal BP, 1 for intermediate BP, and 2 for hypertension), and a score of 0-1 for diabetes (0= no, 1= yes). Thus, participants could have a score that ranged from 0 (minimum) to 5 (maximum). Three strata of the risk score were empirically defined as 0-1 (low risk factor burden), 2-3 (intermediate), 4-5 (high risk factor burden).

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**Supplemental Table 3. Prevalence of major and minor criteria for HF in the two epochs**

| | Epoch 1 | Epoch 2 | P* for Epoch 1 vs. 2 |
|---|---|---|---|
| **Major Criteria, %** | | | |
| Paroxysmal nocturnal dyspnea or Orthopnea | 83% | 73% | 0.02 |
| Distended neck veins | 66% | 50% | <0.001 |
| Hepatojugular reflux | 61% | 49% | 0.16 |
| Rales | 92% | 88% | 0.04 |
| S3 gallop | 51% | 19% | <0.001 |
| Treatment induced weight loss >10lbs/5 days | 44% | 63% | 0.11 |
| Enlarged heart by X-ray | 44% | 46% | 0.75 |
| Acute pulmonary edema on chest X-ray | 45% | 46% | 0.69 |
| **Minor Criteria, %** | | | |
| Pleural effusion by X-ray | 65% | 68% | 0.38 |
| Pulmonary vascular engorgement by X-ray | 73% | 71% | 0.58 |
| Heart rate > 120/minute | 17% | 22% | 0.15 |
| Hepatomegaly | 49% | 8% | <0.001 |
| Ankle edema | 77% | 72% | 0.11 |
| Dyspnea on ordinary exertion | 96% | 98% | 0.17 |
| Night cough | 24% | 41% | 0.11 |

*by Chi-square test

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**Supplemental Table 4. Published estimates of RLR for HF at age 45/50 years.**

| Study, Year, reference | Calendar period | Sample size | F/U Person-yrs | Median F/u, years | HF events | HF adjudicated / criteria | RLR of HF in men | RLR of HF in women |
|---|---|---|---|---|---|---|---|---|
| Framingham Heart Study, 2002 (17) | 1971-1996 | 8229 | 124 262 | N/A | 583 | FHS criteria; central adjudication | 20.9 (11.6 without MI) | 20.5 (15.5 without MI) |
| Rotterdam Study*, 2004 (10) | 1989-1993 (baseline)-2000 | 7734 | 50268 | 7.1 | 725 | Adjudicated RS criteria | 33.0 | 28.5 |
| Physicians Health Study, 2009 (11) | 1982-1983 through 2008 | 20,900 | N/A | 22.4 | 1200 | Self-report | 13.8 (11.5 without antecedent MI) | Not applicable |
| ARIC, 2012 (16) | 1987-1989 (baseline) -2008 | 14709 | NA | 17.6 | 2102 | ICD9, adjudicated | 32.8 (Blacks), 25.9 whites); estimates for pooled sexes | |
| Chicago Heart Association, 2013 (13) | 1967-1973 (baseline)-2003 | 19391 | 501,127 | N/A | 3,972 | ICD9 Medicare discharge | 30.2 in whites (26.1 without MI)<br>20.1 in Blacks (18.6 without MI) | 32.3 in white (28.7 without MI)<br>23.7 in Blacks (22.7 without MI) |
| ARIC†, 2013 (13) | 1987-1989 (baseline) - 2005 | 15732 | 168,516 | N/A | 1010 | ICD9, adjudicated | 19.1 in whites (14.2 without MI)<br>21.3 in Blacks (15.9 without MI) | 13.4 in whites (10.6 without MI)<br>23.9 in Blacks (19.9 without MI) |
| Cardiovascular Health Study**, 2013 (13) | 1989-1993 (baseline) -2004 | 4455 | 47,333 | N/A | 1001 | Adjudicated review of medical records | 41.6 in whites (26.4 without MI)<br>29.1 in Blacks | 38.5 in whites (29.9 without MI)<br>46.1 in Blacks |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | (22.1 without MI) | (36.3 without MI) |
| CALIBER, 2014 (15) | 1997-2010 | 1,258,006 | N/A | 5.2 | 10437 | CPRD and ICD 10 codes | 5% | 8%¶ |
| ARIC, 2015 (12) | 1987-1989 (baseline), to 2011 | 13462 | N/A | 22.5 | 2218 | ICD-9 | 25.5 (21.3 without antecedent MI) Estimates for pooled sexes, pooled race | |
| Cardiovascular Health Study** + MESA, 2018 (14) | 1989-1993 (baseline for CHS); 2000-2002 baseline for MESA) | 12417 | NA | 11.6 | 2178 | adjudicated | 27.4 (20 without MI; estimates for pooled sexes) | 23.8 |

***at age 55 years **at age 65 years † follow-up up to 75 years. ¶at age 30, extrapolated from Appendix, between normal BP and HTN. CPRD= clinical practice research datalink. N/A = not available in the publication. ARIC= Atherosclerosis Risk in Communities. CALIBER= CArdiovascular research using LInked Bespoke studies and Electronic Health Records. MESA= MultiEthnic Study of Atherosclerosis.**

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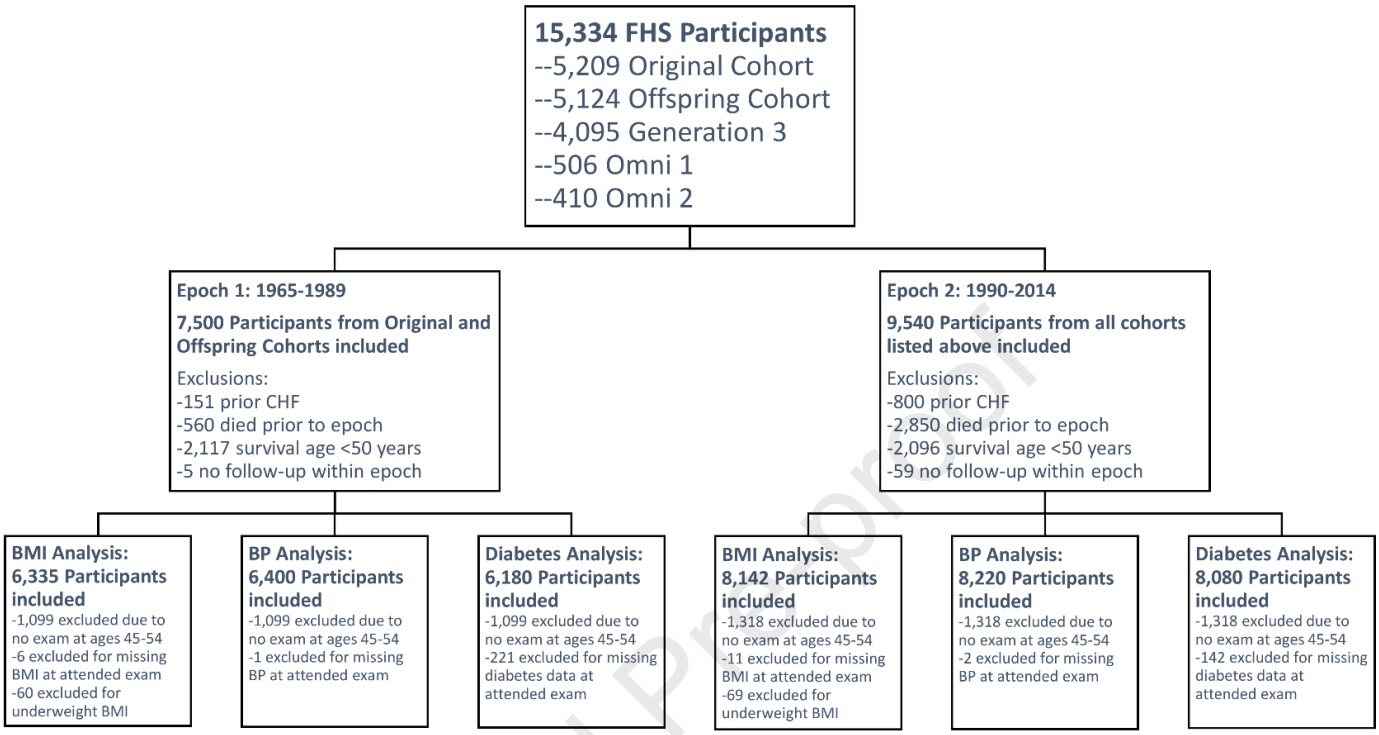
**Supplemental Figure 1.** Derivation of sample sizes in the two epochs (overall and for risk factor strata).

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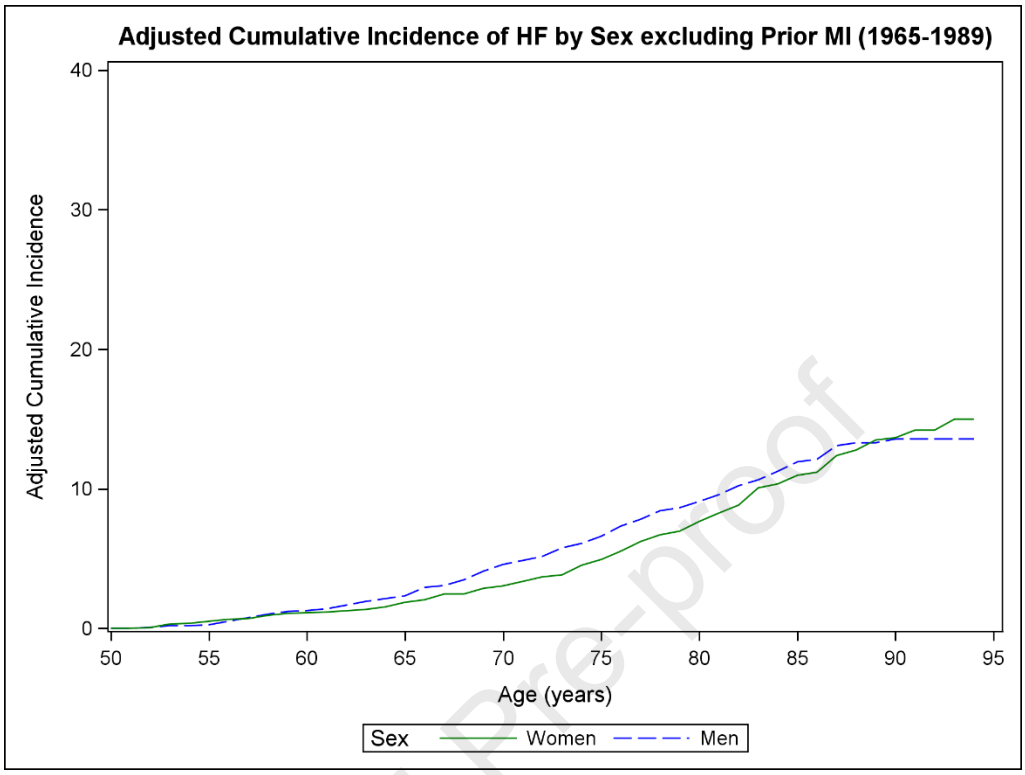
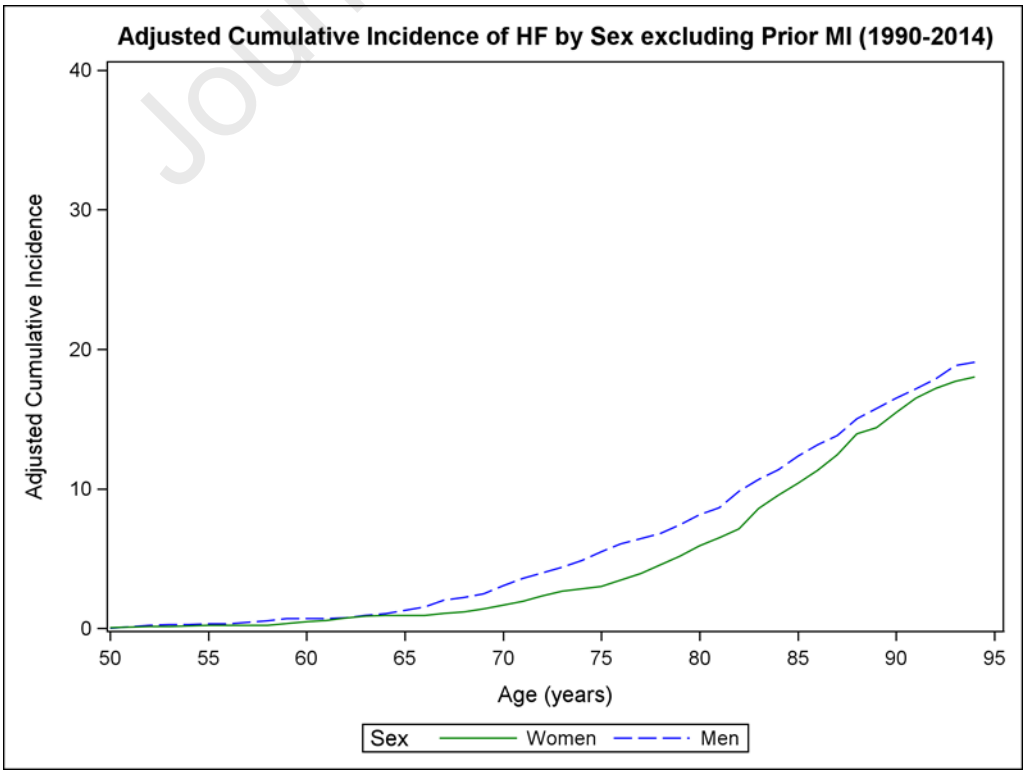
**Supplemental Figure 2. RLR of HF (%) at age 50 according to risk factor strata in *participants without prior MI*: comparison between the two epochs.**

**Panel A.**




**Panel B.**

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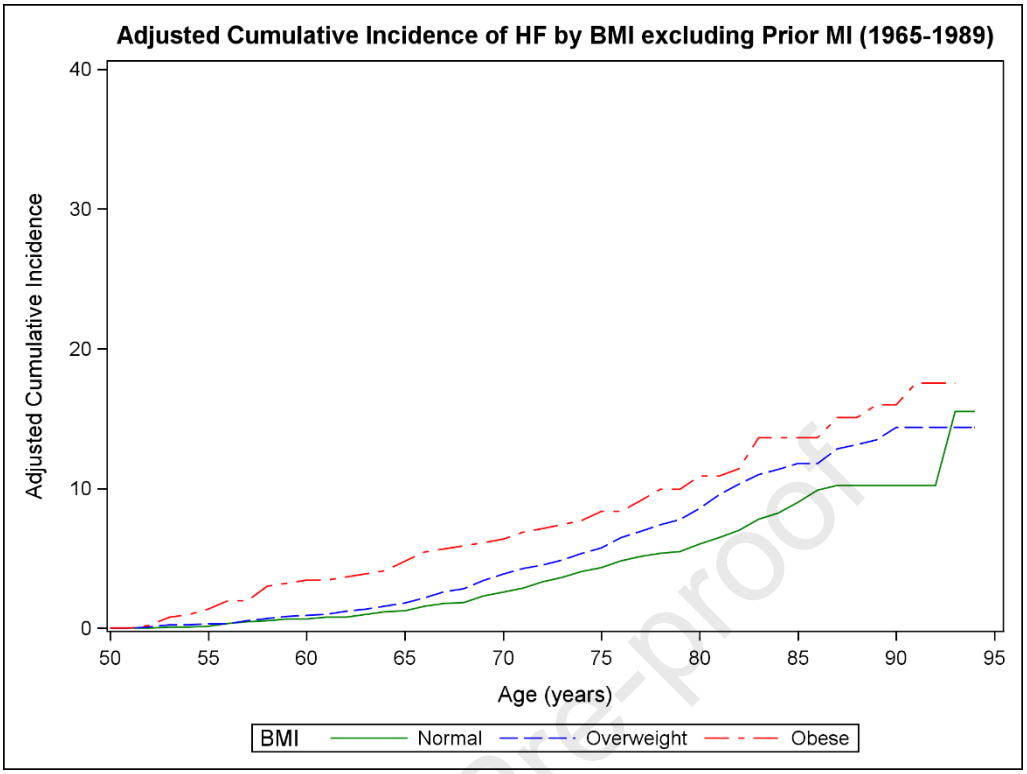
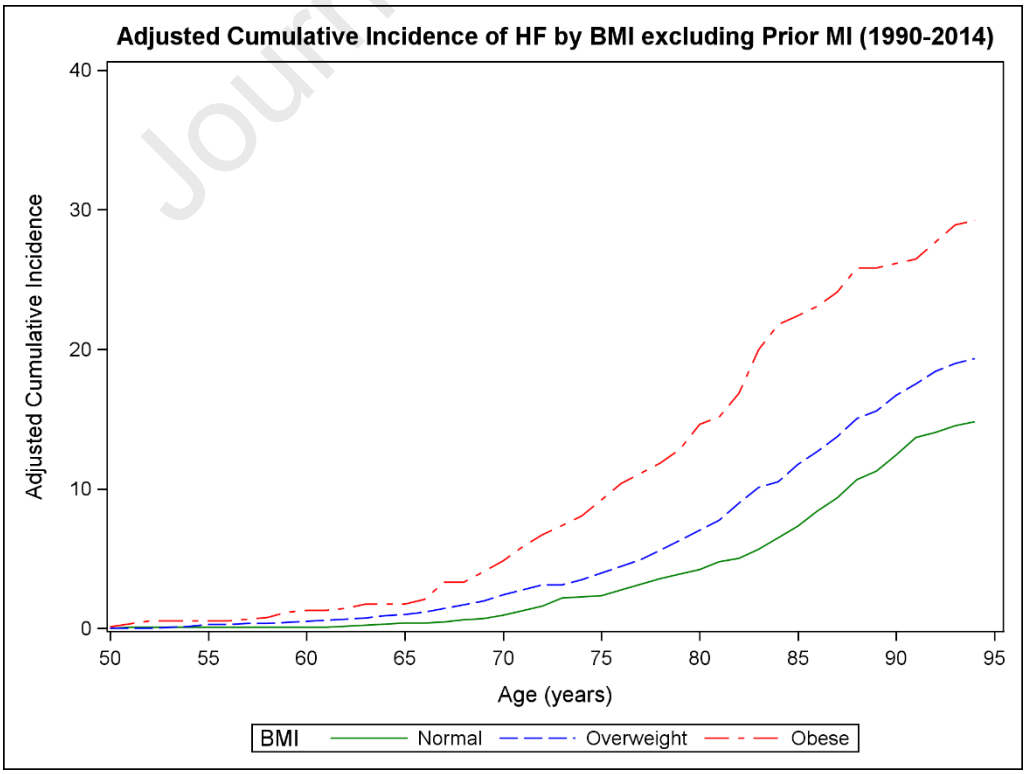
**Panel C.**




**Panel D.**

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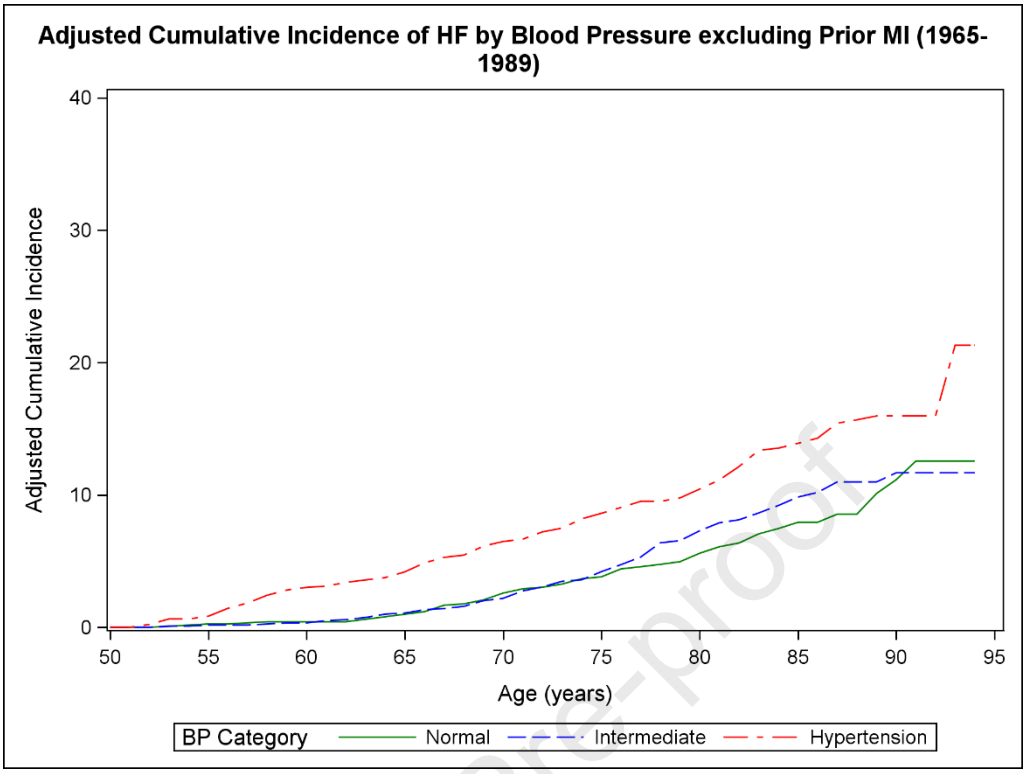
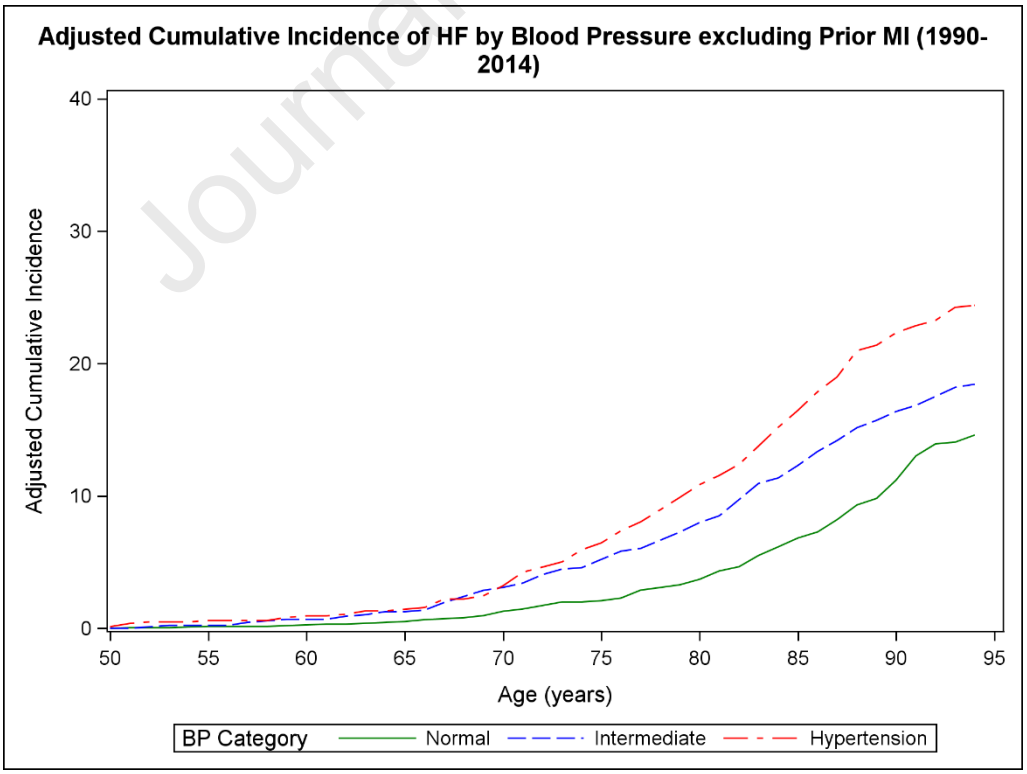
**Panel E.**




**Panel F.**

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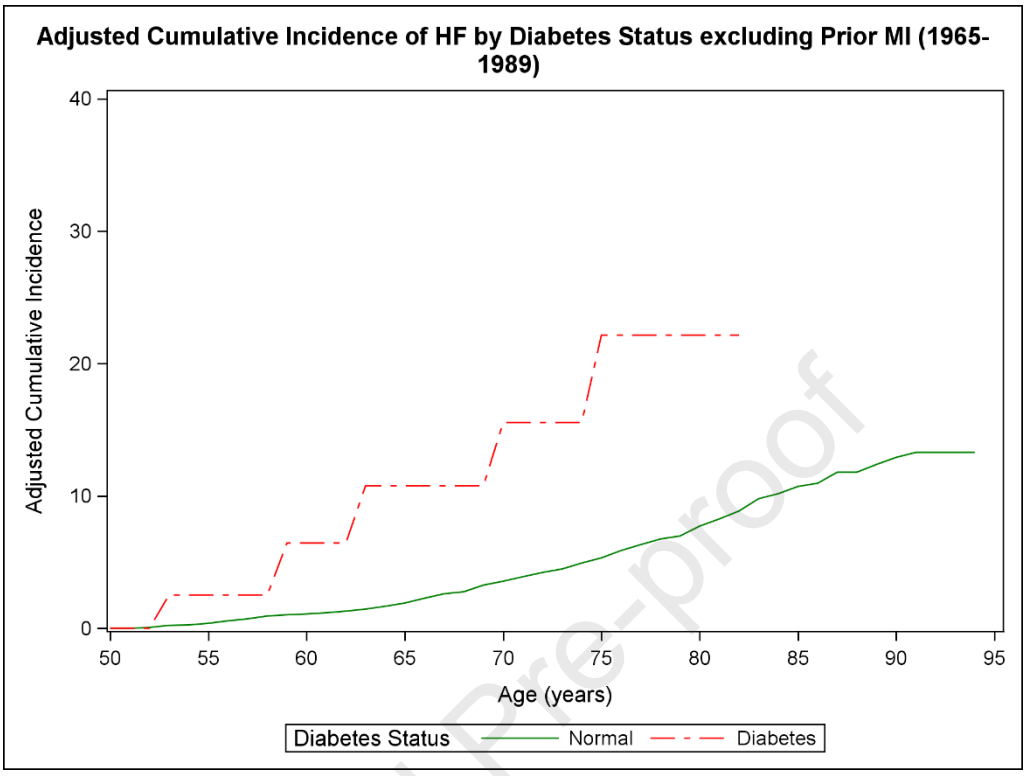
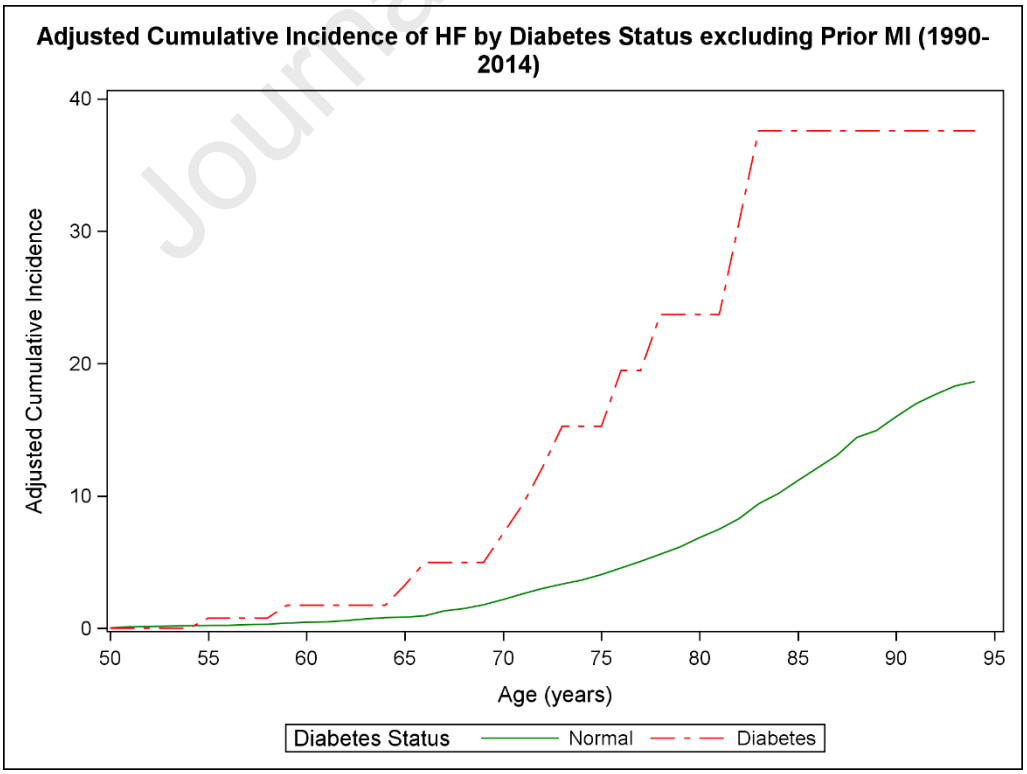
**Panel G.**




**Panel H.**

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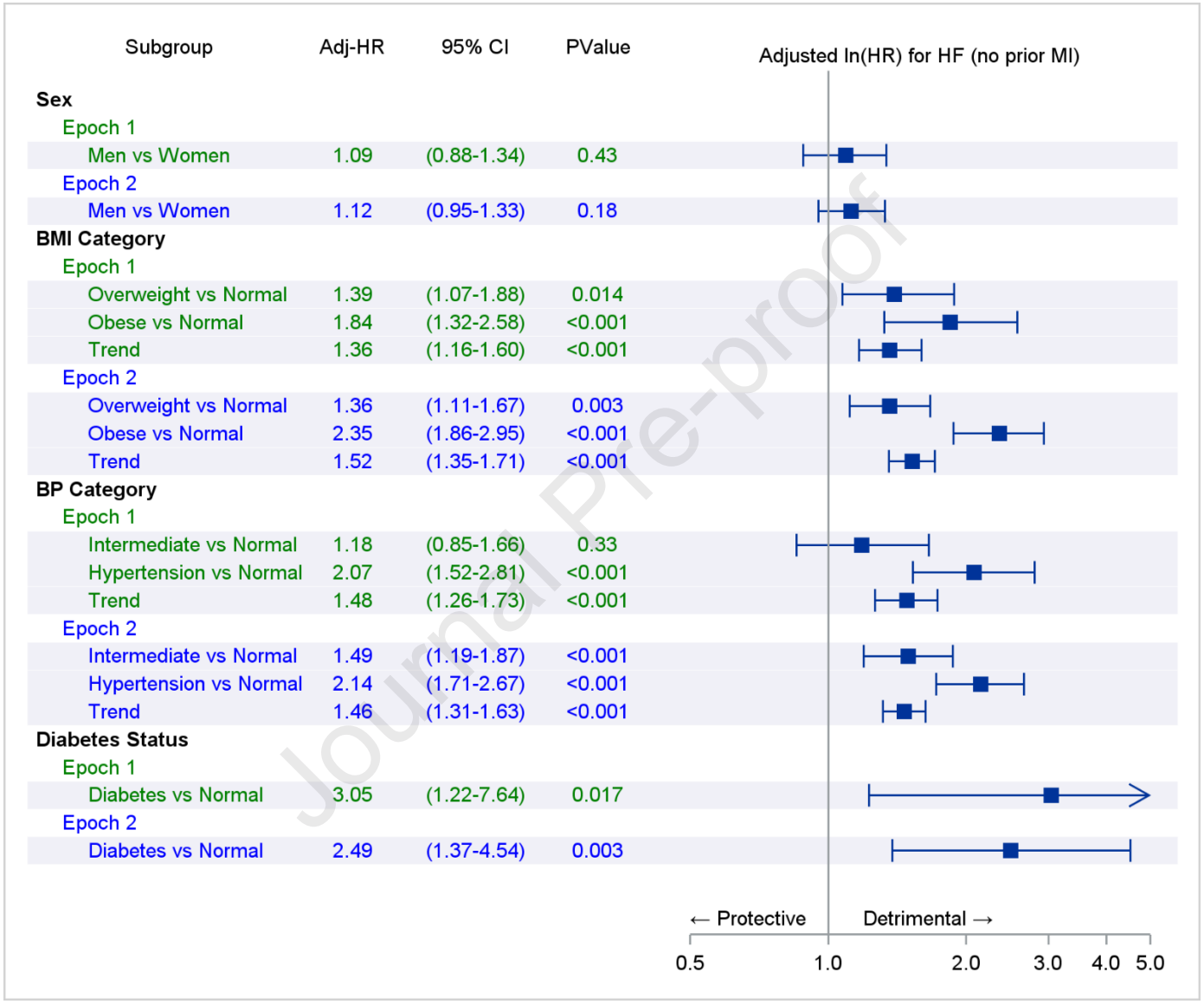
**Supplemental Figure 3. Association of risk factors with HF incidence using Fine-Gray subdistribution hazards regression models in the two epochs in *participants without prior MI*. Panel A** represents comparisons within each epoch, and **Panel B** represents comparisons of hazards ratios associated with a risk factor stratum in epoch 2 vs. epoch 1.

**Panel A.**

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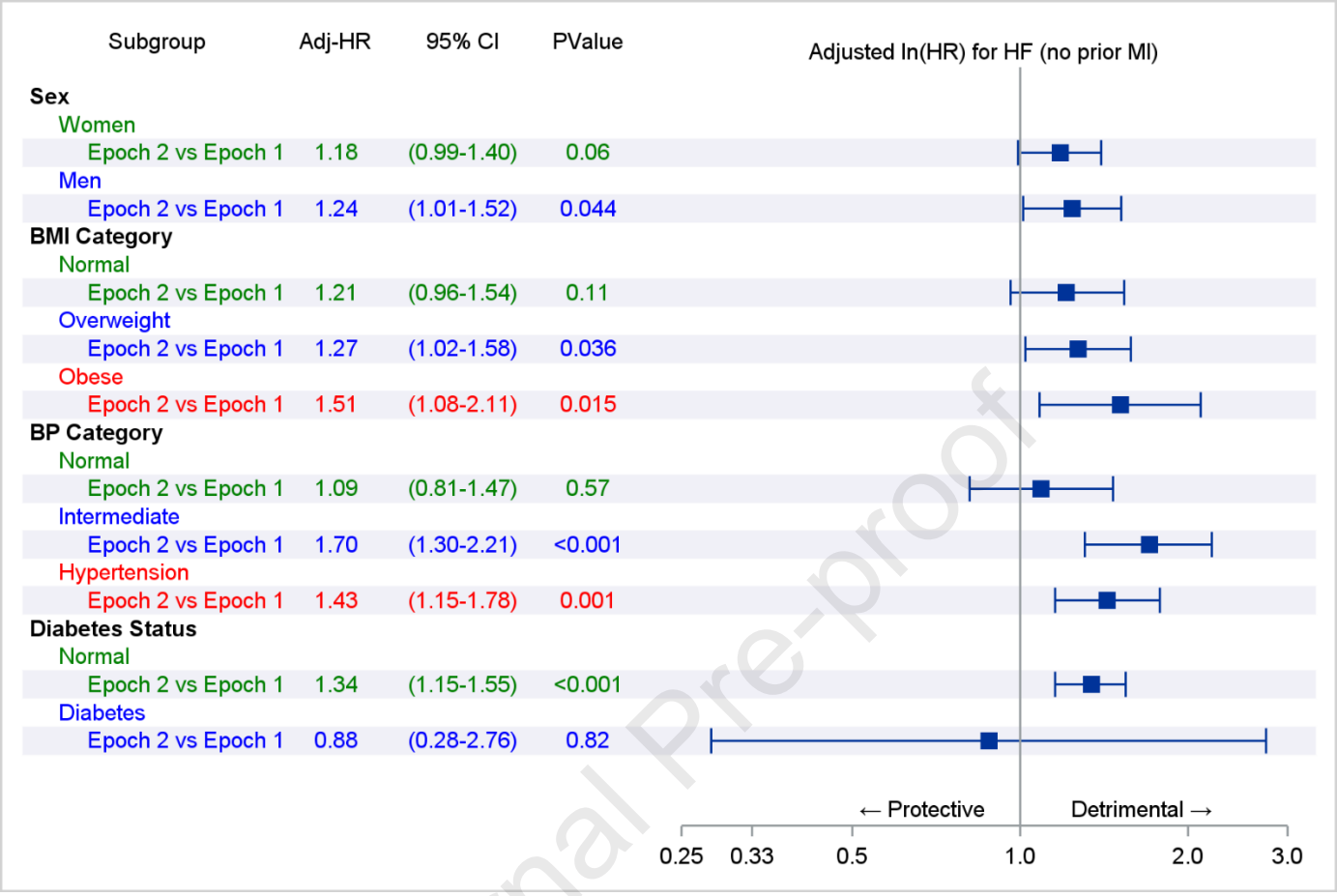
**Panel B.**

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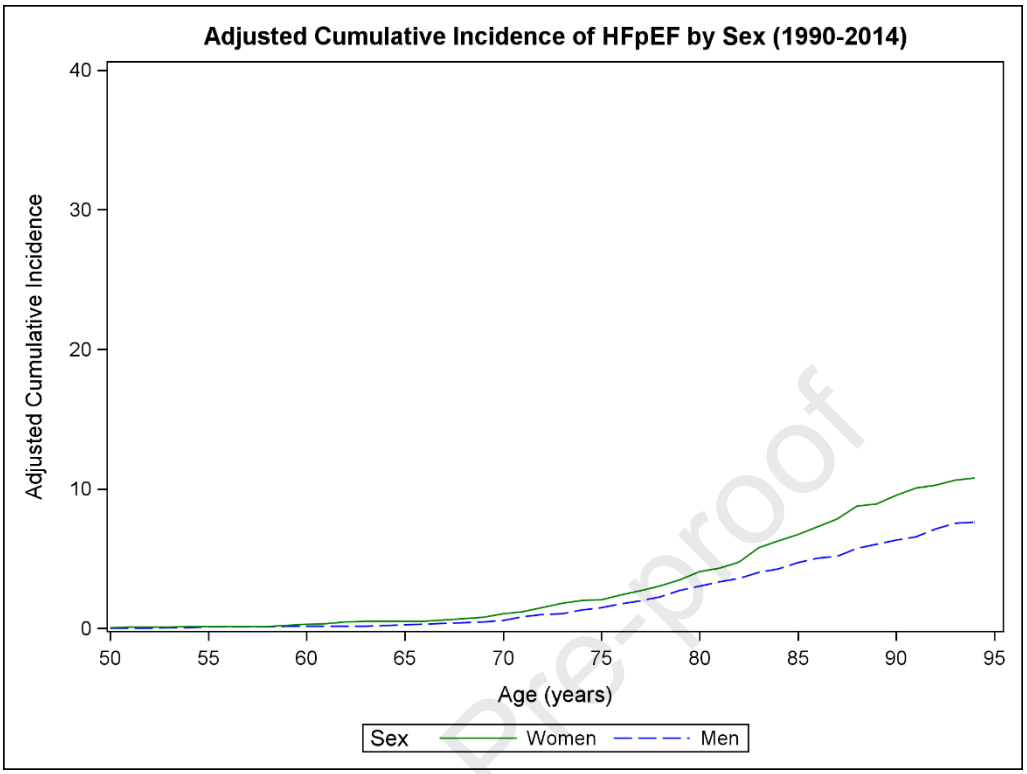
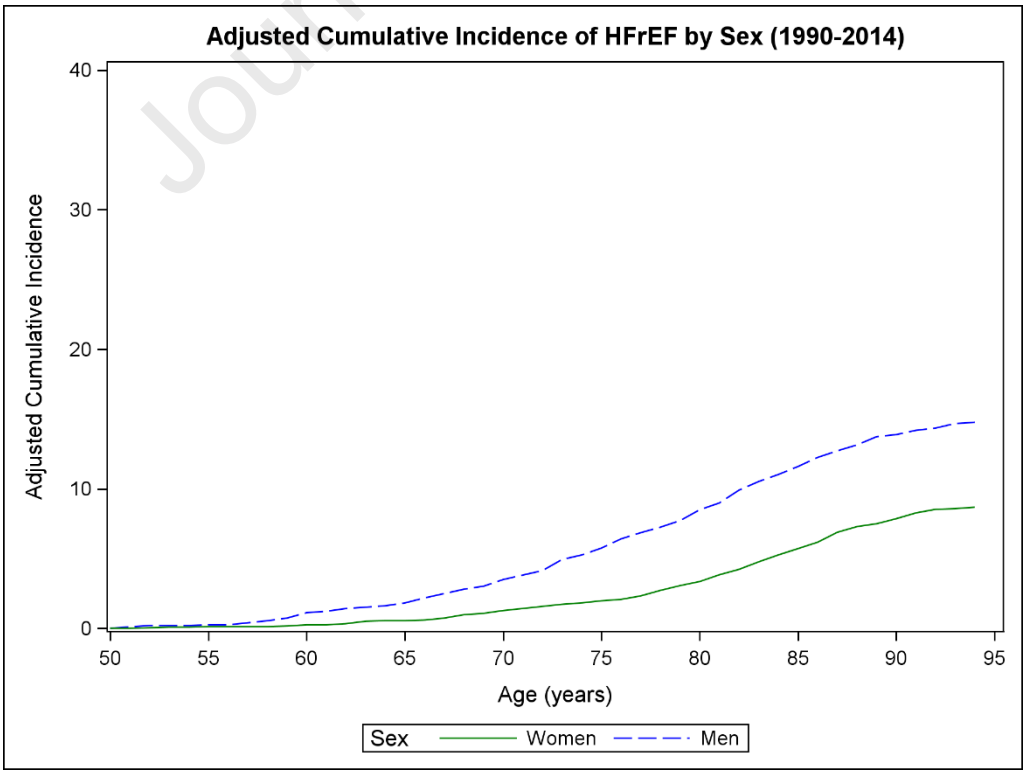
**Supplemental Figure 4. RLR (%) of HFpEF and HFrEF at age 50 years according to risk factor strata in the second epoch**

**Panel A.**




**Panel B.**

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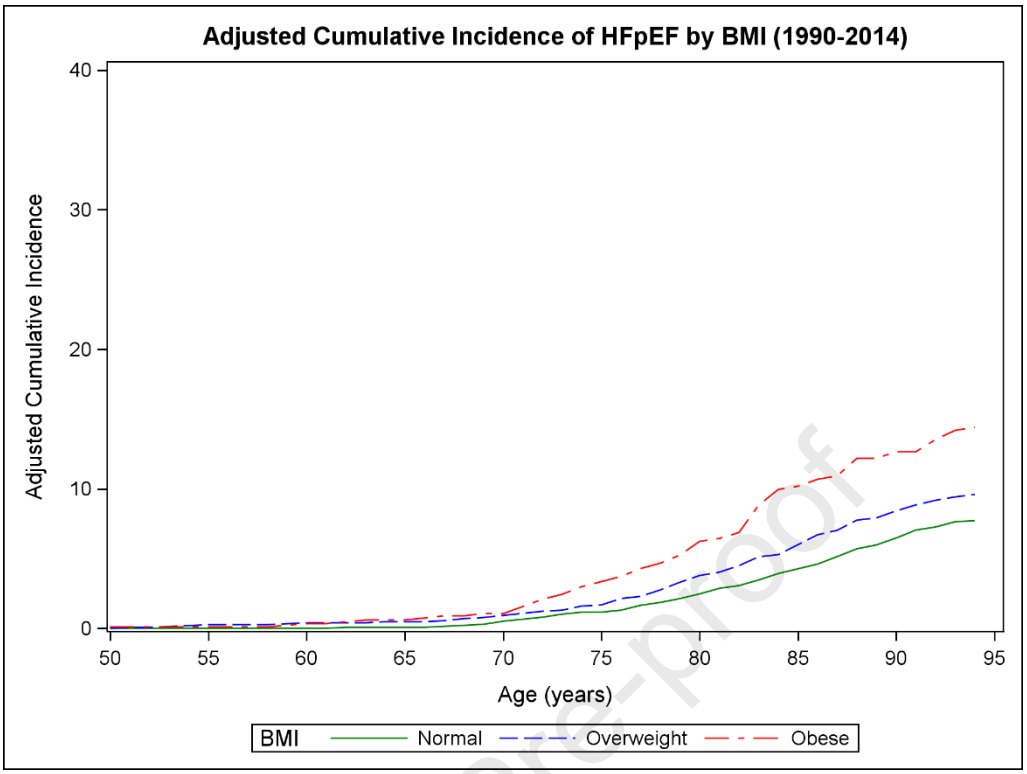
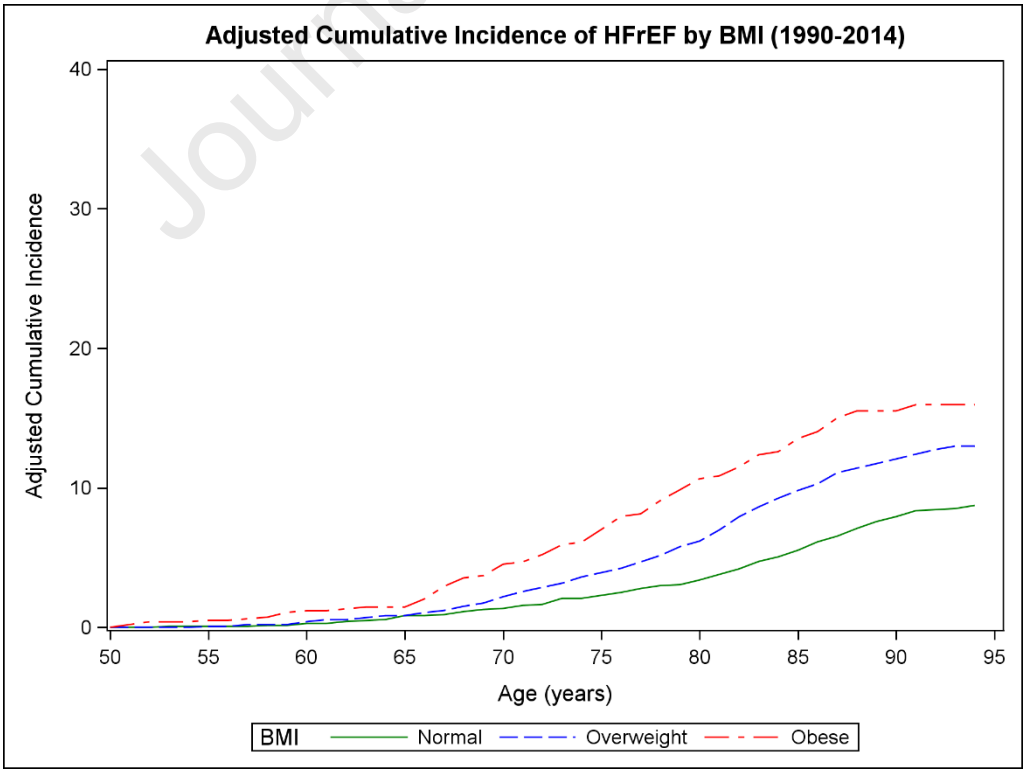
**Panel C.**




**Panel D.**

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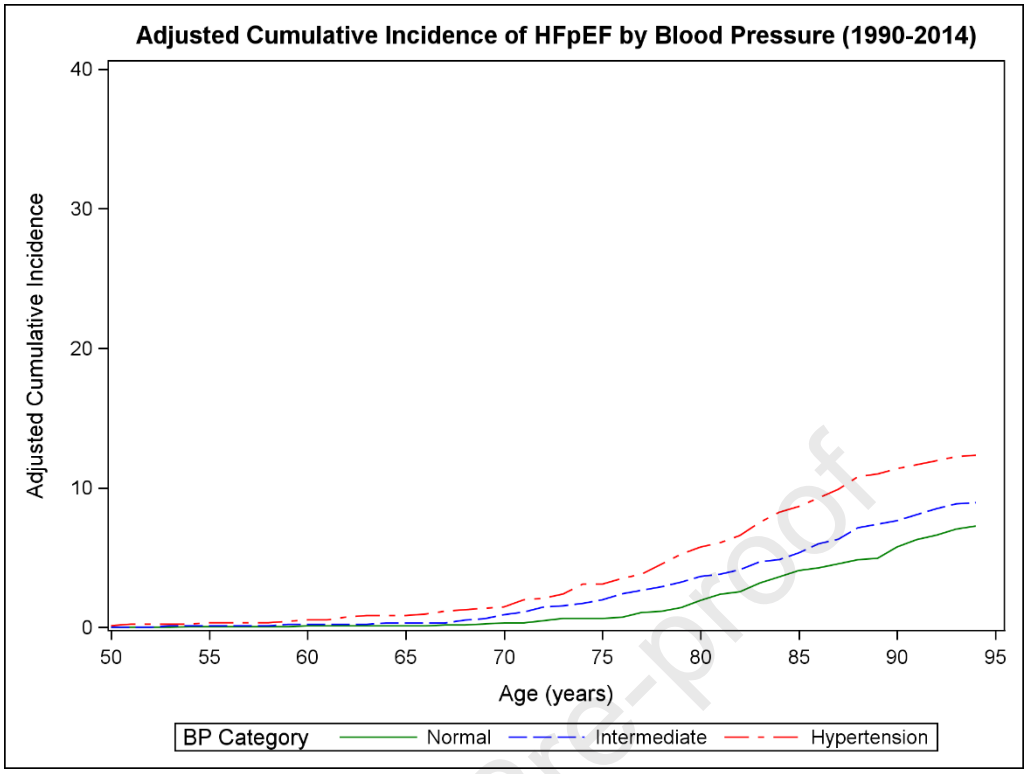
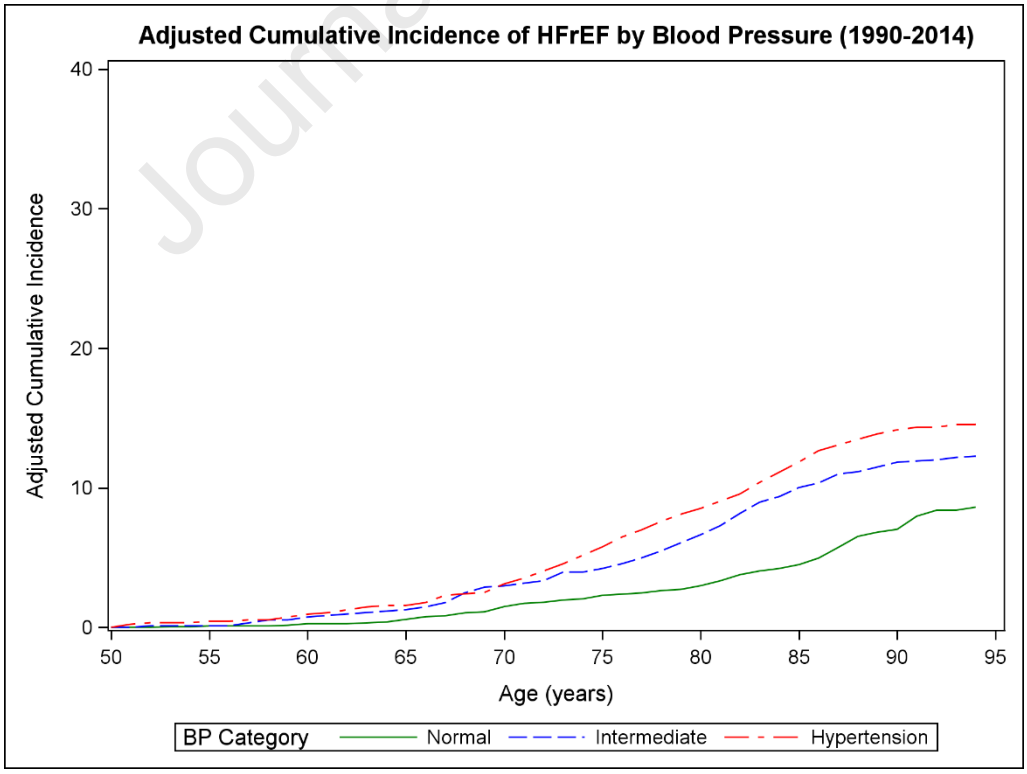
**Panel E.**




**Panel F.**

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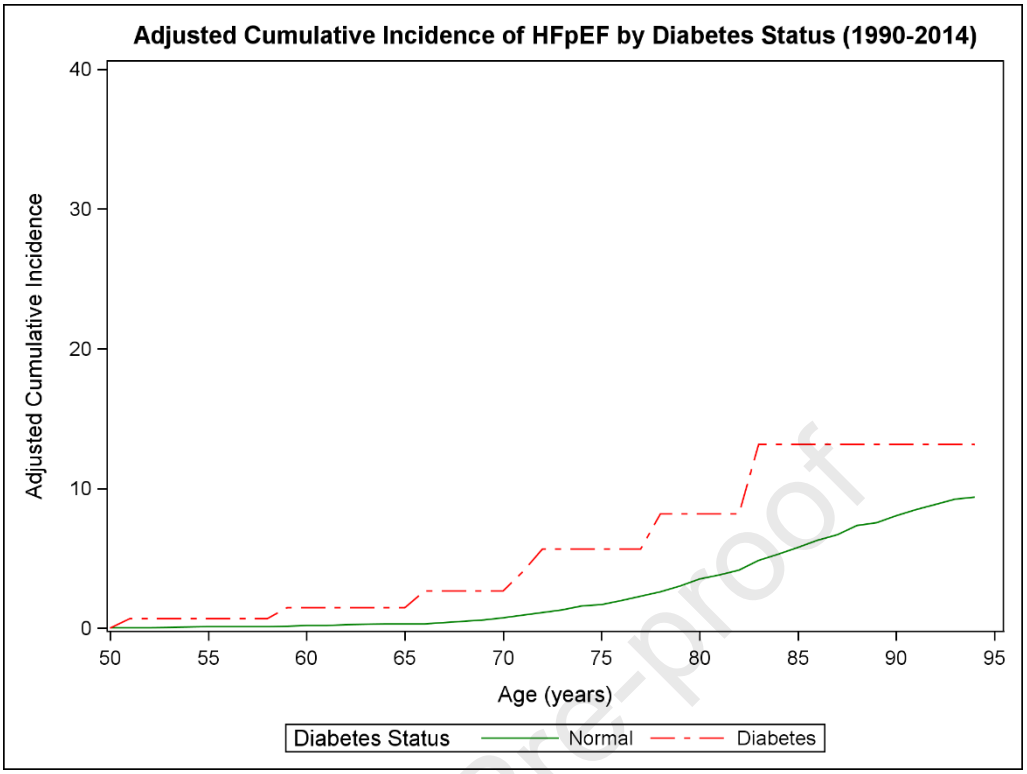
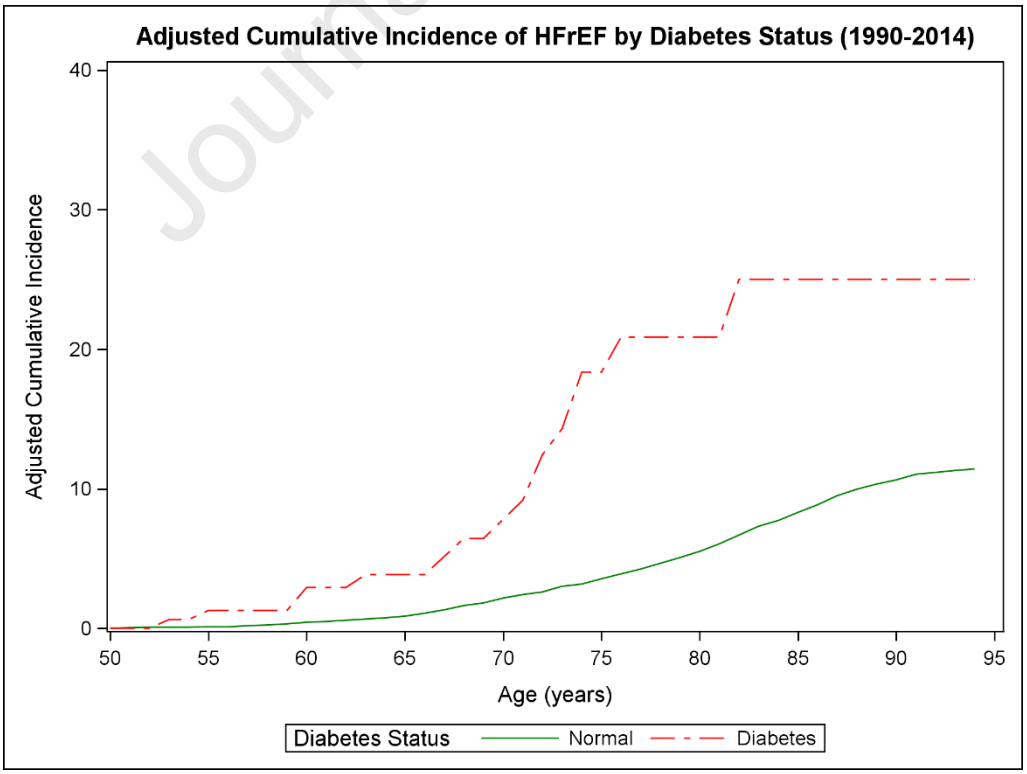
**Panel G.**




**Panel H.**

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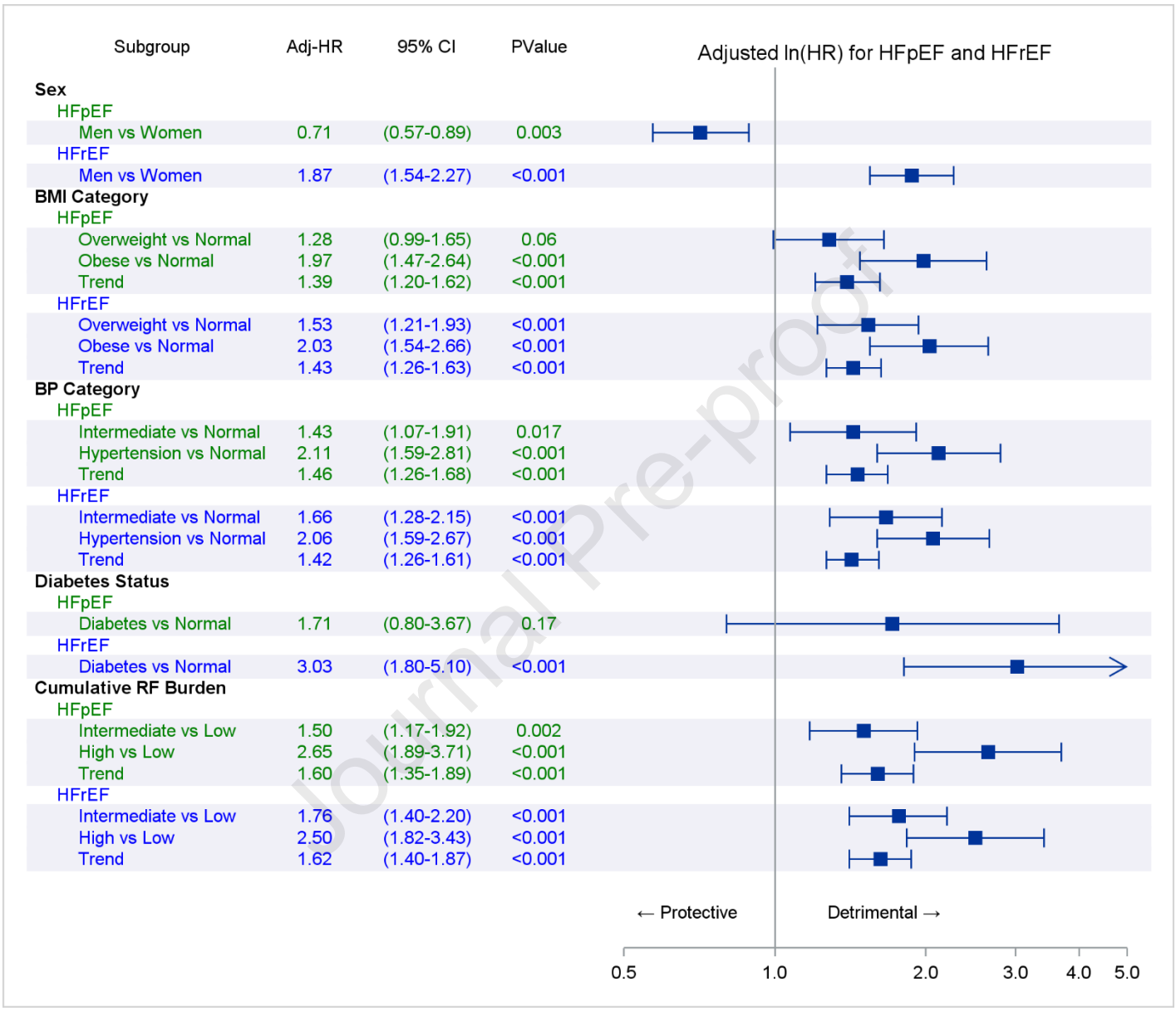
**Supplemental Figure 5.** Association of risk factors with HFpEF and HFrEF incidence using Fine-Gray subdistribution hazards regression models: results for participants in the second epoch.

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