

SUPPLEMENTARY DATA

Hypoglycemia Risk Factors

Supplementary Table S1. Hazard Ratios from Interactions by Race for Traditional Risk Factors of Severe Hypoglycemia, n=1206.

| | Model 1* | | | Model 2* | | |
|--|-----------------------|------------------------|---------------|-----------------------|-----------------------|-----------|
| | Black HR (95% CI) | White HR (95% CI) | p- value** | Black HR (95% CI) | White HR (95% CI) | p-value** |
| Age, per 5 years | 1.38 (1.15 – 1.67) | 1.48 (1.23 – 1.77) | 0.63 | 1.22 (1.00 – 1.47) | 1.28 (1.05 – 1.55) | 0.72 |
| Sex | 0.90 (0.56 – 1.47) | 0.97 (0.66 – 1.43) | 0.82 | 1.14 (0.70 – 1.86) | 1.02 (0.69 – 1.52) | 0.73 |
| Obese*** | 1.74 (1.07 – 2.82) | 1.31 (0.88 – 1.94) | 0.36 | 1.61 (0.99 – 2.61) | 1.15 (0.77 – 1.71) | 0.29 |
| Fructosamine Middle tertile | 3.15 (1.28 – 7.73) | 2.14 (1.26 – 3.66) | <0.0001 | 2.71 (1.10 – 6.68) | 1.55 (0.90 – 2.67) | 0.21 |
| Highest tertile | 6.05 (2.60 – 14.1) | 3.16 (1.87 – 5.32) | | 4.38 (1.87 – 10.3) | 1.89 (1.10 – 3.26) | |
| Diabetes duration ≥9 years | 1.58 (1.02 – 2.46) | 1.92 (1.29 – 2.84) | 0.52 | 1.14 (0.72 – 1.81) | 1.19 (0.78 – 1.82) | 0.88 |
| Diabetes Medications Oral only | 2.09 (0.99 – 4.38) | 4.04 (1.91 – 8.50) | <0.0001 | 1.62 (0.77 – 3.44) | 2.88 (1.35 – 6.15) | 0.43 |
| Any Insulin use | 3.07 (1.49 – 6.31) | 9.11 (4.26 – 19.46) | | 2.10 (1.00 – 4.38) | 4.24 (1.90 – 9.46) | |
| eGFR <60 mL/min/1.73 m ² | 1.92 (1.07 – 3.44) | 2.07 (1.23 – 3.48) | 0.84 | 1.44 (0.79 – 2.65) | 1.36 (0.79 – 2.34) | 0.89 |
| Albumin to Creatinine Ratio 30 – < 300mg/g | 1.13 (0.60 – 2.10) | 1.94 (1.17 – 3.23) | <0.0001 | 0.88 (0.47 – 1.64) | 1.48 (0.89 – 2.48) | 0.39 |
| ≥300mg/g | 2.28 (1.24 – 4.17) | 4.34 (2.39 – 7.88) | | 1.68 (0.90 – 3.14) | 2.26 (1.21 – 4.23) | |
| DSST****, per 1 lower race- specific standard deviation | 1.69 (1.32 – 2.18) | 1.68 (1.38 – 2.04) | 0.96 | 1.58 (1.22 – 2.04) | 1.58 (1.29 – 1.93) | 0.99 |

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*Model 1 included age and sex. Model 2 included all variables in Model 1 plus all covariates listed in the table. **P-value for interaction from a model with only that variable's interaction terms in the model. ***Overweight and normal weight were collapsed into one reference group due to small numbers of normal weight participants.

****DSST: Digit Symbol Substitution Test

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Supplementary Table S2. Hazard Ratios and 95% Confidence Intervals for Non-Traditional Risk Factors for Hypoglycemia (n=1144, 169 people with hypoglycemia, numerical table of results from Figure 2)

| | Model 1 HR (95% CI) | Model 2 HR (95% CI) |
|-----------------------------------|--------------------------------|--------------------------------|
| <i>Disability</i> | | |
| Any ADL difficulty | 2.15 (1.57, 2.95) | 1.95 (1.41, 2.69) |
| Any IADL difficulty | 1.63 (1.18, 2.25) | 1.37 (0.99, 1.90) |
| Number of ADLs/IADLs (ref=0) | | |
| 1 ADL/IADL | 1.16 (0.76, 1.78) | 1.03 (0.67, 1.58) |
| 2 ADLs/IADLs | 1.67 (1.03, 2.72) | 1.48 (0.91, 2.42) |
| 3+ ADLs/IADLs | 2.89 (1.94, 4.30) | 2.17 (1.44, 3.28) |
| <i>General Health</i> | | |
| Poor/fair self-rated health | 1.46 (1.06, 1.99) | 1.08 (0.78, 1.49) |
| Unintentional weight loss | 1.47 (0.89, 2.44) | 1.17 (0.70, 1.95) |
| Prevalent CHD | 1.91 (1.31, 2.78) | 1.42 (0.94, 2.13) |
| Prevalent stroke | 1.54 (0.78, 3.01) | 1.17 (0.59, 2.33) |
| Number of comorbidities (ref=0) | | |
| 1 comorbidity | 1.41 (0.97, 2.06) | 1.28 (0.87, 1.89) |
| 2 comorbidities | 1.58 (0.99, 2.52) | 1.15 (0.71, 1.87) |
| 3+ comorbidities | 2.75 (1.60, 4.71) | 1.73 (0.99, 3.05) |
| <i>Biomarkers</i> | | |
| 1,5-AG, per 5ug/mL | 1.47 (1.30, 1.66) | 1.22 (1.05, 1.41) |
| NT-proBNP, per log-transformed SD | 1.39 (1.18, 1.65) | 1.17 (0.98, 1.39) |
| hs-cTnT, per log-transformed SD | 1.55 (1.33, 1.80) | 1.09 (0.90, 1.32) |
| hsCRP, per log-transformed SD | 1.06 (0.90, 1.24) | 0.89 (0.75, 1.07) |
| <i>Medications</i> | | |
| Beta-Blockers | 0.95 (0.60-8.82) | 0.95 (0.59-1.52) |
| Anti-Depressants | 1.78 (1.08-2.93) | 1.83 (1.11-3.04) |
| <i>Demographics</i> | | |
| Family history of diabetes | 1.28 (0.92, 1.78) | 1.20 (0.86, 1.68) |
| Medicaid insurance | 2.09 (1.41, 3.10) | 1.70 (1.14, 2.53) |
| Education (ref = some college) | | |
| High school graduate | 1.29 (0.86, 1.95) | 1.10 (0.72, 1.67) |
| Less than high school graduate | 2.01 (1.33, 3.04) | 1.33 (0.85, 2.08) |

SUPPLEMENTARY DATA

Supplementary Table S3. Baseline Characteristics of Black and White ARIC Study Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B Coverage (Visit 4, 1996-1998)

| | Overall (n=463) | Blacks (n=139) | Whites (n=324) |
|--------------------------------------|-------------------------------|-------------------------------|-------------------------------|
| | Mean (SD) or n (%) | Mean (SD) or n (%) | Mean (SD) or n (%) |
| Age | 69.0 (2.53) | 68.9 (2.65) | 69.0 (2.48) |
| Female sex | 242 (52.3) | 101 (72.7) | 141 (43.5) |
| BMI | | | |
| Overweight, % | 176 (38.0) | 48 (34.5) | 128 (39.5) |
| Obese, % | 236 (51.0) | 78 (56.1) | 158 (48.8) |
| Diabetes duration \geq 9 years | 225 (48.6) | 80 (57.6) | 145 (44.8) |
| Diabetes Medications | | | |
| No medication use | 109 (23.5) | 28 (20.1) | 81 (25.0) |
| Oral medication use only | 222 (48.0) | 53 (38.1) | 169 (52.2) |
| Any insulin use | 132 (28.5) | 58 (41.7) | 74 (22.8) |
| Fructosamine | | | |
| Middle tertile (299-347 μ mol/L) | 154 (33.3) | 46 (33.1) | 108 (33.3) |
| Highest tertile (>347 μ mol/L) | 154 (33.3) | 60 (43.2) | 94 (29.0) |
| eGFR <60 mL/min/1.73 m ² | 85 (18.4) | 29 (20.9) | 56 (17.3) |
| Albumin to Creatinine Ratio | | | |
| 30 - <300mg/g | 71 (15.3) | 23 (16.7) | 48 (14.8) |
| \geq 300mg/g | 34 (7.3) | 14 (10.1) | 20 (6.2) |
| Digit Symbol Substitution Test | 34.0 (12.9) | 23.1 (10.2) | 38.7 (11.0) |

SUPPLEMENTARY DATA

Supplementary Table S4. Adjusted* Hazard Ratios and 95% Confidence Intervals for Traditional Risk Factors in ARIC Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B (n=463, 76 hypoglycemic events)

| | Model 1* HR (95% CI) | Model 2* HR (95% CI) |
|--|---------------------------------------|---------------------------------------|
| Age, per 5 years | 1.49 (0.95 – 2.33) | 1.34 (0.83 – 2.15) |
| Female sex | 0.96 (0.60 – 1.53) | 1.07 (0.66 – 1.72) |
| Black race | 2.00 (1.25 – 3.21) | 1.48 (0.91 – 2.40) |
| Obese | 1.44 (0.90 – 2.31) | 1.22 (0.75 – 1.98) |
| Fructosamine (vs. lowest tertile) | | |
| Middle tertile (299-347 $\mu\text{mol/L}$) | 1.38 (0.71 – 2.66) | 1.06 (0.54 – 2.09) |
| Highest tertile (>347 $\mu\text{mol/L}$) | 2.63 (1.44 – 4.83) | 1.68 (0.90 – 3.14) |
| Diabetes duration ≥ 9 years | 1.86 (1.15 – 2.99) | 1.15 (0.68 – 1.93) |
| Diabetes Medication (vs. none) | | |
| Oral only | 2.40 (0.99 – 5.77) | 2.27 (0.92 – 5.61) |
| Any insulin use | 6.18 (2.59 – 14.72) | 4.72 (1.92 – 11.63) |
| eGFR <60 mL/min/1.73 m ² | 2.32 (1.38 – 3.89) | 1.92 (1.09 – 3.40) |
| Albumin to Creatinine Ratio | | |
| 30 – <300 mg/g | 1.17 (0.59 – 2.31) | 0.74 (0.36 – 1.52) |
| ≥ 300 mg/g | 4.01 (2.10 – 7.68) | 2.97 (1.49 – 5.89) |
| DSST**, per 1 lower race-specific standard deviation | 1.66 (1.30 – 2.13) | 1.55 (1.21 – 1.99) |

*Model 1 included age, sex, and race. Model 2 included all variables in Model 1 plus all covariates listed in the table.

**DSST: Digit Symbol Substitution Test

SUPPLEMENTARY DATA

Supplementary Table S5. Hazard Ratios and 95% Confidence Intervals for Traditional Risk Factors in ARIC Participants with Diagnosed Diabetes, excluding individuals with insulin only use at all four study visits (possible type 1) (n=1138, 158 hypoglycemic events)

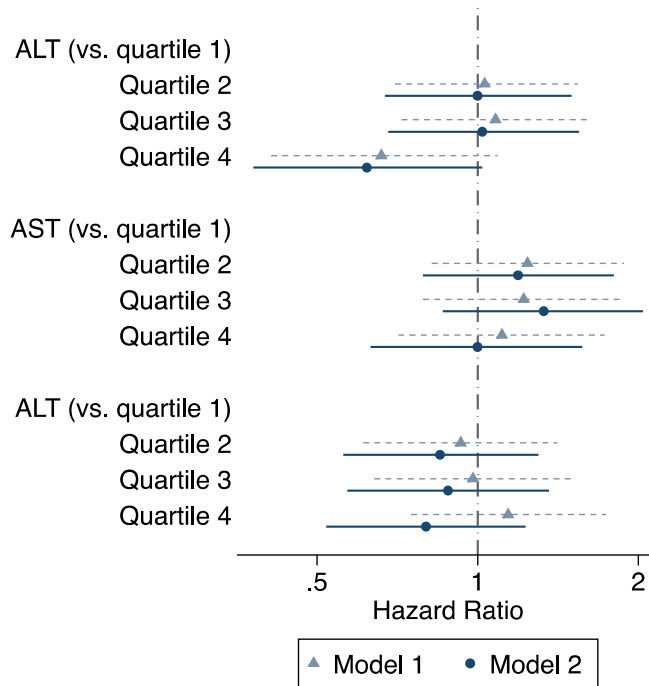
| | Model 1* HR (95% CI) | Model 2* HR (95% CI) |
|--|--------------------------------|--------------------------------|
| Age, per 5 years | 1.39 (1.21 – 1.61) | 1.26 (1.08 – 1.47) |
| Female sex | 0.95 (0.69 – 1.32) | 0.98 (0.70 – 1.37) |
| Black race | 1.76 (1.27 – 2.45) | 1.31 (0.94 – 1.84) |
| Obese | 1.67 (1.20 – 2.33) | 1.62 (1.15 – 2.15) |
| Fructosamine (vs. lowest tertile) | | |
| Middle tertile (296-350 $\mu\text{mol/L}$) | 1.91 (1.19 – 3.06) | 1.54 (0.95 – 2.50) |
| Highest tertile (>350 $\mu\text{mol/L}$) | 3.83 (2.47 – 5.94) | 2.67 (1.69 – 4.21) |
| Diabetes duration ≥ 9 years | 1.47 (1.07 – 2.01) | 1.14 (0.82 – 1.61) |
| Diabetes Medications (vs. none) | | |
| Oral only | 3.02 (1.79 – 5.09) | 2.14 (1.25 – 3.67) |
| Any insulin use | 4.58 (2.65 – 7.93) | 2.66 (1.49 – 4.73) |
| eGFR <60 mL/min/1.73 m ² | 1.98 (1.28 – 3.08) | 1.57 (0.99 – 2.51) |
| Albumin to Creatinine Ratio | | |
| 30 – <300mg/g | 1.75 (1.16 – 2.62) | 1.43 (0.95 – 2.15) |
| $\geq 300\text{mg/g}$ | 3.16 (1.91 – 5.23) | 2.26 (1.33 – 3.85) |
| DSST**, per 1 lower race-specific standard deviation | 1.64 (1.38 – 1.94) | 1.55 (1.30 – 1.84) |

*Model 1 included age, sex, and race. Model 2 included all variables in Model 1 plus all covariates listed in the table.

** DSST: Digit Symbol Substitution Test

SUPPLEMENTARY DATA

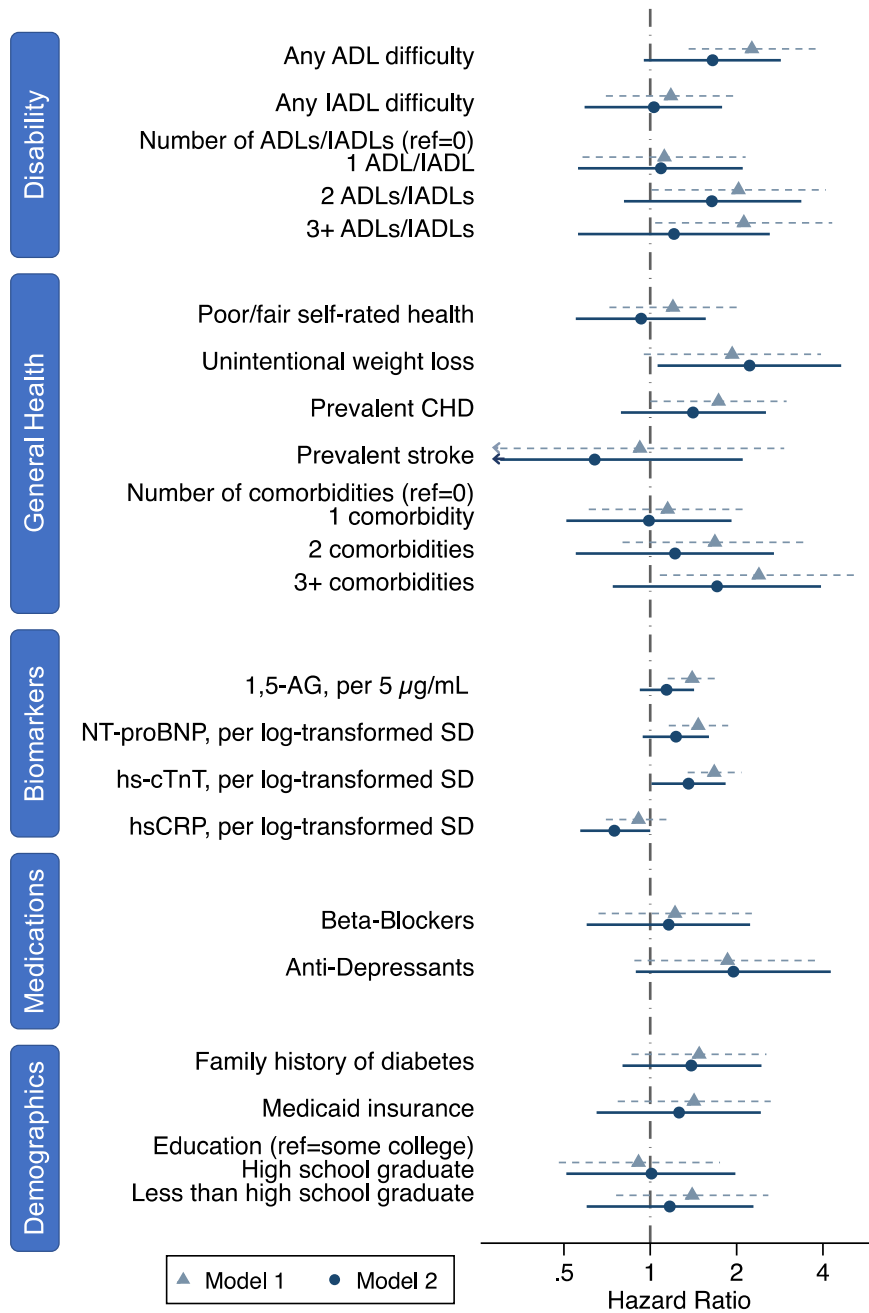
Supplementary Figure S1. Hazard Ratios and 95% Confidence Intervals for Liver Enzymes for Severe Hypoglycemia (n =1144, 169 people with hypoglycemia)



Quartiles of ALT were quartile 1: 1-10U/L, quartile 2: 11-14U/L, quartile 3: 15-19U/L, quartile 4: ≥ 20 U/L. Quartiles of AST were quartile 1: 5-14U/L, quartile 2: 15-17U/L, quartile 3: 18-21U/L, quartile 4: ≥ 22 U/L. Quartiles of GGT were quartile 1: 1-19U/L, quartile 2: 20-27U/L, quartile 3: 28-40U/L, quartile 4: ≥ 41 U/L. Model 1 was adjusted for age, sex, and race. Model 2 was adjusted for all traditional risk factors (age, sex, race, obesity, fructosamine tertiles, diabetes duration ≥ 9 years, diabetes medication use (no medication, oral only, any insulin), eGFR < 60 mL/min/1.73 m², albuminuria (< 30 mg/g, 30- < 300 mg/g, ≥ 300 mg/g), DSST race-specific z-score).

SUPPLEMENTARY DATA

Supplementary Figure S2. Hazard Ratios and 95% Confidence Intervals for Novel Risk Factors for Hypoglycemia in ARIC Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B (n=429, 67 hypoglycemic events)



Fully adjusted models were adjusted for all traditional risk factors (age, sex, race, obesity, fructosamine tertiles, diabetes duration ≥ 9 years, diabetes medication use (no medication, oral only, any insulin), eGFR < 60 mL/min/1.73 m², albuminuria (< 30 mg/g, 30 - < 300 mg/g, ≥ 300 mg/g), DSST race-specific z-score).

SUPPLEMENTARY DATA

Supplementary Figure S3. Incidence Rate of Severe Hypoglycemia among ARIC Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B, Adjusted for Sex.

