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# The Bi-directional Association between Depression and Severe Hypoglycemic and Hyperglycemic Events in Type 1 Diabetes

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## Supplementary Table 1. Definition of covariates based off electronic medical record

| Health condition | ICD-9 Codes |
|---|---|
| Neuropathy | 354.x, 355.x |
| Myocardial infartion | 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 |
| Stroke | 431.x, 430.x, 433.x1, 434.x, 435.x excluding 435.2x |
| Peripheral artieral disease | 440.x, 441.x, 442.0, 442.3, 443.81, 443.9, |

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**Supplementary Table 2. Hazards ratio of depression predicting time to dysglycemic events adjusting for baseline confounders**

| Adjusted for: | Severe Hyperglycemic Event HR (95% CI) | Severe Hypoglycemic Event HR (95% CI) |
|---|---|---|
| **Severe dysglycemic events any time after depression** | | |
| # eligible severe glycemic events | 376 | 641 |
| Demographics | 2.46 (1.97, 3.08) | 1.98 (1.66, 2.37) |
| Demographics & microvascular complications | 2.47 (1.97, 3.09) | 1.97 (1.65, 2.35) |
| Demographics & macrovascular complications | 2.48 (1.98, 3.11) | 1.96 (1.65, 2.34) |
| Demographics & micro- and macro-complications | 2.49 (1.98, 3.12) | 1.95 (1.63, 2.32) |
| Demographics, micro- and macro-complications, & HbA1c | 2.52 (2.02, 3.16) | 1.95 (1.64, 2.33) |

**Notes:** Depression defined as a diagnosis of major depressive disorder, depressive type psychosis, or dysthymic disorder. demographics: age, sex, race; microvascular complications: neuropathy, peripheral artery disease; macrovascular complications: myocardial infarction, stroke

**Supplementary Table 3. Hazards ratio of depression predicting time to dysglycemic events adjusting for demographics, baseline micro- and macro-complications, and quintiles of HbA1c**

| Adjusted for: | Severe Hyperglycemic Event HR (95% CI) | Severe Hypoglycemic Event HR (95% CI) |
|---|---|---|
| Severe dysglycemic events any time after depression | 2.44 (1.98, 3.02) | 1.89 (1.60, 2.12) |
| Severe dysglycemic events within 6 months of depression | 7.09 (5.26, 9.57) | 5.59 (4.46, 7.01) |
| Severe dysglycemic events within first year of depression | 5.12 (3.84, 6.81) | 4.06 (3.27, 5.05) |
| Severe dysglycemic events 1+ years after depression | 1.43 (1.13, 1.81) | 1.09 (0.90, 1.31) |

Notes: demographics: age, sex, race; microvascular complications: neuropathy, peripheral artery disease; macrovascular complications: myocardial infarction, stroke

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**Supplementary Table 4. Hazards ratio of depression predicting time to dysglycemic events adjusting for baseline confounders including baseline dysglycemic event**

| Adjusted for: | Severe Hyperglycemic Event HR (95% CI) | Severe Hypoglycemic Event HR (95% CI) |
|---|---|---|
| **Severe dysglycemic events any time after depression** | | |
| # eligible severe glycemic events | 541 | 888 |
| Demographics & baseline dysglycemic event | 2.25 (1.88, 2.69) | 1.96 (1.71, 2.25) |
| Demographics, baseline dysglycemic event & microvascular complications | 2.22 (1.86, 2.66) | 1.93 (1.68, 2.21) |
| Demographics, baseline dysglycemic event & macrovascular complications | 2.25 (1.88, 2.69) | 1.93 (1.68, 2.21) |
| Demographics, baseline dysglycemic event, & micro- and macro-complications | 2.23 (1.86, 2.66) | 1.90 (1.66, 2.18) |
| Demographics, baseline dysglycemic event,micro- and macro-complications, & HbA1c | 2.31 (1.93, 2.77) | 1.91 (1.66, 2.19) |
| **Severe dysglycemic events within 6 months of depression** | | |
| # eligible severe glycemic events | 332 | 586 |
| Demographics & baseline dysglycemic event | 7.91 (6.21, 10.07) | 5.84 (4.80, 7.10) |
| Demographics, baseline dysglycemic event & microvascular complications | 7.77 (6.10, 9.90) | 5.73 (4.71, 6.97) |
| Demographics, baseline dysglycemic event & macrovascular complications | 7.91 (6.22, 10.06) | 5.78 (4.85, 6.90) |
| Demographics, baseline dysglycemic event, & micro- and macro-complications | 7.78 (6.12, 9.90) | 5.70 (4.78, 6.80) |
| Demographics, baseline dysglycemic event,micro- and macro-complications, & HbA1c | 7.82 (6.15, 9.94) | 5.68 (4.77, 6.76) |
| **Severe dysglycemic events within first year of depression** | | |
| # eligible severe glycemic events | 341 | 596 |
| Demographics & baseline dysglycemic event | 5.59 (4.41, 7.09) | 4.24 (3.51, 5.13) |
| Demographics, baseline dysglycemic event & microvascular complications | 5.50 (4.31, 7.01) | 4.17 (3.45, 5.05) |
| Demographics, baseline dysglycemic event & macrovascular complications | 5.58 (4.40, 7.07) | 4.20 (3.47, 5.07) |
| Demographics, baseline dysglycemic event, & micro- and macro-complications | 5.50 (4.33, 6.98) | 4.14 (3.49, 4.92) |
| Demographics, baseline dysglycemic event,micro- and macro- | 5.62 (4.42, 7.15) | 4.14 (3.49, 4.92) |

| | | |
|---|---|---|
| complications, & HbA1c | | |
| **Severe dysglycemic events 1+ years after depression** | | |
| # eligible severe glycemic events | 440 | 735 |
| Demographics & baseline dysglycemic event | 1.38 (1.13, 1.69) | 1.28 (1.10, 1.49) |
| Demographics, baseline dysglycemic event & microvascular complications | 1.33 (1.09, 1.63) | 1.19 (1.02, 1.39) |
| Demographics, baseline dysglycemic event & macrovascular complications | 1.38 (1.13, 1.68) | 1.19 (1.02, 1.39) |
| Demographics, baseline dysglycemic event, & micro- and macro-complications | 1.34 (1.10, 1.63) | 1.17 (1.00, 1.37) |
| Demographics, baseline dysglycemic event,micro- and macro-complications, & HbA1c | 1.38 (1.13, 1.69) | 1.17 (1.01, 1.37) |

Notes: Models with severe hypoglycemic events as the outcome adjusted for history of severe hypoglycemic event prior to baseline and models with severe hyperglycemic events as the outcome adjusted for history of severe hyperglycemic events prior to baseline. demographics: age, sex, race; microvascular complications: neuropathy, peripheral artery disease; macrovascular complications: myocardial infarction, stroke

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**Supplementary Table 5. Risk of severe dysglycemic event any time after baseline associated with depression stratified by demographics, diabetes complications, and baseline HbA1c levels**

| | Severe Hyperglycemic Event | | | Severe Hypoglycemic Event | | |
|---|---|---|---|---|---|---|
| | # cases | # obs | HR (95% CI) | # cases | # obs | HR (95% CI) |
| **Sex** | | | | | | |
| Males | 166 | 2,035 | 2.91 (2.12, 3.98) | 311 | 1,874 | 2.01 (1.59, 2.53) |
| Females | 210 | 1,872 | 2.03 (1.53, 2.69) | 330 | 1,783 | 1.74 (1.39, 2.18) |
| **Race** | | | | | | |
| Asian | 20 | 153 | 5.71 (1.03, 31.50) | 23 | 143 | 1.80 (0.72, 4.51) |
| White | 316 | 3,133 | 2.44 (1.94, 3.08) | 516 | 2,907 | 1.77 (1.48, 2.12) |
| Other | 53 | 517 | 2.01 (1.15, 3.51) | 97 | 503 | 2.69 (1.76, 4.10) |
| Neuropathy | | | | | | |
| Yes | 38 | 475 | 2.70 (1.26, 5.78) | 78 | 411 | 1.60 (0.98, 2.61) |
| No | 338 | 3,432 | 2.35 (1.89, 2.93) | 563 | 3,246 | 1.89 (1.59, 2.24) |
| PAD | | | | | | |
| Yes | 27 | 230 | 1.67 (0.68, 4.07) | 41 | 216 | 1.36 (0.67, 2.78) |
| No | 349 | 3,677 | 2.46 (1.98, 3.06) | 600 | 3,441 | 1.90 (1.61, 2.25) |
| MI | | | | | | |
| Yes | Too Few | | | Too Few | | |
| No | 371 | 3,843 | 2.44 (1.97, 3.02) | 632 | 3,590 | 1.89 (1.61, 2.22) |
| **Stroke** | | | | | | |
| Yes | <20 | 137 | 1.93 (0.44, 8.50) | 27 | 123 | 1.09 (0.47, 2.52) |
| No | <370 | 3,770 | 2.39 (1.93, 2.96) | 614 | 3,534 | 1.91 (1.62, 2.45) |
| **HbA1c*** | | | | | | |
| <5 | Too Few | | | Too Few | | |
| 5-7 | 44 | 739 | 2.54 (1.34, 4.81) | 106 | 634 | 1.71 (1.15, 2.55) |
| 8-9 | 129 | 1,284 | 2.22 (1.54, 3.20) | 204 | 1,114 | 1.70 (1.29, 2.26) |
| 9+ | 78 | 660 | 2.56 (1.59, 4.15) | 123 | 688 | 2.06 (1.37, 3.09) |

Notes: Models adjusted for baseline age, sex, race, micro- and macro-complications. Model stratifying by baseline HbA1c excludes individuals missing baseline HbA1c. PAD=peripheral artery disease; MI=myocardial infarction