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Ambient Heat and Risk of Serious Hypoglycemia in Older Adults With Diabetes Using Insulin in the U.S. and Taiwan: A Cross-National Case-Crossover Study

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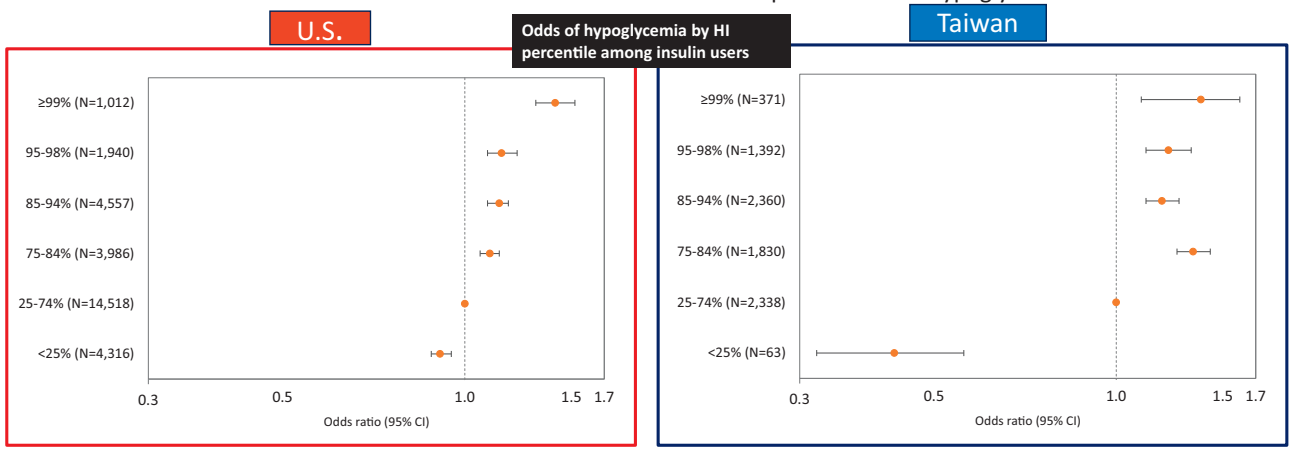
Higher ambient temperature was associated with increased hypoglycemia events in national samples of U.S. and Taiwan older adults using insulin.

Heat → cutaneous vasodilation → increased insulin absorption → risk of hypoglycemia



Study design: Retrospective, time-stratified, case-crossover study of adults ≥65 years using insulin during summer 2016-2019
Exposure: Heat index (HI), categorized into percentile categories (HI ≥99, 95-98, 85-94, 75-84, 25-74, <25th %tiles) based on ZIP code-level temp. distribution. HI incorporates both relative humidity and absolute temp. A HI of 90, for example, can refer to a temp of 84 F and 70% relative humidity
Outcome: Serious hypoglycemia (based on primary emergency department visit or hospitalization ICD-10 codes)

Patients & providers should be aware that extreme heat may increase risk of hypoglycemia in individuals using insulin

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Older adults with diabetes are vulnerable to extreme heat, but studies examining heat exposure in this population have been limited by ecological study designs and modest sample sizes.

- **What is the specific question we wanted to answer?**
  We measured the association between the heat index and risk of serious hypoglycemic events among older adults prescribed insulin therapy in the U.S. and Taiwan.

- **What did we find?**
  Adults aged ≥65 years using insulin had significantly increased risk of serious hypoglycemic events during periods of extreme heat exposure.

- **What are the implications of our findings?**
  Patients and providers should be aware that extreme heat may increase the risk of hypoglycemia in older adults using insulin, and appropriate precautions should be taken.

Ambient Heat and Risk of Serious Hypoglycemia in Older Adults With Diabetes Using Insulin in the U.S. and Taiwan: A Cross-National Case-Crossover Study

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BRIEF REPORT

OBJECTIVE

To measure the association between ambient heat and hypoglycemia-related emergency department visit or hospitalization in insulin users.

RESEARCH DESIGN AND METHODS

We identified cases of serious hypoglycemia among adults using insulin aged ≥65 in the U.S. (via Medicare Part A/B/D-eligible beneficiaries) and Taiwan (via National Health Insurance Database) from June to September, 2016–2019. We then estimated odds of hypoglycemia by heat index (HI) percentile categories using conditional logistic regression with a time-stratified case-crossover design.

RESULTS

Among ∼2 million insulin users in the U.S. (32,461 hypoglycemia case subjects), odds ratios of hypoglycemia for HI >99th, 95–98th, 85–94th, and 75–84th percentiles compared with the 25–74th percentile were 1.38 (95% CI, 1.28–1.48), 1.14 (1.08–1.20), 1.12 (1.08–1.17), and 1.09 (1.04–1.13) respectively. Overall patterns of associations were similar for insulin users in the Taiwan sample (∼283,000 insulin users, 10,162 hypoglycemia case subjects).

CONCLUSIONS

In two national samples of older insulin users, higher ambient temperature was associated with increased hypoglycemia risk.

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Older adults with diabetes are particularly vulnerable to extreme heat because their thermoregulatory response is often impaired (1,2). Heat can also induce changes in metabolism and hemodynamics that can lead to alterations in insulin sensitivity (2). We measured the association between the heat index (HI)—a combination of ambient temperature and humidity exposures— and the risk of serious hypoglycemic events among older adults prescribed insulin therapy in two nations with distinctly different climates: the U.S. and Taiwan.

RESEARCH DESIGN AND METHODS

For U.S. analyses, we used data for all U.S. Medicare Parts A/B/D-eligible beneficiaries linked to ambient temperature data from the Parameter-elevation Relationships on Independent Slopes (PRISM) model (3,4). The Taiwan analyses used data from the Taiwan National Health Insurance Database (NHID) linked to temperature data from the Atmospheric and Hydrological Research Database. The study periods for both countries were limited to warm-season months (1 June–30 September) from 2016 through 2019.

Our base study populations included unique patients *1*) aged 65–100 years, *2*) with at least 90 days of Part D eligibility or NHID eligibility during the study period, and *3*) at least one dispensing for insulin (including mixed products) during the 90 days of eligibility prior to the case day. We also defined mutually exclusive cohorts of sulfonylurea users (not concomitantly on insulin), defined as at least one prescription for an oral sulfonylurea medication up to 90 days prior to the index date, and a group of metformin users who were not prescribed any other diabetes medications during the Part D eligibility period (U.S. sample) and across all NHID eligibility (Taiwan cohort).

In each of the three cohorts for each country, we identified beneficiaries who developed serious hypoglycemia, defined as a primary emergency department (ED) visit or unplanned inpatient admission for hypoglycemia from 1 June through 30 September using a modified version of the ICD-10–based algorithm originally developed by Ginde et al. (5,6) (Supplementary Materials). Daily HI values were determined for all ZIP codes in the contiguous U.S. using the PRISM model estimates closest to a ZIP code's population centroid. These data were then linked to patient-level data by residential ZIP code (4,7). For the Taiwan sample, postal code-level HI data were linked to the NHID by postal code. We calculated the daily HI for each ZIP/postal code using a regression equation by Rothfusz (8). We determined HI percentile cut points for each ZIP code and day based on the historical distribution of HI in the ZIP code from 1981 through 2010 on the day ± 10 days (7,8). This distribution was then categorized into ≥99th, 95–98th, 85–94th, 75–84th, 25–74th, and <25th percentiles. Average HI in the ≥99th percentile by ZIP code is represented in Supplementary Fig. 1.

Covariates examined included demographic factors (age group, sex, race/ethnicity, climatic region), health care use factors (numbers of hospitalizations, medications, and ED or outpatient visits), comorbidities assessed from ICD-10 codes, and case-related covariates, including case month, year, and type of case (ED visit only vs. inpatient stay following ED admission).

We estimated the association between HI percentile and hypoglycemia among insulin users, sulfonylurea users, and metformin users using conditional logistic regression with a time-stratified case-crossover study design (9), for which we sampled up to five summer control days prior to the case day on the same day of the week within 5 weeks of the case date. We adjusted for time-varying factors (number of hospitalizations, ED visits, outpatient visits, and medications). We also conducted additional analyses stratified by case month and climatic region. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) with a two-sided statistical significance level of 0.05.

RESULTS

In the U.S. sample, among 22,693,486 Medicare beneficiaries, 2,032,759 had at least one insulin prescription (Table 1). Among insulin users, the incidence of hypoglycemic events was 25.6 per 1,000 person-years (Supplementary Fig. 2). The Taiwan NHID covers 4 million older adults, of whom 282,716 had at least one insulin prescription in 2016–2019. Among insulin users, the incidence of serious hypoglycemia was 17.3 per 1,000 person-years (Supplementary Fig. 2). Insulin users in both countries had a high prevalence of cardiometabolic comorbidities, including >30% with diabetes complications (Supplementary Fig. 3). Insulin users had a higher incidence of hypoglycemia than users of metformin (U.S.: 1.5, Taiwan: 4.7 per 1,000 person-years) and sulfonylureas (U.S.: 11.2, Taiwan: 8.3 per 1,000 person-years). Taiwanese patients overall had lower proportions of comorbidities than U.S. patients and were more likely to experience an inpatient hospitalization (Tables 1 and 2).

The risk of a serious hypoglycemic event among insulin users was ∼40% higher on days with a HI ≥99th percentile compared with the 25–74th percentile (unadjusted odds ratio [OR], 1.38 [95% CI 1.28–1.48] for U.S. and 1.40 [1.21–1.62] for Taiwan). These findings remained largely consistent after adjustment for time-varying confounders (Fig. 1 and Supplementary Table 1). Conversely, HI <25th percentile was associated with a lower risk of hypoglycemia (Fig. 1). Among U.S. beneficiaries, adjusted associations were stronger in September than in other summer months (Supplementary Table 2). Among U.S. beneficiaries using only long-acting insulin and among patients with type 1 diabetes, associations were similar to patterns seen in all insulin users (Supplementary Tables 3 and 4). Changing exposure to maximum temperature rather than HI also did not impact risk estimates (Supplementary Table 5). We did not observe substantial differences in overall risk of hypoglycemic events by climatic region (Supplementary Table 6).

Among 92,742 beneficiaries using sulfonylureas only, the unadjusted odds of a serious hypoglycemic event were 38% higher on days with a HI ≥99th percentile compared with a HI in the 25–74th percentile (OR 1.38 [95% CI 1.28–1.53]) for the U.S. (Fig. 2). These significant positive associations and the pattern of increasing risk with a higher HI seen in the U.S. were not seen among case subjects using only metformin (Fig. 2).

CONCLUSIONS

In this study of a large population of adults aged ≥65 years in the U.S. and Taiwan with diabetes using insulin, exposure to a higher HI was associated with increased risk of serious hypoglycemic events. Although sulfonylurea users demonstrated similar increases in risk, metformin users had no significantly increased risk of serious hypoglycemia.

Only a handful of studies—mostly ecological or of limited sample size—have investigated ambient temperature and hypoglycemia (10–12). A small single-center study in Germany (10) assessed the risk of hypoglycemia among patients seen by emergency medical personnel throughout the year and found that hypoglycemia risk was 15–18% higher at temperatures >20°C and <10°C compared

Table 1—Baseline characteristics of insulin users experiencing hypoglycemia and overall insulin user populations

	U.S.		Taiwan	
	Hypoglycemia case subjects *n* = 32,461	All insulin users *n* = 2,032,759	Hypoglycemia case subjects *n* = 10,162	All insulin users *n* = 282,716
Age, years				
65–74	17,088 (53)	1,232,122 (60)	4,707 (46)	143,094 (51)
75–84	11,412 (35)	590,580 (29)	4,057 (40)	94,210 (33)
≥85	3,961 (12)	210,057 (10)	1,398 (14)	45,412 (16)
Female sex	19,147 (59)	1,100,891 (54)	5,564 (55)	149,112 (53)
Race/ethnicity				
White	23,382 (72)	1,559,382 (77)	NA	NA
Black	6,368 (20)	278,943 (14)	NA	NA
Other	469 (1)	37,665 (2)	NA	NA
Asian	728 (2)	57,967 (3)	NA	NA
Hispanic	1,208 (4)	81,376 (4)	NA	NA
Native American	306 (1)	17,426 (1)	NA	NA
Comorbidities (*n* = 20,053)*				
Type 2 diabetes	19,526 (97)	1,171,517 (92)	9,747 (96)	247,970 (88)
Type 1 diabetes	5,166 (25)	261,808 (21)	282 (3)	4,626 (2)
Acute renal disease	5,107 (25)	183,301 (14)	338 (3)	9,507 (3)
Atrial fibrillation	4,745 (24)	222,206 (18)	367 (4)	12,969 (5)
Alcohol use disorder	365 (2)	16,870 (1)	66 (0.6)	1,575 (0.6)
Anemias	8,841 (44)	415,233 (33)	1,073 (11)	28,239 (10)
Stable angina	2,016 (10)	100,722 (8)	703 (7)	17,750 (6)
Unstable angina	1,314 (7)	56,507 (4)	312 (3)	8,030 (3)
Anxiety	3,602 (18)	187,422 (14)	932 (9)	24,246 (9)
Acute mental disorder	8,873 (44)	428,861 (34)	3,139 (31)	79,305 (28)
Asthma	1,703 (9)	105,822 (8)	720 (7)	19,736 (7)
Bipolar disorder	605 (3)	26,954 (2)	61 (0.6)	1,735 (0.6)
Cancer	6,436 (32)	373,752 (29)	1,026 (10)	29,321 (10)
Cardiac conduction disorder	2,699 (13)	113,603 (9)	54 (0.5)	1,703 (0.6)
Cardiomyopathy	1,832 (9)	74,868 (6)	26 (0.3)	735 (0.3)
Chronic kidney disease	9,081 (45)	395,917 (31)	2,664 (26)	61,670 (22)
Chronic obstructive pulmonary disease	4,795 (24)	231,338 (18)	954 (9)	30,941 (11)
Other cerebrovascular disease	2,021 (10)	81,135 (6)	684 (7)	20,114 (7)
Dementia	5,169 (25)	201,676 (16)	1,335 (13)	36,976 (13)
Depression	3,844 (19)	206,624 (16)	593 (6)	14,590 (5)
Diabetes with				
Peripheral circulatory disorder	4,988 (25)	215,747 (17)	433 (4)	8,466 (3)
Nephropathy	8,324 (42)	341,188 (27)	3,946 (39)	86,219 (31)
Neuropathy	8,918 (44)	447,668 (35)	1,533 (15)	30,311 (11)
Retinopathy	5,847 (29)	290,939 (23)	1,241 (12)	29,466 (10)
Other dysrhythmia	7,286 (36)	336,617 (26)	790 (8)	27,334 (10)
Edema	5,789 (29)	254,162 (20)	957 (9)	21,251 (8)
Electrolyte disorder	8,214 (41)	342,542 (27)	1,059 (10)	34,482 (12)
Epilepsy	639 (3.2)	28,653 (2)	89 (0.9)	3,864 (1)
Heart failure	7,247 (36)	301,441 (24)	1,454 (14)	38,850 (14)
Hypertension	18,508 (92)	1,084,421 (85)	7,680 (76)	204,121 (72)
Hypothyroidism	5,916 (29)	315,933 (25)	130 (1)	4,014 (1)
Dyslipidemia	15,244 (76)	937,141 (74)	4,851 (48)	131,619 (47)
Liver disease	2,123 (11)	108,632 (9)	1,228 (12)	38,668 (14)
Myocardial infarction	1,434 (7)	53,703 (4)	235 (2)	7,000 (3)
Obesity	5,431 (27)	346,227 (27)	36 (0.4)	1,051 (0.4)
Obstructive sleep apnea	2,807 (14)	175,575 (14)	5 (0)	252 (0.1)
Osteoarthritis	4,337 (22)	256,871 (20)	2,582 (25)	61,112 (22)
Peripheral vascular disease	5,335 (27)	262,199 (21)	460 (5)	9,988 (4)
Other ischemic heart disease	9,400 (47)	476,020 (37)	2,023 (20)	52,917 (19)
Renal insufficiency	5,407 (27)	234,918 (18)	1,639 (16)	43,433 (15)
Smoking	3,526 (18)	211,812 (17)	89 (0.9)	2,707 (1)
Ischemic stroke	4,394 (22)	195,887 (15)	1,475 (15)	38,801 (14)
Transient ischemic attack	1,218 (6)	46,412 (4)	353 (4)	8,144 (3)

Data are presented as *n* (%). NA, not applicable. *Comorbidities were determined in a subset of case subjects with at least 1 year Part A/B/D eligibility in order to more sensitively estimate prevalence.

Table 2—Hypoglycemia event characteristics among insulin users experiencing hypoglycemia

	U.S.		Taiwan	
	No.	Percent	No.	Percent
Total	32,461		10,162	
Visit type				
ED only	25,326	76	6,829	67
Inpatient hospitalization	7,135	22	3,333	33
Primary diagnosis				
E09.649	188	0.6	4	0.04
E10.649	1,597	5	10	0.1
E11.641	306	0.9	914	9
E11.649	25,174	78	1,658	16
E13.649	143	0.4	18	0.2
E16.0	322	1	128	1
E16.2	2,259	7	5,598	55
T38.3X1A	2,011	6	43	0.4
T38.3X5A	209	0.6	137	1
Others	252	0.8	1,823	18
Case month				
June	8,362	26	2,698	27
July	8,244	25	2,627	26
August	8,141	25	2,595	26
September	7,714	24	2,242	22
Case year				
2016	9,586	30	2,413	24
2017	8,604	27	2,588	26
2018	7,368	23	2,444	24
2019	6,903	21	2,717	27

with 10–20°C, whereas an ecological study in Taiwan (11) assessing correlations between monthly average ambient temperatures and hypoglycemia ED visits showed higher rates of serious hypoglycemia during winter months compared with summer months; however, within the summer months, higher temperatures were associated with greater monthly incidence of hypoglycemia, which is in line with our findings.

Physiologically, high temperatures, in a fashion akin to exercise, can increase peripheral and cutaneous vasodilation and insulin sensitivity (13). The combination of vasodilation, which can increase insulin delivery to peripheral tissues, and insulin sensitivity can result in significant drops in plasma glucose. The paradoxical increases in risk of hypoglycemia at colder temperatures in prior studies may be in part due to *1*) increases in metabolic rate in cold temperatures consuming glucose, *2*) reactive hypoglycemia after a stress/shiver response, or *3*) changes in exogenous insulin absorption at colder temperatures.

Our study had several peculiar findings, most notably, the marked differences in risk of hypoglycemia by summer month, especially in September. We speculate that the higher risk in September in the U.S. is in part due to overall cooler, average temperatures decreasing physiological and behavioral preparedness for extreme heat (13). We speculate that Taiwan's higher risk in June/July may be in part due to decreased humidity and rainfall in August and September and greater adaptability to high temperatures.

Our study has several limitations. Individuals with hypoglycemia were older, more frequently non-Hispanic Black in the U.S, and had more comorbidities than those without hypoglycemia. Since we used a case-only design, caution should be exercised in generalizing our results to broader populations and mild/moderate hypoglycemia that may be asymptomatic. We were unable to capture sociobehavioral variables, such as outdoor activity, exercise, and diet, or changes in these variables and insulin dosing from control to case days, all of which can alter the risk of serious hypoglycemia. Furthermore, although the risk of exposure misclassification due to our short study period is low, there may still be differential misclassification of insulin use (e.g., a single dispensing may not reflect adherence or medication use across all 90 days of eligibility).

Our study also has several strengths. We conducted a patient-level analysis

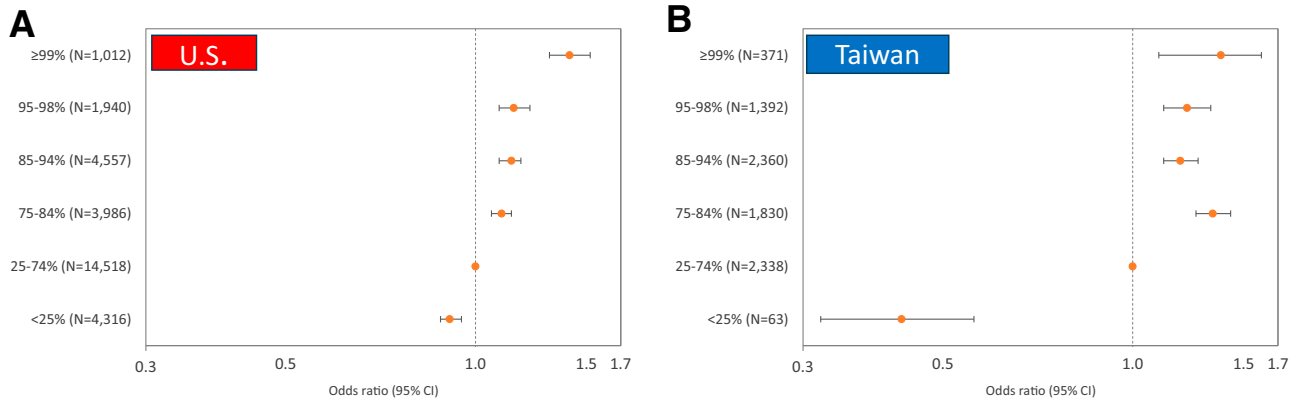

Figure 1—The odds of hypoglycemia among insulin users are presented by percentile category of heat exposure, relative to the 25th to 74th percentile HI in the U.S. (*A*) and Taiwan (*B*). ORs are adjusted for the number of inpatient hospitalizations, ED visits, outpatient visits, and medications in the 5-week span during which the case day and up to 5 preceding control days were sampled.

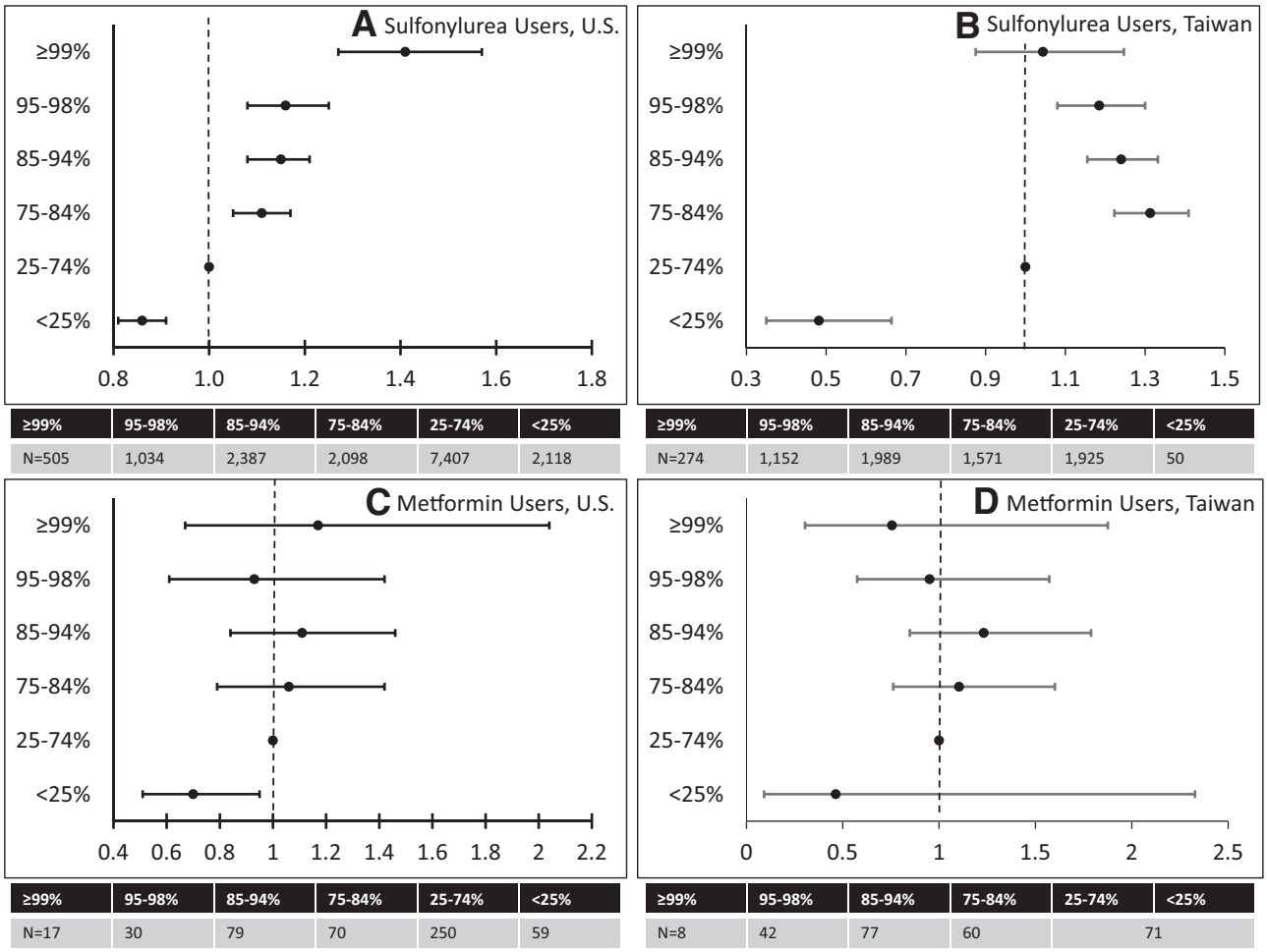

Figure 2—The odds of hypoglycemia are shown by category of HI exposure by percentile (P) among sulfonylurea users in the U.S. (*A*) and Taiwan (*B*) and metformin users in the U.S. (*C*) and Taiwan (*D*). Metformin users were restricted to those using only metformin and no other antidiabetes medications. Sulfonylurea users were restricted to those who did not concurrently use insulin (but could have used other medications such as metformin).

using two large, national samples and incorporating medication use, which has not been addressed previously. We also matched on all measured and unmeasured time-invariant covariates using the case-crossover design.

Our finding of elevated risk of hypoglycemia-related ED visits in older adults using insulin and exposed to extreme heat underscores the need for patients and providers to be aware and cautious that extreme heat may increase the risk of hypoglycemia. Future studies should incorporate individual-level glucose data (e.g., continuous glucose monitoring) and temperature data to additionally understand the relationship between climate and mild-to-moderate hypoglycemia.

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Author Contributions. A.V. and S.S. designed the study, conducted data analysis, and drafted the manuscript. S.-P.H. and P.G. curated data and conducted data analysis. C.-C.S. contributed to data acquisition. D.R. and C.-Y.L. contributed to study design and supervision. J.R., B.B., A.P., and M.R. contributed to project administration and supervision. R.N. contributed to funding acquisition, study methodology, and supervision. K.J. contributed to study methodology and project resources. A.K.G. and Y.-H.K.Y. provided project supervision. S.S. acquired funding for the study and contributed to study methodology. All authors contributed to writing, reviewing, and editing the article and approved the final version of the manuscript. Y.-H.K.Y. and S.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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