SUPPLEMENT

Table of Contents

Supplemental Table 1. Baseline* characteristics of persons with type 2 diabetes

Panel A. Among N = 713,464 persons with exposure to the antidiabetes prescription drugs of interest

	N (%**)
DEMOGRAPHICS	
Age in years, median | 25th, 75th percentiles	60.7 (48.8-71.5)
Sex, female	413,199 (59.2%)
Race/ethnicity	
White	246,488 (34.5%)
Black or African American	108,046 (15.1%)
Hispanic/Latino	158,256 (22.2%)
Asian	54,675 (7.7%)
Other/unknown	145,999 (20.5%)
State of residence	
California	302,080 (42.3%)
Florida	98,581 (13.8%)
New York	207,968 (29.1%)
Ohio	53,567 (7.5%)
Pennsylvania	51,268 (7.2%)
MEASURES OF INTENSITY OF HEALTHCARE USE	
Number of prescriptions dispensed, median | 25th, 75th percentiles	6.0 (0.0-24.0)
Number of outpatient diagnosis codes, median | 25th, 75th percentiles	6.0 (3.0-19.0)
Number of inpatient diagnosis codes, median | 25th, 75th percentiles	0.0 (0.0-0.0)
COMORBIDITIES†	
Circulatory system disorder (ICD-CM: 390–459)	89,782 (12.6%)
Digestive system disorder (ICD-CM: 520–579)	16,394 (2.3%)
Genitourinary system disorder (ICD-CM: 580–629)	21,167 (3.0%)
Infectious and parasitic disease (ICD-CM: 001–139)	18,395 (2.6%)
Mental, behavioral, or neurodevelopmental disorder (ICD-CM: 290–319)	44,056 (6.2%)
Neoplasm (ICD-CM: 140–239)	14,067 (2.0%)
Nervous system or sense organ disorder (ICD-CM: 320–389)	43,733 (6.1%)
Respiratory system disorder (ICD-CM: 460–519)	32,659 (4.6%)

ICD-CM = International Classification of Diseases, 9th Revision, Clinical Modification

* Demographics assessed on date of cohort entry. Measures of intensity of healthcare use and comorbidities assessed in the 364 days preceding and on the date of cohort entry.

** Unless otherwise noted

† Determined by presence of ≥1 International Classification of Diseases 9th Revision Clinical Modification code in any position on any claim type.

Panel B. Among the included subset of persons in Panel A with complete data on sex and date of birth (N = 697,678) vs. the excluded subset of persons in Panel A with missing sex or date of birth (N = 15,786)

	Included	Excluded	
	N (%**)	N (%**)	Standardized difference
DEMOGRAPHICS			
Age in years, median | 25th, 75th percentiles	60.7 (48.8-71.5)	67.0 (60.7-78.7)	0.58
Sex, female	413,197 (59.2%)	††	0.19
Race/ethnicity			2.92
White	246,488 (35.3%)	0 (0.0%)	
Black or African American	108,046 (15.5%)	0 (0.0%)	
Hispanic/Latino	158,255 (22.7%)	††	
Asian	54,675 (7.8%)	0 (0.0%)	
Other/unknown	130,214 (18.7%)	15,785 (100.0%)	
State of residence			0.60

California	299,266 (42.9%)	2,814 (17.8%)	
Florida	95,214 (13.6%)	3,367 (21.3%)	
New York	200,561 (28.7%)	7,407 (46.9%)	
Ohio	52,617 (7.5%)	950 (6.0%)	
Pennsylvania	50,020 (7.2%)	1,248 (7.9%)	
MEASURES OF INTENSITY OF HEALTHCARE USE			
Number of prescriptions dispensed, median | 25th, 75th percentiles	6.0 (0.0-24.0)	6.0 (0.0-22.0)	0.05
Number of outpatient diagnosis codes, median | 25th, 75th percentiles	6.0 (3.0-19.0)	5.0 (2.0-15.0)	0.05
Number of inpatient diagnosis codes, median | 25th, 75th percentiles	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.00
COMORBIDITIES†			
Circulatory system disorder (ICD-CM: 390–459)	87,606 (12.6%)	2,176 (13.8%)	0.04
Digestive system disorder (ICD-CM: 520–579)	16,051 (2.3%)	343 (2.2%)	0.01
Genitourinary system disorder (ICD-CM: 580–629)	20,769 (3.0%)	398 (2.5%)	0.03
Infectious and parasitic disease (ICD-CM: 001–139)	18,021 (2.6%)	374 (2.4%)	0.01
Mental, behavioral, or neurodevelopmental disorder (ICD-CM: 290–319)	42,980 (6.2%)	1,076 (6.8%)	0.03
Neoplasm (ICD-CM: 140–239)	13,807 (2.0%)	260 (1.6%)	0.02
Nervous system or sense organ disorder (ICD-CM: 320–389)	42,728 (6.1%)	1,005 (6.4%)	0.01
Respiratory system disorder (ICD-CM: 460–519)	32,018 (4.6%)	641 (4.1%)	0.03

ICD-CM = International Classification of Diseases, 9th Revision, Clinical Modification

* Demographics assessed on date of cohort entry. Measures of intensity of healthcare use and comorbidities assessed in the 364 days preceding and on the date of cohort entry.

** Unless otherwise noted

† Determined by presence of ≥1 International Classification of Diseases 9th Revision Clinical Modification code in any position on any claim type.

†† Suppressed in accordance with the Centers for Medicare and Medicaid Services cell suppression policy (HHS-0938-2020-F-7420)

Supplemental Table 2. Outcome counts and occurrence rates without regard to maximum ambient temperature exposure, by antidiabetes drugs forming the sub-cohorts of interest

		Serious hypoglycemia*		**Diabetic ketoacidosis**		**Sudden cardiac arrest / ventricular arrhythmia**	
Antidiabetes Class	Antidiabetes Agent	Outcomes, n	Rate**, per 1,000 p-y	Outcomes, n	Rate**, per 1,000 p-y	Outcomes, n	Rate**, per 1,000 p-y
Sulfonylureas	glimepiride	4,900	25.1	NA	NA	749	3.8
	glipizide	11,465	25.0	NA	NA	2,156	4.4
	glyburide	15,487	28.7	NA	NA	2,059	3.6
	overall	**31,852**	**26.8**	NA	NA	**4,964**	**4.0**
Meglitinides	nateglinide	NA	NA	NA	NA	136	6.3
	repaglinide	NA	NA	NA	NA	163	6.3
	overall	NA	NA	NA	NA	**299**	**5.9**
DPP-4is	saxagliptin	NA	NA	not estimable	not estimable	†	4.4
	sitagliptin	NA	NA	64	0.6	284	2.8
	overall	NA	NA	**65**	**0.6**	†	**2.8**
GLP1RAs	exenatide	NA	NA	13	0.9	19	1.4
	liraglutide	NA	NA	not estimable	not estimable	†	2.8
	overall	NA	NA	**13**	**0.8**	†	**1.4**

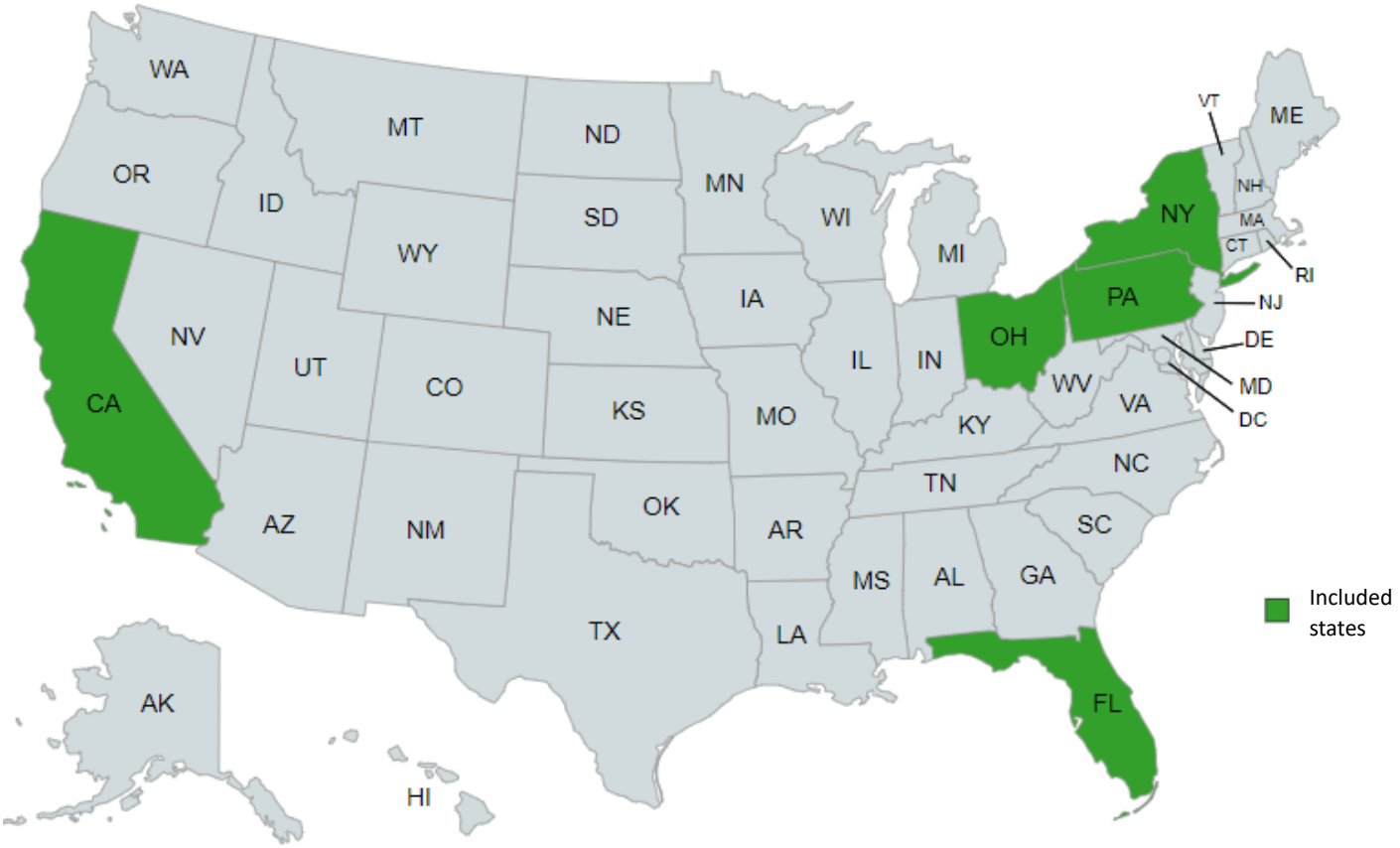
* The preplanned sensitivity analysis excluding follow-up time upon initiation of insulin included the study of 3,899, 9,374, and 13,405 outcomes and had occurrence rates of 22.4, 23.9, and 26.8 per 1,000 p-y for glimepiride, glipizide, and glyburide respectively

** Age and sex adjusted occurrence rates; obtained from generalized estimating equation Poisson regression models and estimated at the mean age and sex. Rates were calculated as outcomes occurring during person-days exposed to the antidiabetes drug/class of interest. Please note that the sudden cardiac arrest / ventricular arrhythmia occurrence rate for liraglutide is not adjusted for age and sex, as such a model failed to converge.

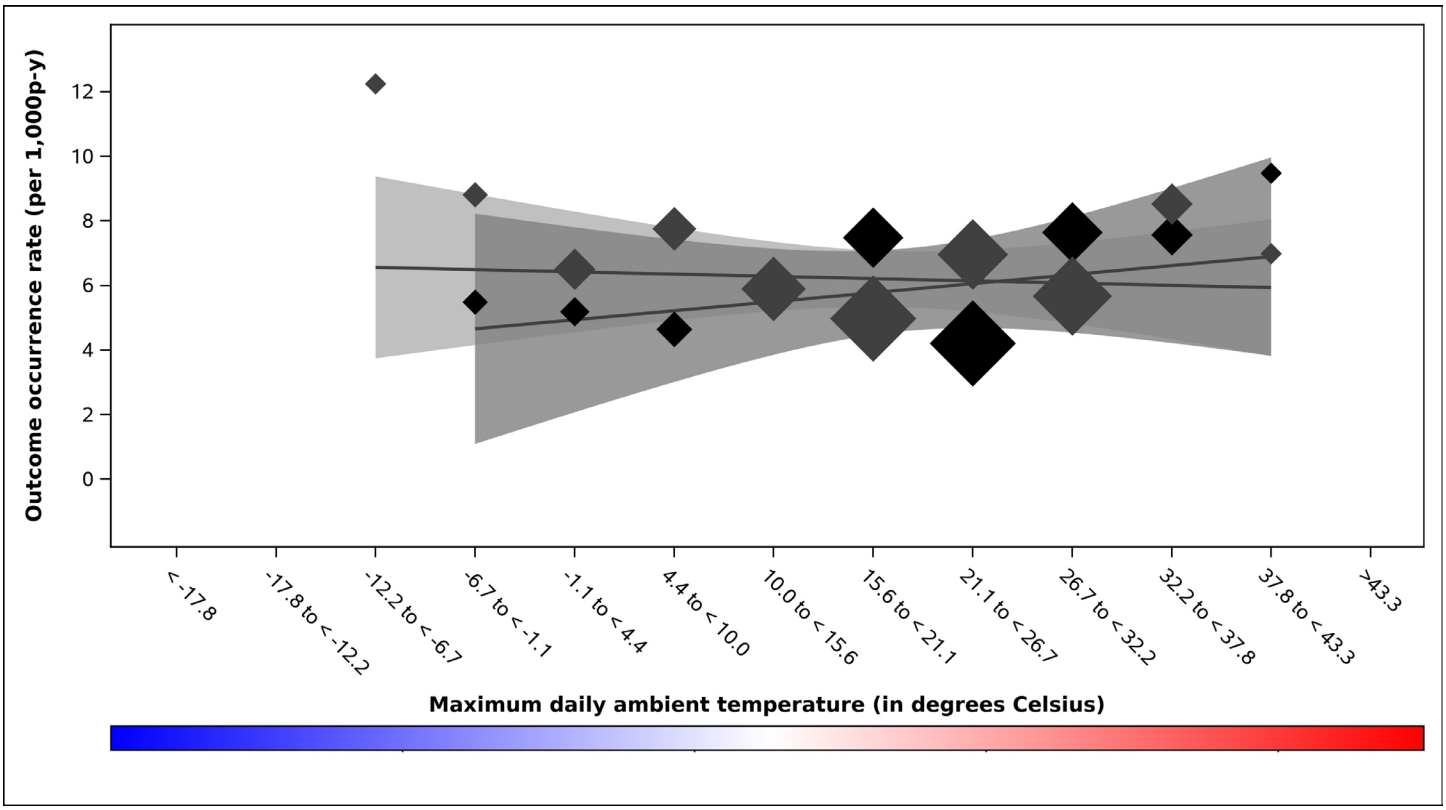
† Cell count <11 or would enable back-calculation of a cell <11, therefore value suppressed to comply with the US Department of Health and Human Services *CMS Cell Suppression Policy* (HHS-0938-2020-F-7420)

DPP-4is = dipeptidyl peptidase-4 inhibitors; GLP1RAs = glucagonlike peptide 1 receptor agonists; NA = not applicable, i.e., drug-class-outcome pair was not prespecified as 'of interest'; p-y = person years

Supplemental Figure 1. US states from which Medicaid data was eligible for study inclusion.



Supplemental Figure 2. Sudden cardiac arrest / ventricular arrhythmia occurrence rates by prespecified strata of maximum daily ambient temperature, in degrees Celsius, among meglitinide users enrolled in five US state Medicaid programs.



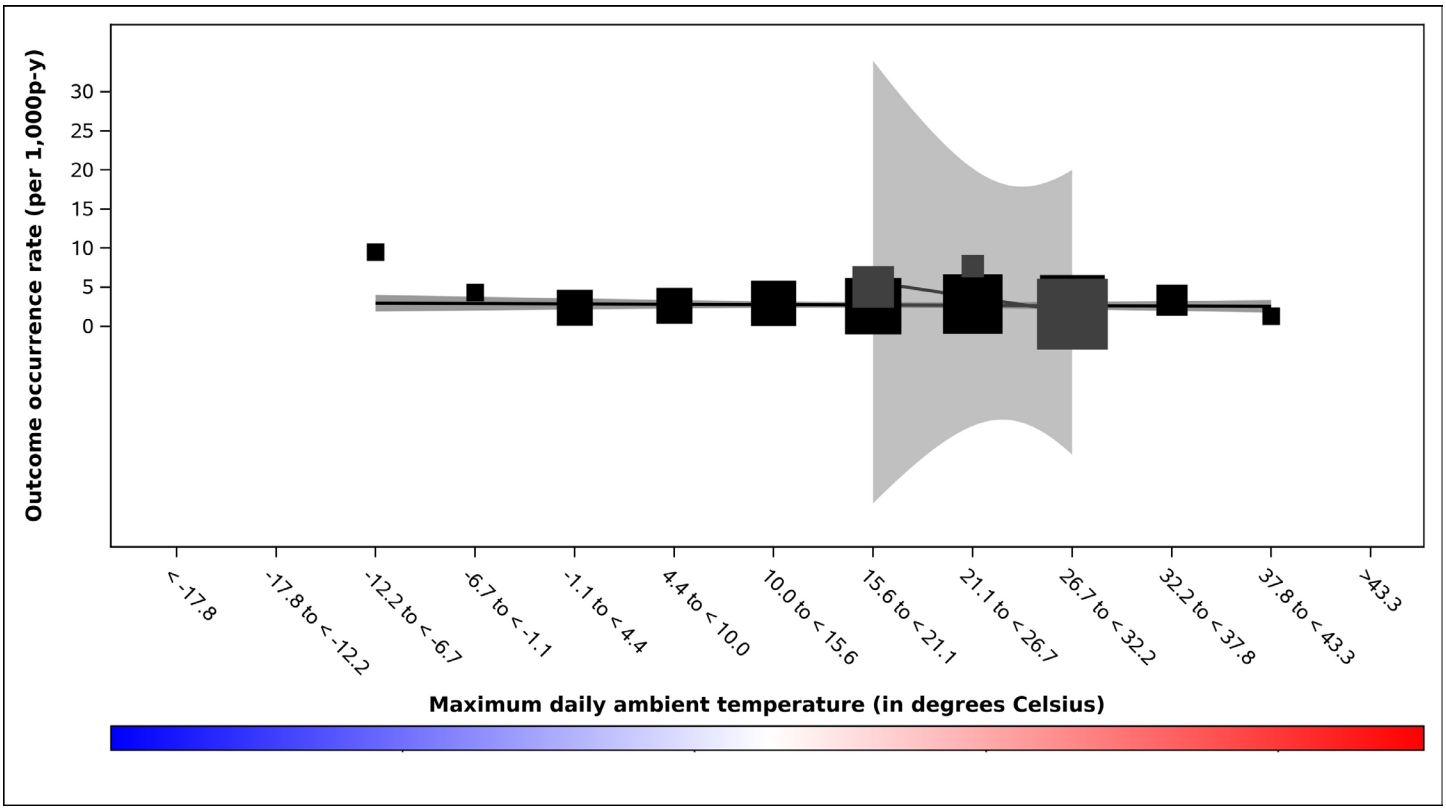
Occurrence rates (i.e., outcomes among exposed person-days) for meglitinides are represented by diamonds. We scaled the size of each data point to reflect its weight, using the inverse of the variance estimate.

Black-to-gray tones distinguish meglitinides. Black diamonds = nateglinide. Dark gray diamonds = repaglinide. Corresponding 95% confidence bands are dark gray and light gray, respectively.

P-values for **quadratic terms** for maximum daily ambient temperature were 0.715 and 0.313 for nateglinide and repaglinide, respectively. P-values for **linear terms** for maximum daily ambient temperature were 0.313 and 0.914 for nateglinide and repaglinide, respectively; Wald test for **interaction** among these meglitinides: p = 0.410.

P-y: person-years.

Supplemental Figure 3. Sudden cardiac arrest / ventricular arrhythmia occurrence rates by prespecified strata of maximum daily ambient temperature, in degrees Celsius, among dipeptidyl peptidase-4 inhibitor users enrolled in five US state Medicaid programs.



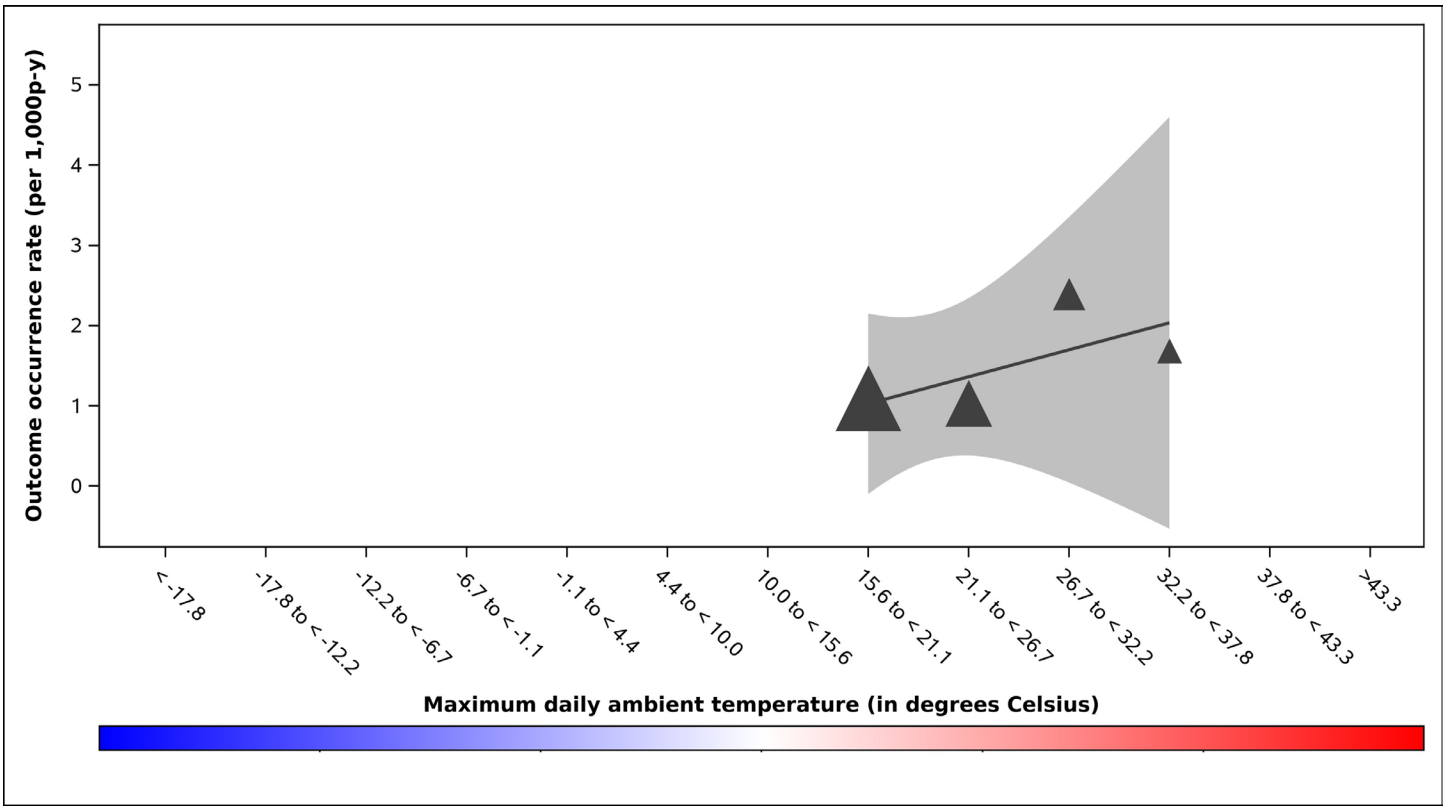
Occurrence rates (i.e., outcomes among exposed person-days) for dipeptidyl peptidase-4 inhibitors are represented by squares. We scaled the size of each data point to reflect its weight, using the inverse of the variance estimate.

Black-to-gray tones distinguish dipeptidyl peptidase-4 inhibitor. Black squares = sitagliptin. Dark gray squares = saxagliptin. Corresponding 95% confidence bands are dark gray and light gray, respectively.

P-values for **quadratic terms** for maximum daily ambient temperature were 0.362 and 0.856 for sitagliptin and saxagliptin, respectively. P-values for **linear terms** for maximum daily ambient temperature were 0.366 and 0.521 for sitagliptin and saxagliptin, respectively; Wald test for **interaction** among these dipeptidyl peptidase-4 inhibitors: p = 0.438.

P-y: person-years.

Supplemental Figure 4. Sudden cardiac arrest / ventricular arrhythmia occurrence rates by prespecified strata of maximum daily ambient temperature, in degrees Celsius, among exenatide (GLP1RA) users enrolled in five US state Medicaid programs.



Occurrence rates (i.e., outcomes among exposed person-days) for exenatide (a glucagonlike peptide 1 receptor agonist) are represented by triangles. We scaled the size of each data point to reflect its weight, using the inverse of the variance estimate.

P-value for **quadratic term** for maximum daily ambient temperature was 0.909. P-value for **linear term** for maximum daily ambient temperature was 0.074.

P-y: person-years.