**Protocol Title:** Association between extreme temperature and heat-related outcomes among people with mental conditions

**Introduction**

Climate change is a global issue that has led to increased occurrences of extreme heat temperatures in many countries. Heatwaves occur more frequent and last longer in recent years. Current evidence suggests that high ambient temperature increases the risk of heat-related mortality.1 Previous studies have also shown that heatstroke poses negative effects on both central nervous system and cardiovascular system, including increased risk of delirium and myocardial infarction.1-4 It was also shown that increasing temperature would increase the risk of mental health hospitalisation in people with mental conditions.5 6 Additionally, with aging populations in high-income countries and rapid urbanisation in low-income nations, the health consequences of hot weather are emerging as a significant global public health challenge for the 21st century.7

Individuals with psychiatric disorders often require psychotropic medications. Certain psychotropic medications can interfere with normal thermoregulatory functions, thereby increasing the risk of heat-related health issues.1 8 The use of antipsychotics was reported to be associated with an increased risk of hyperthermia or heat stroke during heatwaves, particularly among the elderly.9 It was also shown that antipsychotics could lead to more hospitalisations related to heat, even outside of heatwave periods.10 Existing studies have primarily focused on older individuals and the overall effect of psychotropics, and the associations for specific psychotropics have not been systematically investigated. Given that studies showed that heatwave was associated with mental health hospitalisation in people with mental conditions, current studies have not investigated whether there was synergistic harmful effect of psychotropics in people with underlying mental illness.

Electronic health insurance claims records contain valuable clinical data that can be utilised to address this question. In this study, we will use readily available electronic records from Japan, linked with publicly available meteorological data, including daily temperature. We will employ self-controlled case series (SCCS) and case-crossover study designs to examine the associations between extreme heat and heat-related clinical outcomes among individuals undergoing psychotropic treatment with mental conditions. In the SCCS, we will compare, within individuals, risk of heat-related clinical outcomes (i.e., disorders of fluid electrolyte and acid-base balance, and heatstroke; myocardial infarction; delirium) in periods of extreme heat compared to baseline time. This will allow us to establish whether and how extreme heat temperatures affect the effects of psychiatric illness and/or psychotropic medications on heat-related clinical outcomes.

**Aim and objectives**

***Aim***

To examine the associations between heatwave and heat related-illness, myocardial infarction, and delirium among individuals with mental conditions.

***Objectives***

1. to determine the associations between heatwave and (a) heat related-illness, (b) myocardial infarction, and (c) delirium among people with mental conditions

2. to identify people with mental conditions at high risk of (a) heat related-illness, (b) myocardial infarction, and (c) delirium according to age, sex, and concurrent use of psychotropic medications.

3. to determine the associations between heatwaves and (a) heat related-illness, (b) myocardial infarction, and (c) delirium among people with/without being prescribed antipsychotics and antidepressants respectively; and how these associations differ between individual antipsychotics and antidepressants among people with mental conditions.

**Methods**

***Data source***

We will use Japanese claim data of Ibaraki prefecture. With the Japanese health insurance system11, there is a mandatory insurance coverage under three insurance programs based on the enrollee’s employment status, age, and residence: 1) employer-based health insurance (for individuals aged <75 years with regular employment and their dependents), 2) municipally administered National Health Insurance (for individuals aged <75 years without regular employment), and 3) Late Elders’ Health Insurance (for individuals aged 75 years or older and individuals aged 65–74 years with a certified disability). The benefits and co-payments remain consistent across all programs. We used claims data between 1/1/2014 and 31/12/2021 from the National Health Insurance and Late Elders’ Health Insurance in Ibaraki prefecture. The claims data contains records of approximately 2 million people including demographics, prescriptions, and diagnoses from primary and secondary care settings in Ibaraki prefecture, Japan. We will use publicly available meteorological data in Japan from Japan Meteorological Agency (https://www.data.jma.go.jp/risk/obsdl/index.php) to determine the daily mean temperature during the study period (1/1/2014-31/12/2021). It has been used to study the risk of mortality in people with mental conditions.12

***Study population***

People with severe mental illness, and depression.

***Descriptive analyses***

We will report the crude incidence of outcomes of interest among those with mental conditions, and those with psychotropic medication.

***Study design***

The SCCS method was developed to eliminate time-invariant confounding among participants as it compares the incidence rates during pre-defined risk periods with a baseline period within the same individual.13 We will also use case-crossover study design to compare the SCCS findings. Case-crossover study design is also a within-person study design by compare the odds of exposure in the pre-defined hazard periods with the control periods within an individual.14

***Outcome***

We will identify delirium, myocardial infarction and heat-related illness (including disorders of fluid electrolyte and acid-base balance, and heatstroke) using International Classification of Diseases 10th Revision-10 during the study period. We allow multiple event occurrence for each outcome. We will define incident event for each outcome as at least 30 days apart between diagnoses (on separate days).

***Planned analyses***

*Prescribing trend of psychotropics*

We will present the annual prescribing trend of patients receiving psychotropic drugs by drug class and drug substance and undertake descriptive analyses for age, sex, and region in Ibaraki prefecture. We will also report the seasonal prescribing trend of psychotropic prescriptions. Clinical and prescribing details including their co-morbidities (ischaemic heart disease, cerebrovascular disease, diabetes, heart failure, cancer, venous thromboembolism, hypertension, schizophrenia, depression, bipolar disorder, chronic obstructive pulmonary disease, chronic renal disease) and within 90 days of co-prescribed medications (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta-blockers, diuretics, oral anticoagulants, statins, antibiotics, proton pump inhibitors) before the first psychotropic drug will also be reported.

*Linked meteorological data*

A total of 44 municipalities are geographically located in 5 major regions of Ibaraki prefecture. We will link the data on mean daily temperatures of 6 municipalities available from Japan Meteorological Agency to individual data by city code. We will select 6 municipalities including Kitaibaraki, Hitachi, Mito, Kashima, Tsukuba, Shimotsuma which are geographical centre of the 5 major regions in Ibaraki prefecture. Notably, the landscape of Kitaibaraki is different from other municipalities in the northern part (80% area is made up of mountains and wilderness). Therefore, unlike other four major regions, two municipalities (Kitaibaraki & Hitachi) will be selected in the northern part of Ibaraki.

*Self-controlled case series*

We will include people with a diagnosis of mental conditions (including severe mental illness and depression) and ever had their outcome of interest during the study period. Observation period will start from the latest of people entering the database, the first diagnosis of mental conditions, study start date (1/1/2014), until the earliest of patient death, leaving the database, and study end date (31/12/2021). We will then stratify the person-time by taking psychotropics or not (Figure 1) . This would allow us to estimate the risk of outcomes in people taking psychotropics and those without taking psychotropics. Where there were treatment breaks of ≤30 days, patients were assumed to be exposed to psychotropic drugs continuously, accounting for any potential medication stockpiling and non-adherence. Using the meteorological data, we will define extreme temperature (i.e. heatwave) as at least 2 consecutive days with daily mean temperature exceeding 95% percentile of that particular year-round.15 Within the observation period, we will divide the observation period as 5-day pre-exposure period, heatwave exposure period, and 5-day post-exposure period and all other periods (baseline). We will report the number of events and person-time in each specified period. We chose to add these pre- and post-exposure periods as this can detect if there is any difference in risk in the lead up to a heatwave and shortly after the heatwave. The incidence rate ratio (IRR) of each outcome will be estimated by comparing the incidence of each outcome between pre-exposure/exposure/post-exposure period with baseline period using conditional Poisson regression. We will further control for time-varying confounders by adjusting for seasonal effect and age. We will introduce the product term of heatwave exposure and taking psychotropics as the interaction in the regression to estimate the IRRs for each outcome associated with heatwave among people with and those without psychotropics respectively. We will separate the analyses by antipsychotics in people with severe mental illness and antidepressants in people with depression for each outcome. We will also repeat the analysis by stratifying on individual psychotropic medication. We will stratify psychotropics medications into the 5 most used antipsychotics and antidepressants respectively and all other individual psychotropics will be grouped as one category as “other psychotropics”. In this analysis, we will start the observation period from entering the database, diagnosis of mental condition, study start date, or start taking antipsychotics/antidepressants and end the observation period when they leave the database, study end date, and discontinuation of the treatment. We will also remove people who had psychotropic drug 180 days before their first prescription identified during the study period.

*Case-crossover study*

We will use case-crossover study design to compare the SCCS findings as triangulation (Figure 2). We will compare the odds of exposure (occurrence of heatwave) in the hazard period (defined as 5 days) on/prior to event date to the 5-day control period. We will also define 9-day washout period between hazard and control period so that the day of the week for the hazard period and control period can be matched. We will estimate the odds ratio for each outcome using conditional logistic regression.

***Subgroup analyses***

We will conduct subgroup analysis to study whether the associations differ by age group, sex, and concurrent use of psychotropic medications and will perform likelihood ratio test to investigate if the associations differ across subgroups.

***Sensitivity analysis***

To test the robustness of the outcome definition, we will identify first recorded delirium, myocardial infarction and heat-related illness during the study period. Second, we will exclude people who only had an inpatient record during the study period, that might indicate they were hospitalised for long time, therefore unlikely to be exposed to heatwave.

**Strength and limitations**

The utilisation of the SCCS and/or case-crossover study design in this study provides a robust method for mitigating time fixed confounding among individuals. Additionally, the extensive data available enables us to investigate the prescribing trends of psychotropics and explore potential effect modifications by the use of psychotropics and other subgroups including age, sex, and concurrent use of other psychotropics. However, it is important to acknowledge that the use of electronic records to identify drug exposure introduces the possibility of misclassification bias, as we cannot ascertain whether patients actually took the prescribed drugs. To minimise this bias, we will employ the assumption of continuous exposure for treatment breaks of ≤30 days. Further, as the data of their outdoor physical activity and the availability of air-conditioner at home is not available, misclassification of exposure to heatwave is possible. Due to the lack of temperature daily data on all municipalities and definition of heatwave, it could also lead to misclassification of exposure. Notably, we will add pre-exposure and post-exposure periods to test the robustness of the results. Moreover, as we used claims data to define outcome, there may be misclassification of outcome if the patient did not see the doctors for their condition. Notably, our study will capture outcome that are of more severe condition and thus are of clinical significance.

**Figure legend**

Figure 1. Illustration of self-controlled case series (SCCS)

A diagram of a patient's schedule

Description automatically generated

The upper panel illustrates the SCCS analysis for people with severe mental illness; while the lower panel illustrates the SCCS analysis for people with depression

Figure 2. Illustration of case-crossover study



**References**

1. Ban J, Xu D, He MZ, et al. The effect of high temperature on cause-specific mortality: A multi-county analysis in China. *Environ Int* 2017;106:19-26.

2. Ebi KL, Exuzides KA, Lau E, et al. Weather changes associated with hospitalizations for cardiovascular diseases and stroke in California, 1983-1998. *Int J Biometeorol* 2004;49(1):48-58.

3. Epstein Y, Yanovich R. Heatstroke. *N Engl J Med* 2019;380(25):2449-59.

4. Xu R, Huang S, Shi C, et al. Extreme Temperature Events, Fine Particulate Matter, and Myocardial Infarction Mortality. *Circulation* 2023;148(4):312-23.

5. Bundo M, de Schrijver E, Federspiel A, et al. Ambient temperature and mental health hospitalizations in Bern, Switzerland: A 45-year time-series study. *PLoS One* 2021;16(10):e0258302.

6. Hansen A, Bi P, Nitschke M, et al. The effect of heat waves on mental health in a temperate Australian city. *Environ Health Perspect* 2008;116(10):1369-75.

7. Hajat S, O'Connor M, Kosatsky T. Health effects of hot weather: from awareness of risk factors to effective health protection. *Lancet* 2010;375(9717):856-63.

8. Westaway K, Frank O, Husband A, et al. Medicines can affect thermoregulation and accentuate the risk of dehydration and heat-related illness during hot weather. *J Clin Pharm Ther* 2015;40(4):363-7.

9. Martin-Latry K, Goumy MP, Latry P, et al. Psychotropic drugs use and risk of heat-related hospitalisation. *Eur Psychiatry* 2007;22(6):335-8.

10. Layton JB, Li W, Yuan J, et al. Heatwaves, medications, and heat-related hospitalization in older Medicare beneficiaries with chronic conditions. *PLoS One* 2020;15(12):e0243665.

11. Matsuda R. The Japanese Health Care System: In: Tikkanen, R., Osborn, R., Mossialos, E., Djordjevic, A., Wharton, G. (Eds.), International Profiles of Health Care Systems. The Commonwealth Fund, New York, pp. 127–136. 2020.

12. Kuroda N, Tamiya N. Excess mortality among adults with mental disorders treated in psychiatric and general medical settings: A population-based cohort study using municipal medical claims data in Japan. *Asian J Psychiatr* 2023;88:103719.

13. Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;25(10):1768-97.

14. Lewer D, Petersen I, Maclure M. The case-crossover design for studying sudden events. *BMJ Med* 2022;1(1):e000214.

15. Guo Y, Gasparrini A, Li S, et al. Quantifying excess deaths related to heatwaves under climate change scenarios: A multicountry time series modelling study. *PLoS Med* 2018;15(7):e1002629.