Exploring the relationship between medications and heat-related community deaths during the 2021 heat dome: a hybrid approach using machine learning

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Summary

Background Extreme heat events (EHEs) are a growing threat to health worldwide. To date, only a limited number of studies have evaluated medications as risk or protective factors for mortality during EHEs.

Methods We explored the relationship between dispensed pharmaceuticals and heat-related community deaths using linked administrative health data and both logistic regression (LR) and machine learning (ML) models. We conducted a case-control study during the 2021 EHE in British Columbia, Canada, including 504 community deaths from heat exposure as cases and 2520 similar controls who survived the EHE. We used medications dispensed 30, 60 and 90 days prior to death (or 30, 60 and 90 days before the end of the EHE for controls) as predictors, grouped by Anatomical Therapeutic Chemical (ATC) classification at level 2 for LR (28 classes) and level 4 for ML (270 subclasses). Models were adjusted for multiple covariates, including common chronic diseases.

Findings Results from LR showed increased odds of mortality associated with dispensations of antiepileptics, anti-Parkinson drugs, psycholeptics, diuretics, drugs for diabetes, beta blocking agents, analgesics, urologicals and drugs for treatment of bone diseases. We observed a protective association with dispensations of calcium channel blockers and ophthalmologicals. Results varied by sex, age, and other covariates. The ML model highlighted the most computationally important subclasses of medications within each of the ATC level 2 classes.

Interpretation This study leveraged both LR and ML to generate insights about medications and mortality during EHEs. The results add to the existing evidence on pharmaceutical risks during EHEs and provide new avenues for further research. They can be used to help develop more targeted messages to inform individuals whose medications put them at greater risk during EHEs.

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Introduction

Climate change is increasing the intensity and frequency of extreme heat events (EHEs) worldwide.[1] EHEs result in a range of health impacts, with significant excess mortality being the most severe.[2–6] That said, most EHE-related health effects can be avoided by correctly identifying risks factors and implementing prevention measures for the populations most at risk.[7,8] Age, sex, comorbidities, poverty and characteristics of the built environment such as lack of neighbourhood greenness are among the risk factors most associated with EHE mortality.[9,10] Medication use is also an important factor, but it has been less well studied than other characteristics.[8]

Many medications affect thermoregulation and thirst, which can put users at risk during EHEs.[11–14] Medications identified as higher risk include psychotropics, anticholinergics, antihistamines, diuretics, cardiovascular agents, non-steroidal anti-inflammatory drugs and anticoagulants.[8,15–17] However, there is still limited evidence on medication use and adverse health outcomes during EHEs, partially because the exposure

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Research in context

Evidence before this study

Current public health messages emphasize that many classes of medications increase the risk of adverse health outcomes during extreme heat. However, there are a limited number of studies that provide supporting evidence. We searched PubMed, Web of Science and Google Scholar from inception to March 2025 for studies on "medications", "prescribed drugs" or "pharmaceuticals" during "extreme heat", "hot temperature" or "heatwave", and their effects on health outcomes such as "mortality", "death" or "morbidity". Most studies have focussed on morbidity outcomes or only studied specific classes of medications such as psychotropics. The few studies on mortality mainly looked at in-care mortality. No studies have examined the potential protective effects of different classes of drugs.

Added value of this study

This study looked at the effects of several classes and subclasses of medications on heat-related community deaths during the 2021 extreme heat event in British Columbia, Canada. We found an increased risk of mortality associated with antiepileptics, anti-Parkinson drugs, psycholeptics, diuretics, drugs for diabetes, beta blocking agents, analgesics, urologicals and drugs for treatment of bone diseases. We also found a protective association with dispensations of calcium channel blockers and ophthalmologicals.

Implications of all the available evidence

This study shows that some drugs are strongly associated with an increased risk of mortality during extreme heat events, with differences between age, sex, dispensation windows and drug subclasses. In addition, some medications may have a protective effect. These results add to the existing evidence on medications and heat-related mortality, that can be used by health authorities to develop more targeted messages to pharmacists, physicians and the general population to reduce the increasing heat-related health burden due to climate change.

is challenging to measure without systematic, individual-level data on medication prescriptions, dispensations or use. Indeed, a recent literature review on hyperthermia associated with prescribed drugs identified 11 studies and only found evidence for psychotropics to increase risk of hyperthermia-related mortality.[15] Another recent systemic review of the effect of medications on core temperature during heat stress highlighted that the evidence did not support current messages about medication use during EHEs.[11]

Much of the available evidence on medications and EHEs comes from studies of drug-related morbidity.[18–24] While these studies provide important information about medication risks, more evidence is needed on medications associated with more severe mortality outcomes. Some mortality during EHEs has been studied in clinical settings, including after initial presentation to the emergency department,[25] hospital[26–28] or intensive care unit.[29] However, many deaths during EHEs occur in the community,[30] and studies on the role of medications in such deaths are scarce.[16,31,32]

In 2021, an unprecedented EHE occurred in western North America[5] and was associated with an estimated 740 excess deaths[30,33] and 619 heat-related deaths[34] in the province of British Columbia (BC), Canada. Two previous studies found that schizophrenia and poverty were most strongly associated with mortality risk and noted a protective effect of angina.[35,36] The authors hypothesized that some common pharmaceutical therapy for angina (e.g., nitrates, beta blockers or calcium channel blockers) might have protective properties, but neither of these studies examined the effects of medications.

In this study, we investigate the relationship between dispensed medications and heat-related community deaths during the 2021 EHE in BC using a case-control design. We leverage a state-of-the-art analytics platform that links multiple health databases at the individual level, including all medications dispensed by community pharmacies. First, we used logistic regression to identify broad classes of medications associated with heat-related mortality risk during the EHE. Second, we trained a machine learning model using more precise subclasses of medications to validate and further refine the results obtained with logistic regression. The objective was to generate evidence that will help public health authorities, clinicians and pharmacists better understand the role of medications during EHEs and inform the development of more tailored messages to reduce the mortality burden.

Methods

Study context

British Columbia (BC) is the westernmost Canadian province, with a population of approximately 5 million people in 2021. The EHE occurred towards the end of June, just after the summer solstice. Daytime high temperatures throughout BC were 15–25 °C higher than historical norms and, in many cases, 5 °C higher than previously recorded.[5] As in previous work, we defined the study period as June 25 to July 2, 2021, which includes the 8 days when population mortality was statistically higher than expected based on historical data.[35,36] The mortality peaked around the 5th day of the EHE (June 29), with 300 of the excess deaths recorded on that date. There was also a significant increase in mortality up to three days after the peak of the EHE, which may have been due to persistent indoor

overheating.[33,37] During the EHE, there were an estimated 740 excess deaths. The BC Coroners Service (BCCS) directly attributed 619 deaths to heat exposure based on circumstantial reviews and 98% of the fatal heat-related injuries occurred in private residences.[34] As per the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans of Canada, this project and the data used to support it are exempt from research ethics board.[38]

Data sources

All data were extracted and analysed using R version 4.3.1. We used multiple administrative health datasets (Table S1) linked within the BC Provincial Health Services Authority Platform for Analytics & Data (PANDA). All data available in PANDA are developed and maintained by the BC Ministry of Health, and they capture complete data for all BC residents enrolled in the provincial single-payer Medical Services Plan (MSP) insurance program, which is mandatory. Information from different datasets was merged using the Patient Master Key (PMK), an anonymized and randomly assigned unique identifier. The PMK is consistent across the de-identified datasets in PANDA and thus allows records for the same individual to be linked.

The Vital Statistics database was used to extract deaths during the study period. Vital Statistics are the official records of mortality across BC, covering all deaths within the province. The underlying and contributing causes of death are coded according to the International Classification of Disease 10th revision (ICD-10). The records also include information about sex, age and where each death occurred, such as acute care facility, long-term care facility or private residence. The MSP Client Roster was used to identify potential controls, which includes basic demographic (i.e., age, sex) and geographic information for all enrollees. For the geographic information, we used the 16 Health Service Delivery Areas, referred to herein as the health region. The sex variable in Vital Statistics and the Client Roster generally capture biological sex at birth rather than gender, and no data on race/ethnicity are available in PANDA.

The Health System Matrix (HSM) for the 2020–2021 fiscal year (April to March) was used to assign a population segment for each subject, which represents individual healthcare needs based on diagnoses or use of specific services. It includes 14 segments, ranging from non-users (PS01) to people near the end of life (PS14). In addition to the HSM, we used the 25 administrative Chronic Disease Registries to identify subjects with chronic conditions based on their individual patterns of healthcare use.

The main database used for the study was PharmaNet, which includes records of all medications dispensed to MSP registrants from community pharmacies, including whether the prescription was dispensed under any of the BC PharmaCare coverage plans.[39] We used coverage by PharmaCare plans C (*income assistance*) and G (*psychiatric medications assistance*) as a proxy for low-income status.[36] Plan C covers 100% of prescription costs for individuals enrolled in the BC Employment and Assistance program, while Plan G covers 100% of eligible costs for certain psychiatric medications for BC residents with clinical and financial need.

Study design and subject selection

We used a population-based case-control design to compare adults who died during the EHE with similar people who survived the event. To select the cases, we first extracted all deaths during the study period from Vital Statistics. Then, we excluded deaths with missing information on age, sex, health region or HSM population segment, as well deaths among those aged ≤18 years. Next, we excluded deaths that occurred in acute or long-term care facilities in order to focus on out-of-care community deaths.[30] Finally, we selected deaths that were directly attributed to heat exposure by BCCS, meaning the underlying cause of death was coded as ICD-10 X30.

The pool of potential controls included all BC residents available in the MSP Client Roster who (1) survived the EHE to at least August 1, 2021, (2) did not live in a residential care facility, (3) had complete information on age, sex, health region and population segment, and (4) were aged 19 years or older. We used the same method described by McLean et al. to identify those living in residential care.[36] For each case, we randomly selected 5 controls from the pool with the same 5-year age group, sex, health region and HSM population segment (Fig. S1). This ratio was chosen to maximize statistical precision while minimizing the number of strata with insufficient controls.[40] Matching on the HSM population segment ensured that cases and controls had similar healthcare needs.

Medications and chronic diseases

We used PharmaNet to extract all medications dispensed 30 days prior to death for cases and 30 days prior to the end of the EHE for controls. We also tested 60- and 90-day windows in the sensitivity analyses, described in more detail below. These periods were chosen based on common dispensation frequencies, from a short-term dispensation window (1 month) to a longer one (3 months). Medications were then classified using the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization,[41] previously used to study drugs and heat-related illnesses in Australia.[19] The ATC classification includes 16, 94, 235, 718 and 2262 classes for levels 1–5, respectively. Within each ATC level, we created binary indicators for each class. The indicator was set to 1 if the subject had any medication dispensed within that class

during the 30-day window, or 0 otherwise. In addition, we classified the subject as low income if they had any medications dispensed under Plan C or Plan G in the year prior to the study period. We extracted information about chronic diseases for all subjects from the 25 Chronic Disease Registries. If a subject had an incidence date in any registry prior to the EHE, the disease was categorized as present and, otherwise, absent. After applying the method described in McLean et al., 21 chronic diseases were included.[36]

Logistic regression modelling and sensitivity analyses

Unconditional logistic regression (LR) was used to quantify the association between dispensed ATC level 2 classes of medications and odds of heat-related death during the 2021 EHE (Fig. 1). We chose unconditional regression to align with the machine learning model (described below), which cannot accommodate conditional analyses, and because it can be more precise and equally valid as conditional analyses.[42] For the LR model, we excluded all ATC level 2 classes that had less than 2% prevalence among cases or controls to reduce uncertainty in the estimated odds ratios (OR). The primary model in eq. (1) was also adjusted for age, sex, health region, HSM population segment and the 21 chronic diseases (CD):

$$\begin{aligned}\text{Heat-related community death during the EHE} &= \text{Med}_{\text{ATClevel2class1}} + \ldots + \text{Med}_{\text{ATClevel2classN}} + \text{Sex} \\ &\quad + \text{Age group} + \text{Health region} \\ &\quad + \text{HSM Population segment} + \text{CD}_1 + \ldots + \text{CD}_{21}\end{aligned} \tag{1}$$

We performed several sensitivity and subgroup analyses on the primary model. First, we removed the chronic diseases from the primary model. Second, we adjusted the primary model for low-income status. Third, we changed the medication dispensation window from 30 to 60 and then to 90 days prior to death for cases and prior to the end of the EHE for controls. We also stratified the primary model by sex (male or female) and age categories (≤75 or ≥76 years). This split was used because 76 years was the median age at death for the cases. Finally, we ran the main model using a conditional logistic regression as in eq. (1), adding a stratum for each case-control group and removing the matching factors (sex, age, health region and HSM population segment).

Machine learning modelling

Results obtained with LR were further assessed and refined by introducing a machine learning (ML) model (Fig. 1). ML models, and especially tree-based approaches, are being increasingly used in pharmacoepidemiology to include a large number of medications and predict drug-related health outcomes.[43,44] A Light Gradient Boosting Model (LGBM) was selected for the study. LGBM is an ensemble tree-based method that uses trees with few leaves (called weak learners) that are sequentially added to the ensemble based on the residuals of the last tree(s), thus being less prone to overfitting than other ML models such as Random Forest.[45,46] In addition, LGBM was promising compared with other ML and statistical approaches for modelling heat–health relationships in previous studies.[47,48]

LGBM was fitted using the ATC level 4 rather than the ATC level 2 used in the LR model. We used the ATC level 4 in LGBM because this model can handle many more predictors than the LR model by performing variable selection during the training process (i.e., selecting only the most predictive subclasses of medications). We included all ATC level 4 subclasses for which there was

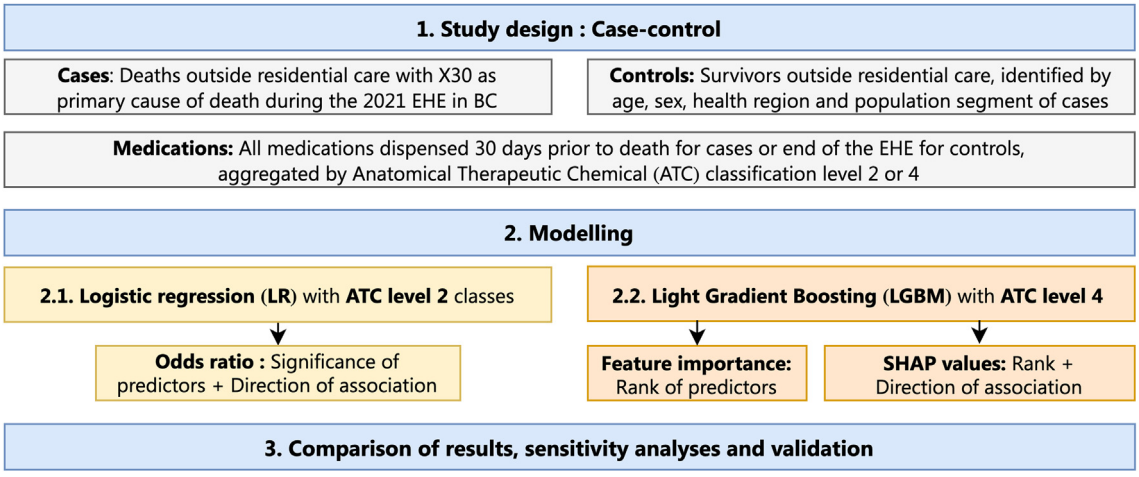

Fig. 1: Overview of the methodology.

at least one subject who was dispensed a medication within that subclass. Otherwise, the model followed the same structure as eq. (1), with mortality during the EHE (1 = *yes*, 0 = *no*) as the response variable using the logit link function. The LGBM was trained with 80% of the dataset and validated with the remaining 20%. The split was performed randomly while keeping the cases and their corresponding controls together in either the training or validation set. Different values of learning rates were tested (0.1, 0.01, 0.001) to ensure the training was not too fast or too slow on the validation set. The other tuned hyperparameter was the number of trees, which we optimized to minimize the cross-entropy on the validation dataset. We set the feature fraction to 70% to limit overfitting. The other hyperparameters were kept at their default values, which are expected to perform best in most cases.[46] For example, the maximum number of leaves was 31, allowing up to 5 orders interaction in the underlying trees while limiting overfitting with trees that are too deep, which can happen in Random Forest models. Once the optimal learning rate and number of trees were found using the validation set, the model was retrained with the whole dataset prior to extracting the descriptive and explanatory metrics.

We used two metrics to explain the LGBM machine learning model. First, we computed feature importance (FI) based on the gain in accuracy for each predictor (referred to as FI gain). FI gain is an easy and straightforward method to identify the predictors that contribute most to the prediction success in an ensemble tree-based model.[47,49] Second, we computed SHapley Additive exPlanations (SHAP) values. SHAP is a method based on cooperative game theory that calculates the contribution of each individual predictor to the prediction(s) of the algorithm.[50,51] Both metrics express how computationally important each predictor (i.e., medication) is for modelling the mortality risk during the EHE. To facilitate comparisons, the FI gain and SHAP values were expressed as ranks, with the first being the most important medication for each metric. In addition, the SHAP values illustrate the direction of the association, thus allowing us to interpret whether the medication may be a potential risk or protective factor in the LGBM.

Note that FI gain and SHAP are different from the ORs obtained in the LR model, which reflect the magnitude of the effect of medication classes on EHE mortality. The ML metrics identify the most important medications to differentiate between the people who died and those who survived. They are sensitive to variable frequency, meaning that drugs with low dispensations rates may have lower importance in the ML model, but could have a high or low OR in the LR model. Importance metrics should not be interpreted as effect estimates, but rather as indicators of medication sub-classes that require further investigation.

Role of the funding source

The funders did not have any role in the study design, data collection, data analyses, interpretation, or writing.

Results

Subject characteristics

There were 504 cases and 2520 controls (Fig. S1). Cases were 49.4% male with a mean age of 75.1 years (Table 1). Most resided in the Fraser North (25.0%), Fraser South (18.1%), Vancouver (17.9%) and Fraser East (10.3%) health regions. The health status of cases based on HSM population segment was mostly high chronic conditions without frailty (31.0%) or with frailty (9.9%), followed by medium (24.4%) and low (12.9%) chronic conditions. A smaller proportion of cases were frail in the community (6.3%) or had severe mental health and substance use disorders (5.8%). Other cases were either healthy adults or non-users of the healthcare system (5.4%), or people near the end of life or with cancer (3.4%). The controls were selected based on the sex, age groups, health regions and HSM population segments of the cases, so they had the same distributions for these variables (Table 1).

The females who died during the EHE were older (mean age of 78.1 years) than the males who died (71.8 years old) (Table S2). There were more deaths among females than males in the dense urban area of greater Vancouver, but more deaths among males in most other parts of the province. Finally, the female decedents had

	Cases (*n* = 504)	Controls (*n* = 2520)
Basic demographics		
Mean age in years (standard deviation)	75.1 (12.7)	74.9 (12.7)
Male	49.4%	*Same*
Health region (Health Service Delivery Area)		
Fraser North (22)	25.0%	*Same*
Fraser South (23)	18.1%	
Vancouver (32)	17.9%	
Fraser East (21)	10.3%	
Okanagan (13)	6.2%	
Thompson Cariboo Shuswap (14)	4.8%	
Central Vancouver Island (42)	3.8%	
South Vancouver Island (41)	3.6%	
Northern Interior (52)	2.8%	
Other (11, 12, 31, 33, 43, 51, 53)	7.8%	
Health system matrix population segment		
PS10–High chronic without frailty	31.0%	*Same*
PS06–Medium chronic conditions	24.4%	
PS05–Low chronic conditions	13.9%	
PS11–High chronic with frailty	9.9%	
PS09–Frail in the community	6.3%	
PS07–Severe mental health and substance use	5.8%	
PS01–Non-users or PS03–Adult Major Age 18+	5.4%	
PS14–End of life or PS12–Cancer	3.4%	

Table 1: **Characteristics of the subjects selected for this study.**

a higher prevalence of high and medium chronic conditions than males. Males had a higher prevalence of low chronic diseases, severe mental illness, and more were near the end of life or had cancer than females (Table S2).

Of the 94 drug classes in ATC level 2, there were 28 for which more than 2% of cases or controls received a dispensation and were therefore included in the LR model (Table 2, Fig. S2). Lipid modifying agents (C10) were the most frequently dispensed medication among cases (22.8%), and the second most dispensed among controls (20.2%). Renin-angiotensin system agents (C09) were the most frequently dispensed medication among controls (22.1%), and the third most dispensed among cases (21.6%). Both psychoanaleptics (N06) and psycholeptics (N05) were highly dispensed among cases with ~22% prevalence (ranked respectively #2 and #3), but less frequently dispensed among controls (~10–14%). For almost all classes of medication, there were more dispensations among cases than controls, except for renin-angiotensin system agents (C09), calcium channel blockers (C08) and ophthalmologicals (S01).

Medication class (ATC level 2)	% among cases	% among controls
Lipid modifying agents (C10)	22.8%	20.2%
Psychoanaleptics (N06)	22.2%	13.9%
Psycholeptics (N05)	21.6%	9.5%
Renin-angiotensin system agents (C09)	21.6%	22.1%
Beta blocking agents (C07)	18.3%	13.3%
Drugs for acid related disorders (A02)	18.1%	12.7%
Antithrombotic agents (B01)	17.9%	13.8%
Analgesics (N02)	17.5%	11.0%
Diuretics (C03)	16.3%	11.3%
Drugs used in diabetes (A10)	15.1%	11.2%
Calcium channel blockers (C08)	12.3%	12.4%
Drugs for obstructive airway diseases (R03)	11.3%	7.0%
Thyroid therapy (H03)	10.7%	7.2%
Antiepileptics (N03)	9.5%	2.9%
Antianemic preparations (B03)	8.1%	4.3%
Urologicals (G04)	7.7%	6.4%
Antibacterials for systemic use (J01)	5.8%	5.1%
Anti-parkinson drugs (N04)	4.2%	1.4%
Cardiac therapy (C01)	4.2%	2.8%
Antigout preparations (M04)	3.6%	2.9%
Drugs for treatment of bone diseases (M05)	3.2%	2.2%
Corticosteroids, dermatological preparation (D07)	2.8%	1.9%
Drugs for constipation (A06)	2.8%	1.2%
Muscle relaxants (M03)	2.6%	1.3%
Corticosteroids for systemic use (H02)	2.6%	2.4%
Mineral supplements (A12)	2.6%	1.5%
Vitamins (A11)	2.2%	1.8%
Ophthalmologicals (S01)	2.0%	4.4%

Refer to Fig. S2 for a graph of these frequencies.

Table 2: **Medications dispensed based on ATC level 2 classification.**

Of the 21 chronic diseases included in the study, chronic kidney disease, COPD, depression, epilepsy, heart failure, schizophrenia and substance use disorder were more prevalent among the cases, while osteoarthritis, mood and anxiety disorders and hospitalized transient ischaemic attack were more prevalent among the controls (Table S3). For the 11 other chronic diseases, the prevalence was similar for both cases and controls. In the year preceding the EHE, cases were more likely to have been dispensed pharmaceuticals under PharmaCare Plans C or G (25.2%) than controls (9.3%), indicating a higher prevalence of low income among the deceased (Table S3).

Logistic regression results

In the LR model of eq. (1), the medications most clearly associated with higher odds of heat-related community death during the EHE were anti-Parkinson drugs (N04), antiepileptics (N03) and psycholeptics (N05) with respective ORs [95% confidence interval] of 2.36 [1.15, 4.81], 2.16 [1.32, 3.51] and 1.43 [1.00, 2.02] (Fig. 2, Table S4). Some other classes of medications also had elevated ORs, such as drugs for constipation (A06), antianemic preparation (B03) and drugs used in diabetes (A10). Two categories of drugs had protective effects, namely calcium channel blockers (C08) and ophthalmologicals (S01) with respective ORs of 0.69 [0.48, 0.98] and 0.34 [0.16, 0.67]. ORs less than 1.0 were also estimated for renin-angiotensin system agents (C09) and corticosteroids for systemic use (H02). Results from the conditional regression model were similar to the unconditional model (Fig. S3).

When the primary model was not adjusted for chronic conditions, the ORs observed for anti-Parkinson drugs (N04), antiepileptics (N03) and psycholeptics (N05) were higher (Table 3a, Fig. S4). In addition, there was a marked increase in ORs for antianemic preparations (B03), drugs used in diabetes (A10) and drugs for obstructive airway diseases (R03). When adjusting the primary model for low-income status using PharmaCare plans C and G (Table 3c, Fig. S5), the OR for psycholeptics (N05) was decreased. Sensitivity analyses for longer dispensation windows of 60 and 90 days showed generally the same drugs being identified as with the 30-day window, but with some differences (Table 3d, e, Fig. S6). Drugs used in diabetes (A10), diuretics (C03) and drugs for treatment of bone disease (M05) all had increased effect estimates at longer windows. This increased effect was particularly marked for the latter class of medications (i.e., M05). On the other hand, the OR for psycholeptics (N05) at longer dispensation windows was adjusted towards the null.

Stratified analysis by sex showed marked differences between males and females (Table 3f, g, Fig. S7). For example, dispensations of anti-Parkinson drugs (N04), beta blocking agents (C07), analgesics (N02) and urologicals (G04) were associated with higher odds of

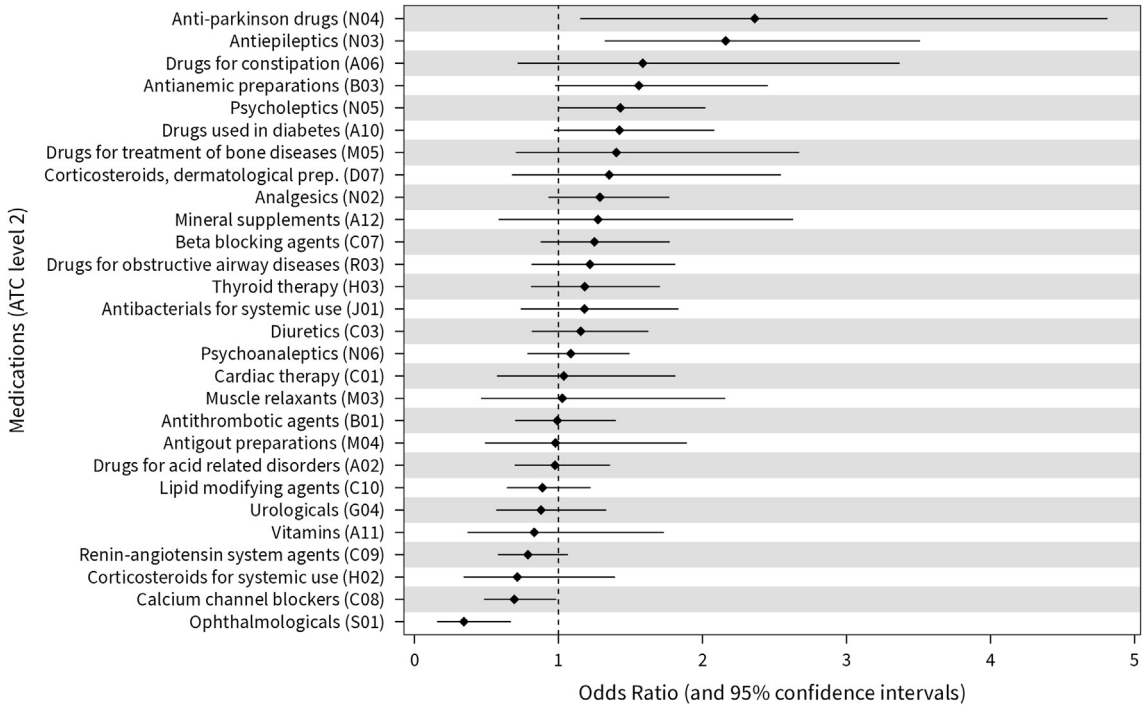

Fig. 2: **Odds ratios from the logistic regression based on the 28 classes of medications from ATC level 2 dispensed 30 days prior to death (or end of the extreme heat event for controls), adjusted for age group, sex, health region, Health System Matrix population segment and chronic diseases**. Refer to Table S4 for numeric values.

mortality among females. Among males, medications for diabetes (A10) were associated with higher risk and urologicals (G04) were associated with lower risk. The effects of antiepileptics (N03) and ophthalmologicals (S01) remained consistent for both sexes. Stratified analyses by age showed that the mortality risk associated with dispensations of neurological medications such as anti-Parkinson (N04), antiepileptics (N03) and

Medications (ATC level 2)	W/o chron. diseases (a)	Prim. model (b)	Adj. low income (c)	Med. 60 days (d)	Med. 90 days (e)	Sex Male (f)	Sex Female (g)	Age ≤75 (h)	Age ≥76 (i)
Antiepileptics (N03)	2.45	2.16	1.87	2.55	2.43	2.36	2.27	2.59	0.96
Anti-parkinson drugs (N04)	2.42	2.36	2.37	2.14	2.03	1.75	3.46	3.27	0.87
Psycholeptics (N05)	2.05	1.43	1.34	1.27	1.19	1.52	1.53	2.01	0.93
Drugs for constipation (A06)	1.84	1.59	1.65	1.32	1.07	1.65	2.35	1.54	1.52
Antianemic preparations (B03)	1.72	1.56	1.46	1.30	1.44	1.37	1.71	1.85	1.35
Drugs for obstructive airway diseases (R03)	1.55	1.22	1.22	1.42	1.27	1.82	1.01	1.75	0.85
Drugs used in diabetes (A10)	1.40	1.42	1.42	1.40	1.46	1.97	1.13	1.74	1.07
Beta blocking agents (C07)	1.35	1.25	1.26	1.22	1.23	0.93	1.66	1.62	0.95
Analgesics (N02)	1.33	1.29	1.22	1.23	1.23	0.90	1.59	1.59	1.10
Diuretics (C03)	1.28	1.16	1.14	1.18	1.38	0.94	1.26	0.62	1.71
Drugs for treatment of bone diseases (M05)	1.20	1.40	1.48	2.05	1.94	6.19	1.24	1.60	1.54
Urologicals (G04)	0.89	0.88	0.90	0.96	1.00	0.53	2.98	0.69	1.11
Renin-angiotensin system agents (C09)	0.76	0.79	0.82	0.84	0.90	0.98	0.67	0.80	0.76
Calcium channel blockers (C08)	0.74	0.69	0.71	0.66	0.70	0.79	0.66	0.90	0.70
Ophthalmologicals (S01)	0.34	0.34	0.35	0.41	0.57	0.23	0.39	0.19	0.39

Risk (pval<0.05) | Risk (0.05≤pval<0.10) | Protective (pval <0.05) | Protective (0.05≤pval<0.10) | Non-sign. (pval>0.10)

Only ATC level 2 medication classes with at least one OR with a p-value <0.10 are shown. Refer to Figs. S4–S8 for detailed results. (a) Primary model without chronic diseases. (b) Primary model of eq. (1). (c) Primary model adjusted for low income. (d) Primary model with 60-day medication dispensation window rather than 30 days. (e) Primary model with 90-day dispensation window. (f and g) Primary model stratified by sex. (h and i) Primary model stratified by age.

Table 3: **Sensitivity analyses to contextualize findings from the primary model (eq. 1, column b).**

psycholeptics (N05) was higher in the younger (≤75 years) group (Tables 3h and i, Fig. S8). In the older (≥76 years) group, only diuretics (C03) were associated with increased risk. The protective effect of ophthalmologicals (S01) was present in both age groups, but more pronounced in the ≤75 group.

Machine learning results

Of the 780 subclasses of ATC level 4, there were 270 subclasses with at least one subject who was dispensed a medication within the subclass in the 30 days prior to death (or end of the EHE for controls). We used LGBM with these 270 ATC level 4 subclasses to identify the most computationally important medications for heat-related mortality. The optimal hyperparameters values found on the validation dataset for the learning rate and the number of trees were respectively 0.01 and 217. Diazepines, oxazepines, thiazepines and oxepines (N05AH), plain sulfoamides (C03CA) and non-selective monoamine reuptake inhibitors (N06AA) were the three most important medication subclasses based on both FI gain and SHAP values (Fig. 3). Angiotensin II receptor blockers (plain) (C09CA) was ranked 2nd based on SHAP values and 7th based on FI gain. The subclass of other antipsychotics (N05AX) was ranked 3rd based on FI gain and 6th based on SHAP values. The top 20 subclasses identified by LGBM were from the following ATC level 2 classes (presented in order of importance): psycholeptics (N05), diuretics (C03), psychoanaleptics (N06), renin-angiotensin system agents (C09), antithrombotic agents (B01), calcium channel blockers (C08), antianemic preparations (B03), anti-Parkinson drugs (N04), drugs used in diabetes (A10), urologicals (G04), antiepileptics (N03), lipid modifying agents (C08), analgesics (N02), drugs for obstructive airway diseases (R03) and beta blocking agents (C07).

We used SHAP values to further refine the results of LGBM by estimating the direction of association between ATC level 4 subclasses of medications and odds of mortality during the EHE (Fig. 4). Most of the medications previously identified by LGBM had a positive association with mortality, except for angiotensin II receptor blockers (C09CA) and dihydropyridine derivatives (C08CA), which had potentially protective effects. In addition, the directions of the associations were unclear for plain ace inhibitors (C09AA) and HMG-CoA reductase inhibitors (C10AA). All protective and unclear associations were from the calcium channel blockers (C08), renin-angiotensin system agents (C09) and lipid modifying agents (C10) in the ATC level 2 classification.

Results summary and comparison

For each ATC level 2 class, LGBM could effectively identify which ATC level 4 subclasses were the most computationally important based on the FI gain or SHAP values and the potential direction of the association (Table 4). For example, the ATC level 2 class of psycholeptics (N05) had an OR from the LR of 1.43 [1.00, 2.02], while the ATC level 4 subclass of N05AH was

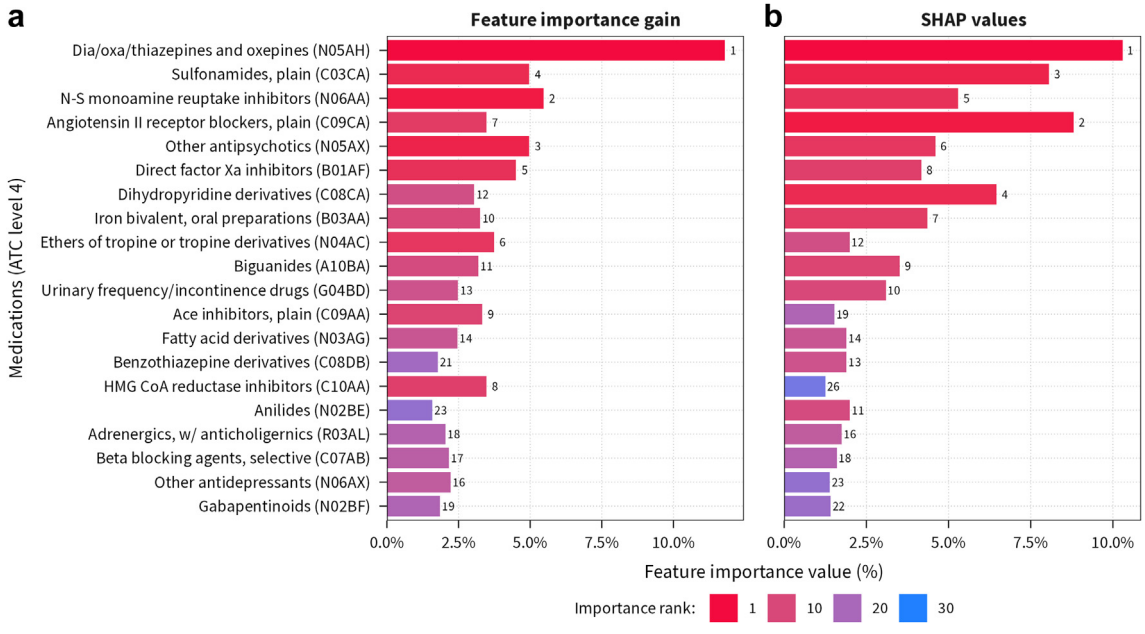

Fig. 3: **Top 20 most important medication predictors (out of 270) from the machine learning model and ATC level 4 medication subclasses based on a) feature importance gain in accuracy for each predictor and b) SHapley Additive exPlanations (SHAP) values.** Results are based on the model trained on the whole dataset. Medications are ordered based on the mean rank between the feature importance gain and SHAP values.

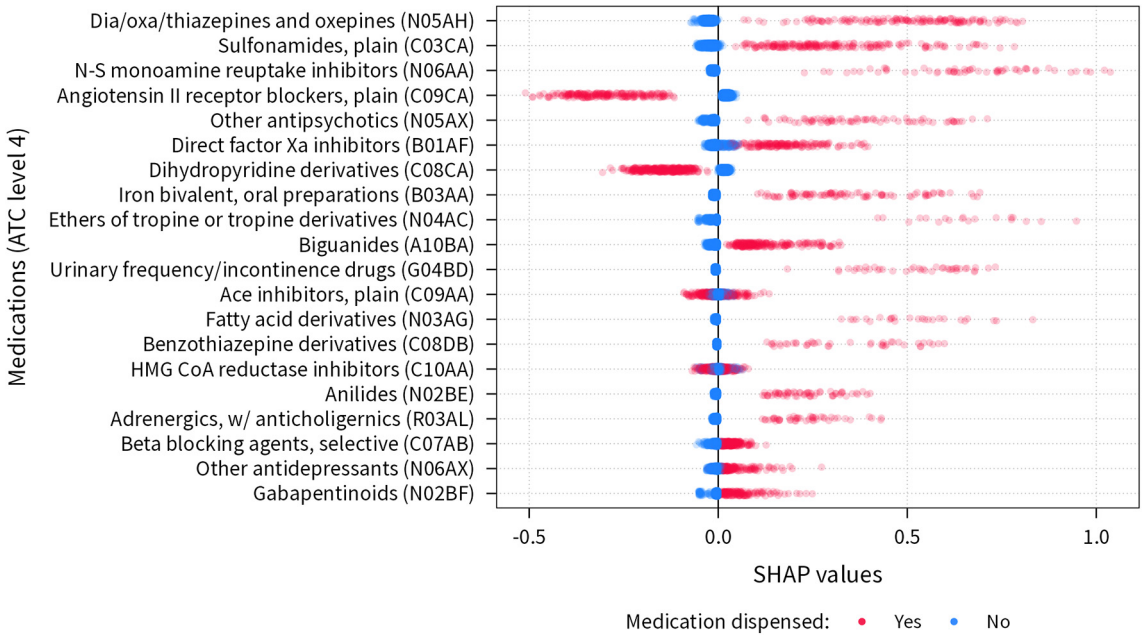

Fig. 4: **Direction of association based on SHapley Additive exPlanations (SHAP) values for the top 20 ATC level 4 medication subclasses previously identified by the machine learning model**. Results are based on the model trained on the whole dataset. Red dots represent individuals who were dispensed the medication subclass, while blue dots represent individuals who were not dispensed the medication. Red dots with positive SHAP values indicate a positive association of a dispensation of the medication subclass with heat-related mortality, while negative SHAP values indicate a negative association associated with the dispensation. Blue dots with positive SHAP values indicate a positive association of a non-dispensation of the medication subclass with heat-related mortality, while negative SHAP values indicate a negative association with a non-dispensation.

ranked #1 for both FI gain and SHAP values and subclass N05AX was ranked #3 and #6, respectively (refer to Table S5 for examples of medications within each subclass). The OR for urologicals (G04) was <1.0 for males and >1.0 for females in stratified analyses (Table 3). The LGBM identified two important ACT level 4 subclasses: G04BD with a potential positive association, and G04CA with a negative association. These diverging results could be attributed to the differences between males and females. The negative relationship between calcium channel blockers (C08) and heat-related mortality was observed for only one ATC level 4 subclass (C08CA), while a positive association was found for another subclass (C08DB) when using LGBM. Finally, the ophthalmologicals (S01) had a consistent protective effect across all LR analyses. The most important ATC level 4 subclass was medications to treat glaucoma (S01EE) in LGBM. However, this subclass was only ranked #33 based on SHAP values. The difference between the LR and LGBM results can be explained by the low number of subjects (<5%) dispensed ophthalmologicals among both cases and controls.

Discussion

This study introduced a hybrid approach using logistic regression (LR) and machine learning (ML) models to examine the relationship between dispensed pharmaceuticals and community heat-related deaths during the 2021 EHE in BC. Among the 28 ATC level 2 medication classes, LR identified anti-Parkinson medications, antiepileptics and psycholeptics as risk factors for mortality, and calcium channel blockers and ophthalmologicals as protective factors. There were some differences by age, sex, and the length of the dispensation window used for the analysis. ML identified more precise ATC level 4 subclasses of medications as risk or protective factors within the ATC level 2 classes (Table 4). Also, ML highlighted other potential risk factors (e.g., psychoanaleptics, antithrombotic agents, antianemic preparations and drugs for obstructive airway diseases) and protective factors (e.g., renin-angiotensin system agents) not identified by LR. Combining LR and ML approaches allowed us to study the relationship between a large number of dispensed pharmaceuticals and heat-related mortality during the 2021 EHE.

Methodological differences in our study limit the specificity of comparisons we can make within the existing literature. These differences include health outcomes considered (e.g., mortality *vs.* morbidity), medications studied (e.g., all classes *vs.* psychotropics), care settings (e.g., community *vs.* in care) and demographic characteristics. For example, Nordon et al.

Logistic regression		Light gradient boosting model			
Medication class (ATC level 2)	OR	Medication subclass (ATC level 4)	FI gain rank	SHAP rank	SHAP direction
Anti-Parkinson drugs (N04)	2.36*	Ethers of tropine or tropine derivatives (N04AC)	**6**	12	+
		Dopa and dopa derivatives (N04BA)	59	64	+
Antiepileptics (N03)	2.16*	Fatty acid derivatives (N03AG)	14	14	+
		Hydantoin derivatives (N03AB)	32	34	+
Antianemic preparations (B03)	1.56·	Iron bivalent, oral preparations (B03AA)	**10**	**7**	+
		Vitamin B12 (cyanocobalamin/analogue) (B03BA)	50	44	+
Psycholeptics (N05)	1.43*	Dia/oxa/thiazepines and oxepines (N05AH)	**1**	**1**	+
		Other antipsychotics (N05AX)	**3**	**6**	+
Drugs used in diabetes (A10)	1.42·	Biguanides (A10BA)	11	**9**	+
		Sulfonylureas (A10BB)	26	20	+
Analgesics (N02)	1.29	Anilides (N02BE)	23	11	+
Beta blocking agents (C07)	1.25	Beta blocking agents, selective (C07AB)	17	18	+
Drugs for obstructive airway diseases (R03)	1.22	Adrenergics, w/anticholinergics (R03AL)	18	16	+
Diuretics (C03)	1.16	Sulfonamides, plain (C03CA)	**4**	**3**	+
Psychoanaleptics (N06)	1.09	N–S monoamine reuptake inhibitors (N06AA)	**2**	**5**	+
Antithrombotic agents (B01)	0.99	Direct factor Xa inhibitors (B01AF)	**5**	**8**	+
Lipid modifying agents (C10)	0.89	HMG CoA reductase inhibitors (C10AA)	**8**	26	+/–
Urologicals (G04)	0.88	Urinary frequency/incontinence drugs (G04BD)	13	**10**	+
		Alpha-adrenoreceptor antagonists (G04CA)	28	15	–
Renin-angiotensin system agents (C09)	0.79	Angiotensin II receptor blockers, plain (C09CA)	**7**	**2**	–
		Ace inhibitors, plain (C09AA)	**9**	19	+/–
Calcium channel blockers (C08)	0.69*	Dihydropyridine derivatives (C08CA)	12	**4**	–
		Benzothiazepine derivatives (C08DB)	21	13	+
Ophthalmologicals (S01)	0.34*	Prostaglandin analogues (S01EE)	41	33	–
		Corticosteroids, plain (S01BA)	55	47	–

For ATC level 4, all medications in the top 10 based on feature importance (FI) gain or SHapley Additive exPlanations (SHAP) ranks are shown (the top 10 ranks are in bold), in addition to at least two subclasses for each corresponding ATC level 2 class that had p-values <0.05 (*) or <0.10 (·) in LR. ATC level 2 results (OR) were added if at least one ATC level 4 subclass was identified in the top 10 most important medications based on LGBM. SHAP direction refers to the association between dispensations of medications and heat-related mortality in the LGBM (+ for positive, – for negative, and +/– for unclear). Refer to Table S5 for examples of drugs in each ATC level 4 subclass.

Table 4: **Comparison of selected results between Logistic Regression (LR) with ATC level 2 medication classes and Light Gradient Boosting Model (LGBM) with ATC level 4 subclasses.**

studied psychotropic use and risk of dying during the 2003 European EHE in France using a population-based case-control study and found elevated risk for antidepressants (OR = 1.71, 95% CI = 1.57–1.86) and antipsychotics (OR = 2.09, 95% CI = 1.89–2.35).[31] Here we report an OR of 2.05 (95% CI = 1.50–2.78) for psycholeptics when not adjusting the model for chronic diseases. Thompson et al. studied multiple risk factors associated with heat-related mortality in a time-stratified case-crossover study, including some cardiovascular medications.[32] They reported elevated risk for vasodilators (OR = 1.83, 95% CI = 1.19–2.80), which fall into multiple of the ATC level 2 classes we examined. They also noted increased ORs for cardiac glycosides, diuretics, beta blockers, ace inhibitors and non-steroidal anti-inflammatory drugs with ORs ranging from 1.00 to 1.25, but exact OR values and 95% CIs were not provided for these drugs.

Bouchama et al. reviewed 6 studies on risk factors for heatwave-related mortality published between 1982 and 2005 and only found evidence of increased risk for psychotropic medications.[16] Similarly, Bongers et al. reviewed drug-related hyperthermia studies and linked psychotropics to increased risk of mortality, though most of the studies included only in-care mortality.[15] More recently, Hospers et al. conducted a meta-analysis on the effect of medications on core body temperature during heat stress and identified increases associated with anticholinergics, non-selective beta blockers, adrenaline and anti-Parkinson's agents.[11] However, most subjects in the reviewed studies were healthy young males. Our study adds to this body of evidence by combining LR and ML and provides detailed results on the specific medications associated with heat-related community deaths during the 2021 EHE in BC. This was only possible by leveraging the state-of-the-art PANDA platform. We were able to assess the complete history of medications dispensed to all study subjects and to adjust medication effects for important potential confounders, such as specific chronic conditions and poverty.

There are many mechanisms by which medications can increase risk of mortality during EHEs. Anti-Parkinson drugs have strong anticholinergic effects that alter thermoregulation and inhibit the muscarinic sweat glands, which can lead to increased core temperature and heat-related illness.[11,13,15] In addition, these medications can impair mobility, putting people who use them at higher risk during EHEs.[12] Anti-epileptics can cause sedation and cognitive impairment, thus reducing the alertness and perception of hot weather,[14] but there is no evidence they impair sweating or effect core temperature.[11] Psycholeptics impair sweating, alter thermoregulation and can increase the hypothalamic temperature set point,[14] which limits the capacity of the body to maintain core temperature.[12]

Although we identified these medications (and others) as risk factors for heat-related mortality, we did not compare their substantial benefits to their negative heat-related outcomes. This study is epidemiological, not clinical, and cannot provide evidence to suggest or support changing or discontinuing pharmaceutical therapy during an EHE. However, the results can provide valuable information to physicians and pharmacists to better communicate with their patients about pharmaceutical risks during hot weather. There are many ways to reduce heat risks, such as spending time in cool indoor environments, performing routine health checks, limiting social isolation and decreasing economic marginalization, among others.[7,15]

While many studies have reviewed heat risks associated with medications, no previous reviews have discussed which medications might be protective for mortality during EHEs. Indeed, most studies only considered a limited number of preselected medications that were assumed to be risk factors.[19,32] Using the data-driven approach described here, we were able to examine all pharmaceuticals dispensed to the study subjects, and our findings can be used to generate hypotheses about potentially protective medications that require further examination. Our previous research on chronic conditions consistently identified protective effect estimates for hospitalized transient ischaemic attack and angina during the 2021 EHE.[35,36] Here, we found that dispensations of calcium channel blockers and renin-angiotensin system agents were associated with lower odds of heat-related mortality, though different subclasses had diverging results in the ML model for calcium channel blockers.

One hypothesis is that individuals taking calcium channel blockers or renin-angiotensin system agents associated with cardiovascular diseases were receiving more medical care than others, resulting in a protective effect during the EHE. Another hypothesis is that some subclasses of these drugs have physiological effects that lead to lower risk. A recent review discussed the risk associated with cardiovascular medications during EHEs, but did not point out any potential benefits.[17] However, two recent studies identified statins, part of lipid modifying agents (C10) in ATC level 2 classification, as protective for mortality during EHEs.[52,53] While the LR model showed a little protective effect for C10 (OR = 0.89, 95% CI = 0.64–1.22), the ML model identified statins (C10AA) as particularly important, but with mixed results in terms of the direction of the association. More studies are needed to understand the complex mechanisms of these different cardiovascular medications on mortality during EHEs.

We also found a consistent and strong protective effect of ophthalmologicals, and more specifically, medications to treat glaucoma. Glaucoma is asymptomatic in the earlier stages of the disease and routine eye examinations are required to identify it before significant damage to the optic nerve has occurred. Because of this, patients who are dispensed ophthalmologicals could also be the types of patients who are more likely to seek medical care. In addition, there is some evidence that ophthalmologicals may have systemic effects.[54,55] Prostaglandin analogues promote vasodilation, which might improve thermoregulation. On the other hand, corticosteroids reduce inflammation, which is associated with multiple health endpoints. More research is needed to understand whether the protective effects of ophthalmologicals in this study are observed elsewhere and, if so, the roles of these medications in reducing risk of mortality during EHEs.

Our study highlighted some differences by sex and age groups. For example, none of the neurological drugs were significant risk factors among older individuals (i.e., ≥76 years old). This may be explained by a better care of older patients with chronic neurological conditions by family members or community services, compared with the younger age group (i.e., ≤75 years old), or by survivor bias. In the older age group, diuretics were identified as a strong risk factor, but not in the younger age group. This is aligned with past evidence that diuretics do not increase core temperature in younger adults.[11] Analyses by sex showed that females had stronger effects for anti-Parkinsonians, beta-blocking agents and analgesics. Unfortunately, evidence specific to females is lacking[11] because most previous epidemiological studies have not stratified by sex.[15] Finally, urologicals were a protective factor for men, but a strong risk factor for women. Oxybutynin, a drug for urinary incontinence, was identified previously in a case report to have potentially led to a female heat-related death.[56] We also identified drugs for urinary incontinence, including oxybutynin, as a risk factor in the ML model. All the above results of stratified analyses must be interpreted with caution given the relatively small sample sizes and the lack of past evidence on medications and heat-related outcomes in such age and sex subgroups.

This study has several strengths. First, it used a case-control design with 504 heat-related community deaths

during the 2021 BC EHE and 2520 controls, which is more subjects than in most previous studies on medications and heat-related health outcomes. Second, the available administrative databases provided a complete history of all dispensed medications for each subject, the presence of chronic diseases and indicators of low-income status. This made it possible to adjust the primary model for comorbidities, perform sensitivity analyses for low-income status and different dispensation windows, and stratify analyses by age and sex. Third, the use of two different approaches allowed us to derive ORs for broader classes of medications with LR and feature importance metrics for subclasses with ML. Finally, the results from both approaches were complementary, with the ML approach providing more detailed information on the subclasses of medications associated with heat-related mortality, but without providing effect estimates comparable with the LR output.

There are also limitations that need to be acknowledged. First, the analyses relied on administrative data that are not collected for research purposes and may have quality concerns that affected study results. For example, the PharmaNet database contains information on dispensed pharmaceuticals, but there is no way to know whether the study subjects used the medications. Another example was that race/ethnicity is not available in PANDA. Thus, we could not perform stratified analyses for such subgroups. Second, we used a binary indicator for each ATC class capturing whether any medication in that class was dispensed, rather than looking at the quantity of medications dispensed. We did this because fields related to quantity and duration of medications dispensed in PharmaNet are unreliable (internal communication). However, the impacts are evident in the sensitivity analyses by exposure dispensation windows, where some medications have substantively different ORs for the 60- and 90-day windows (Table 3), especially drugs to treat bone diseases (M05). This suggests that some drugs may be dispensed on longer refill cycles and were misclassified by the 30-day window used in the primary model. Third, we did not investigate potential interactions, though it is known that some patients are on multiple high-risk drugs. Future research could use ML clustering methods to examine risk of common medication groupings on mortality during EHEs. Fourth, the 2021 EHE occurred before glucagon-like peptide-1 (GLP-1) agonists (e.g., Ozempic) became available in BC. This important new class of drugs is now being widely used and has been associated with many protective benefits,[57] but we cannot comment on its association with heat-related mortality during this event. Finally, this study was based on a single EHE event, and the people who died may have different characteristics than those who die during other EHEs, so results may not be fully generalizable to other events or locations. Increasing the sample size would help generate more robust results, especially for the ML model, and would also allow more fulsome subgroup analyses.

Based on the results of the fully adjusted primary model, the medications that increased the odds of heat-related community death during the 2021 EHE in BC were anti-Parkinson drugs, antiepileptics and psycholeptics, while calcium channel blockers and ophthalmologicals reduced this risk. Supplementary analyses by age and sex strata, different dispensation windows and subclasses of medications using a ML approach also identified other potential risk factors such as diuretics, drugs used in diabetes, beta blocking agents, analgesics, urologicals, drugs for treatment of bone diseases, psychoanaleptics, antithrombotic agents, antianemic preparations and drugs for obstructive airway diseases, as well as potentially protective effects for agents acting on the renin-angiotensin system. In the context of climate change, this study can help to identify patients whose medications place them at higher risk during EHEs. Additionally, this methodology can be applied in other regions to generate more evidence on medication use and heat-related health outcomes. Finally, in the context of the existing evidence on medications and EHE mortality, these results can help support the development of tailored messages for clinicians, pharmacists and the population to reduce the mortality burden of extreme heat.

Contributors

All authors read and approved the final version of the manuscript. **JB**: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft, Funding acquisition. **KEM**: Conceptualization, Investigation, Methodology, Software, Writing-review & editing. **SBH**: Conceptualization, Investigation, Methodology, Writing-review & editing, Funding acquisition, Project administration. **JB** and **KEM** have verified the data supporting this study.

Data sharing statement

The data that support the findings of this study are available upon reasonable request from the Data Stewards.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Over the past three years, JB has received travel grants from the Canadian Institutes of Health Research (CIHR) and Columbia University to attend summer schools and workshops.

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research projects through the Data Stewards or their designated service providers. All inferences, opinions and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Stewards. Data source citations are available in Table S1. This work was funded through a travel scholarship from the *Ministère de l'Enseignement supérieur du Québec* (no grant number). BC Centre for Disease Control supported this study in-kind, and with a small trainee stipend (no grant number). The first author also received funding from the Natural Sciences and Engineering Research Council of Canada (Vanier Scholarship #CGV-180821), the Canadian Institutes of Health Research (Health System Impact Fellowship #IF1-184093), Ouranos (Real-Décoste Excellence Scholarship #RDX-317725) and *Institut national de santé publique du Québec* (no grant number).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105788.

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