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# Seasonal variation of serum potassium and related prescription pattern: an ecological time series

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## ABSTRACT

### Aims

To assess if ambient temperature-related effects on serum potassium levels impact clinical decision-making.

### Methods

This study is an ecological time series consisting of 1 218 453 adult patients with at least one ACE inhibitor (ACEI) prescription who participate in a large UK primary care dataset.

Descriptive statistics and a quasi-Poisson regression model using time series data at regular time intervals (monthly) were undertaken to examine the association between potassium measurements and ACEI/potassium supplement prescriptions.

**Results** It is noted that correlating with lower ambient temperature, serum potassium values follow a seasonal pattern; peaks in winter months and troughs in summer. During summer months, there are clear annual spikes in the number of potassium prescriptions suggesting a change in prescribing practice during periods of potentially spurious hyperkalaemia. The converse pattern is seen in the ACEI prescription proportion which spikes annually during the winter period with lower average ambient temperatures. Our time series modelling demonstrated that each one unit increase in potassium is associated with a 33% increased rate of ACEI prescriptions (risk ratio, RR 1.33; 95% CI 1.12 to 1.59) and 63% decreased rate of potassium supplements (RR 0.37; 95% CI 0.32 to 0.43).

**Conclusions** Our findings highlight the seasonal pattern in serum potassium and we observe a corresponding alteration in prescribing practice for potassium sensitive medications. These findings demonstrate the importance of educating clinicians on the presence of seasonal potassium variability in addition to standard measurement error, and its potential impact on their prescribing activity.

## INTRODUCTION

In the UK, clinicians working in primary and secondary care have access to analytical laboratories where serum blood testing is commonly conducted. In 2015/2016, an average of 4.5 laboratory tests per patient were requested in primary care, the majority of which were serum blood tests. This represents a threefold increase in testing since 2000/2001, potentially in response to the emphasis placed on blood monitoring in clinical performance measures.<sup>1</sup>

Specifically, serum potassium is an important test for clinicians to request to investigate and monitor renal function. The standard reference range

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Serum potassium is a useful test for clinicians to request to investigate renal function and disease. However, previous work on small samples has identified that spurious potassium results can occur (which can lead to pseudohypokalaemia or pseudohyperkalaemia) and occur more apparently during summer and winter months.

## WHAT THIS STUDY ADDS

⇒ First, this study confirms on a large nationally representative sample the inverse association between ambient temperature and average serum potassium recordings. Second, for the first time, this study identifies an association between seasonal fluctuations in potassium values and prescribing activity for potassium supplements and ACE inhibitors.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study clearly identifies the need to educate clinicians as to the impact of ambient temperature on the accuracy of blood test results. Second, there are policy considerations regarding the potential need to adopt novel approaches such as centrifugation on site in general practices to avert ambient temperature-related clinical prescribing errors.

for serum potassium concentration in the UK is between 3.5 and 5.3 mEq/L (equivalent to mmol/L for potassium)<sup>2–3</sup> and abnormalities in potassium levels can be associated with significant morbidity and mortality, most notably cardiac anomalies and arrest in extreme cases.<sup>4</sup> There is no standard definition for hyperkalaemia (raised potassium in the blood) or hypokalaemia (low blood potassium), but typically clinical review would be triggered if levels were above 5.5 mEq/L or below 3.0 mEq/L.<sup>5–6</sup> When undertaking potassium testing, spurious results can occur, resulting in pseudohypokalaemia or pseudohyperkalaemia. This may be due to the transcellular movement of ions during phlebotomy or contamination of blood samples.<sup>7</sup> Phlebotomy techniques such as prolonged tourniquet application<sup>8</sup> or fist clenching<sup>9–10</sup> and can lead to significant increases in the serum concentrations of potassium in collected samples. Phlebotomist retraining and monitoring programmes appear to reduce the number of pseudohyperkalaemic samples, demonstrating



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impact of erroneous results from poor practice and potential mitigation strategies.<sup>11 12</sup>

Of note, another reason for erroneous results could relate to the stark seasonal variation of potassium measurement values. It has been demonstrated in different global settings that background ambient temperature appears to affect potassium samples as they are transported to the centrifuge for testing.<sup>13</sup> During periods where temperature falls, such as winter, the measured mean daily serum potassium concentration rises.<sup>14</sup> Although the shift in mean potassium values appears modest (0.2–0.3 mEq/L) and is roughly in line with total allowable error,<sup>15</sup> it results in a doubling of the number of tests being classified as hyperkalaemic, and therefore, requiring urgent clinical review.<sup>14</sup> These erroneous readings caused by seasonal variation can lead to significant issues for primary care providers. Inaccurate results may lead to clinicians-making incorrect clinical decisions, or if an erroneous result is suspected, require rebleeding of the patient, all of which negatively affects patient care and practice resources.

The problem caused by these erroneous results is thought to be so significant that there have been movements to encourage centrifuges to be placed on site within general practice surgeries.<sup>16</sup> In the region covered by National Health Service (NHS) Grampian, where seasonal effects are more pronounced due to greater distance between practices and processing laboratories, this solution has been adopted.<sup>17</sup> This has reduced the effect of seasonal variation<sup>17</sup> and led to a significant reduction in samples displaying marked hyperkalaemia.<sup>18</sup> However, this approach has not been adopted universally across the UK, therefore, this problem may still persist. There has yet to be any literature exploring the relationship of the spurious results due to seasonal variation and the impact this may have on prescribing practice. Many medications, most notably ACE inhibitors (ACEIs), are known to impact renal potassium excretion, with regular blood sample monitoring undertaken and dose adjustment advised in patients who are experiencing hyperkalaemia.<sup>19 20</sup> ACEIs are the most commonly prescribed medication for the treatment of high blood pressure, with 9% of UK adults taking them.<sup>21</sup> ACEIs are also used frequently for cardiovascular disease secondary prevention, heart failure and diabetic nephropathy.<sup>22</sup> Alternatively, for patients who are found to be hypokalaemic, even if mild, clinicians may treat with a course of potassium replacement agents.<sup>23</sup>

Since there is evidence to suggest seasonal inaccuracies in potassium values exist, it is important to identify what impact this has on prescribing practice. Given this particularly affects patients on ACEI we chose to investigate this in a population of patients on ACEI.

## METHODS

### Study design, data source and study population

To explore this phenomenon, we have undertaken an ecological time series analysis exploring the relationship between serum potassium measurements (in patients prescribed ACEIs

and in those prescribed potassium supplements) and Met Office recorded temperature levels. Clinical data were derived from a nationally representative UK primary care dataset (IQVIA Medical Research Data (IMRD-UK)) between the 1 January 2003 to 31 December 2016.<sup>24</sup>

The IMRD-UK database (previously named ‘The Health Improvement Network’) is an anonymised patient record database derived from UK general practices using Vision electronic medical records software. The IMRD-UK database contains records taken from over 800 general practices including over 15 million patients which are thought to be representative of the UK population in terms of demographic structure and prevalence of key comorbidities.<sup>24–26</sup> The database consists of clinically recorded information on patient characteristics, drug prescriptions, diagnoses, consultations and diagnostic test results including blood serum testing results. Data extraction, transformation and loading of IMRD-UK were facilitated by the automated clinical epidemiology Data extraction for epidemiological research (DExtER) platform.<sup>27</sup> Data relating to the monthly average temperature for the UK have been taken from 1 January 2003 to 31 December 2016 from the UK Meteorological Office.<sup>28</sup>

In order to reduce under-recording of events, general practices were included 12 months following their instalment of electronic practice records or from the practices’ acceptable mortality recording date.<sup>29</sup> We only included adults (aged at least 18 years) on at least one ACEI or potassium supplement in our respective study population.

### Study variables

To monitor seasonal trends, we aggregated for monthly data on all potassium concentration values (a variable that has been extensively studied in UK primary data)<sup>30–33</sup> in patients with at least one ACEi prescription or potassium supplement. Extreme values of potassium were excluded (<1 mEq/L, >10 mEq/L). Whilst isolated potassium readings outside of this range have been reported in hospitalised cardiac arrest patients,<sup>34 35</sup> it is implausible that such samples would be taken in primary care and as such were assumed to be erroneous values. Primary care data recorded in the UK do not contain information on the specific dose change of a medication, but does include information on whether the medication was prescribed. Therefore, our primary outcome is a proportion describing the number of ACEI prescriptions given less than 15 days after a prior ACEI prescription divided by the total number of ACEI prescriptions in that calendar month. Fifteen days is a sufficient period for a clinician to receive the results of an investigation, for these results to be actioned and then for any changes in prescribing to be made. Where patients experience hyperkalaemia, the usual clinical decision in patients already taking ACEI would depend on the severity of hypokalaemia. The clinical response would be either a dose reduction, medication discontinuation or pause awaiting a repeat sample.<sup>36</sup>

**Table 1** Potassium measurements and total number of prescriptions for potassium supplement and ACEI

	England	Northern Ireland	Scotland	Wales	UK
Potassium measurements	7 357 129	565 818	1 406 139	1 351 739	10 680 825
ACEI prescriptions Repeated prescriptions within 15 days of a previous ACEI prescription	4 404 063	79 426	223 703	893 549	5 600 741
Potassium supplement prescriptions	64 438	3861	9134	5534	82 967
ACEI, ACE inhibitor.					

Alternatively, when patients on ACEI experience hypokalaemia, provided no other cause was identified they may be prescribed potassium supplements.<sup>23</sup> Therefore, our secondary analysis examined the aggregated frequency of potassium supplements given in each month.

### Analysis

The study analysis has been conducted using the R statistical package (R Core Team, 2013). Initially, a linear model was undertaken to describe the relationship between UK ambient temperature and average potassium values per month.

Following this, simple descriptive statistics have been used to present the characteristics of the data. The data are displayed graphically describing trends over time during the study period.

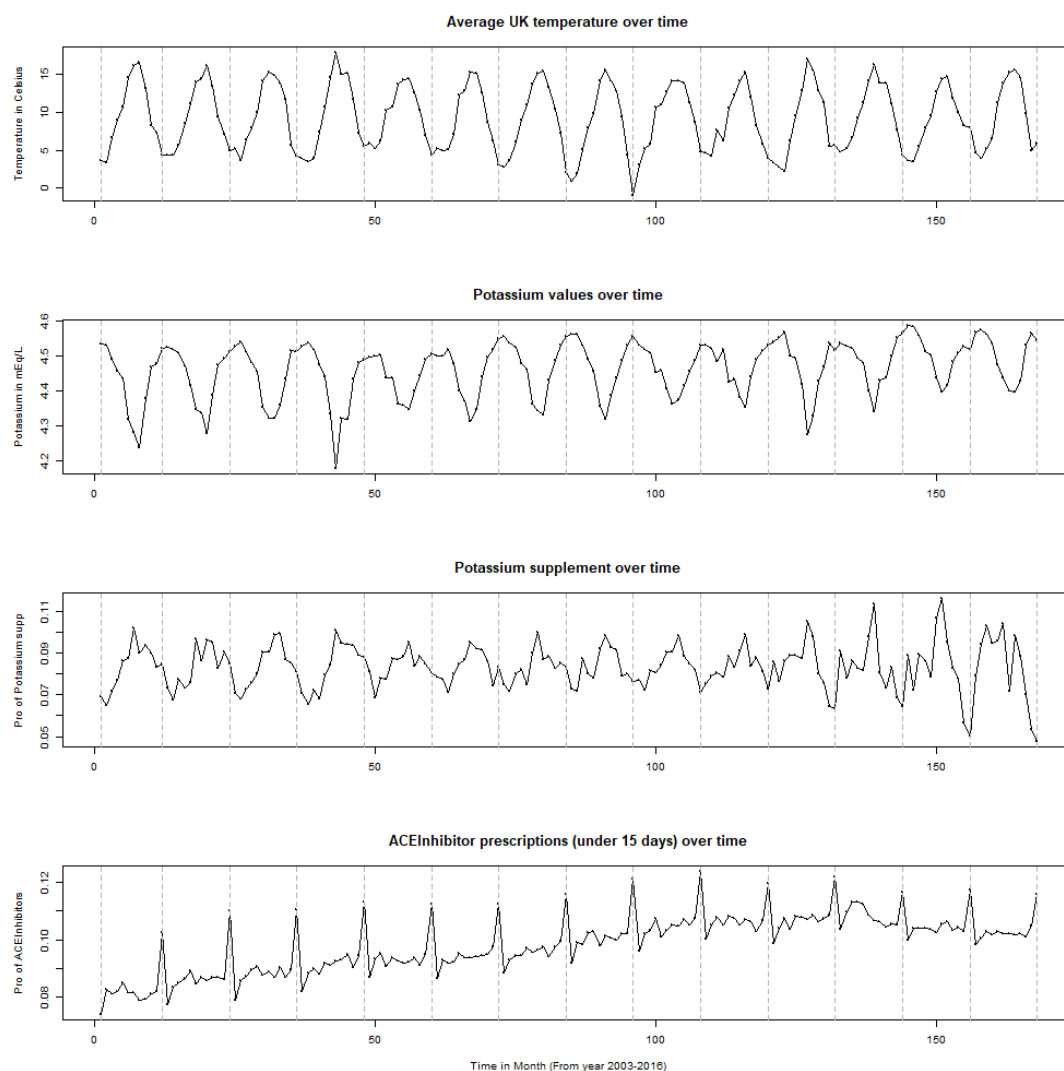
A quasi-Poisson regression model using time series data at regular time intervals (monthly) was then undertaken to examine the association between potassium measurements and the proportion of ACEI within 15 days of a previous ACEI. This model was used to estimate incidence rate ratios and their corresponding 95% CIs to describe this risk.

## RESULTS

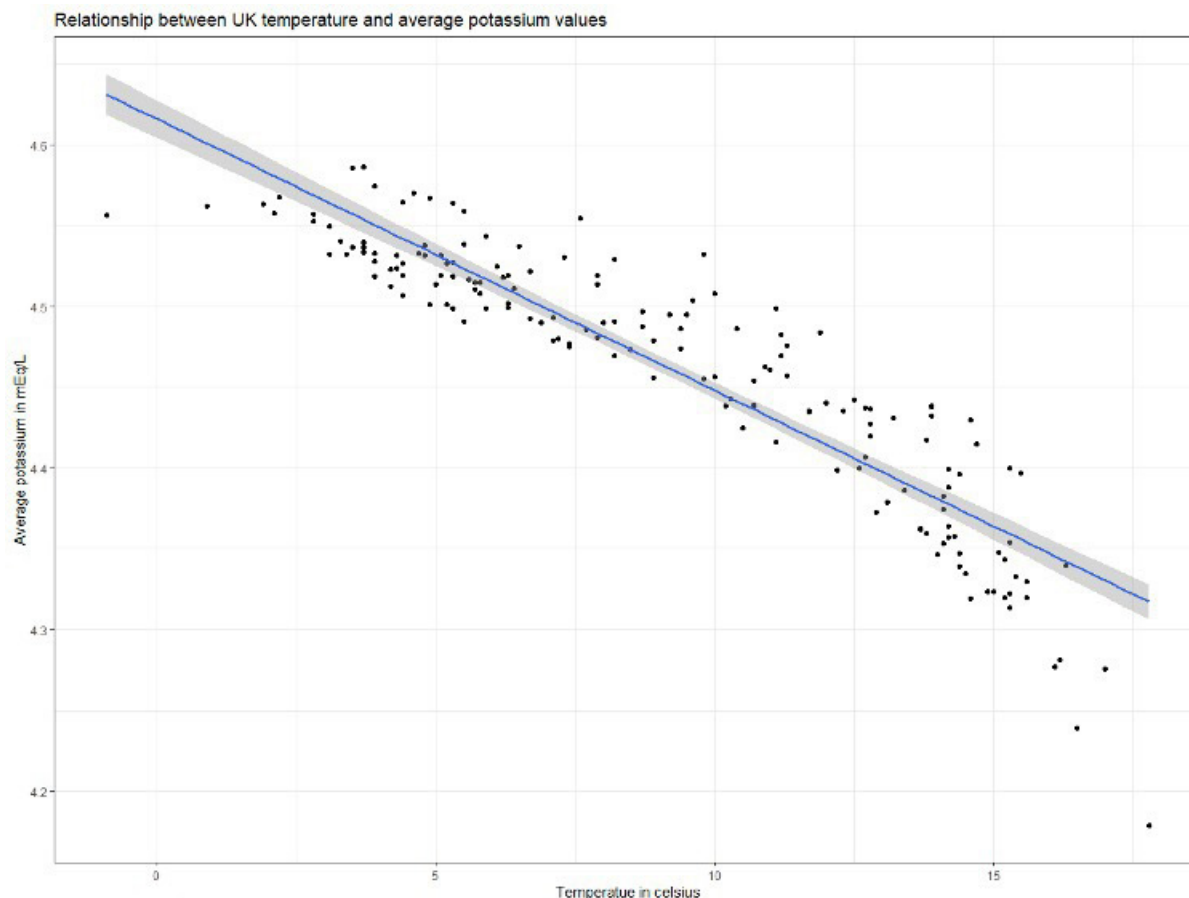
### Trends in potassium measurement and ACEI prescriptions

During the study period, the eligible study population included 1 218 453 UK wide patients with at least one ACEI prescription, with a total of 5 600 741 and 82 967 prescriptions for ACEI and potassium supplements, respectively, prescribed. A total of 10 680 825 potassium measurements were taken during this period for 1 169 400 included patients (1569 measurements were excluded due to extreme/improbable values). Table 1 describes the potassium measurements, supplements and ACEI/potassium supplement data per UK region; England, Scotland, Wales and Northern Ireland.

Figure 1 demonstrates that as in other recorded studies, correlating with lower ambient temperature, serum potassium values follow a seasonal pattern; peaks in winter months and troughs in summer.<sup>13 14</sup> Then, during summer months, there are clear annual spikes in the proportion of potassium prescriptions given suggesting a change in prescribing practice during periods of potentially spurious hyperkalaemia. The converse pattern is seen in the ACEI prescription proportion which annual spikes during the winter period with lower average ambient temperatures.



**Figure 1** Temperatures (degrees Celsius), potassium measurements (mEq/L), the proportion of Potassium supplements and ACE Inhibitor prescriptions within 15 days of a previous ACE Inhibitor prescriptions in that calendar month between January 1st 2003 and December 31st 2016.



**Figure 2** Relationship between UK temperature and average potassium values.

To explore the relationship further between serum potassium and ambient temperature, we undertook a linear model (coefficient =  $-0.02$ , intercept =  $4.62$ ). The relationship can be seen in figure 2 and  $R^2$  was  $0.8335$  suggesting that potassium values explained  $83.35\%$  of the variation in the temperature in the model.

### Time series models

The main aim of the time series regression model was to investigate whether some of the short-term variation in the outcome (proportion of ACEI/supplement prescriptions) is associated by changes in the exposures (aggregated potassium concentration).

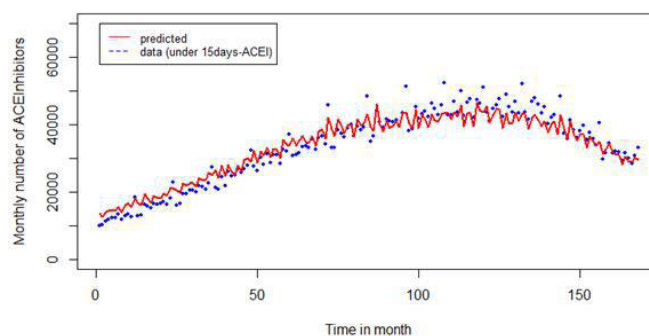
The quasi-Poisson regression model for ACEI prescriptions under 15 days with offset as total prescriptions within potassium concentration as an independent variable shows that each  $1$  mEq/L increase in potassium concentration is associated with an ACEI risk ratio of  $1.33$  (95% CI  $1.12$  to  $1.59$ ,  $p=0.001$ ). This translates into a  $33\%$  increase in the proportion of ACEI prescriptions given within 15 days of a previous ACEI when the serum potassium goes up by  $1$  mEq/L, which can be seen in figure 3.

The quasi-Poisson regression model for potassium supplement prescriptions under 15 days with offset as total prescriptions within potassium concentration as an independent associated variable, shows that each  $1$  mEq/L increase in potassium concentration is associated with an ACEI risk ratio of  $0.37$  (95% CI  $0.32$  to  $0.43$ ,  $p<0.001$ ). This translates into a  $63\%$  decreased risk in the proportion of potassium supplement prescriptions given within 15 days of an ACEI prescription when the serum potassium goes up by  $1$  mEq/L, which can be seen in figure 4.

### DISCUSSION

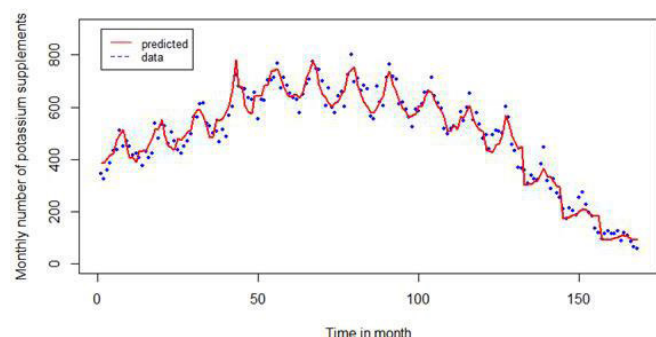
We see as in other recorded studies, correlating with lower ambient temperature, serum potassium values follow a seasonal pattern; peaks in winter months and troughs in summer. We also identify that, during summer months, there are annual spikes in the proportion of potassium prescriptions given suggesting a change in prescribing practice during these periods. The converse pattern is seen in the ACEI prescription proportion which annual spikes during the winter period with lower average ambient temperatures. These descriptive findings are confirmed when applied to time series modelling.

Our study is limited by the unavailability of free text in the medical notes, hence we could not make patient-level inferences as to exact reasons why their medications were amended. Second,



**Figure 3** The plot showing ACE inhibitor (ACEI) prescriptions under 15 days with predicted values over time from 2003 to 2016.





**Figure 4** The plot showing potassium supplement prescriptions under 15 days with predicted values over time from 2003 to 2016.

attempts to identify discontinuation of a prescription for a short period of time using anonymised dataset is challenging. Therefore, we will not be able to state general practitioners (GPs) are stopping or pausing patients on ACEi during the study period, but we are able to say that there has been some form of change to their prescription, indicating a prescribing decision has taken place. Third, our approved protocol and study dataset did not allow us to evaluate the concurrent effect of other blood parameters on potassium levels, such as renal function, platelet count and leucocyte count. Fourth, the effect of seasonal changes in blood pressure on prescribing activity was not part of our study protocol but could be influencing the prescribing patterns seen in ACEi and certainly warrants further investigation.<sup>37</sup>

Despite these limitations, our findings demonstrate the importance of educating clinicians on the extent of measurement error present in their serum sampling requests and subsequent prescribing decisions. Our findings also suggest further investigation is needed to explore the clinical effects of facilitating centrifugation or newer approaches such as multiple panel point of care testing at the site of venepuncture to minimise spurious potassium measurements.<sup>16 17</sup> It is clear that there is an associated clinical implication related to these erroneous results which is significant. Consideration should be given to the adoption of approaches in the region covered by NHS Grampian (where GP surgeries are provided centrifuges on site),<sup>17</sup> where significant reductions in erroneous samples have been achieved.<sup>18</sup> This would be aided by formal cost-benefit analyses of these approaches, which is so far lacking in the literature.

In conclusion, our study demonstrates there are observable shifts in prescribing activity temporally associated with ambient temperature-related changes in serum potassium levels. Clinicians should be educated as to the breadth of this issue and consider these findings when interpreting biochemistry results at different points throughout the year.

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**Contributors** RT, KN and JSC were responsible for study conception. RT, KN, KMG and JSC were responsible for data extraction and statistical analysis. RT, KN and JSC were responsible for initial drafting of the manuscript. All authors (RT, KN, KMG, NJA, RH and JSC) were responsible for ongoing drafts and final review of the manuscript. All authors have read and approved the final manuscript. JSC is the guarantor of the manuscript and work undertaken.

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**Competing interests** JSC, KN and KMG are codirectors of DEXTER operating division which is part of the University of Birmingham. DEXTER operating division supports the extraction and preparing of healthcare data to support epidemiological analyses such as those seen in this article.

**Patient and public involvement statement** Patients were not involved in the conception, design, analysis or drafting of this research/manuscript. However, findings of this published manuscript will be shared with our press office to co-produce a lay language summary which will be shared on social media and through the media.

**Patient consent for publication** Not applicable.

**Ethics approval** Anonymised data were used throughout the study provided by the data provider to the University of Birmingham. Studies using IMRD-UK database have had initial ethical approval from the NHS South-East Multicentre Research Ethics Committee, subject to prior independent scientific review. The Scientific Review Committee (IQVIA) approved the study protocol (SRC Reference Number: SRC19THIN036).

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**Data availability statement** Data may be obtained from a third party and are not publicly available.

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