Seasonal pattern of incidence and outcome of Acute Kidney Injury: A National study of Welsh AKI electronic alerts.

Dafydd Phillips*[1], Oliver Young*[1], Jennifer Holmes MSc[2], Lowri A Allen MB BCh[1], Gethin Roberts MSc[3], John Geen PhD[4/5], John D Williams MD[1], and Aled O Phillips MD[1]
On behalf of the Welsh AKI steering group.
*Made an equal contribution to this manuscript

[1] Institute of Nephrology, Cardiff University School of Medicine, Cardiff, U.K.
[2] Welsh Renal Clinical Network, Cwm Taf University Health Board.
[3] Department of Clinical Biochemistry, Hywel Dda University Health Board.
[4]Department of Clinical Biochemistry, Cwm Taf University Health Board, Merthyr, U.K.
[5] Faculty of Life Sciences and Education, University of South Wales, U.K.

Corresponding Author;
Professor Aled Phillips
Institute of Nephrology
Cardiff University School of Medicine
University Hospital
Heath Park
Cardiff, CF14 4XN
Tel: +44 2920 748467
E-mail: Phillipsao@cf.ac.uk

Abstract

Objectives: To identify any seasonal variation in the occurrence of, and outcome following Acute Kidney Injury.

Methods: The study utilised the biochemistry based AKI electronic (e)-alert system established across the Welsh National Health Service to collect data on all AKI episodes to identify changes in incidence and outcome over one calendar year (1st October 2015 and the 30th September 2016).

Results: There were are total of 48,457 incident AKI alerts. **The highest proportion of AKI episodes was seen in the quarter of January to March (26.2%), and the lowest in the quarter of October to December (23.3%, p<0.001).** The same trend was seen for both community-acquired and hospital-acquired AKI sub-sets. Overall 90-day mortality for all AKI was 27.3%. In contrast to the seasonal trend in AKI occurrence, 90-day mortality after the incident AKI alert was significantly higher in **the quarters of January to March** and **October to December** compared to the **quarters of April to June** and **July to September (p<0.001)** consistent with excess winter mortality reported for likely underlying diseases which precipitate AKI.

Conclusion: In summary we report for the first time in a large national cohort, a seasonal variation in the incidence and outcomes of AKI. The results demonstrate distinct trends in the incidence and outcome of AKI.

What is known.
Seasonal variation in diseases associated with the development of AKI has been previously reported.
What this study adds.
This is the first study to describe seasonal variation in the number of AKI cases and associated mortality.

Introduction

AKI is a clinical syndrome characterized by rapid loss of kidney function, and is associated with adverse patient outcomes [1-5]. It is estimated to occur in up to 15% of hospitalized patients and up to 60% of critically ill patients [2, 3, 6] . The estimated cost of AKI to NHS England is £1 billion/year or roughly 1% of the total NHS budget [7].

Significant weaknesses in patient management have been widely reported [8, 9]. In the U.K. the National Confidential Enquiry report highlighted sub-optimal care of AKI patients which may subsequently translate into episodes of preventable harm [10]. This has driven initiatives to facilitate early detection and intervention in order to improve patient outcomes. In response the Royal College of Physicians, at a consensus conference in the UK, recommended the adoption of an e-alert system to aid in the early identification of AKI [11]. The presumed benefits of early detection of AKI has led to the development of an automated an AKI electronic alert system in in Wales, and the other home countries of the United Kingdom [12]. Electronic alerts are generated by comparing a single serum creatinine measurement with previous measurements for the same patient, and flagging any results which represent a rise in creatinine equating AKI [13]. In addition to prompting clinicians to intervene at an early stage, this also provides a valuable source of data regarding the epidemiology of AKI. We have previously used this data set to report the incidence and outcome of AKI in adult [14] and paediatric patients [15] in Wales (U.K.). More recently we have demonstrated the significance of the electronic AKI alert in primary care [16].

Despite advances in health care, the incidence of AKI is increasing both in the UK [17, 18] and USA [19, 20]. Potential explanations for this increase may be related to increasingly aggressive medical and surgical therapies in a largely aging population with multiple comorbid conditions [21]. In the majority of cases AKI is a secondary to other disease states and critical illness rather than a reflection of primary intrinsic renal disease. Alterations in the patterns of these underlying diseases may therefore also contribute to the increased incidence of AKI. Seasonal variations have been described in many diseases which may precipitate AKI. In contrast to date there are no studies which address seasonal variations in the incidence and outcome of AKI. Using our data set generated from electronic AKI alerts in this manuscript we describe the seasonal trends for AKI over a one-year period. The data captures all cases of AKI in both community and hospital settings with AKI being defined by change in creatinine criteria.

Methods

Electronic Reporting of AKI: The previously described (and validated) Welsh electronic AKI reporting system [22], utlitises the Welsh Laboratory Information Management System (LIMS), (InterSystems TrakCare Lab) to automatically compare in real time measured creatinine values on an individual patient against previous results. This generates electronic AKI alerts, derived from a nationally agreed algorithm based on KDIGO AKI criteria [12].

The study was approved under Service Evaluation Project Registration.

Data Collection: Data was collected for all cases of adult (≥18yrs of age) AKI in Wales between 1st October 2015 and the 30th September 2016, and organised into quarters. **The "calendar" year was divided into four quarters: January to March (Jan-Mar), April to June (Apr-Jun), July to September (Jul-Sep) and October to December (Oct-Dec).** Clinical location, patient age, AKI stage and the rule under which the AKI alert was generated was collected together with all measurements of renal function for up to 30 days following the AKI alert. To prevent inclusion of known patients receiving renal replacement therapy, alerts transmitted by patients from a renal, renal transplant, or dialysis setting, and by patients who had a previous blood test in a dialysis unit were excluded.

Mortality data were collected from the Welsh Demographic Service (WDS). Patients were censored at 1 year for survival analysis.

Data analysis: All patients for which the first alert was issued during a hospital admission who also had a normal SCr value generated in a hospital setting within the preceding seven days were defined as Hospital acquired (HA)-AKI. Patients alerting in a non-inpatient setting (including Accident and Emergency/Acute assessment units) and not alerting in primary care were classified as non-primary care community acquired (CA)-AKI. Primary care and non-primary care CA-AKI therefore collectively represent CA-AKI. Hospitalisation of CA-AKI, was defined as a measurement of renal function in a hospital setting within 7 days following the AKI e-alert. 4399 (9.1%) patients whilst alerting in an in-patient setting had no results for the previous 7 days. As these patients did not therefore fall into either CA- or HA- definitions, they were excluded from the subgroup analysis.

An incident AKI episode was defined as 30 days i.e. any AKI e-alert for the same patient within 30 days the incident alert was not considered a new episode. Progression of AKI was defined as a peak AKI stage higher than that associated with incident e-alert or for stage 3 alerts an increase ≥50% from the SCr generating the alert. Pre-existing chronic kidney disease (PeCKD) was defined as an eGFR (calculated by CKDEpi eGFR formula [23]) <60ml/min/1.73m^2 derived from the baseline SCr.

Statistical significance was determined by one way ANOVA, student t test and Chi^2 test as appropriate. The influence of age, sex and pre-existing CKD on AKI incidence was assessed by logistic regression. P values less than 0.05 were considered statistically significant.

Results

Seasonal trends in AKI episodes:

Over the study period there were a total of 48,457 incident AKI alerts, and a progressive fall in the number of AKI episodes in each quarter of the **calendar** year (Table 1 and Figure 1A), with the proportion of AKI falling from 26.2% in the **quarter of Jan-Mar** to 23.3% in the **quarter of Oct-Dec** ($p<0.001$). The seasonal trend in AKI occurrence was not associated with differences in basic patient demographic as assessed by sex, age or pre-existing CKD (Table 1). In a logistic regression model age, gender and pre-existing CKD had no influence on the

primary outcome i.e. seasonal variation in AKI. As a results age adjusted incidence of AKI in each season also demonstrated a fall from 25.9% in **Jan-Mar** to 23.8% in **Oct-Dec** ($p<0.001$).

Incidence of CA-AKI: Of all AKI which occurred during the study period 49.9% were CA-AKI alerts (Table 2). This represents a total of 24,178 alerts. The number of CA-AKI episodes varied across the year (Figure 1B). The highest number (6265) was seen in **Jan-Mar,** and there were significantly fewer episodes (5632) during the **Oct-Dec** compared to each of the preceding quarters ($p<0.001$ for comparison of **Oct-Dec** vs. each of the other quarters)**.**

31.5% of CA-AKI represented alerts generated in Primary care (GP-AKI), and 48.4% represented patients alerting at the hospital front door (A&E AKI). Both cohorts demonstrated the same seasonal trends with a significantly lower number of AKI alerts in **Oct-Dec** (Table 2). Only 42.9% of all CA-AKI were admitted to hospital following the alert. The same seasonal trends seen in the whole cohort (with the lowest number seen in **Oct-Dec**) was also seen in both the admitted and non-admitted groups (Table 2).

Incidence of HA-AKI: Of all AKI that occurred during the study period 41.0% were HA-AKI alerts (Table 3). This represents a total of 19,880 alerts. The number of hospital acquired AKI episodes varied across the year (Figure 2C). The number of HA-AKI episodes in **Jan-March (5334**), was statistically greater than the number of episodes in all other quarters. The comparative fall in each quarter was statistically significant, with the lowest number of cases being seen in the **quarter of Oct-Dec (4569)**. The seasonal trend in AKI occurrence was not associated with differences in basic patient demographic as assessed by sex, age or pre-existing CKD.

In the absence of clinical data, to provide insight into the nature of HA-AKI we analysed the seasonal incidence of AKI in relation to the clinical speciality in which the alert was generated (Table 4). Only specialities in which ≥200 AKI episodes were documented during the year were included in this analysis. The decreasing trend of AKI incidence throughout the calendar year was significant in the majority of the medical specialties, the exceptions being hematology/oncology and endocrinology. It should however be noted that these two specialties also had the fewest number of episodes. Within the surgical specialties the pattern of falling numbers was seen in General surgical and urology locations only, and no seasonal changes in AKI occurrence was seen related to Trauma, Obstetrics and Gynecology nor Cardiothoracic location codes.

Seasonal trends in AKI outcomes

Overall 90-day mortality for all AKI was 27.3% (Table 1). 90-day mortality after the incident AKI alert **was significantly higher in the quarters of Jan-March and Oct-Dec** compared to the **Apr-Jun and Jul-Sep quarters (p<0.001).**

CA-AKI: 90-day mortality was also significantly higher following an incident CA-AKI alert, in the **Jan-Mar and Oct-Dec quarters** (Table 2). CA-AKI severity was

also highest in these quarters with a higher proportion of AKI stage 2/3. ICU admission was also used as a surrogate marker of disease severity. In the same two quarters a higher proportion of AKI episodes required support in an Intensive Care Unit (ICU) setting.

HA-AKI: As with CA-AKI, 90-day mortality was significantly higher following an alert in the **Jan-Mar and Oct-Dec quarters** (Table 3). For this subgroup however, there was no significant difference in AKI severity throughout the year, as assessed by AKI stage at presentation, and the proportion of patients requiring support in the ICU.

Discussion

The majority of publications of large series characterising AKI rely on making and recording an accurate diagnosis of AKI through hospital coding or retrospective review of hospital records [24-27]. As a result most studies of AKI focus on hospitalised patients [4, 8, 24, 26-29], and do not include all community acquired AKI, as a significant proportion of AKI in these settings do not result in hospitalisation [30-34]. We have previously demonstrated that using the electronic AKI data set provides a comprehensive characterisation of AKI across both community and hospital settings [14]. Our data therefore provides a comprehensive overview of trends of all cases of AKI defined by changes in serum creatinine. It should be noted however that any patients for which there are no results on the system existing from the previous 365 days will not be identified, although these cases may represent AKI. Currently any abnormal serum creatinine result with no baseline creatinine comparator is highlighted as an abnormal result requiring clinician scrutiny, but is not included in our data.

The data presented represent the first study to describe the seasonal variation in the number of episodes of AKI in a large national cohort. Whilst seasonal changes in disease patterns have been described for a number of illnesses, there is no published data regarding whether this affects the seasonal incidence of AKI. Our data demonstrates that there is a significant seasonal variation in the incidence of all AKI with a significant decreasing trend in the incidence throughout the calendar year.

In this manuscript it is evident that the seasonal patterns for AKI are similar for both CA-AKI and HA-AKI. For CA-AKI the trend is consistent for both the cases admitted and managed in the community, as well as those cases detected in primary care and at the hospital front door. This pattern therefore does not reflect the widely reported winter rise in emergency medical pressures in NHS hospitals across the United Kingdom which is accepted to reflect admissions related to respiratory and cardiovascular illness [35]. Within the HA-AKI AKI cohort, and in the absence of clinical data, we used the location of the AKI alerts to provide some insight into the potential causes of AKI. The seasonal trend for a fall in incidence was consistent across the majority of medical specialties. Within surgical specialties however the fall in the number of episodes throughout the year was seen for alerts generated in general surgical and urology location codes only and not in in trauma nor cardiothoracic locations. It is interesting to speculate that in the latter two specialties clinical activity in not a reflection of

"illness". Trauma cases relate to "human behavior patterns" rather than disease and tend to reflect patterns of weather and temperature whilst cardiothoracic surgery activity generally reflects elective planned surgery which leads to a consistent number of procedures throughout the year. In contrast, for medical specialties and general surgery, clinical activity is more closely associated to "illness" rather than elective activity, although we are unable to distinguish between elective and emergency cases and this therefore remains speculative.

Whilst demonstrating a significant trend our data does not however provide a clear explanation for this trend as the e-alert system is IT driven and based on creatinine values only. There is therefore no clinical context which precludes inclusion of clinical information, such as patient co-morbidity and linkage to primary care data sets. It also lacks the detail of the cause of AKI. In the majority of cases AKI does not represent intrinsic kidney disease but rather a response to other primary illness which leads to reduced renal perfusion. The seasonal variation in AKI incidence is therefore likely to reflect that common causes/precipitants of AKI demonstrate seasonal variation. Seasonal variation in disease presentations and hospital admissions is a well-described phenomenon. For example, acute myocardial infarction is more common during winter and spring [36, 37]. Whilst the explanation for this remains unclear it is postulated that the likely link is the association between variation in temperature and biological factors which contribute to disease pathogenesis such as blood pressure [38] and other metabolic factors [39, 40]. Epidemiological studies in diabetes have demonstrated that hypoglycaemic episodes are more common during summer months, whilst hyperglycaemic complications are more common in the first months of the year, with said patterns ascribed to changes in calorie consumption and physical activity [41-43]. Increased incidence of Gram-negative bacteraemia has been reported in summer months and associated with elevated monthly outdoor temperatures [44-46]. Community acquired pneumonia in contrast is more common in the spring and winter, as a result of the combination of circulating respiratory bacteria being more prevalent during colder seasons, and people spending more time indoors during colder months [47, 48]. Trauma is another potential predisposing factor for the development of AKI. Studies have shown that in paediatric cohorts, admissions relating to trauma are highest during summer months, presumably as children spend more time playing outdoors during these warmer months. In contrast, adults are more likely to be admitted with significant trauma during winter months, due to an increase in falls and accidents relating to ice/snow [49]. It is likely that each of these aforementioned diseases influence the seasonal variation of AKI and further studies are required focusing on the precipitating factors which lead to AKI to provide a robust link between disease aetiology and the seasonal variation that we have described. A striking and somewhat unexpected observation in this study however is the consistency of the seasonal trend across all of the sub-groups of AKI that we have examined.

In addition to the seasonal effect of disease incidence we have also found and temporal association with outcome following AKI. There was however a

disconnect between seasonal trends in incidence and outcome as mortality was highest in the first and fourth quarters of the **calendar** year, that is during the winter months. This is again consistent across CA- and HA-AKI. For CA-AKI mortality was associated with disease severity at presentation as the AKI stage at presentation was also higher in these two quarters, as was the need for ICU support. This association with AKI severity as assessed by these simple parameters were not however apparent for HA-AKI patients. This pattern of mortality is reflective of the accepted patterns of mortality associated with "winter pressures". Excess winter mortality has been described in studies dating back over a century [50], with an increase in all cause mortality, mortality related to cardiovascular disease, stroke, respiratory disease and gram negative bacteraemia all being reported [51-53] . In the majority of cases AKI does not represent intrinsic renal disease but occurs as a result of dysfunction of other organs leading to septic, ischemic or toxic insults to the kidneys. Although without additional clinical information our data set does not shed light on the cause of death, it is likely that the seasonal trends in mortality reflect different patterns of mortality associated with the primary underlying diseases which precipitate AKI.

In summary we report for the first time in a large national cohort, a seasonal variation in the incidence and outcomes of AKI. The results demonstrate distinct trends in the incidence and outcome of AKI. Incidence of AKI fell throughout the four quarters of the calendar year whilst mortality was higher in the **quarters of January to March and October to December** reflecting well described excess winter mortality association with numerous primary illnesses which may precipitate AKI. This study was derived from a biochemical data set. Further studies are therefore needed, in which data on clinical diagnosis and cause of death are captured to provide a detailed understanding of these reported trends.

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There are no competing interests

Legends

Figure 1: Total incidence of AKI per quarter.

A: Total number of all cause AKI episodes per quarter. *, $p<0.001$ vs. all other quarters. **B:** Total number of hospital acquired AKI episodes per quarter. *, $p<0.001$ vs. all other quarters; #, $p<0.001$ vs. **Jan-Mar**; §, $p<0.05$ vs. **Jan-Mar**. **C:** Total number of community acquired AKI episodes per quarter. *, $p<0.001$ vs. all other quarters; #, $p<0.001$ vs. **Oct-Dec** and **Jan-Mar**; §, $p<0.05$ vs. **Jul-Sep** and $p=0.008$ vs. **Jan-Mar**.

References:

1. Ali T, Khan I, Simpson W et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007; **18**: 1292-8.
2. Bagshaw SM, Laupland KB, Doig CJ et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Crit Care* 2005; **9**: R700-9.
3. Lo LJ, Go AS, Chertow GM et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int* 2009; **76**: 893-9.
4. Pannu N, James M, Hemmelgarn B, Klarenbach S. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin J Am Soc Nephrol* 2013; **8**: 194-202.
5. Wald R, Quinn RR, Adhikari NK et al. Risk of chronic dialysis and death following acute kidney injury. *Am J Med* 2012; **125**: 585-93.
6. Waikar SS, Wald R, Chertow GM et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J Am Soc Nephrol* 2006; **17**: 1688-94.
7. Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. *Nephrol Dial Transplant* 2014; **29**: 1362-8.
8. Aitken E, Carruthers C, Gall L et al. Acute kidney injury: outcomes and quality of care. *QJM* 2013; **106**: 323-32.
9. Wilson FP, Bansal AD, Jasti SK et al. The impact of documentation of severe acute kidney injury on mortality. *Clin Nephrol* 2013; **80**: 417-25.
10. National Confidential Enquiry into Patient Outcome and Death [NCEPOD] Report Acute Kidney Injury: Adding Insult to Injury. 2009.
11. Feehally J, Gilmore I, Barasi S et al. RCPE UK consensus conference statement: Management of acute kidney injury: the role of fluids, e-alerts and biomarkers. *J R Coll Physicians Edinb* 2013; **43**: 37-8.
12. Available from: https://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf
13. Holmes J, Roberts G, Meran S et al. Understanding Electronic AKI Alerts: Characterization by Definitional Rules. *Kidney International Reports*.
14. Holmes J, Rainer T, Geen J et al. Acute Kidney Injury in the Era of the AKI E-Alert. *Clin J Am Soc Nephrol* 2016; **11**: 2123-31.
15. Holmes J, Roberts G, May K et al. The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based electronic alert. *Kidney Int* 2017; **In Press**.
16. Holmes J, Allen N, Roberts G et al. Acute Kidney Injury Electronic alerts in Primary Care - Findings from a large population cohort. *QJM* 2017.
17. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. *BMJ* 1993; **306**: 481-3.
18. Metcalfe W, Simpson M, Khan IH et al. Acute renal failure requiring renal replacement therapy: incidence and outcome. *QJM* 2002; **95**: 579-83.
19. Hou SH, Bushinsky DA, Wish JB et al. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; **74**: 243-8.
20. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; **39**: 930-6.

21. Coca SG. Acute kidney injury in elderly persons. *Am J Kidney Dis* 2010; **56**: 122-31.
22. Holmes J, Rainer T, Geen J et al. Acute Kidney Injury in the era of the AKI e-alert: A National Survey. *Clin J Am Soc Nephrol* 2016; **In Press**.
23. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-12.
24. Bucaloiu ID, Kirchner HL, Norfolk ER et al. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012; **81**: 477-85.
25. Hsu CY, Chertow GM, McCulloch CE et al. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol* 2009; **4**: 891-8.
26. Hsu CY, McCulloch CE, Fan D et al. Community-based incidence of acute renal failure. *Kidney Int* 2007; **72**: 208-12.
27. Liangos O, Wald R, O'Bell JW et al. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. *Clin J Am Soc Nephrol* 2006; **1**: 43-51.
28. Tian J, Barrantes F, Amoateng-Adjepong Y, Manthous CA. Rapid reversal of acute kidney injury and hospital outcomes: a retrospective cohort study. *Am J Kidney Dis* 2009; **53**: 974-81.
29. Zhang JH, Palevsky PM, Chertow GM et al. Piecewise analysis of patient survival after onset of AKI. *Clin J Am Soc Nephrol* 2013; **8**: 1679-84.
30. Alavijeh OS, Bansal J, Hadfield K et al. Implementation of an Automated Primary Care Acute Kidney Injury Warning System: A Quantitative and Qualitative Review of 2 Years of Experience. *Nephron* 2017; **135**: 189-95.
31. Barton AL, Mallard AS, Parry RG. One Year's Observational Study of Acute Kidney Injury Incidence in Primary Care; Frequency of Follow-Up Serum Creatinine and Mortality Risk. *Nephron* 2015; **130**: 175-81.
32. Schissler MM, Zaidi S, Kumar H et al. Characteristics and outcomes in community-acquired versus hospital-acquired acute kidney injury. *Nephrology (Carlton)* 2013; **18**: 183-7.
33. Talabani B, Zouwail S, Pyart RD et al. Epidemiology and outcome of community-acquired acute kidney injury. *Nephrology (Carlton)* 2014; **19**: 282-7.
34. Wonnacott A, Meran S, Amphlett B et al. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol* 2014; **9**: 1007-14.
35. Afza M, Bridgman S. Winter emergency pressures for the NHS: contribution of respiratory disease, experience in North Staffordshire district. *J Public Health Med* 2001; **23**: 312-3.
36. Rumana N, Kita Y, Turin TC et al. Seasonal pattern of incidence and case fatality of acute myocardial infarction in a Japanese population (from the Takashima AMI Registry, 1988 to 2003). *Am J Cardiol* 2008; **102**: 1307-11.
37. Manfredini R, Manfredini F, Boari B et al. Seasonal and weekly patterns of hospital admissions for nonfatal and fatal myocardial infarction. *Am J Emerg Med* 2009; **27**: 1097-103.
38. MacMahon S, Peto R, Cutler J et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure:

prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765-74.
39. Mavri A, Guzic-Salobir B, Salobir-Pajnic B et al. Seasonal variation of some metabolic and haemostatic risk factors in subjects with and without coronary artery disease. *Blood Coagul Fibrinolysis* 2001; **12**: 359-65.
40. Gordon DJ, Trost DC, Hyde J et al. Seasonal cholesterol cycles: the Lipid Research Clinics Coronary Primary Prevention Trial placebo group. *Circulation* 1987; **76**: 1224-31.
41. Hashimoto T, Morita A, Hashimoto Y et al. Seasonal variation of severe hypoglycemia in hospitalized patients 60 years of age or older presenting to an emergency center hospital between 2004 and 2010. *Intern Med* 2013; **52**: 2721-6.
42. Tsujimoto T, Yamamoto-Honda R, Kajio H et al. Seasonal variations of severe hypoglycemia in patients with type 1 diabetes mellitus, type 2 diabetes mellitus, and non-diabetes mellitus: clinical analysis of 578 hypoglycemia cases. *Medicine (Baltimore)* 2014; **93**: e148.
43. Clemens KK, Shariff S, Richard L et al. Seasonal variation in hospital encounters with hypoglycaemia and hyperglycaemia. *Diabet Med* 2017.
44. Deeny SR, van Kleef E, Bou-Antoun S et al. Seasonal changes in the incidence of Escherichia coli bloodstream infection: variation with region and place of onset. *Clin Microbiol Infect* 2015; **21**: 924-9.
45. Eber MR, Shardell M, Schweizer ML et al. Seasonal and temperature-associated increases in gram-negative bacterial bloodstream infections among hospitalized patients. *PLoS One* 2011; **6**: e25298.
46. Alcorn K, Gerrard J, Macbeth D, Steele M. Seasonal variation in health care-associated bloodstream infection: increase in the incidence of gram-negative bacteremia in nonhospitalized patients during summer. *Am J Infect Control* 2013; **41**: 1205-8.
47. Cilloniz C, Ewig S, Gabarrus A et al. Seasonality of pathogens causing community-acquired pneumonia. *Respirology* 2017.
48. Murdoch KM, Mitra B, Lambert S, Erbas B. What is the seasonal distribution of community acquired pneumonia over time? A systematic review. *Australas Emerg Nurs J* 2014; **17**: 30-42.
49. Parsons N, Odumenya M, Edwards A et al. Modelling the effects of the weather on admissions to UK trauma units: a cross-sectional study. *Emerg Med J* 2011; **28**: 851-5.
50. Guy W. On the annual fluctuaations in the number of deaths from various diseases, compared with like fluctuations in crime, and in other events within and beyond the control of the human will. *J Stat Soc London* 1858; **21**: 52-86.
51. Abernethy JK, Johnson AP, Guy R et al. Thirty day all-cause mortality in patients with Escherichia coli bacteraemia in England. *Clin Microbiol Infect* 2015; **21**: 251 e1-8.
52. Zeka A, Browne S, McAvoy H, Goodman P. The association of cold weather and all-cause and cause-specific mortality in the island of Ireland between 1984 and 2007. *Environ Health* 2014; **13**: 104.
53. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. The Eurowinter Group. *Lancet* 1997; **349**: 1341-6.

Table 1: Seasonal changes in number, patient characteristics, AKI stage and outcome of All AKI episodes.

	Annual total	**Jan- Mar**	**Apr-Jun**	**Jul-Sep**	**Oct-Dec**	P value
Number of episodes, n (% of total)	48457	12674 (26.2)	12329 (25.4)	12116 (25.0)	11338 (23.4)	P<0.001
Mean age (yrs)	70.4	70.8	70.1	70.2	70.2	n/s
Proportion of males, n (%)	22861 (47.2)	5990 (47.3)	5853 (47.5)	5669 (46.8)	5349 (47.2)	n/s
% with pre-existing CKD	33.1	34.2	32.3	32.9	32.9	n/s
AKI stage, n (%)						
AKI1	37405 (77.2)	9655 (76.2)	9476 (76.9)	9510 (78.5)	8767 (77.3)	n/s
AKI2	7157 (14.8)	1924 (15.2)	1873 (15.2)	1679 (13.9)	1681 (14.8)	
AKI3	3895 (8.0)	1098 (8.7)	980 (7.9)	927 (7.7)	890 (7.8)	
90-day mortality, n (%)	13080 (27.3)	3694 (29.4)	3179 (26.1)	3061 (25.6)	3146 28.1)	P<0.001 **Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep**

Table 2: Seasonal changes in number, patient characteristics, AKI stage and outcome of CA-AKI episodes.

	Annual total	**Jan- Mar**	**Apr-Jun**	**Jul-Sep**	**Oct-Dec**	P value
Number of episodes, n (% of total)	24178	6265 (25.9)	6129 (25.4)	6152 (25.5)	5632 (23.3)	P<0.001 **Oct-Dec vs. Jan-Mar/Apr-Jun/Jul-Sep**
Mean age (yrs)	69.4	70.1	69.2	69.0	69.1	n/s
Proportion of males, n (%)	10995 (45.5)	2860 (45.7)	2799 (45.7)	2787 (45.3)	2549 (45.3)	n/s
% with pre-existing CKD	33.2	34.0	32.3	33.1	33.7	n/s
AKI stage, n (%)						
AKI1	17931	4559 (72.8)	4584 (74.8)	4663 (75.8)	4125 (73.2)	P=0.002 AKI1 vs. AKI2/3 **Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep**
AKI2	3898	1048 (16.7)	975 (15.9)	923 (15.0)	952 (16.9)	
AKI3	2349	658 (10.5)	570 (9.3)	566 (9.2)	555 (9.9)	
AKI associated with ICU admission, n (%)	1191 (4.9)	320 (5.1)	294 (4.8)	269 (4.4)	308 (5.5)	P=0.04 **Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep**
90-day mortality, n (%)	5206 (21.8)	1482 (23.9)	1218 (20.1)	1198 (19.7)	1308 (23.6)	P<0.001 **Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep**
CA-AKI sub-group seasonal incidence						
GP-AKI, n (%)	7626	1915 (25.1)	2024 (26.5)	2022 (26.5)	1665 (21.8)	P<0.001 **Oct-Dec vs. Jan-Mar/Apr-Jun/Jul-Sep**
A&E AKI, n (%)	11693	3197 (27.3)	2867 (24.5)	2873 (24.6)	2756 (23.6)	P<0.001 **Oct-Dec vs. Jan-Mar/Apr-Jun/Jul-Sep**

AKI admitted, n (%)	10368	2784 (26.9)	2568 (24.8)	2535 (24.5)	2481 (23.9)	P<0.001 **Oct-Dec vs. Jan-Mar/Apr-Jun/Jul-Sep**
CA-AKI Not admitted, n (%)	13810	3481 (28.9)	3561 (25.8)	3617 (26.2)	3151 (22.8)	P<0.001 **Oct-Dec vs. Jan-Mar/Apr-Jun/Jul-Sep**

Table 3: Seasonal changes in number, patient characteristics, AKI stage and outcome of HA-AKI episodes.

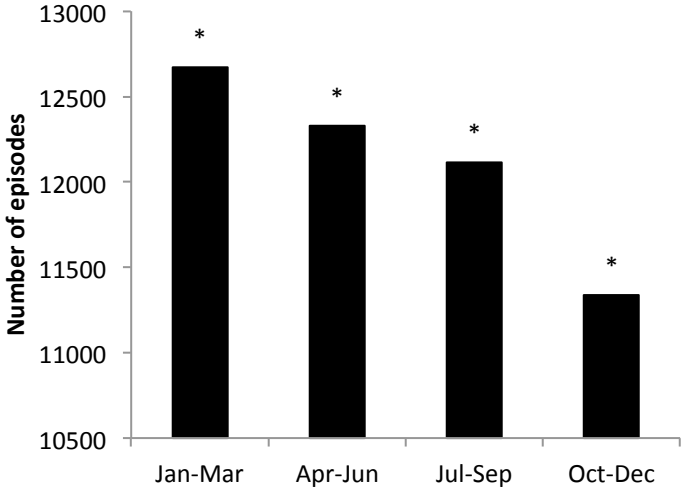
	Annual total	**Jan- Mar**	**Apr-Jun**	**Jul-Sep**	**Oct-Dec**	P value
Number of episodes, n (% of total)	19878	5333 (26.8)	5120 (25.8)	4857 (24.4)	4568 (22.9)	P<0.001 **Oct-Dec vs. Jan-Mar/Apr-Jun/Jul-Sep**
Mean age (yrs)	69.4	70.1	69.2	69.0	69.1	n/s
Proportion of males, n (%)	9554 (48.1)	2567 (48.1)	2467 (48.2)	2291 (47.2)	2229 (48.8)	n/s
% with pre-existing CKD	33.8	35.2	33.4	33.8	32.6	n/s
AKI stage, n (%)						
AKI1	16279 (81.9)	4355 (81.6)	4128 (80.6)	4010 (82.6)	3786 (82.9)	n/s
AKI2	2495 (12.6)	666 (12.5)	698 (13.6)	593 (12.2)	538 (11.8)	
AKI3	1106 (5.6)	313 (5.9)	294 (5.7)	254 (5.2)	245 (5.4)	
AKI associated with ICU admission, n (%)	1028 (5.4)	284 (5.6)	245 (5.0)	237 (5.0)	262 (5.9)	n/s
90-day mortality, n (%)	6924 (33.2)	1855 (35.1)	1636 (32.3)	1530 (31.9)	1503 (33.2)	P=0.003 **Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep**

Table 4: Seasonal variation in HA-AKI by location (Medical specialty) of AKI alert: n (% in quarter).

	Annual total	**Jan- Mar**	**Apr-Jun**	**Jul-Sep**	**Oct-Dec**	P value
Medical Specialties						
Internal Medicine	5000	1342 (26.8)	1258 (25.2)	1265 (25.3)	1135 (22.7)	P<0.001
Care of the elderly	1946	533 (27.4)	492 (25.3)	483 (24.8)	438 (22.5)	P=0.005
Cardiology	1730	470 (27.2)	444 (25.7)	413 (23.9)	403 (23.3)	P=0.03
Gastroenterology	915	229 (25.0)	251 (27.4)	239 (26.1)	196 (21.4)	P=0.02
Thoracic Medicine	876	252 (28.8)	245 (27.9)	214 (24.4)	165 (18.8)	P<0.001
Haem/Oncology	529	136 (25.7)	133 (25.1)	119 (22.5)	141 (26.5)	n/s
Endocrinology	318	90 (28.3)	85 (26.7)	79 (24.8)	64 (20.1)	n/s
Surgical Specialties						
General Surgery	2511	682 (27.2)	630 (25.1)	596 (23.3)	603 (24.1)	P=0.02
Trauma & Orthopaedic	1694	427 (25.2)	414 (28.7)	422 (24.9)	431 (25.4)	n/s
Urology	703	177 (25.2)	202 (28.7)	171 (24.2)	153 (21.7)	P=0.02
Gynaecology	244	65 (26.6)	62 (25.4)	58 (23.8)	59 (24.2)	n/s
Obstetrics	246	58 (23.6)	79 (32.1)	53 (21.5)	56 (22.8)	n/s
Cardiothoracic Surgery	237	64 (27.0)	63 (26.6)	54 (22.8)	56 (23.6)	n/s
Anaesthetics /ICU	218	59 (27.1)	67 (30.7)	51 (23.4)	41 (18.8)	P=0.02

FIGURE 1

A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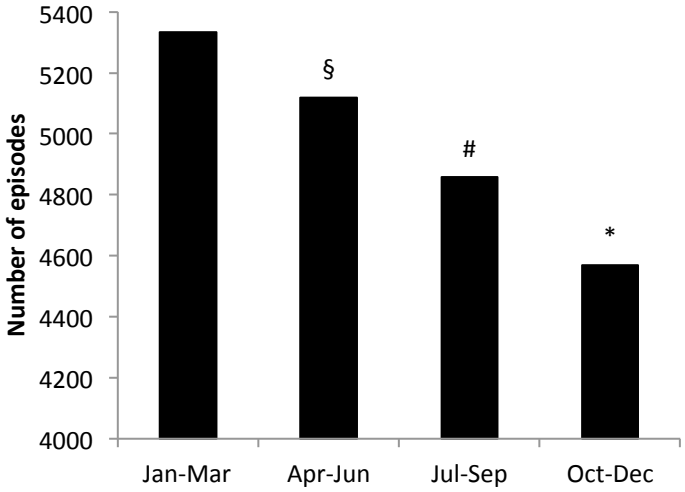
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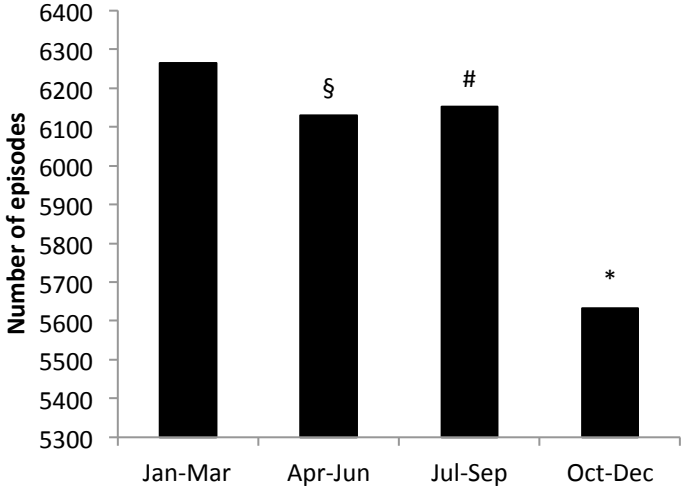
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