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Inpatient Hospitalization and Mortality Rate Trends from 2004 – 2014 in the United States: A Propensity Score-Matched Case-Control Study of Hyperkalemia

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Keywords: Hyperkalemia, potassium, National Inpatient Sample, hospitalization, mortality, heart failure, kidney disease, diabetes mellitus

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Abstract

Objective: To study the trends of hyperkalemia in United States inpatient hospitalization records with heart failure (HF), chronic kidney disease (CKD), acute kidney injury (AKI), and/or type II diabetes mellitus (T2DM) from 2004-2014 with respect to prevalence and inpatient mortality

Design: Observational cross-sectional and propensity score-matched case-control study

Setting: The National Inpatient Sample (representing up to 97% of inpatient hospital discharge records in the United States) from 2004-2014

Participants: 120,513,483(±2,312,391) adult inpatient hospitalization records with HF, CKD/ESRD, AKI, and/or T2DM

Exposure: Hyperkalemia, defined as the presence of an ICD-9-CM code of '276.7' in any of the first 15 diagnostic codes

Primary and Secondary Outcome Measures: The outcomes of interest are the annual rates of hyperkalemia prevalence and inpatient mortality.

Results: Among 120,513,483(±2,312,391) adult inpatient hospitalizations with HF, CKD/ESRD, AKI, and/or T2DM, we found a 28.9% relative increase of hyperkalemia prevalence from 4.94% in 2004 to 6.37% in 2014 ($p<0.001$). Hyperkalemia was associated with an average of 4 percentage points higher rate of inpatient mortality (1.71 post-matching, $p<0.0001$). Inpatient mortality rates decreased from 11.49%±0.17% to 6.43%±0.08% and 9.67%±0.13% to 5.05%±0.07% for matched cases with and without hyperkalemia, respectively ($p<0.001$).

Conclusions: Hyperkalemia prevalence increased over time and was associated with greater inpatient mortality, even after accounting for presentation characteristics. We detected a decreasing trend in inpatient mortality risk, regardless of hyperkalemia presence.

Keywords: Hyperkalemia, potassium, National Inpatient Sample, hospitalization, mortality, heart failure, kidney disease, diabetes mellitus

Article Summary

In this study of 120,513,483(±2,312,391) adult inpatient hospitalization records with heart failure, chronic kidney disease, end stage renal disease, acute kidney injury, and/or type II diabetes mellitus, we found a relative increase of 28.9% in hyperkalemia prevalence (from 4.94% in 2004 to 6.37% in 2014). We found that hospitalizations in which hyperkalemia occurred were far more likely to be severe in nature and that the presence of hyperkalemia was associated with a higher rate of inpatient mortality. After controlling for primary diagnosis, severity of illness, comorbidities, hospital characteristics, and socio-demographics via propensity score matching, we found that the presence of hyperkalemia was still associated with a higher mortality rate (average absolute difference=1.71%, average relative difference=25.3%, $p < 0.0001$), and the rate decreased similarly between groups over time, decreasing from 11.49%±0.17% to 6.43%± 0.08% for cases with hyperkalemia and from 9.67%±0.13% to 5.05%± 0.07% for cases without hyperkalemia.

Strengths and Limitations

- This is a large study, representing up to 120,513,483 (±2,312,391) inpatient discharges in the United States across 11 years.
- Neither medication nor laboratory information was available in the data source.
- We overcame the inherent imbalance of characteristics between hospitalizations with vs. without hyperkalemia by performing additional analyses on a propensity score matched data set, which made our conclusions more robust.

INTRODUCTION

Hyperkalemia, potassium levels above the upper limit of normal, is rare in the general population, but may be a concern for individuals with renal insufficiency, type II diabetes mellitus (T2DM), and/or congestive heart failure (HF) as a natural consequence of disease or corresponding medication.[1] Many of the medications used to treat these comorbidities may induce hyperkalemia either by altering the cellular shift of potassium or by impairing the kidneys' ability to excrete it.[2] Although mild hyperkalemia may be asymptomatic, when potassium levels are very high (>6.5 mmol/L), life-threatening cardiac arrhythmias, muscle weakness, and/or paralysis may occur; even mild hyperkalemia can cause permanent damage, if left untreated.[1,3,4] Because the comorbidity burden and subsequent requirement for chronic medications has amplified in America as the population has become increasingly older, it is imperative to study the trends of hyperkalemia in America over time.[5,6,7] Hence, the purpose of this paper is to study the trends of hyperkalemia in Americans hospitalized with HF, chronic kidney disease (CKD)/end stage renal disease (ESRD), acute kidney injury (AKI), and/or T2DM from 2004-2014 with respect to prevalence and inpatient mortality.

MATERIALS AND METHODS

This research was approved by the Baylor Scott & White Research Institute's Institutional Review Board via expedited review and was found to be exempt due to being secondary research; informed consent was not required. Neither patients nor the public were involved in the design, conduct, reporting, dissemination plans of this research.

Data

Data Source

The NIS is the largest database developed for the Healthcare Cost and Utilization Project, comprised of approximately 20% of hospitals in the United States, housing approximately 8 million discharge records per year, allowing inferences to be made on approximately 97% of U.S. population.[8] The NIS has a complex sample design. From 1998 – 2011, 100% of discharges were collected from 20% of U.S. hospitals; from 2012 onward, a 20% national patient-level sample has been utilized.[9, 10] To calculate national estimates, users must account for hospital clusters, stratification, and sample weights (accounting for the sample design change in 2012, if performing a trend analysis).[11] The database may be used to evaluate inpatient mortality. [12]

Key Variables:

This cross-sectional observational study was designed to examine any hospital discharge in the NIS from 2004-2014 for adults (age ≥ 18 years) with HF, CKD/ESRD, AKI, and/or T2DM. We used methodology described in Healthcare Cost and Utilization Project (HCUP) documentation to search for diagnoses of interest, as documented with ICD-9-CM codes, through the 15th diagnostic position. For example, if the code '428.X' was present in any of the first 15 listed diagnoses associated with the hospitalization, we flagged the record as having HF and included it in this analysis. We modified the Elixhauser diabetes comorbidities code sets to select cases specifically with T2DM, and to combine 'complicated and uncomplicated' classes. Similarly, we identified the primary condition of interest, hyperkalemia, by searching through the 15th diagnostic position for the ICD-9-CM code '276.7.' We were then able to calculate prevalence using the binary indicator variable for hyperkalemia. We also incorporated information from the severity files available from NIS which contain information on Elixhauser comorbidities. The endpoint of inpatient mortality was all available on the yearly NIS core files provided from HCUP.

Data cleaning

The data required a minimal amount of cleaning prior to matching and analyses. Due to sparse categories, we combined levels of primary payor so that 'self-pay', 'no charge', and 'other' were combined into 1 group. We did the same for race/ethnicity, combining Asian, Native American, other, and unknown. Finally, we did the same for the All-Patient Refined Diagnosis Related Groups (APR-DRG) severity variable, such that those with no loss of function and those with minor loss of function were combined into 1 group. Data were missing at low rates and were imputed as follows. If weekend admission was missing, we assigned a value of 0 (this occurred nearly 0%). If gender was missing, we designated female as the default – we did so because there were slightly more women in the sample, and gender was missing at a very small rate (0.03%). Median income quartile was missing at the highest rate (2.06%) and we created an imputation rule with a multivariable model using factors that were found to be significantly associated with it (race, gender, T2DM, hospital region, hospital location/teaching status, and hospital bed size).

Propensity Score Matching

We conducted the matched case-control portion of the study using a greedy nearest neighbor matching algorithm such that 1 record with hyperkalemia was matched without replacement to the 1 record without hyperkalemia having the closest propensity score (PS). We set a caliper boundary of 0.25 to achieve reasonable matches (if the closest possible match had a difference in score > 0.25, the case was unmatched and excluded from analyses). Following the work of potassium-specific analyses and NIS-specific analyses, such as those by Basnet and colleagues, Tanenbaum and colleagues, and Ahmed and colleagues, we created the regression model (using hyperkalemia as the outcome) based on the following independent predictors: age,

gender, race/ethnicity, median zip code income quartile, weekend admission, primary payor, smoking status, HF, CKD/ESRD, T2DM, APRDRG severity, hypertension (HTN), obesity, hospital region, hospital location/teaching status, hospital bed size.[13,14,15] Because it was our intention from the beginning of this project to conduct subgroup analyses according to primary diagnosis and to draw inferences on trends over time, we conducted the matching within year-specific files by primary diagnosis. Doing so ensured a PS-matched dataset with balanced allocation by year and primary diagnosis. To improve model convergence for the relatively small subgroup of CKD/ESRD primary diagnosis, we did not match on HTN, obesity, smoking, gender, or hospital location; these factors did not differ according to hyperkalemia presence. We excluded records with a primary diagnosis of hyperkalemia prior to matching.

Statistical Analyses

Due to the complex design of the NIS, as well as its re-structuring in 2012, the calculation of summary statistics for this trend study required additional steps compared to a cross-sectional analysis. We applied specialized discharge weights provided from HCUP ('trendwt' for years 2004-2011 and 'discwt' for years 2012-2014) to calculate the statistics. We used the 'surveymeans' and 'surveyfreq' procedures in SAS to account for clustering by hospital, stratification by 'NIS stratum,' and discharge record weight assignment. Categorical results are presented as percent and standard error. To compare characteristics between groups, we followed the work of Rosenbaum and Rubin, considering an absolute value of the standardized difference > 0.10 to be significantly different.[16] We utilized the 'surveylogistic' procedure to evaluate a trend in prevalence over time, as well as to assess the significance of hyperkalemia presence on trends in inpatient mortality rates over time.

RESULTS:

Unmatched analysis

To achieve our objective regarding prevalence, we required the use of an unmatched data set. There was a total of 24,941,608 discharge records of patients aged ≥ 18 years in the NIS from 2004-2014 with presence of CHF, CKD/ESRD, AKI, or T2DM, which represent a total of 120,513,483 (±2,312,391) inpatient discharges in the US. In this cohort we found a total of 1,397,573 records containing hyperkalemia, which represent a total of 6,761,577 (±149,409) discharges in the US. This corresponds to an average annual prevalence of 5.61%, which increased over time from 4.94% ± 0.07% in 2004 to 6.37% ± 0.04% in 2014, a relative increase of 28.9% ($p<0.0001$, Figure 1). Partly due to the large sample size, significant differences between groups were observed in every variable examined (Table 1); however, the distributions of age, gender, HF, and hospital characteristics were similar between those who did vs. did not have hyperkalemia. African Americans and Hispanics had a higher risk of hyperkalemia than Caucasians. Hospitalizations including hyperkalemia had higher rates of renal dysfunction (acute and chronic) and major/extreme loss of function (APR-DRG severity).

Inpatient mortality rates were significantly higher for cases with vs. without hyperkalemia (average absolute difference = 4.0%, average relative difference=97.81%, $p < 0.0001$), and the rate decreased non-uniformly between groups over time, decreasing at a faster rate for cases with hyperkalemia (10.91%±0.17% to 6.23%± 0.08%) than for cases without hyperkalemia (4.81%±0.05% to 3.8%±0.03%) ($p_{year} < 0.0001$, $p_{interaction} < 0.0001$, Figure 2).

Matched Analysis

To achieve our objective regarding inpatient mortality rates while accounting for confounders, we performed PS-matching. After matching, we had a total of 2,606,462 records,

representing 12,517,269 (±174,562) hospital discharges. The unweighted records reflect the 1:1 matching (i.e., 1,303,231 records in each group), but they represent an odd number of discharges due to records having unequal weights. Patient characteristics were well balanced, with standardized differences all < 0.10 (Table 1). Note that because we excluded cases of hyperkalemia as the primary diagnosis for the matched analyses, the cases with hyperkalemia and their characteristics are not identical to those in the unmatched cohort.

Inpatient mortality rates were significantly higher for cases with vs. without hyperkalemia (average absolute difference=1.71%, average relative difference=25.3%, p < 0.0001), and the rate decreased uniformly between groups over time, decreasing from 11.49%±0.17% to 6.43%± 0.08% for cases with hyperkalemia and from 9.67%±0.13% to 5.05%± 0.07% for cases without hyperkalemia (p < 0.0001, Figure 3).

DISCUSSION

In this study considering adult inpatient hospitalizations with HF, CKD/ESRD, AKI, and/or T2DM, we found a relative increase of 28.9% in hyperkalemia prevalence (from 4.94% in 2004 to 6.37% in 2014). We found that hospitalizations in which hyperkalemia occurred were far more likely to be severe in nature. Accordingly, we found that the presence of hyperkalemia was associated with a higher rate of inpatient mortality. Further, after controlling for primary diagnosis, severity of illness, comorbidities, hospital characteristics, and socio-demographics, we found that the presence of hyperkalemia continued to play a significant role in inpatient mortality risk. We also observed significant reductions in inpatient mortality over time.

Our work reiterates and extends findings from Betts and colleagues, who determined that the prevalence of hyperkalemia among patients with CKD and/or HF increased from 4.95% to 6.35% (a relative increase of 28.2%) using insurance claims records and laboratory test results

from 2010-2014 in the Truven MarketScan claims and encounters database.[17] The nearly 30% increase in hyperkalemia prevalence in Betts' study, as well as in our current examination of inpatient hospitalizations may be partially explained by the aging population, increasing comorbidity burden, and need for chronic/multiple medications.[3,4] Additionally, our timeframe is large enough such that improved abilities and/or standards of documentation may have been adopted by hospitals over time.[18] For example, it is possible that the implementation of specialized tools within electronic health systems over time may have made the documentation of multiple diagnoses easier.[19] Similarly, another possible explanation is that general awareness of hyperkalemia may have increased over time and that physicians became more likely to screen for it. For example, searching PubMed for the term 'hyperkalemia' yields 206 and 357 papers for 2004 and 2014, respectively.

Our findings extend those of Singer and colleagues' cross-sectional study which determined that hyperkalemia was independently associated with greater risk of inpatient admission (80% vs. 39% from patients in the emergency department with moderate hyperkalemia vs. normal potassium levels, respectively) and mortality (5.5% vs. 0.8% among those with moderate hyperkalemia vs. normal potassium levels, respectively).[20] Similarly, Davis and colleagues found that having severe hyperkalemia increased the risk of inpatient mortality by 58.5% compared to having mild hyperkalemia (19.5% vs 12.3%).[21] Cheunpasitporn and colleagues found mild hyperkalemia to carry an associated 22% increased risk of inpatient mortality among those with CKD, after adjusting for confounders.[22] While we do not know the severity of hyperkalemia in our study, our results are similar in that the presence of hyperkalemia was associated with an average 25% increase in the risk for mortality in the matched analysis and a 98% increase in the unmatched analysis. In general, hyperkalemia's association with increased

risk of mortality may simply be reflective of a more severe overall presentation, or it may contribute to death by complicating an already difficult-to-treat disease state, or even more directly by inducing life-threatening cardiac arrhythmias.[23,1] Our observation of mortality rates declining over time may be reflective of the large percentage of records with CKD in this study, as it has been shown that CKD mortality rates in Medicare beneficiaries have declined over time but remain significantly higher than the rates observed in patients without CKD.[24] Further, the declining rates may be partially attributable to advancements in technology and medical care delivery. For example, increased use of point-of-care potassium testing could have resulted in faster delivery of care.[25]

Although we observed a significant increase in its prevalence, as well as a higher mortality rate for those who have it, preventing and treating hyperkalemia is possible. In some cases, particularly patients with CKD at risk for chronic hyperkalemia, a potassium-restricted diet may be beneficial.[26] For cases of drug-induced hyperkalemia, interrupting the prescription may be a solution; however, new challenges may arise if the medication was for the management of a chronic condition, which is often true.[2] Alternatively, diuretics may be used to increase potassium excretion via urine and dialysis may be used to remove excess potassium from blood. In the setting of a hyperkalemic emergency, an intravenous infusion of calcium and insulin may be used to both protect the heart and cause a cellular shift of potassium. Another treatment for hyperkalemia is potassium-binding medication, which expels excess potassium through fecal matter.[27] One such drug is sodium polystyrene sulfonate (SPS), which has been used since the late 1950's, but is associated with serious gastrointestinal side effects (and even colonic necrosis in rare cases) and has a relatively low adherence rate.[28] Two additional drugs, sodium zirconium cyclosilicate and patiromer, help patients achieve and maintain normal potassium levels.[29] These

have advantages over SPS in that they are associated with fewer side effects and they may be efficacious regardless of RAASi and/or diet.[25] These newer drugs received FDA approval after our study timeframe, so they do not explain our observed reduction in mortality rate; however, it is of interest to determine whether these rates have further declined since their availability.

The study was designed to examine any record with HF, CKD/ESRD, AKI, or T2DM. Doing so provided a very large and rich dataset for studying hyperkalemia trends in in-patient hospitalizations. Due to the broad inclusion criteria of these analyses, this work did not shed light on comparisons within specific types of hospitalizations (i.e., according to primary diagnosis). In this paper, we overcame the inherent imbalance of characteristics between hospitalizations with vs. without hyperkalemia by performing additional analyses on a PS-matched data set, which made our conclusions more robust. Further, we conducted the PS-matching within specific primary diagnoses because it is our intention to perform subgroup analyses according to primary diagnosis in future work.

Limitations of this study include that the timeframe under evaluation ended in 2014; this was due to availability of data and to maintain consistency with ICD-9-CM coding. We acknowledge that there may be additional epidemiological changes to the data since then, particularly following the introduction of newer therapies for hyperkalemia. Hence, it may be of interest to conduct this study using more recent data. Additionally, because the NIS is de-identified, it is possible that an individual may be present in the data more than once without means to identify such an occurrence; for that reason, the data are interpreted as independent hospital discharges, not as patients. Additionally, laboratory results are not available in the NIS. As such, the definition of hyperkalemia in this study was based on its ICD code and limits our conclusions regarding potential causes of mortality, as the severity of hyperkalemia is unknown.

Similarly, medications are not available in the NIS and we are unable to make inferences regarding the effects of therapies received. Further, cause of death is not available in this data source. Finally, there were instances in which there was only 1 cluster within a stratum, so the standard error could not be calculated; however, this happened in less than 1% of the data. While this work's data source represents up to 97% of United States hospital discharges, more work is needed to understand whether these findings generalize to other countries.

CONCLUSION

In this large 10-year study of inpatient hospitalizations, hyperkalemia became more prevalent and was associated with greater illness severity and inpatient mortality than hospitalizations without hyperkalemia. Inpatient mortality rates decreased in this timeframe, regardless of hyperkalemia presence; however, the risk of death remained higher when hyperkalemia was present.

Author Contributions:

KMT – Design, data acquisition, analyses, interpretation, drafting, critical revision, approval, and accountability.

RAB – Interpretation, critical revision, approval, and accountability.

LC – Interpretation, critical revision, approval, and accountability.

PMC – Design, interpretation, critical revision, approval, and accountability.

Data Availability

The National Inpatient Sample data files are available for purchase through the Online HCUP Central Distributor; all HCUP data users must complete the HCUP Data Use Agreement Training Tool, and read and sign the Data Use Agreement for Nationwide Databases.

Conflicts of Interest

The authors have nothing to disclose.

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Figure Headers

Figure 1. Prevalence of hyperkalemia in inpatient hospitalizations including congestive heart failure, chronic kidney disease (and end stage renal disease), acute kidney injury, and/or type II diabetes mellitus

Figure 2. Annual in-hospital mortality rates (with standard error bars) for the unmatched cohort according to presence of hyperkalemia in hospitalizations including congestive heart failure, chronic kidney disease (and end stage renal disease), acute kidney injury, and/or type II diabetes mellitus

Figure 3. Annual in-hospital mortality rates (with standard error bars) for the propensity score-matched cohort according to presence of hyperkalemia in hospitalizations including congestive heart failure, chronic kidney disease (and end stage renal disease), acute kidney injury, and/or type II diabetes mellitus

Table 1. Patient characteristics of the unmatched and matched cohorts according to hyperkalemia presence

	Unmatched Cohort			Matched Cohort		
	Hyperkalemia			Hyperkalemia		
Characteristic	Yes	No	Standardized Difference	Yes	No	Standardized Difference
Age Group						
18 - 44	9.05 (0.1)	7.76 (0.07)	0.3999	8.64 (0.1)	8.14 (0.09)	0.0179
45 - 54	11.67 (0.09)	11.97 (0.08)	-0.0990	11.43 (0.09)	10.82 (0.09)	0.0192
55 - 64	18.28 (0.08)	18.4 (0.06)	-0.0426	18.09 (0.08)	16.85 (0.08)	0.0322
65 - 74	21.65 (0.06)	22.56 (0.05)	-0.3623	21.72 (0.06)	22.13 (0.06)	-0.0099
75+	39.35 (0.23)	39.32 (0.19)	0.0066	40.12 (0.23)	42.06 (0.22)	-0.0397
Gender (female)	49.34 (0.09)	51.79 (0.07)	-0.8118	49.43 (0.09)	49.95 (0.08)	-0.0103
Race/ethnicity						
White	53.45 (0.59)	58.94 (0.58)	-0.7165	54.23 (0.59)	55.42 (0.57)	-0.0239
Black	18.62 (0.43)	14.48 (0.33)	0.6359	18.29 (0.42)	17.79 (0.39)	0.0128
Hispanic	9.74 (0.32)	7.98 (0.26)	0.3115	9.4 (0.3)	8.99 (0.3)	0.0140
Other	18.19 (0.64)	18.6 (0.62)	-0.0517	18.08 (0.64)	17.8 (0.63)	0.0074
Heart failure	38.6 (0.16)	37.41 (0.12)	0.2958	39.26 (0.16)	39.33 (0.15)	-0.0013
CKD/ESRD	56.84 (0.18)	28.36 (0.12)	6.6531	55.42 (0.18)	54.53 (0.16)	0.0179
Acute kidney injury	49.53 (0.18)	20.12 (0.11)	6.955	51.04 (0.18)	42.31 (0.16)	0.1746
T2DM	47.28 (0.13)	60.07 (0.11)	-3.4897	46.92 (0.14)	46.69 (0.13)	0.0047
Hypertension	61.95 (0.16)	67.85 (0.12)	-1.4971	60.5 (0.16)	60.81 (0.15)	-0.0065
Obesity	11.4 (0.1)	13.92 (0.09)	-0.8082	11.93 (0.1)	11.18 (0.09)	0.0231
Smoker	7.68 (0.08)	9.69 (0.08)	-0.7077	7.58 (0.08)	6.86 (0.07)	0.0272
Primary Diagnosis						
Acute kidney Injury	15.01 (0.08)	2.91 (0.02)	4.1859	15.89 (0.09)	15.9 (0.1)	-0.0003
Heart failure	7.99 (0.05)	8.7 (0.04)	-0.3278	8.49 (0.05)	8.51 (0.05)	-0.0006
CKD/ESRD	0.34 (0.01)	0.1 (0)	0.2619	0.36 (0.01)	0.36 (0.01)	0.0002
Other	73.2 (0.09)	84.99 (0.05)	-3.9621	71.6 (0.09)	71.59 (0.1)	0.0003
T2DM	3.45 (0.03)	3.31 (0.02)	0.0840	3.66 (0.03)	3.65 (0.03)	0.0005
Primary payer						
Medicare	70.96 (0.22)	66.93 (0.2)	0.8573	71.07 (0.21)	72.9 (0.2)	-0.0405
Medicaid	10.44 (0.16)	9.07 (0.13)	0.3396	10.25 (0.15)	9.52 (0.14)	0.0239
Private insurance	13.48 (0.14)	17.96 (0.14)	-1.2035	13.59 (0.14)	12.89 (0.13)	0.0205
Other	5.12 (0.15)	6.03 (0.12)	-0.2395	5.09 (0.13)	4.69 (0.1)	0.0186
Zipcode income quartile						
First quartile	33.22 (0.49)	31.3 (0.44)	0.2751	32.9 (0.49)	32.95 (0.46)	-0.0011
Second quartile	27.41 (0.33)	27.78 (0.32)	-0.0646	27.32 (0.34)	27.21 (0.33)	0.0025
Third quartile	22.4 (0.29)	22.8 (0.27)	-0.0745	22.52 (0.29)	22.39 (0.28)	0.0030
Fourth quartile	16.97 (0.44)	18.11 (0.44)	-0.1720	17.26 (0.45)	17.45 (0.43)	-0.0049
Hospital region						
Northeast	17.72 (0.52)	19.39 (0.51)	-0.2331	18.12 (0.53)	18.13 (0.49)	-0.0004

Midwest	23.76 (0.58)	23.7 (0.53)	0.0088	23.17 (0.59)	23.12 (0.56)	0.0013
South	40.33 (0.74)	39.84 (0.71)	0.0574	40.54 (0.75)	41.07 (0.73)	-0.0108
West	18.18 (0.52)	17.07 (0.48)	0.1552	18.17 (0.52)	17.68 (0.5)	0.0127
Hospital setting						
Rural	11.29 (0.38)	13.1 (0.37)	-0.2952	11.16 (0.38)	11.15 (0.36)	0.0003
Urban nonteaching	41.14 (0.7)	41.02 (0.66)	0.0146	41.56 (0.71)	41.49 (0.68)	0.0015
Urban teaching	47.57 (0.71)	45.88 (0.68)	0.2017	47.28 (0.72)	47.36 (0.7)	-0.0017
Hospital bed size						
Small	12.13 (0.31)	13.31 (0.3)	-0.2116	12.03 (0.32)	11.58 (0.28)	0.0140
Medium	25.26 (0.52)	25.23 (0.48)	0.0042	25.32 (0.53)	24.92 (0.49)	0.0093
Large	62.61 (0.61)	61.46 (0.58)	0.1475	62.64 (0.62)	63.5 (0.58)	-0.0177
Weekend admission	21.83 (0.05)	20.68 (0.04)	0.5302	21.99 (0.05)	21.15 (0.05)	0.0203
Function Loss						
None/minor	0.83 (0.02)	10.25 (0.06)	-6.2509	0.76 (0.02)	0.62 (0.01)	0.0163
Moderate	16.51 (0.12)	37.44 (0.1)	-6.0681	15.39 (0.11)	14.51 (0.08)	0.0244
Major	60.75 (0.1)	39.51 (0.09)	6.7972	61.03 (0.1)	62.22 (0.08)	-0.0245
Extreme	21.91 (0.13)	12.8 (0.08)	2.4879	22.83 (0.14)	22.65 (0.12)	0.0041

CKD = chronic kidney disease; ESRD = end stage renal disease; T2DM = type II diabetes mellitus

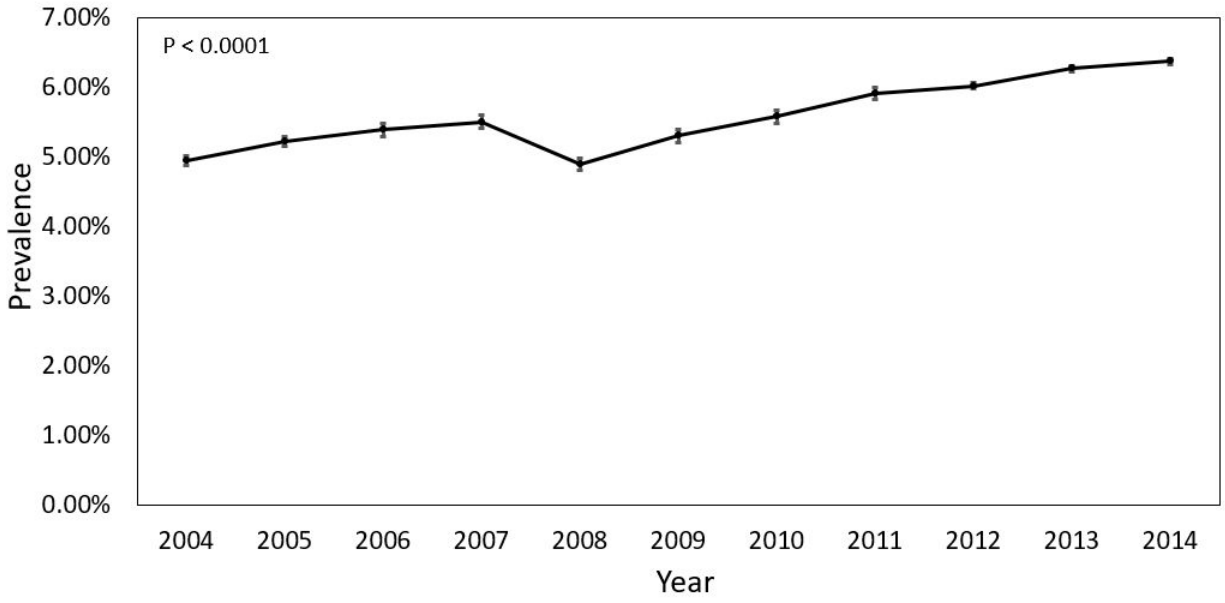

Figure 1.

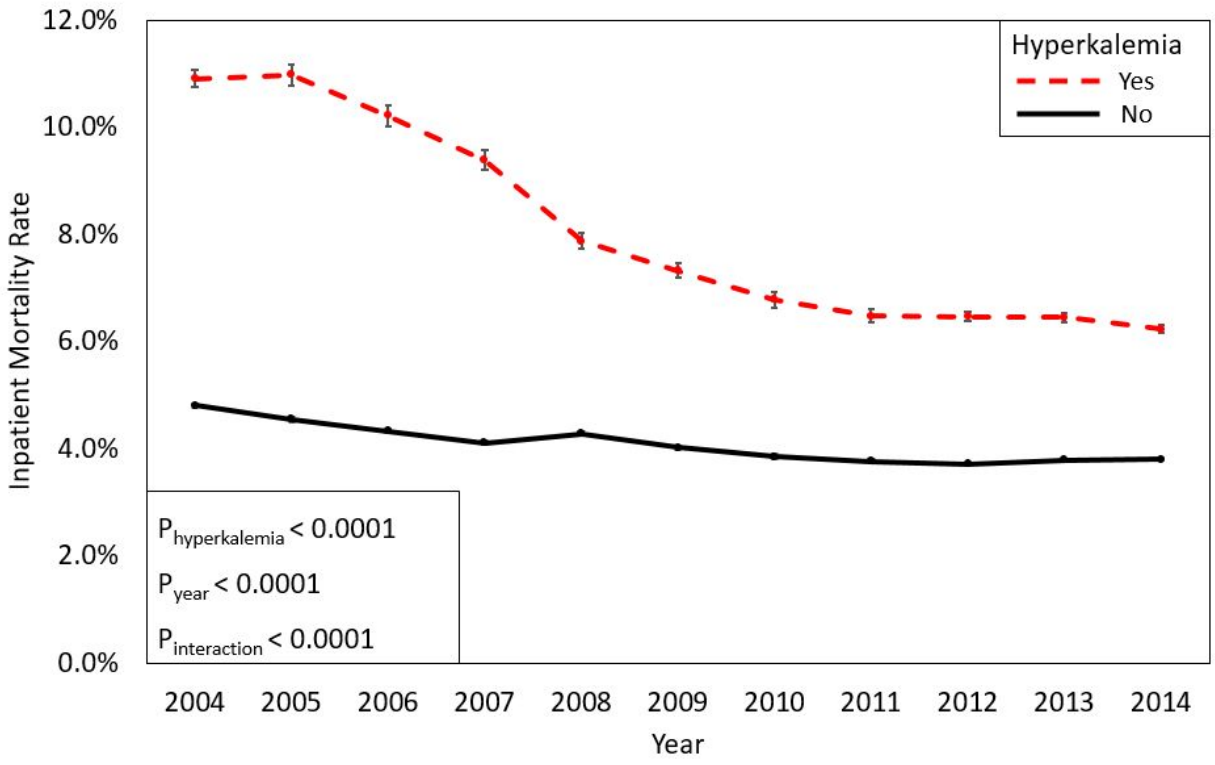

Figure 2.

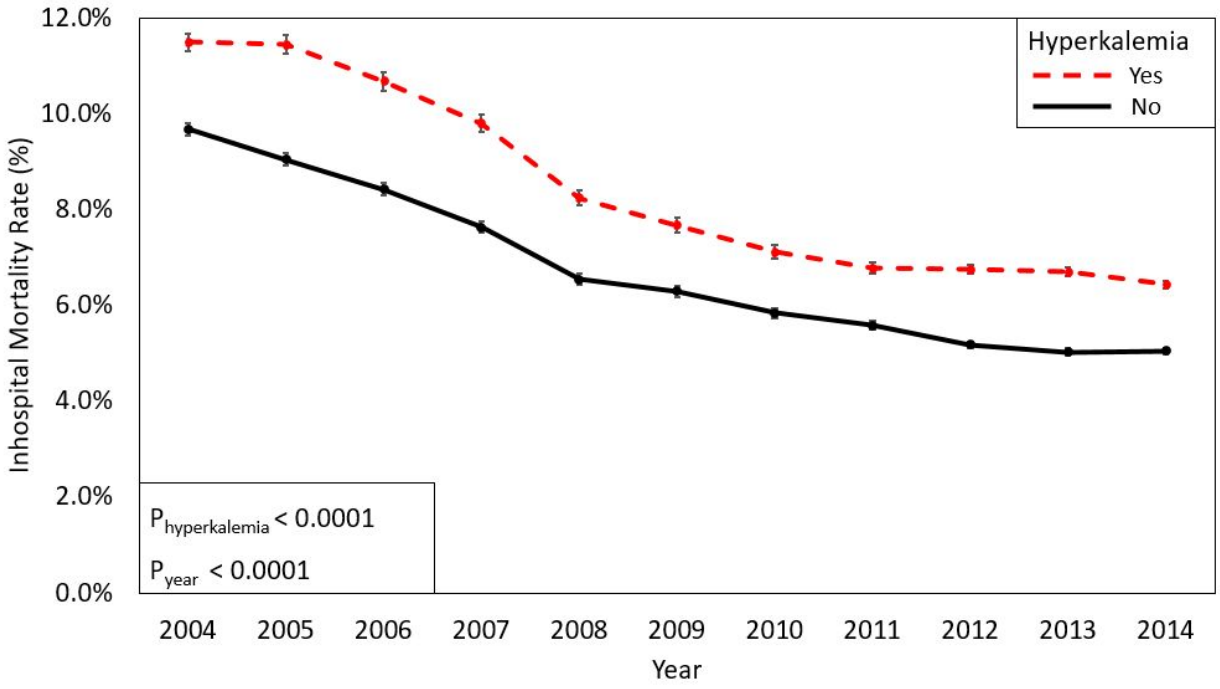

Figure 3.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	2, 6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Case-control: 7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8 (interaction)
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Table 1
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10; Figures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Inpatient Hospitalization and Mortality Rate Trends from 2004 – 2014 in the United States: A Propensity Score-Matched Case-Control Study of Hyperkalemia

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Keywords: Hyperkalemia, potassium, National Inpatient Sample, hospitalization, mortality, heart failure, kidney disease, diabetes mellitus

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Abstract

Objective: To study the trends of hyperkalemia in United States inpatient hospitalization records with heart failure (HF), chronic kidney disease (CKD), acute kidney injury (AKI), and/or type II diabetes mellitus (T2DM) from 2004-2014 with respect to prevalence and inpatient mortality

Design: Observational cross-sectional and propensity score-matched case-control study

Setting: The National Inpatient Sample (representing up to 97% of inpatient hospital discharge records in the United States) from 2004-2014

Participants: 120,513,483(±2,312,391) adult inpatient hospitalization records with HF, CKD/ESRD, AKI, and/or T2DM

Exposure: Hyperkalemia, defined as the presence of an ICD-9-CM code of '276.7' in any of the first 15 diagnostic codes

Primary and Secondary Outcome Measures: The outcomes of interest are the annual rates of hyperkalemia prevalence and inpatient mortality.

Results: Among 120,513,483(±2,312,391) adult inpatient hospitalizations with HF, CKD/ESRD, AKI, and/or T2DM, we found a 28.9% relative increase of hyperkalemia prevalence from 4.94% in 2004 to 6.37% in 2014 ($p<0.001$). Hyperkalemia was associated with an average of 4 percentage points higher rate of inpatient mortality (1.71 post-matching, $p<0.0001$). Inpatient mortality rates decreased from 11.49%±0.17% to 6.43%±0.08% and 9.67%±0.13% to 5.05%±0.07% for matched cases with and without hyperkalemia, respectively ($p<0.001$).

Conclusions: Hyperkalemia prevalence increased over time and was associated with greater inpatient mortality, even after accounting for presentation characteristics. We detected a decreasing trend in inpatient mortality risk, regardless of hyperkalemia presence.

Keywords: Hyperkalemia, potassium, National Inpatient Sample, hospitalization, mortality, heart failure, kidney disease, diabetes mellitus

Strengths and Limitations

- This is a large study, representing up to 120,513,483 (±2,312,391) inpatient discharges in the United States across 11 years.
- Neither medication nor laboratory information is available in the National Inpatient Sample.
- We did not study hypokalemia separately from normokalemia.
- We overcame the inherent imbalance of characteristics between hospitalizations with vs. without hyperkalemia by performing additional analyses on a propensity score matched data set, which made our conclusions more robust.

INTRODUCTION

Hyperkalemia, potassium levels above the upper limit of normal, is rare in the general population, but may be a concern for individuals with renal insufficiency, type II diabetes mellitus (T2DM), and/or congestive heart failure (HF) as a natural consequence of disease or corresponding medication.[1] Many of the medications used to treat these comorbidities may induce hyperkalemia either by altering the cellular shift of potassium or by impairing the kidneys' ability to excrete it.[2] Although mild hyperkalemia may be asymptomatic, when potassium levels are very high (>6.5 mmol/L), life-threatening cardiac arrhythmias, muscle weakness, and/or paralysis may occur; even mild hyperkalemia can cause permanent damage, if left untreated.[1,3,4] Because the comorbidity burden and subsequent requirement for chronic medications has amplified in America as the population has become increasingly older, it is imperative to study the trends of hyperkalemia in America over time.[5,6,7] Hence, the purpose of this paper is to study the trends of hyperkalemia in Americans hospitalized with HF, chronic kidney disease (CKD)/end stage renal disease (ESRD), acute kidney injury (AKI), and/or T2DM from 2004-2014 with respect to prevalence and inpatient mortality.

MATERIALS AND METHODS

This research was approved by the Baylor Scott & White Research Institute's Institutional Review Board via expedited review and was found to be exempt due to being secondary research; informed consent was not required.

Patient and Public Involvement

No patient or public involvement.

Data

Data Source

The National Inpatient Sample (NIS) is the largest database developed for the Healthcare Cost and Utilization Project, comprised of approximately 20% of hospitals in the United States, housing approximately 8 million discharge records per year, allowing inferences to be made on approximately 97% of U.S. population.[8] The NIS has a complex sample design. From 1998 – 2011, 100% of discharges were collected from 20% of U.S. hospitals; from 2012 onward, a 20% national patient-level sample has been utilized.[9, 10] To calculate national estimates, users must account for hospital clusters, stratification, and sample weights (accounting for the sample design change in 2012, if performing a trend analysis).[11] The database may be used to evaluate inpatient mortality. [12]

Key Variables:

This cross-sectional observational study was designed to examine any hospital discharge in the NIS from 2004-2014 for adults (age ≥ 18 years) with HF, CKD/ESRD, AKI, and/or T2DM. We used methodology described in Healthcare Cost and Utilization Project (HCUP) documentation to search for diagnoses of interest, as documented with ICD-9-CM codes, through the 15th diagnostic position. For example, if the code '428.X' was present in any of the first 15 listed diagnoses associated with the hospitalization, we flagged the record as having HF and included it in this analysis. We modified the Elixhauser diabetes comorbidities code sets to select cases specifically with T2DM, and to combine 'complicated and uncomplicated' classes. Similarly, we identified the primary condition of interest, hyperkalemia, by searching through the 15th diagnostic position for the ICD-9-CM code '276.7.' We were then able to calculate prevalence using the binary indicator variable for hyperkalemia. We also incorporated information from the severity files available from NIS which contain information on Elixhauser

comorbidities. The endpoint of inpatient mortality was all available on the yearly NIS core files provided from HCUP.

Data cleaning

The data required a minimal amount of cleaning prior to matching and analyses. Due to sparse categories, we combined levels of primary payor so that 'self-pay', 'no charge', and 'other' were combined into 1 group. We did the same for race/ethnicity, combining Asian, Native American, other, and unknown. Finally, we did the same for the All-Patient Refined Diagnosis Related Groups (APR-DRG) severity variable, such that those with no loss of function and those with minor loss of function were combined into 1 group. Data were missing at low rates and were imputed as follows. If weekend admission was missing, we assigned a value of 0 (this occurred nearly 0%). If gender was missing, we designated female as the default – we did so because there were slightly more women in the sample, and gender was missing at a very small rate (0.03%). Median income quartile was missing at the highest rate (2.06%) and we created an imputation rule with a multivariable model using factors that were found to be significantly associated with it (race, gender, T2DM, hospital region, hospital location/teaching status, and hospital bed size).

Propensity Score Matching

We conducted the matched case-control portion of the study using a greedy nearest neighbor matching algorithm such that 1 record with hyperkalemia was matched without replacement to the 1 record without hyperkalemia having the closest propensity score (PS). We set a caliper boundary of 0.25 to achieve reasonable matches (if the closest possible match had a difference in score > 0.25, the case was unmatched and excluded from analyses). Following the

work of potassium-specific analyses and NIS-specific analyses, such as those by Basnet and colleagues, Tanenbaum and colleagues, and Ahmed and colleagues, we created the regression model (using hyperkalemia as the outcome) based on the following independent predictors: age, gender, race/ethnicity, median zip code income quartile, weekend admission, primary payor, smoking status, HF, CKD/ESRD, T2DM, APRDRG severity, hypertension (HTN), obesity, hospital region, hospital location/teaching status, hospital bed size.[13,14,15] Because the NIS maintains each year of data in a separate file and our goal was to study trends over time (with future study of primary diagnosis), we conducted the matching according to primary diagnosis within year-specific files prior to combining the data. Doing so ensured a PS-matched dataset with balanced case-control representation for each year and primary diagnosis. To improve model convergence for the relatively small subgroup of CKD/ESRD primary diagnosis, we did not match on HTN, obesity, smoking, gender, or hospital location; these factors did not differ according to hyperkalemia presence. We excluded records with a primary diagnosis of hyperkalemia prior to matching.

Statistical Analyses

Due to the complex design of the NIS, as well as its re-structuring in 2012, the calculation of summary statistics for this trend study required additional steps compared to a cross-sectional analysis. We applied specialized discharge weights provided from HCUP ('trendwt' for years 2004-2011 and 'discwt' for years 2012-2014) to calculate the statistics. We used the 'surveymeans' and 'surveyfreq' procedures in SAS to account for clustering by hospital, stratification by 'NIS stratum,' and discharge record weight assignment. Categorical results are presented as percent and standard error. To compare characteristics between groups, we followed the work of Rosenbaum and Rubin, considering an absolute value of the standardized difference

> 0.10 to be significantly different.[16] We utilized the 'surveylogistic' procedure to evaluate a trend in prevalence over time, as well as to assess the significance of hyperkalemia presence on trends in inpatient mortality rates over time.

RESULTS:

Unmatched analysis

To achieve our objective regarding prevalence, we required the use of an unmatched data set. There was a total of 24,941,608 discharge records of patients aged ≥ 18 years in the NIS from 2004-2014 with presence of CHF, CKD/ESRD, AKI, or T2DM, which represent a total of 120,513,483 (±2,312,391) inpatient discharges in the US. In this cohort we found a total of 1,397,573 records containing hyperkalemia, which represent a total of 6,761,577 (±149,409) discharges in the US. This corresponds to an average annual prevalence of 5.61%, which increased over time from 4.94% ± 0.07% in 2004 to 6.37% ± 0.04% in 2014, a relative increase of 28.9% ($p<0.0001$, Figure 1). Partly due to the large sample size, significant differences between groups were observed in every variable examined (Table 1); however, the distributions of age, gender, HF, and hospital characteristics were similar between those who did vs. did not have hyperkalemia. African Americans and Hispanics had a higher risk of hyperkalemia than Caucasians. Hospitalizations including hyperkalemia had higher rates of renal dysfunction (acute and chronic) and major/extreme loss of function (APR-DRG severity).

Inpatient mortality rates were significantly higher for cases with vs. without hyperkalemia (average absolute difference = 4.0%, average relative difference=97.81%, $p < 0.0001$), and the rate decreased non-uniformly between groups over time, decreasing at a faster

rate for cases with hyperkalemia (10.91%±0.17% to 6.23%± 0.08%) than for cases without hyperkalemia (4.81%±0.05% to 3.8%±0.03%) ($p_{year} < 0.0001$, $p_{interaction} < 0.0001$, Figure 2).

Matched Analysis

To achieve our objective regarding inpatient mortality rates while accounting for confounders, we performed PS-matching. After matching, we had a total of 2,606,462 records, representing 12,517,269 (±174,562) hospital discharges. The unweighted records reflect the 1:1 matching (i.e., 1,303,231 records in each group), but they represent an odd number of discharges due to records having unequal weights. Patient characteristics were well balanced, with standardized differences all < 0.10 (Table 1). Note that because we excluded cases of hyperkalemia as the primary diagnosis for the matched analyses, the cases with hyperkalemia and their characteristics are not identical to those in the unmatched cohort.

Inpatient mortality rates were significantly higher for cases with vs. without hyperkalemia (average absolute difference=1.71%, average relative difference=25.3%, p < 0.0001), and the rate decreased uniformly between groups over time, decreasing from 11.49%±0.17% to 6.43%± 0.08% for cases with hyperkalemia and from 9.67%±0.13% to 5.05%± 0.07% for cases without hyperkalemia (p < 0.0001, Figure 3).

DISCUSSION

In this study considering adult inpatient hospitalizations with HF, CKD/ESRD, AKI, and/or T2DM, we found a relative increase of 28.9% in hyperkalemia prevalence (from 4.94% in 2004 to 6.37% in 2014). We found that hospitalizations in which hyperkalemia occurred were far more likely to be severe in nature. Accordingly, we found that the presence of hyperkalemia was associated with a higher rate of inpatient mortality. Further, after controlling for primary

diagnosis, severity of illness, comorbidities, hospital characteristics, and socio-demographics, we found that the presence of hyperkalemia continued to play a significant role in inpatient mortality risk. We also observed significant reductions in inpatient mortality over time.

Our work reiterates and extends findings from Betts and colleagues, who determined that the prevalence of hyperkalemia among patients with CKD and/or HF increased from 4.95% to 6.35% (a relative increase of 28.2%) using insurance claims records and laboratory test results from 2010-2014 in the Truven MarketScan claims and encounters database.[17] The nearly 30% increase in hyperkalemia prevalence in Betts' study, as well as in our current examination of inpatient hospitalizations may be partially explained by the aging population, increasing comorbidity burden, and need for chronic/multiple medications.[3,4] Additionally, our timeframe is large enough such that improved abilities and/or standards of documentation may have been adopted by hospitals over time.[18] For example, it is possible that the implementation of specialized tools within electronic health systems over time may have made the documentation of multiple diagnoses easier.[19] Similarly, another possible explanation is that general awareness of hyperkalemia may have increased over time and that physicians became more likely to screen for it. For example, searching PubMed for the term 'hyperkalemia' yields 206 and 357 papers for 2004 and 2014, respectively.

Our findings extend those of Singer and colleagues' cross-sectional study which determined that hyperkalemia was independently associated with greater risk of inpatient admission (80% vs. 39% from patients in the emergency department with moderate hyperkalemia vs. normal potassium levels, respectively) and mortality (5.5% vs. 0.8% among those with moderate hyperkalemia vs. normal potassium levels, respectively).[20] Similarly, Davis and colleagues found that having severe hyperkalemia increased the risk of inpatient mortality by

58.5% compared to having mild hyperkalemia (19.5% vs 12.3%).[21] Cheunpasitporn and colleagues found mild hyperkalemia to carry an associated 22% increased risk of inpatient mortality among those with CKD, after adjusting for confounders.[22] While we do not know the severity of hyperkalemia in our study, our results are similar in that the presence of hyperkalemia was associated with an average 25% increase in the risk for mortality in the matched analysis and a 98% increase in the unmatched analysis. In general, hyperkalemia's association with increased risk of mortality may simply be reflective of a more severe overall presentation, or it may contribute to death by complicating an already difficult-to-treat disease state, or even more directly by inducing life-threatening cardiac arrhythmias.[23,1] Our observation of mortality rates declining over time may be reflective of the large percentage of records with CKD in this study, as it has been shown that CKD mortality rates in Medicare beneficiaries have declined over time but remain significantly higher than the rates observed in patients without CKD.[24] Further, the declining rates may be partially attributable to advancements in technology and medical care delivery, including medications. For example, increased use of point-of-care potassium testing could have resulted in faster delivery of care.[25]

Although we observed a significant increase in its prevalence, as well as a higher mortality rate for those who have it, preventing and treating hyperkalemia is possible. In some cases, particularly patients with CKD at risk for chronic hyperkalemia, a potassium-restricted diet may be beneficial.[26] For cases of drug-induced hyperkalemia, interrupting the prescription may be a solution; however, new challenges may arise if the medication was for the management of a chronic condition, which is often true.[2] Alternatively, diuretics may be used to increase potassium excretion via urine and dialysis may be used to remove excess potassium from blood. In the setting of a hyperkalemic emergency, an intravenous infusion of calcium and insulin may

be used to both protect the heart and cause a cellular shift of potassium. Another treatment for hyperkalemia is potassium-binding medication, which expels excess potassium through fecal matter.[27] One such drug is sodium polystyrene sulfonate (SPS), which has been used since the late 1950's, but is associated with serious gastrointestinal side effects (and even colonic necrosis in rare cases) and has a relatively low adherence rate.[28] Two additional drugs, sodium zirconium cyclosilicate and patiromer, help patients achieve and maintain normal potassium levels.[29] These have advantages over SPS in that they are associated with fewer side effects and they may be efficacious regardless of RAASi and/or diet.[25] These newer drugs received FDA approval after our study timeframe, so they do not explain our observed reduction in mortality rate; however, it is of interest to determine whether these rates have further declined since their availability. For patients taking medication for chronic diseases, incorporating a pharmacist into a team-based management approach may help protect against hyperkalemia.[30]

The study was designed to examine any record with HF, CKD/ESRD, AKI, or T2DM. Doing so provided a very large and rich dataset for studying hyperkalemia trends in in-patient hospitalizations. Due to the broad inclusion criteria of these analyses, this work did not shed light on disease-specific inferences. It is possible that the trends observed in this overall cohort may not hold for each specific disease group. In this paper, we overcame the inherent imbalance of characteristics between hospitalizations with vs. without hyperkalemia by performing additional analyses on a PS-matched data set, which made our conclusions more robust. Further, we conducted the PS-matching within specific primary diagnoses because it is our intention to perform subgroup analyses according to primary diagnosis in future work.

Limitations of this study include that the timeframe under evaluation ended in 2014; this was due to availability of data and to maintain consistency with ICD-9-CM coding. We

acknowledge that there may be additional epidemiological changes to the data since then, particularly following the introduction of newer therapies for hyperkalemia. Hence, it may be of interest to conduct this study using more recent data. Since our interest was strictly in studying the presence or absence of elevated potassium (hyperkalemia), our reference group was comprised of both normo- and hypokalemic patients; however, it may be of interest in the future to study them separately, as others have shown differential mortality rates.[13] Additionally, because the NIS is de-identified, it is possible that an individual may be present in the data more than once without means to identify such an occurrence; for that reason, the data are interpreted as independent hospital discharges, not as patients. Additionally, laboratory results are not available in the NIS. As such, the definition of hyperkalemia in this study was based on its ICD code and limits our conclusions regarding potential causes of mortality, as the severity of hyperkalemia is unknown. Hence, as with any study utilizing ICD codes, our study may be subject to misclassification bias. Similarly, medications are not available in the NIS and we are unable to make inferences regarding the effects of therapies received before and/or after hyperkalemia diagnosis. Finally, there were instances in which there was only 1 cluster within a stratum, so the standard error could not be calculated; however, this happened in less than 1% of the data. While this work's data source represents up to 97% of United States hospital discharges, more work is needed to understand whether these findings generalize to other countries.

CONCLUSION

In this large 10-year study of inpatient hospitalizations, hyperkalemia became more prevalent and was associated with greater illness severity and inpatient mortality than hospitalizations without hyperkalemia. Inpatient mortality rates decreased in this timeframe,

regardless of hyperkalemia presence; however, the risk of death remained higher when hyperkalemia was present.

Author Contributions:

KMT – Design, data acquisition, analyses, interpretation, drafting, critical revision, approval, and accountability.

RAB – Interpretation, critical revision, approval, and accountability.

LC – Interpretation, critical revision, approval, and accountability.

PMC – Design, interpretation, critical revision, approval, and accountability.

Data Availability

The National Inpatient Sample data files are available for purchase through the Online HCUP Central Distributor; all HCUP data users must complete the HCUP Data Use Agreement Training Tool, and read and sign the Data Use Agreement for Nationwide Databases.

Conflicts of Interest

The authors have nothing to disclose.

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Figure Headers

Figure 1. Prevalence of hyperkalemia in inpatient hospitalizations including congestive heart failure, chronic kidney disease (and end stage renal disease), acute kidney injury, and/or type II diabetes mellitus

Figure 2. Annual in-hospital mortality rates (with standard error bars) for the unmatched cohort according to presence of hyperkalemia in hospitalizations including congestive heart failure, chronic kidney disease (and end stage renal disease), acute kidney injury, and/or type II diabetes mellitus

Figure 3. Annual in-hospital mortality rates (with standard error bars) for the propensity score-matched cohort according to presence of hyperkalemia in hospitalizations including congestive heart failure, chronic kidney disease (and end stage renal disease), acute kidney injury, and/or type II diabetes mellitus

Table 1. Patient characteristics of the unmatched and matched cohorts according to hyperkalemia presence

	Unmatched Cohort			Matched Cohort		
	Hyperkalemia			Hyperkalemia		
Characteristic	Yes	No	Standardized Difference	Yes	No	Standardized Difference
Age Group						
18 - 44	9.05 (0.1)	7.76 (0.07)	0.3999	8.64 (0.1)	8.14 (0.09)	0.0179
45 - 54	11.67 (0.09)	11.97 (0.08)	-0.0990	11.43 (0.09)	10.82 (0.09)	0.0192
55 - 64	18.28 (0.08)	18.4 (0.06)	-0.0426	18.09 (0.08)	16.85 (0.08)	0.0322
65 - 74	21.65 (0.06)	22.56 (0.05)	-0.3623	21.72 (0.06)	22.13 (0.06)	-0.0099
75+	39.35 (0.23)	39.32 (0.19)	0.0066	40.12 (0.23)	42.06 (0.22)	-0.0397
Gender (female)	49.34 (0.09)	51.79 (0.07)	-0.8118	49.43 (0.09)	49.95 (0.08)	-0.0103
Race/ethnicity						
White	53.45 (0.59)	58.94 (0.58)	-0.7165	54.23 (0.59)	55.42 (0.57)	-0.0239
Black	18.62 (0.43)	14.48 (0.33)	0.6359	18.29 (0.42)	17.79 (0.39)	0.0128
Hispanic	9.74 (0.32)	7.98 (0.26)	0.3115	9.4 (0.3)	8.99 (0.3)	0.0140
Other	18.19 (0.64)	18.6 (0.62)	-0.0517	18.08 (0.64)	17.8 (0.63)	0.0074
Heart failure	38.6 (0.16)	37.41 (0.12)	0.2958	39.26 (0.16)	39.33 (0.15)	-0.0013
CKD/ESRD	56.84 (0.18)	28.36 (0.12)	6.6531	55.42 (0.18)	54.53 (0.16)	0.0179
Acute kidney injury	49.53 (0.18)	20.12 (0.11)	6.955	51.04 (0.18)	42.31 (0.16)	0.1746
T2DM	47.28 (0.13)	60.07 (0.11)	-3.4897	46.92 (0.14)	46.69 (0.13)	0.0047
Hypertension	61.95 (0.16)	67.85 (0.12)	-1.4971	60.5 (0.16)	60.81 (0.15)	-0.0065
Obesity	11.4 (0.1)	13.92 (0.09)	-0.8082	11.93 (0.1)	11.18 (0.09)	0.0231
Smoker	7.68 (0.08)	9.69 (0.08)	-0.7077	7.58 (0.08)	6.86 (0.07)	0.0272
Primary Diagnosis						
Acute kidney Injury	15.01 (0.08)	2.91 (0.02)	4.1859	15.89 (0.09)	15.9 (0.1)	-0.0003
Heart failure	7.99 (0.05)	8.7 (0.04)	-0.3278	8.49 (0.05)	8.51 (0.05)	-0.0006
CKD/ESRD	0.34 (0.01)	0.1 (0)	0.2619	0.36 (0.01)	0.36 (0.01)	0.0002
Other	73.2 (0.09)	84.99 (0.05)	-3.9621	71.6 (0.09)	71.59 (0.1)	0.0003
T2DM	3.45 (0.03)	3.31 (0.02)	0.0840	3.66 (0.03)	3.65 (0.03)	0.0005
Primary payer						
Medicare	70.96 (0.22)	66.93 (0.2)	0.8573	71.07 (0.21)	72.9 (0.2)	-0.0405
Medicaid	10.44 (0.16)	9.07 (0.13)	0.3396	10.25 (0.15)	9.52 (0.14)	0.0239
Private insurance	13.48 (0.14)	17.96 (0.14)	-1.2035	13.59 (0.14)	12.89 (0.13)	0.0205
Other	5.12 (0.15)	6.03 (0.12)	-0.2395	5.09 (0.13)	4.69 (0.1)	0.0186
Zipcode income quartile						
First quartile	33.22 (0.49)	31.3 (0.44)	0.2751	32.9 (0.49)	32.95 (0.46)	-0.0011

Second quartile	27.41 (0.33)	27.78 (0.32)	-0.0646	27.32 (0.34)	27.21 (0.33)	0.0025
Third quartile	22.4 (0.29)	22.8 (0.27)	-0.0745	22.52 (0.29)	22.39 (0.28)	0.0030
Fourth quartile	16.97 (0.44)	18.11 (0.44)	-0.1720	17.26 (0.45)	17.45 (0.43)	-0.0049
Hospital region						
Northeast	17.72 (0.52)	19.39 (0.51)	-0.2331	18.12 (0.53)	18.13 (0.49)	-0.0004
Midwest	23.76 (0.58)	23.7 (0.53)	0.0088	23.17 (0.59)	23.12 (0.56)	0.0013
South	40.33 (0.74)	39.84 (0.71)	0.0574	40.54 (0.75)	41.07 (0.73)	-0.0108
West	18.18 (0.52)	17.07 (0.48)	0.1552	18.17 (0.52)	17.68 (0.5)	0.0127
Hospital setting						
Rural	11.29 (0.38)	13.1 (0.37)	-0.2952	11.16 (0.38)	11.15 (0.36)	0.0003
Urban nonteaching	41.14 (0.7)	41.02 (0.66)	0.0146	41.56 (0.71)	41.49 (0.68)	0.0015
Urban teaching	47.57 (0.71)	45.88 (0.68)	0.2017	47.28 (0.72)	47.36 (0.7)	-0.0017
Hospital bed size						
Small	12.13 (0.31)	13.31 (0.3)	-0.2116	12.03 (0.32)	11.58 (0.28)	0.0140
Medium	25.26 (0.52)	25.23 (0.48)	0.0042	25.32 (0.53)	24.92 (0.49)	0.0093
Large	62.61 (0.61)	61.46 (0.58)	0.1475	62.64 (0.62)	63.5 (0.58)	-0.0177
Weekend admission	21.83 (0.05)	20.68 (0.04)	0.5302	21.99 (0.05)	21.15 (0.05)	0.0203
Function Loss						
None/minor	0.83 (0.02)	10.25 (0.06)	-6.2509	0.76 (0.02)	0.62 (0.01)	0.0163
Moderate	16.51 (0.12)	37.44 (0.1)	-6.0681	15.39 (0.11)	14.51 (0.08)	0.0244
Major	60.75 (0.1)	39.51 (0.09)	6.7972	61.03 (0.1)	62.22 (0.08)	-0.0245
Extreme	21.91 (0.13)	12.8 (0.08)	2.4879	22.83 (0.14)	22.65 (0.12)	0.0041

CKD = chronic kidney disease; ESRD = end stage renal disease; T2DM = type II diabetes mellitus

Results shown as percent (standard error)

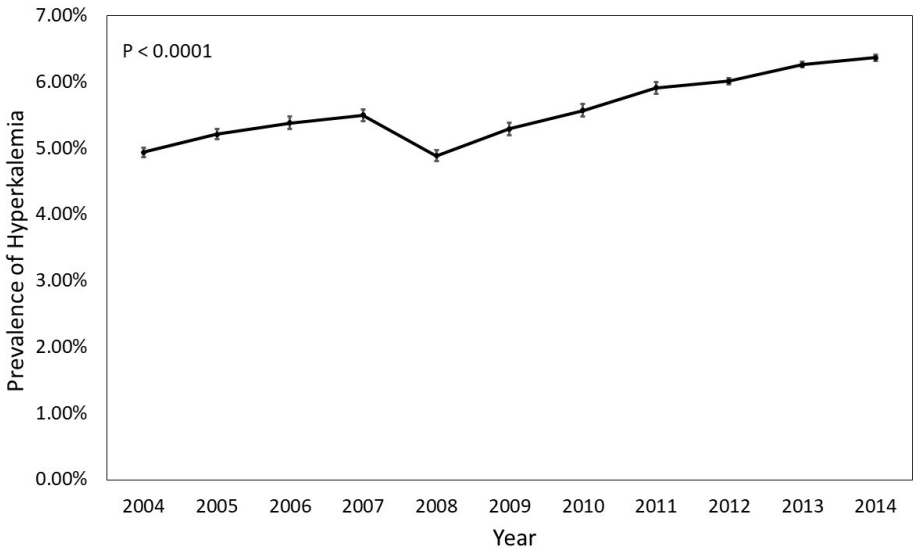

Figure 1

108x60mm (300 x 300 DPI)

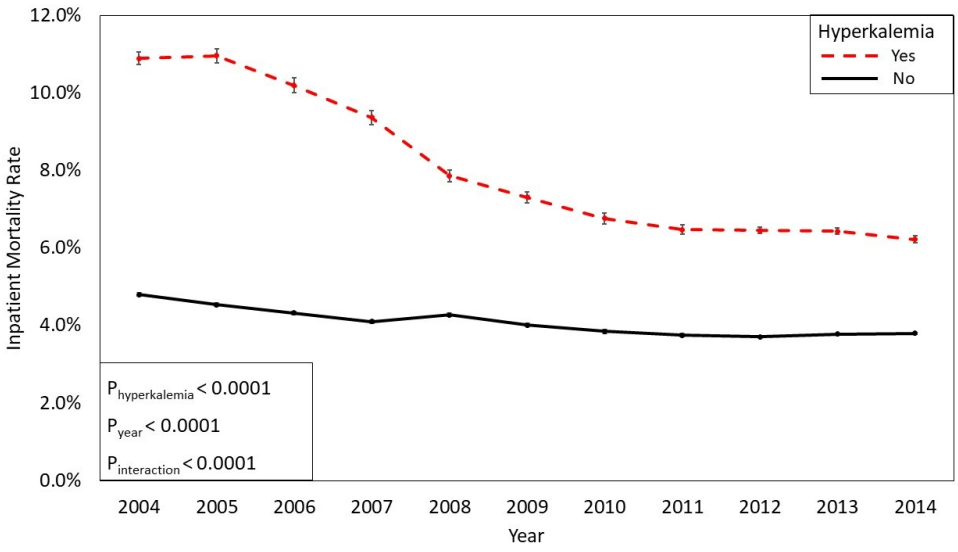

Figure 2

108x60mm (300 x 300 DPI)

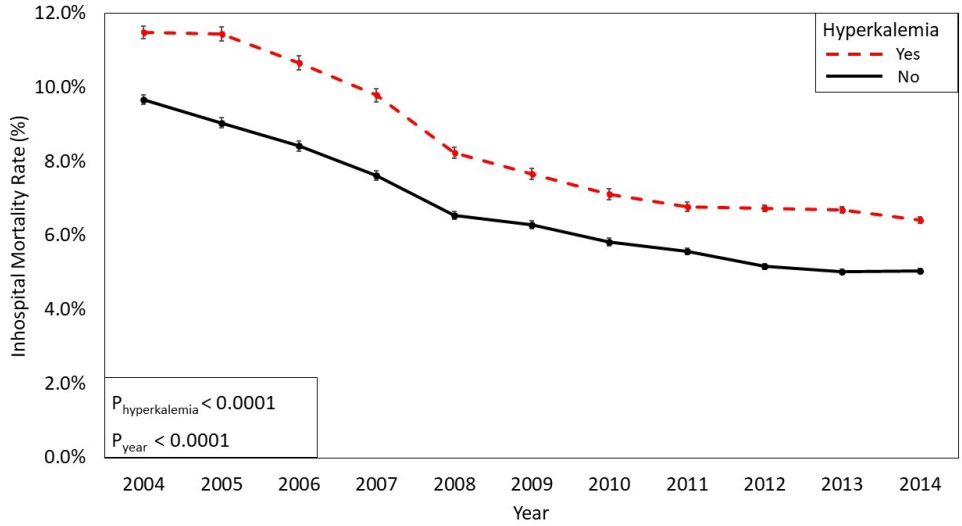

Figure 3

108x60mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	2, 6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Case-control: 7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8 (interaction)
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	-
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Table 1
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10; Figures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.