Predictors and outcome impact of perioperative serum sodium changes in a high risk population

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Running title: Outcomes of perioperative changes in sodium

Abstract

BACKGROUND: The perioperative period may be associated with a marked neurohumoral stress response, significant fluid losses and varied fluid replacement regimes. Acute changes in serum sodium concentration are therefore common, but predictors and outcomes of these changes have not been investigated in a large surgical population.

METHODS: We carried out a retrospective cohort analysis of 27,068 in-patient non-cardiac surgical procedures in a tertiary teaching hospital setting. Data on preoperative conditions, perioperative events, hospital length of stay and mortality were collected, along with preoperative and postoperative serum sodium measurements up to seven days after surgery. Logistic regression was used to investigate the association between sodium changes and mortality, and to identify clinical characteristics associated with a deviation from baseline sodium greater than 5 mmol/l.

RESULTS: Changes in sodium concentration > 5mmol/l were associated with increased mortality risk (adjusted OR 1.49 for a decrease, 3.02 for an increase). Factors independently associated with a perioperative decrease in serum sodium concentration >5 mmol/l included age >60, diabetes mellitus and use of patient-controlled opioid analgesia. Factors associated with a similar increase were preoperative oxygen dependency, mechanical ventilation, central nervous system depression, non-elective surgery and major operative hemorrhage.

CONCLUSIONS: Maximum deviation from preoperative serum sodium value is associated with increased hospital mortality in patients undergoing in-patient non-cardiac surgery. Specific preoperative and perioperative factors are associated with significant serum sodium changes.

Key words: Hospital Mortality, Perioperative Period, Sodium

Introduction

Disorders of plasma sodium concentration are common in hospitalized patients and are associated with increased hospital stay, resource utilization and mortality. Surgical patients may be particularly vulnerable, since the perioperative period is often characterized by a vigorous neurohumoral stress response, significant fluid losses and widely varying fluid replacement regimes. Previous studies have reported hospital outcomes associated with dysnatraemias present on admission, in specific medical or surgical subspecialties, in intensive care, or in mixed medical-surgical populations without reference to the perioperative period.[1-7] Only two studies have focused exclusively on perioperative patients. Leung et al reported increased mortality in patients with preoperative hyponatraemia using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP),[6] and McCausland et al described similar outcomes in dysnatraemic patients after orthopaedic surgery.[7] No previous study has investigated perioperative sodium changes.

While small changes are commonplace and may typically reflect measurement artifact or diurnal variation, [8-10] large changes are often associated with endocrine or iatrogenic factors. These can be harmful in themselves, by inducing osmotic disequilibrium and cerebral dysfunction [11 12], or may reflect an underlying impairment of sodium and water homeostasis that predicts adverse outcomes independently of prevention or treatment. However, both predictors and outcomes of marked changes remain poorly characterized, and the possibility remains that intervention to minimize sodium fluctuations may be beneficial. Hence we investigated a large cohort of patients undergoing intermediate and major in-patient surgery to identify clinical correlates of moderate-to-severe sodium changes, and to quantify any associated increase in mortality. We speculated that

knowledge of these factors, and closer attention to electrolyte monitoring and fluid therapy in patients at increased risk, might attenuate any associated increase in mortality.

Methods

With local research ethics committee approval, we extracted anonymised electronic records of 31,206 in-patient surgical procedures lasting more than one hour at Cambridge University Hospitals between 1 January 1996 and 31 December 2005. This encompassed all specialties with the exception of cardiothoracic surgery. Hospital length of stay and mortality were obtained from the hospital's administrative database, while information on co-morbidities, important preoperative conditions and perioperative events was available from a perioperative audit database, as recorded during each procedure by the attending anaesthetist.

A laboratory database provided measurements of serum sodium concentration, including the latest preoperative value as baseline (no earlier than 14 days preoperatively), and all values in the first 7 days after surgery. The highest and lowest sodium values in the first 7 postoperative days were then compared to baseline to define the following mutually exclusive categories for analysis: no change greater than 5 mmol/l; decrease greater than 5 mmol/l; increase greater than 5 mmol/l; both increase and decrease greater than 5 mmol/l.

Obstetric and paediatric patients (under age 13) were excluded from the study population, as were those missing either preoperative or postoperative sodium measurements, and those without complete data on preoperative conditions and perioperative events. Only the first surgical procedure carried out during an admission was studied.

The above exclusions ensured that we studied a high risk cohort, since all had surgery involving more than one hour of operating time, and all had both preoperative and

postoperative sodium measurements. Preoperative measurement in particular would suggest co-morbidity, major surgery, or both. We were unable to collect data on perioperative fluids from the records obtained.

Statistical analysis

Summary statistics were computed for baseline characteristics and outcomes of the cohort. Hospital admissions were fitted in a multivariate logistic regression model to investigate the association between maximum change in sodium concentration and hospital mortality. The model was adjusted for co-morbidities and other relevant confounders, as well as for possible correlation between admissions of the same patient. Odds ratios were adjusted using the floating absolute risk method to allow comparison between potential confounders, rather than only comparison of each to its absence.[13] Multivariate logistic regression was also used to identify co-morbidities and conditions associated with large changes in sodium (>5 mmol/l).

All models were adjusted by the number of postoperative sodium measurements, to minimise bias related to clinical acuity, and by calendar year to allow for differences in clinical practice over time. Forward selection procedures were used to obtain the most parsimonious model using likelihood ratio tests. All analyses were performed using Stata (version 10.1) and significance was set at 5%.

Results

Study population

Complete data were available for 16,216 admissions (14,942 patients). Exclusions are shown in Online Supplementary Figure 1, the largest number resulting from missing values for physician-entered preoperative and perioperative variables. Baseline characteristics and outcomes are shown in Table 1. In 86.2% of admissions, at least one significant

preoperative condition was present; in 45.8%, ASA Physical Status was assessed as 3 or higher. The most prevalent co-morbidities included hypertension (29.4%), malignancy (16.1%), ischemic heart disease (15.3%) and obesity (11.9%). There were 632 hospital deaths, corresponding to a mortality of 3.9%.

Sodium changes and hospital mortality

Associations between perioperative changes in sodium concentration and hospital mortality are shown in Figure 1. A deviation from the preoperative value of greater than 5 mmol/l in either direction was associated with a higher risk of death than patients with smaller changes. This was strongest with increases, which carried three times the risk (adjusted odds ratio (OR) 3.02; 95% CI, 2.52-3.62) of those with small or no change. Falls in sodium increased mortality by about 50% (OR, 1.49; 95% CI, 1.21-1.83). When preoperative sodium concentration was normal the relationships were more pronounced, with odds ratios of 3.49 and 1.62 for increases and decreases, respectively.

Clinical correlates of large sodium changes

Figures 2 and 3 show the results of multivariate logistic regression investigating clinical correlates of large perioperative decreases and increases, respectively. Figure 2 shows that those more likely to have a large decrease in sodium concentration were older (>60 years, OR 1.34), and had procedures of longer duration (OR 1.30). Those with diabetes (OR 1.30) or liver disease (undergoing transplant, OR 1.74), who were mechanically ventilated (OR 1.41) or receiving oxygen (OR 1.55), and who used patient-controlled analgesia in the postoperative period (OR 1.21), were all more likely to have a large

decrease in sodium than those who were not. Major urological and renal procedures were also associated with this risk (OR 1.35), compared to a reference group comprising all in-patient laparoscopic operations. Obesity appeared to be protective against large decreases (OR .80).

Figure 3 shows the adjusted clinical correlates of large sodium increases. These also included longer operations (OR 2.31), and preoperative ventilation (OR 1.65) or oxygen (OR 2.19). Non-elective surgery (OR 1.97) was predictive, as were the preoperative presence of a neurological (OR 1.33) or endocrine condition (OR 1.27), or central nervous system depression (OR 1.97). Major haemorrhage (> ½ blood volume) during surgery was also powerfully associated with a large sodium increase (OR 2.77). Again, obesity appeared to be protective (OR .77).

Discussion

Sodium homeostasis is achieved by the complex interplay of the renal renin-angiotensin-aldosterone system, sympathetic neural and catecholamine activity, secretion of vasopressin from the neurohypophysis, and release of natriuretic peptides from myocardium.[12] Both osmoreceptors and baroreceptors regulate vasopressin secretion, and the effects of vasopressin on the renal excretion of water are influenced by genetic polymorphisms.[14 15] Aquaporins and ATPases further regulate cell membrane water and sodium flux in the face of changes in extracellular ion concentration. [16 17] In health, thirst ensures adequate intake while renal mechanisms closely control losses. In the perioperative setting, however, many of these systems are affected by inflammation and neuroendocrine responses to surgical stress, and the adaptive capacity of the global homeostatic response may be impaired.[18 19] Little is known about the relative importance

of constitutional versus iatrogenic factors in this context, but available data suggest that both are relevant and that treatment should be carefully individualised. [12 20-22]

Pre-admission and hospital acquired dysnatraemias are known to be associated with increased resource utilization and mortality in mixed medical-surgical and intensive care populations, [1-5 11 23-25] and more recently have been linked to mortality in two large cohorts of post-surgical patients.[6 7] Sodium variability *per se* also predicted increased mortality in patients admitted to a surgical ICU.[26] This study has demonstrated similar outcomes in a large population undergoing in-patient surgery, and has added new data on the predictors and outcomes of perioperative sodium changes.

We have shown that deviations from baseline greater than 5 mmol/l are associated with increased hospital mortality, even when preoperative values are normal. We selected the threshold of >5 mmol/l deviation from preoperative baseline because lesser changes are typical in stable, uncomplicated perioperative patients, and are known to be confounded by diurnal variation, blood glucose and protein concentrations, and laboratory imprecision.[8-10] Also, changes of this magnitude were not found to predict mortality in a large study of patients treated in surgical intensive care.[26] Although dysnatraemias may represent non-causal biomarkers of underlying neuroendocrine or inflammatory disorders, and correction may not necessarily provide benefit, clinical experience and published data strongly suggest that fluid management does affect outcomes and that dysnatraemia may be avoided.[27-32] Thus, sodium values may merit closer attention than they currently receive. While doses of potassium, glucose and even water are regularly adjusted in surgical patients, sodium is delivered at standard concentrations as long as serum values are normal. With greater consideration of the last-recorded sodium measurement and of easily measured sodium losses in urine and drains, some variability may be prevented,

reducing osmotic shifts and associated effects on organ function, and improving outcomes.[27]

In support of this hypothesis, this study has identified some conditions linked to marked sodium changes that may be easily remediable. Diabetes mellitus predicted large decreases, raising concerns about water excess associated with the widespread, protocolised use of 5% glucose with variable-rate intravenous insulin infusion in post-surgical patients. This regime was standard therapy at the time of this study and its use continues. 10% glucose and concurrent balanced electrolyte solutions given via central venous catheter may be safer in this group. Diabetics, along with the elderly, patients on patient-controlled opiate analgesia, and those undergoing major urological procedures would be appropriately targeted for more frequent serum sodium measurements and more variable sodium replacement regimes.

Major operative haemorrhage was a powerful independent predictor of an increase in sodium concentration, supporting other evidence that the sodium load associated with administration of bank blood may be detrimental. This too underscores the potential benefits of prevention in high-risk cases, by prophylactic administration of tranexamic acid, washing of bank blood using cell salvage equipment to reduced citrate-associated sodium loading, or concomitant administration of low-sodium crystalloid. Moreover, the prominence in this study of oxygen therapy and mechanical ventilation as predictors of large sodium changes in the critical care setting, where closer monitoring and more intensive management are easiest to implement, suggests another opportunity for beneficial impact. The importance of frequent monitoring of a rising or falling serum sodium is clear.

The protective effect of obesity in relation to both hypo- and hypernatraemia was an unexpected finding. This suggests enhanced osmoregulation rather than fluid regimes influenced by weight or a higher prevalence of hyperaldosteronism, both of which would protect from only one of these disorders. However, effects of obesity on cytokine profile, chronic inflammation and neuroendocrine function, including renal responses to sodium intake, are well recognized [33] and some may be beneficial. Indeed, since moderate obesity is known to confer a survival advantage in some surgical and critical care settings, a positive effect on sodium homeostasis seems possible.

Another important implication of our findings relates to the approach to the dysnatraemic patient presenting for surgery, which has received little attention in the literature and remains largely arbitrary. Abnormalities of preoperative serum sodium values are common, but few cases are investigated and treated before elective surgery. Most cases of mild preoperative hyponatraemia appear to be related to long term drug treatments. These include thiazide diuretics, angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors, proton pump inhibitors, narcotics and numerous others.[34-38] However, we suggest that when a cause is not apparent any abnormality found before major elective surgery should be investigated, for the following reasons. First, abnormal serum sodium values may worsen perioperatively if the underlying condition is intensified, as may occur in the syndrome of inappropriate antidiuresis (SIAD), the most common cause of perioperative hyponatraemia. Second, if major fluid replacement is needed, especially transfusion of citrated bank blood, rapid changes in serum sodium may lead to dangerous osmotic syndromes, including cerebral edema and demyelination.[39 40] Lastly, underlying disorders that remain undiagnosed may have unpredictable consequences in the perioperative period. These include hypovolaemic states (including renal impairment and cerebral salt-wasting syndrome),

diverse malignancies, hypothyroidism, hypoadrenalism, diabetes, heart failure, liver disease and nephrotic syndrome. Most of these are identifiable with simple screening tests, and are treatable.[28]

A number of features of this study may limit generalisation of our results. Our selection criteria isolated a high risk cohort of patients undergoing intermediate and major surgical procedures, and interpretation of our results should take this into account. Our data was derived from a single center and collected over a 10 year period, so case-mix and management trends may have been idiosyncratic and probably varied over time. Most importantly, we were unable to collect detailed data on perioperative fluid losses and replacement. These parameters may be powerful correlates of serum sodium changes and may be the most readily altered by physician intervention.

Variability in the number of postoperative sodium measurements may have influenced some of our findings, since the number of measurements was undoubtedly an indication of the severity of co-morbid conditions and of the scale of surgery. However, since adjustment for this and for many other indicators of acuity failed to alter the impact of large changes, it is likely that any effect was small.

Although a strength of the study was the reliance on attending and resident physicians for entry of data on preoperative conditions, the numbers we studied were reduced by the failure of many to confirm the absence of chronic co-morbidities on our optically-read forms. Since a clear negative response to this question was a condition of inclusion in our primary analysis, healthy patients may have been excluded and reduced denominators could have exaggerated the incidence and prevalence of sodium conditions. However, by

increasing case-mix severity, these omissions may also have enhanced the study's ability to identify relevant clinical predictors.

We were unable to collect data on preoperative volume status, on postoperative symptoms related to dysnatraemia, nor on neurological outcomes such as osmotic demyelination syndromes, which would have strengthened the predictive value of the analysis greatly. It is also arguable that the collection of data on post-discharge outcomes would have enhanced our understanding of risk in this cohort, although this has been done by others and it is unlikely that our key findings would have been altered.

The absence of routine simultaneous determinations of blood glucose meant that we could not adjust for hyperglycemia. This may have affected the rates of both dysnatraemias.[23] However, Waikar, Mount and Curhan showed that adjustment for glucose concentrations had a very minor effect on prevalence of hyponatraemia and no effect on associations with mortality, so this is unlikely to be important.[3]

In conclusion, this study has confirmed that perioperative dysnatraemias associated with deviations greater than 5 mmol/l from preoperative values, and overall variability of sodium measurements, are associated with significantly increased hospital mortality. Specific preoperative and perioperative factors are independently predictive of these changes. Although the role of perioperative fluid therapy could not be addressed in this study, nor any direct causative link between sodium changes and mortality inferred, these findings enhance risk evaluation in the surgical patient and raise the possibility that both closer monitoring of serum sodium and more careful attention to the volume and content of perioperative fluids may be beneficial in high-risk patients. The definitive determination of

iatrogenic causes and of the value of prevention will require prospective collection of detailed data on fluids and medications, and randomised trials of specific regimes.

Declaration of interests

J.R.K.: None

L.M.: None

E.D.: None

D.K.M: None

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Authors' contributions

J.R.K.: Study design, data collection, interpretation of results, manuscript preparation.

L.M.: Data analysis, interpretation of results, manuscript preparation.

E.D.: Data analysis, interpretation of results.

D.K.M.: Study design, interpretation of results.

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Table 1. Characteristics and outcomes of cohort (16,216 admissions, 14,942 unique patients)

Variable	Subgroup	Mean(range) / N(%)
Age		58 (13 to 104)
Gender	Male	7,563 (46.6)
	Female	8,653 (53.4)
Type of surgery	Elective	11,363 (70.1)
	Non-elective	4,853 (29.9)
ASA score	1	2,873 (17.7)
	2	5,917 (36.5)
	3	6,041 (37.3)
	4	1,289 (7.9)
	5	96 (0.6)
Preoperative sodium concentration (mmol/l)	135-145	14,111 (87.0)
	125-134	1,502 (9.3)
	<125	47 (0.3)
	146-155	550 (3.4)
	>155	6 (0.0004)
Preoperative conditions	Use of cardiovascular drugs	3,787 (23.4)
	Oxygen therapy	648 (4.0)
	Ventilated	479 (3.0)
	Bedridden > 2 weeks	520 (3.2)
	CNS depression	662 (4.1)
Co-morbidities	Obesity	1,927 (11.9)
	Hypertension	4,770 (29.4)
	Smoking	1,645 (10.1)
	Asthma	1,148 (7.1)
	Ischaemic heart disease	2,483 (15.3)
	Structural heart defect	488 (3.0)
	Cardiac failure	594 (3.7)
	Peripheral vascular disease	1,116 (6.9)
	Cerebrovascular disease	1,073 (6.6)
	COAD	638 (3.9)
	Diabetes	1,197 (7.4)
	Steroid use >2 months/other endocrine	1,387 (8.6)
	Liver disease (with transplant)	295 (1.8)
	Liver disease (no transplant)	455 (2.8)
	Renal disease	1,485 (9.2)
	Haematological disease	336 (2.1)
	Seizure disorder	342 (2.1)
	Other CNS disease	1,564 (9.6)
	Malignancy	2,604 (16.1)
	Rheumatoid arthritis	442 (2.7)
No co-morbidities or significant preoperative conditions		2,233 (13.8)
Hospital outcome	Length of postoperative stay* (days)	8 (5-15)
	Died in hospital	632 (3.9)

COAD=chronic obstructive airways disease, CNS=central nervous system, SD=standard deviation. *Median value (with interquartile range) presented instead of mean.

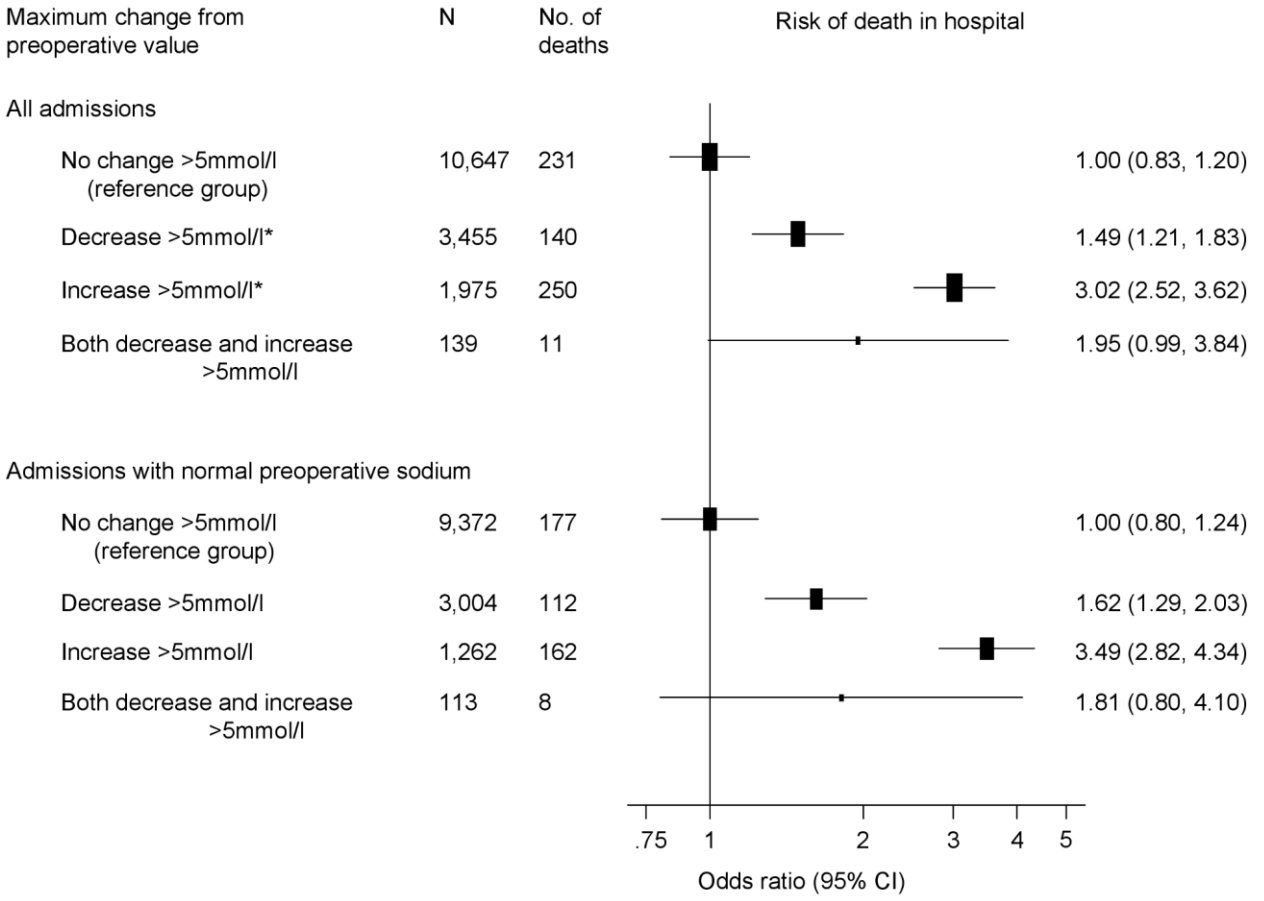


Figure 1. Perioperative sodium changes and hospital mortality

*Decrease and Increase (>5 mmol/l) categories exclude those who also had >5 mmol/l change in the opposite direction. The latter were categorised as “Both decrease and increase >5mmol/l”. Model adjusted by age, ASA score, elective/non-elective surgery, co-morbidities, significant preoperative conditions, preoperative sodium concentration, number of postoperative sodium measurements, type of operation, preoperative length of stay and year of admission.

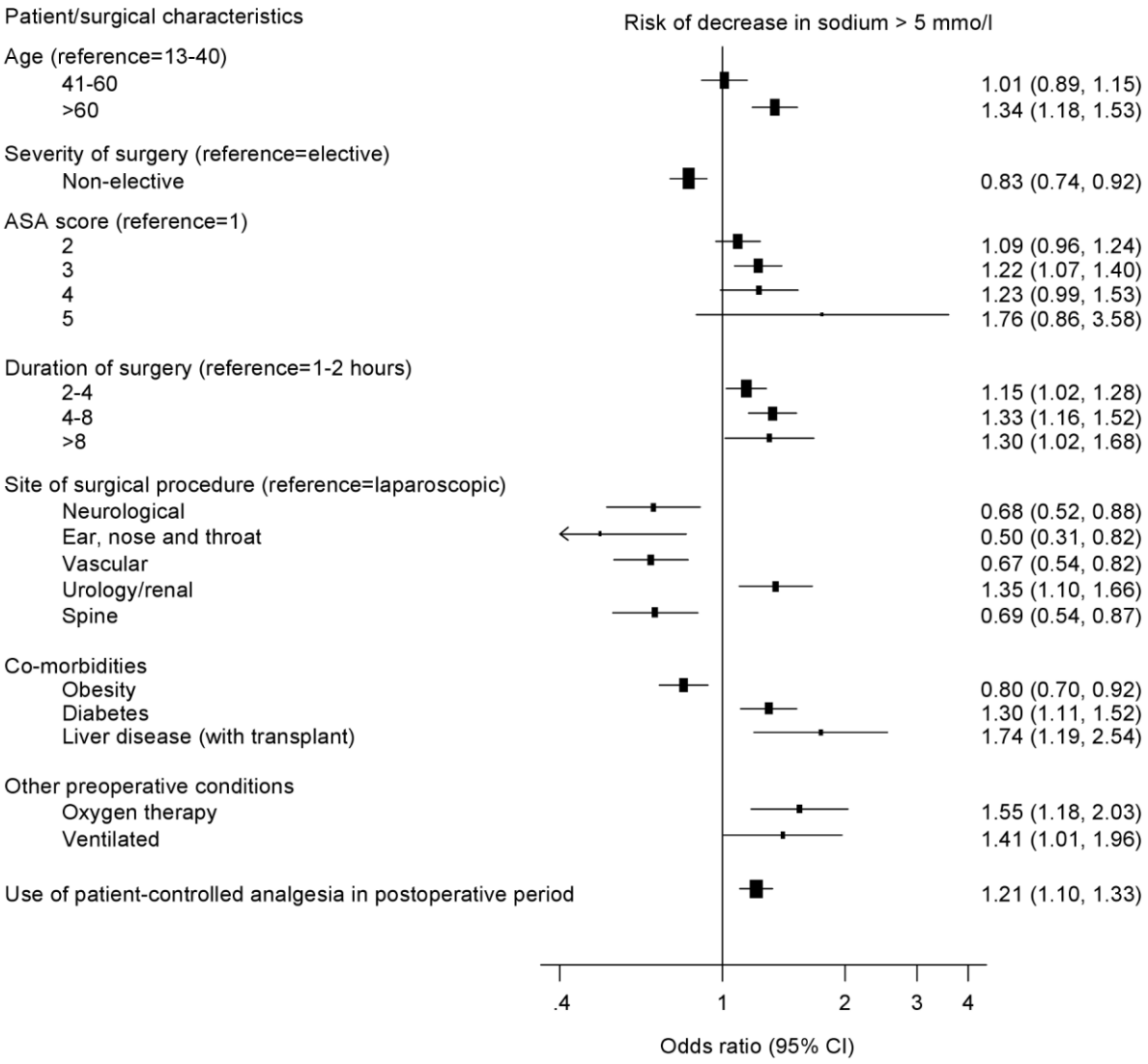


Figure 2. Patient and clinical correlates of sodium decreases >5 mmol/l.

Model adjusted by all variables presented, as well as by calendar year, preoperative length of stay and preoperative sodium concentration. Operative procedures (using OPCS) were fitted as a single categorical variable. Categories were displayed only if they were statistically significant.

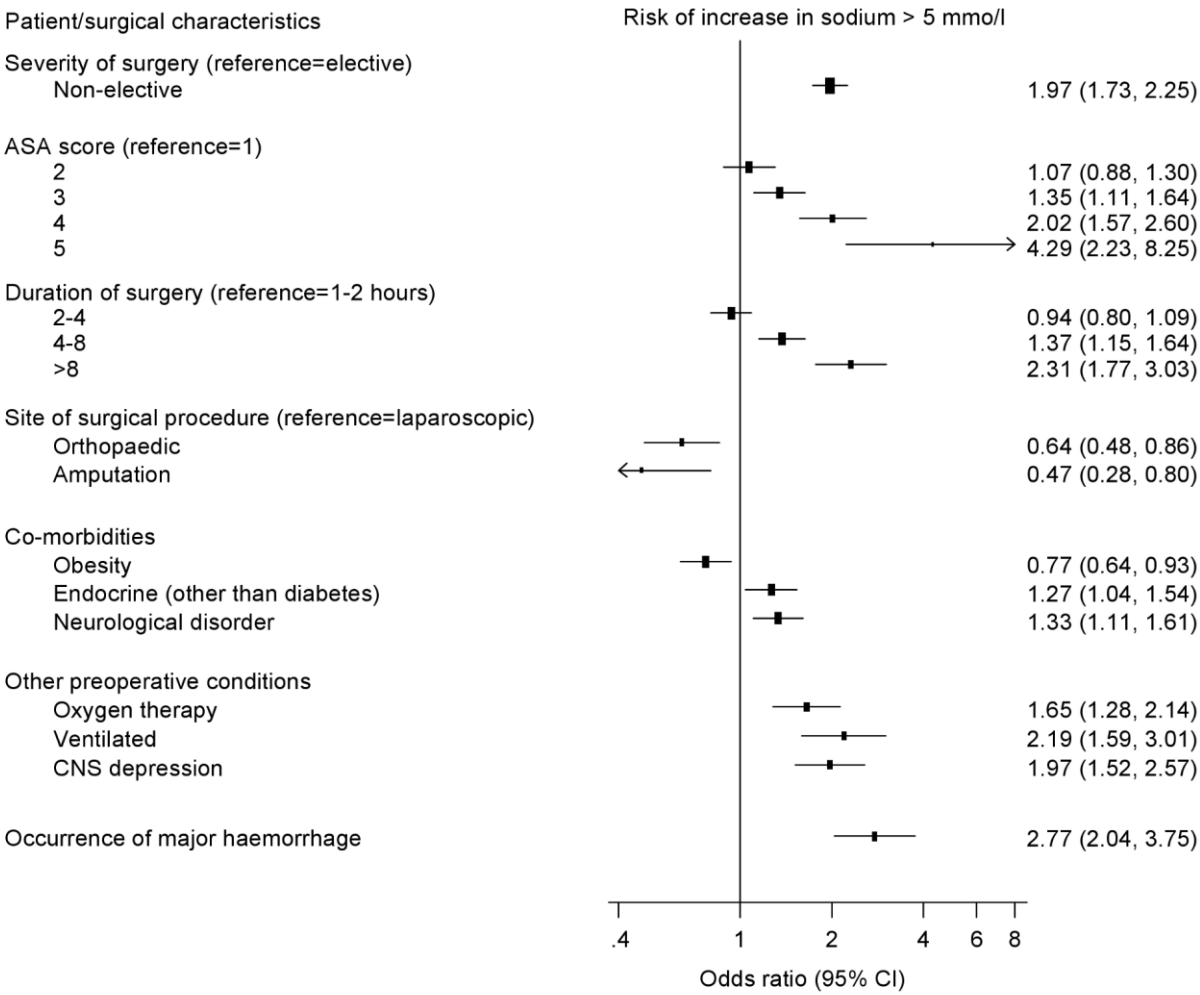
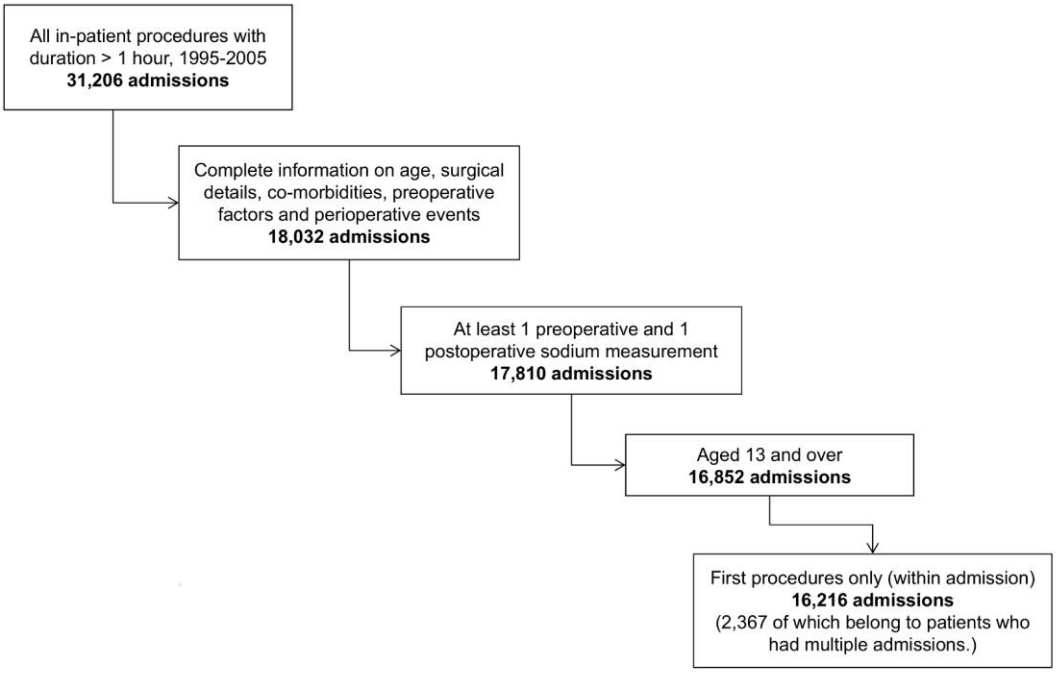


Figure 3. Patient and clinical correlates of increases in sodium >5 mmol/l.

Model adjusted by all variables presented, as well as by calendar year, preoperative length of stay and preoperative sodium concentration. Operative procedures (using OPCS) were fitted as a single categorical variable. Categories were displayed only if they were statistically significant.



Supplementary figure 1. Flow diagram showing exclusions from final data set