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Citation:

Fitzpatrick, D and Walter, E and Leckie, T and Richardson, A and Stacey, M and Hunter, A and Short, S and Hill, N and Woods, D and Grimaldi, R and Galloway, R and Hodgson, L (2020) Association between collapse and serum creatinine and electrolyte concentrations in marathon runners: a 9-year retrospective study. European Journal of Emergency Medicine. ISSN 0969-9546 DOI: <https://doi.org/10.1097/MEJ.0000000000000739>

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Document Version:

Article (Accepted Version)

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Association between collapse and serum creatinine and electrolyte concentrations in marathon runners.

## TITLE PAGE

**Title:** Association between collapse and serum creatinine and electrolyte concentrations in marathon runners: a nine year retrospective study.

**Short title:** Association between collapse and serum creatinine and electrolyte concentrations in marathon runners.

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## **Keywords:**

Creatinine, sodium, potassium, athlete, point-of-care systems

## **Declaration of Interests**

Association between collapse and serum creatinine and electrolyte concentrations in marathon runners.

None declared

**Funding sources** The authors gratefully acknowledge the financial assistance of BASIS in the analysis of samples from the 2019 marathon.

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## **Abstract**

### *Background*

Abnormal biochemical measurements have previously been described in runners following marathons. The incidence of plasma sodium levels outside the normal range has been reported as 31%, and the incidence of raised creatinine at 30%.

### *Objectives*

This study describes the changes seen in electrolytes and creatinine in collapsed ((2010-2019 events) and non-collapsed (during the 2019 event) runners during a UK marathon.

### *Methods*

Point-of-care sodium, potassium, urea and creatinine estimates were obtained from any collapsed runner treated by the medical team during the Brighton Marathons, as part of their clinical care, and laboratory measurements from control subjects.

### *Results*

Results from 224 collapsed runners were available. Serum creatinine was greater than the normal range in 68.9%. 6% of sodium results were below, and 3% above, the normal range, with the lowest 132 mmol/l. 17% of potassium readings were above the normal range; the maximum result was 8.4 mmol/l, but 97% were below 6.0 mmol/l. In the control group mean creatinine was significantly raised in both the collapse and control groups, with 55.4% meeting the criteria for acute kidney injury, but had resolved to baseline after 24 hours. Sodium concentration but not the potassium was significantly raised after the race compared with baseline, but only 15% were outside the normal range.

### *Conclusion*

In this study incidence of a raised creatinine was higher than previously reported. However the significance of such a rise remains unclear with a similar rise seen in collapsed and non-collapsed runners, and resolution noted within 24 hours. Abnormal sodium concentrations were observed infrequently, and severely abnormal results were not seen, potentially reflecting current advice to drink enough fluid to quench thirst.

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## Introduction

Collapse at the end of a marathon common(1,2) and is responsible for 59-85% of all medical presentations(3) to event medical teams. In one series at a half marathon the incidence of severe collapse was 1.53 per 1000 runners. Although the majority of collapses are benign in origin, for example related to orthostatic hypotension or exercise-associated collapse (EAC) (4), there are a number of potentially life-threatening causes that need to be identified and treated promptly. These include cardiac events, exercise-associated hyponatraemia (EAH), and hyper or hypothermia.

As part of the diagnostic process in the field, point-of-care (POC) blood testing for a number of biomarkers is increasingly employed (4). Common tests include sodium, creatinine, urea and troponin (5). POC testing can supplement the initial history and examination to delineate the cause of collapse, such as hyponatraemia, for which early aggressive treatment may be required.

A number of studies have compared creatinine levels between collapsed and non-collapsed endurance runners (6–15). A recent review (16) described an average increase in creatinine levels of 25.7  $\mu\text{mol/l}$  after endurance running events, with 30% of marathon runners in one study having levels above the upper limit of normal (17). What is less clear is whether these increases represent a true renal insult, potentially exacerbated by dehydration or reduced renal blood flow, or due to muscle breakdown or other causes (8) and which runners require further assessment or follow-up. The comparison of creatinine levels in collapsed and non-collapsed runners is an approach that could contribute to the understanding of the significance of creatinine changes following marathon running.

Salt and water loss from prolonged exercise need to be replaced carefully. Historically, runners were encouraged not to drink during exercise. The recognition that dehydration was a problem changed practice, and from 1996, runners were encouraged to drink liberally (18). This policy was complicated by hyponatraemia and cerebral oedema, and in a few cases this was fatal(19). In 2003, the International Marathon Medical Directors Association (IMMDA) adopted more restrictive fluid guidelines of up to 400-800 ml per hour of race. Despite implementation of these guidelines, studies in marathon runners have reported an incidence of hyponatraemia of 6% - 13% (20,21) and of hypernatraemia of 25% (21) with a range of 123–152 mmol/l (21). Current guidelines are to drink according to thirst, suggesting that the body regulates its salt and water balance accurately (22). Even with these guidelines, the incidence of hyponatraemia is reported as between 8.2% (6) and 12.5%, even in asymptomatic volunteers (23). Data on serum potassium concentrations are reported less often, but hyperkalaemia has been reported in 16 % after completing a marathon (17,24).

This study describes the serum sodium, potassium and creatinine changes observed in a cohort of runners immediately after a collapse during the Brighton (UK) Marathon, over a nine-year period (2010-2019). The Brighton Marathon is an annual event which has run since 2010. Around 10,000 runners take part each year. A medical facility with sports medicine and critical care doctors is provided at the finishing line to provide immediate treatment to runners. The study also compares creatinine levels between collapsed and non-collapsed runners at the 2019 marathon, providing the first comparative study of creatinine changes in collapsed and non-collapsed marathon runners.

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## Methods

A total of 307 participants were took part in the Brighton Marathon (Brighton, United Kingdom) over a number of years. These were split into collapse and control groups. The collapse group (n=227) were runners who presented to one of two main medical tents after a collapse between 2010 and 2019. The control group (n=80) took part in the 2019 Brighton Marathon and were prospectively recruited after ethical approval and written consent were obtained. Recruitment was done through email advertisement before the marathon and a physical presence at the pre-marathon exhibition where all runners attended to register for the race. Runners were eligible to participate as long as they did not have any pre-existing medical conditions and self-reported to be in good health at the time of the race. Consent was not taken from the collapsed runners, as the investigations were taken and required for clinical care, and the data pooled and anonymised at source.

Collapsed runners had POC, sodium, potassium, urea and creatinine testing performed using the Abbott i-STAT device (Abbott Diagnostics, Maidenhead, UK). Blood was taken during initial assessment as part of standard medical care and analysed using the i-STAT device onsite in the medical tent. Baseline samples were not obtained as this group were recruited retrospectively following their collapse. This method has been validated against other creatinine measurement methods previously (25–27). The normal reference ranges for this method are as follows; Creatinine 55-115  $\mu\text{mol/l}$ , Urea 2.9-9.4mmol/l, Sodium 138-146mmol/l and potassium 3.5-4.9 mmol/l

The control group had conventional laboratory-based biochemistry testing performed at baseline (within the 48 hours prior to the race) and within 10 minutes of completing the race. A proportion of the control group (28.8% n=23) also provided a sample 24 hours following the marathon. Participants returned for this on a voluntary basis as a large proportion were not able to stay in the locality of the marathon for the 24 hour sample and so were lost to the study at this stage. Blood was taken using a Vacutainer system (BD Medical, New Jersey, USA) and measurement taken from serum. This was then transported, frozen, to the laboratory within two hours of sampling. The normal reference range for creatinine in this laboratory was 50.04-98.1  $\mu\text{mol/l}$  for women and 63.6-110.5  $\mu\text{mol/l}$  for men.

## Statistical analysis

Data on all creatinine and electrolyte samples before and after the marathon in both groups were assessed for normality using the Shapiro-Wilk test. In the control group, the dependent (paired) t-test was used to compare baseline creatinine levels with creatinine levels at the finish line and at 24 hours following race completion. Given the different normal reference ranges for the laboratory creatinine test and POC test, an independent t-test compared the percentage rise above the upper limit of normal between the control and collapsed runners at the 2019 marathon, to control for changes in environmental conditions, and between the entire collapsed cohort and 2019 control group.

Mean values for sodium, potassium and urea were compared using unpaired t test and proportions outside of the normal range were also reported. In addition, relative risk (RR)



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was calculated for the collapse and control groups for creatinine, urea and potassium results above the normal range and sodium results below the normal range.

In the control group, pre- and post-marathon results were compared to establish whether the post-race results met the criteria for acute kidney injury (AKI), defined by the KDIGO criteria as a 50% rise in creatinine or absolute rise of more than 27  $\mu\text{mol/l}$  in a 48-hour period (28).

All values are mean and standard deviation (SD) unless otherwise stated. Statistical analysis was performed using R: A language and environment for statistical computing software, 2019 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was chosen as a p value  $<0.05$ .

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## Results

### Collapsed runners

Two hundred and twenty-seven collapsed runners warranted on-site immediate biochemistry measurement over the nine marathons between 2010 and 2019 (POC data were not collected for the 2016 marathon). The mean number of collapses per year was 25.3 (SD 8.8) and the majority were male (65.6%). The median age (range) was 39.5 years (19–57 years). Collapses per year can be seen as supplementary digital content. Table 1 shows data for electrolytes in control and collapsed runners. Figure 1 shows distribution of results for the different POC tests.

### Control

None of the control group suffered a collapse or reported significant new medical symptoms post-race. Table 1 also contains data for control runners before and after the marathon.

As per table 1, the mean creatinine was significantly elevated between baseline and immediately after completing the marathon ( $p < 0.01$ ). In those tests, creatinine levels were returning to normal after 24 hours; the mean creatinine was not significantly elevated between baseline and the 24 hour post-race sample ( $p = 0.01$ ) (figure 2a).

The baseline sodium concentration was lower than the race sodium concentration immediately after the race in the control group ( $p=0.001$ ). The baseline potassium concentration did not differ from the concentration immediately after the race ( $p=0.35$ ). Baseline urea concentration was significantly lower than the post-marathon urea concentration ( $p<0.001$ ).

Forty-six (55.4%) controls met the KDIGO criteria (28) for AKI immediately following the race. After 24 hours, one patient (4.3 %) still met the AKI criteria. Using a chi-squared test, there was a statistically significant difference in the proportion of participants with an AKI between the two time points ( $p<0.001$ ). This is shown in Table 2.

### Control and collapse

When comparing the control and collapsed runners, the mean rise above the creatinine assay upper limit of normal was not different between the 2019 control group ( $M = 114.6 \mu\text{mol/l}$ ,  $SD 22.9$ ) and the 2019 collapsed runners ( $M = 106.9 \mu\text{mol/l}$ ,  $SD 29.3$ ),  $t(30.18) = 1.17$ ,  $p = 0.25$ , or between the 2019 control group and the entire cohort of collapsed runners ( $M = 119.43 \mu\text{mol/l}$ ,  $SD 32.34$ ),  $t(198.17) = 1.42$ ,  $p = 0.16$ . Figure 2b shows the comparison between creatinine levels immediately after completing the marathon between the control group and the collapsed runners. The former analysis between the 2019 control and collapse group is included as the environmental and other conditions were identical between the groups.

Table 1 shows comparisons between control and collapsed runners for sodium, potassium and urea. When comparing sodium concentration between control and collapsed runners, there was no statistically significant difference ( $p=0.98$ ). The same was true for urea concentration ( $p=0.71$ ); however, serum potassium was higher in collapsed runners when

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compared to controls ( $p < 0.0001$ ). Table 3 details RR for creatinine and electrolyte results outside of the normal range. Of these, only raised serum potassium showed a statistically significant risk.

## **Discussion**

In this large group of marathon runners, we found a large proportion of asymptomatic runners to have an AKI after running a marathon, and a similar proportion of these runners to have a raised creatinine concentration compared to collapsed runners. In the majority of the asymptomatic runners, creatinine levels had returned to near baseline after 24 hours. Additionally, we found similar serum sodium concentrations in these two groups, and a far lower incidence of hyponatraemia in collapsed runners than previously reported.

### Creatinine results in collapsed and non-collapsed runners

A raised serum creatinine level after a marathon is well recognised, but to our knowledge, this is the largest reported cohort of post-race serum creatinine results in collapsed marathon runners. Nearly three quarters of all collapsed runners recorded elevated serum creatinine levels, consistent with some previous smaller studies (16, 24), although others suggest a much lower incidence, around 30-40% of marathon runners (11,17). However, the current study also shows comparisons to non-collapsed runners (controls) completing the same marathon course. A similar proportion of non-collapsed runners demonstrated a post-marathon creatinine level above the normal range, with 55.4 % of these having an AKI, as defined by the KDIGO criteria (28), consistent with existing literature (6,7,9,11,13,15,30). This makes the clinical interpretation and significance if any of a raised creatinine result in the collapsed runner challenging. Consistent with the results in the current study, a previous study (49) also reported a rapid return to normal levels, with only 9% showing persistent abnormal levels after 24 hours. However, a much smaller number of participants provided 24 hour samples and so it is not clear whether all of those with an AKI would have normal results at that time point.

Whilst the likelihood of collapsed runners having an elevated creatinine was not on average different to control runners, when the creatinine was raised, it was on average 11 % higher, relative to the normal range, than in non-collapsed runners. This raises the possibility that these individuals may be at greater risk of subsequent complications or morbidity.

### Potential causes of raised creatinine

The pathophysiology of a raised creatinine in endurance exercise is likely to be multifactorial and has been reviewed by members of this research groups previously(16), However the causes may be related to muscle breakdown and true renal dysfunction. Creatinine has been shown to increase following exercise, suggesting it may be present as part of normal skeletal muscle breakdown following exercise (31). Although levels of creatine kinase in rhabdomyolysis may predict development of significant AKI (32), this is not frequently observed in endurance events (16). However, in the presence of an acidic environment within the renal tubules, high levels of myoglobin precipitate with uromodulin to form casts and AKI ensues, though vasoconstriction, direct toxicity of myoglobin and release of cytokines all probably contribute (34,35). It is likely that in most endurance runners, the physiological response of the kidneys is sufficient to cope with the muscle breakdown

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products and it is only the presence of multiple risk factors that significant injury, requiring medical treatment, can occur(36).

Subclinical renal injury immediately following a marathon does however also exist with levels of cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 in the urine having been observed to rise immediately after a marathon (11). These biomarkers are a more sensitive and are earlier measures of renal filtration than creatinine, suggesting that renal filtration rate falls immediately following a marathon. Runners are therefore at risk of renal dysfunction (37), in the subsequent few days. True renal injury may be due to catecholamine-driven renal hypoperfusion producing a transiently reduced glomerular filtration rate (GFR) and a subsequent increase in serum creatinine (28,29).

Contributory factors common to all runners during an event include relative dehydration from sweat losses (13), preceding/intra-race illness (such as gastroenteritis) the use of NSAIDs (with resulting renal vasoconstriction), diuretics or ACE inhibitors; the combination of the latter three significantly increase the risk of AKI (30,31). High ambient temperatures can also predispose to heat related illness, a common cause of collapse(3) and risk factor for AKI. Increased core temperature itself is associated with increased rates of myoglobinaemia and can cause microvascular changes that induce renal dysfunction (42). In the context of this extreme physiological disturbance, true renal injury may occur with short-term damage and if recurrent, contribute to chronic kidney dysfunction.

### Clinical implications

Overall, there are a number of potential mechanisms for the transient creatinine rise observed in apparently healthy marathon runners in this study. However, this study demonstrates that these runners are as likely to have a raised creatinine as those who collapse. In addition, a proportion of collapsed runners may have further pathological causes for a raised creatinine such as heat illness or rhabdomyolysis(3) which may explain their greater relative rise. Unlike in exertional heatstroke management, where repeated blood tests are performed to ensure resolution of biochemical abnormalities (37), no such guidelines for exertional AKI exist. However, the finding that the majority of raised creatinine levels return to baseline within 24 hours in asymptomatic runners may be reassuring and consistent with previous findings (12, 14, 18). To help guide the need for follow-up, clinical signs and symptoms, the likely underlying cause of the creatinine rise, and co-existing pathologies and medication use will best determine the need for follow up of renal function. AKI following a marathon is, however, on occasion, severe enough to require renal replacement therapy (47, 48). With the high incidence of a raised serum creatinine after marathon running, it would be prudent to advise runners to avoid or minimise any factors, including drugs, which could further increase serum creatinine, or exacerbate potential renal dysfunction.

This study demonstrated that creatinine returns to near normal levels in 24 hours in a cohort of non-collapsed runners. Furthermore, creatinine is an imperfect measurement of renal function (38, 39). Authors of previous studies have suggested that the standard normal ranges are not appropriate for use in an athletic population for this reason (27, 40). However, interpreting a much higher result, particularly if a runner is unwell, is more difficult. A similar effect has been noted by our group in serum troponin rises, normally

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employed to detect myocardial ischaemia (7, 41) For this reason, better biomarkers for AKI are desirable (49). Biomarkers other than creatinine, such as NGAL, KIM-1 and cystatin are more direct measures of renal injury (26, 43) and may have less potential to be increased following endurance exercise (16). Further study in this area, including the response to running a marathon, and patterns seen in collapsed runners, may allow biomarkers to be employed to better risk-stratify runners. This may be significant as it has been postulated that repeated low-grade insults may have long-term implications that should be considered (13), the use of novel biomarkers may help to identify these changes.

### Sodium / Potassium

In the current study, the incidence of abnormal sodium levels was markedly lower than previously reported (7, 8, 11), and severely abnormal results were not seen. None of the results were outside the detectable range of the analyser, and very unlikely to have any clinical effect. Furthermore, when comparing runners who had experienced a collapse and required help from the medical team to asymptomatic volunteers there was no difference in their sodium concentration after the marathon. It is not clear why the current study has more normal results, but it may reflect a previous changes to hydration strategy advice given to marathon runners.

Initial advice was to drink prescribed amounts of water at regular intervals(51) which may have contributed to hyponatraemia secondary to increased total water volume(52). However, in 2006 (53) this advice changed to drinking to thirst, in recognition that individuals lose water at variable rates and so a prescribed amount will be excessive for some and insufficient for others. Despite this change in 2006, a study at the 2010 London Marathon showed only 25.3% of runners were using this strategy, although this increased to 48.7% in 2014(54). The earliest marathon in this study was in 2010 and studies showing a higher incidence of hyponatraemia (20,21) were generally published prior to the change in recommendations. The decreased incidence demonstrated here may be the result of changes in runner behaviours in response to the change in recommendations and education.

Hyponatraemia in runners is thought to be dilutional secondary to increased water consumption during running, or to inappropriate vasopressin secretion (55); current guidelines to drink only to thirst (22,52) may have reduced the incidence of clinically important hyponatraemia. It is generally accepted that the body has good homeostatic mechanisms to maintain accurate salt and water balance, and other methods of assessing hydration during exercise, for example, calculating fluid loss, or assessing the colour of urine, may be over-complicated or less accurate than simply drinking to thirst. A meta-analysis of data from cyclists taking part in time trials concluded that the best strategy for gauging fluid replacement was to rely on thirst (56). There has also been much debate recently on the merits or otherwise of manufactured sports drinks. Recent work (57) suggested that water is as effective, safe and cheaper than commercially available products. The majority of runners in the Brighton Marathon drink water as dictated by thirst (Walter EJ, 2012, unpublished data), so this current study would support advice to drink to thirst, and that water does not cause significant electrolyte derangement.

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Potassium has less often been implicated in collapse in marathon runners, but hyperkalaemia can result in arrhythmias and cardiac arrest. Previous studies have shown a prevalence of 16 % (3, 49); these results are consistent with findings in the current study, which show an incidence of hyperkalaemia above the normal range of 17.4 %, and hypokalaemia of 2.2 %. Although collapsed runners did have a higher average potassium concentration after the marathon, the absolute difference was small and unlikely to be of clinical importance. Of note, the proportion of runners with a clinically importantly raised potassium (defined as greater than 6.0 mmol/l (58)) in the current study was low at 3.1 %. This suggests that whilst most collapsed runners will not need to be treated for hyperkalaemia, a small number may require urgent treatment to prevent cardiac complications. A clinically important hyperkalaemia was therefore uncommon in this study, and severe hyperkalaemia was very rarely seen. These results should be taken with caution, however, as haemolysis cannot be assessed with the i-STAT device, and potassium levels may therefore be overestimated.

### Limitations

This study has a number of limitations. The main analysis was a retrospective analysis of historical POC results in collapsed runners, with the data primarily collected to aid clinical decision-making. Clinical details of collapsed runners were unavailable to the authors and as a result the cause of collapse, and medical and medication history are unclear. Availability of these would allow more detailed analysis including testing the hypothesis that cause of collapse may contribute to the heterogeneity of collapsed runner's creatinine levels. For the collapsed runners, baseline and follow-up creatinine results were absent. These would be useful for an understanding of peri-event renal function. Of note though, only 6.3% of control runners had a pre-race creatinine outside the normal range, meaning prevalence of pre-existing renal disease was likely to be low. However, this could also represent increased muscle bulk in trained athletes. The incidence of changes in urea concentration is low (18 %), suggesting that pre-race AKI is rare.

In addition to this, a far smaller number of participants in the control group provided a 24 hour sample than did immediately following the race. Although creatinine levels returned to near normal at this time point, this result should be interpreted with caution as we were unable to confirm that all abnormal results improved in this way.

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## **Conclusion**

In a nine-year review of a marathon event we have demonstrated a consistent increase in serum creatinine levels immediately following completion of the race. Whilst the prevalence of a post-marathon creatinine rise was similar between collapsed and non-collapsed runners, this study demonstrated that the degree of rise is greater in those who experience a collapse. Additionally, levels return to normal after 24 hours in non-collapsed runners. This means it may be difficult to use post-race creatinine levels to determine those at risk of actual renal injury. Further research is required to validate novel biomarkers of renal injury and to establish the long-term significance of a raised creatinine after running a marathon and who, if any, may be at risk of a longer-term renal injury.

In addition, we have demonstrated a lower prevalence of hyponatraemia and hypernatraemia than had been previously reported. This may be the result of revised hydration guidance for runners preventing dilutional hyponatraemia in particular. In addition, sodium concentrations were similar in collapsed and asymptomatic runners. This may help clinicians providing medical care at marathon events plan for expected cases.

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### Acknowledgements

The authors are grateful to the subjects for enrolling in the study.

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## Figure Legends

*Figure 1: Box and Whisker plots for POC testing in collapsed runners. A-Sodium, B-Potassium, C- Creatinine, D- Urea*

*Figure 2: A- Baseline, finish line and 24-hour post-marathon serum creatinine for control runners. Thick black line represents mean for each group. B- Post-race creatinine as a percentage of the upper normal range*

*Table 1- Data for creatinine, sodium, potassium and urea concentrations. \*Different normal ranges for creatinine measurement in control and collapsed participants*

*Table 2- Creatinine results and AKI status of control runners immediately before, immediately after, and 24h after completing marathon.*

*Table 3- Risk Ratios (RR) for creatinine and electrolyte disturbance comparing control and collapse groups immediately after completing marathon.*