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Mild hyponatremia, hypernatremia and incident cardiovascular disease and mortality in older men: A population-based cohort study

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Abstract *Aim:* To examine the association between serum sodium concentration and incident major cardiovascular disease (CVD) outcomes and total mortality in older men.
Methods and Results: A prospective study of 3099 men aged 60–79 years without a history of cardiovascular disease followed up for an average 11 years during which there were 528 major CVD events (fatal coronary heart disease [CHD] and non-fatal MI, stroke and CVD death) and 873 total deaths. A U shaped relationship was seen between serum sodium concentration and major CVD events and mortality. Hyponatremia (<136 mEq/L) and low sodium within the normal range (136–138 mEq/L) showed significantly increased risk of major CVD events and total mortality compared to men within the upper normal range (139–143 mEq/L) after adjustment for a wide range of confounders and traditional risk factors [adjusted HRs 1.55 (1.13,2.12) and 1.40 (1.14,1.72) for major CVD events respectively and 1.30 (1.02,1.66) and 1.30 (1.11,1.53) respectively for total mortality]. Hyponatremia was associated with inflammation, NT-proBNP, low muscle mass and alkaline phosphatase; these factors contributed to the increased total mortality associated with hyponatremia but did not explain the increased risk of CVD events associated with hyponatremia or low normal sodium concentration. Hypernatremia (≥145 mEq/L) was associated with significantly increased risk of CVD events and mortality due to CVD causes.
Conclusion: Mild hyponatremia even within the normal sodium range and hypernatremia are both associated with increased total mortality and major CVD events in older men without CVD which is not explained by known adverse CV risk factors.

Introduction

Hyponatremia, usually defined as serum sodium concentration <136 mEq/L, is one of the most common electrolyte abnormalities observed in hospitalised patients [1] and in patients with chronic kidney disease (CKD), coronary heart disease (CHD) and heart failure (HF) [2–3]. Several clinical and epidemiological studies have shown hyponatremia to be associated with increased total mortality in these patients [4–6]. In recent years, attention has turned to the possibility that mild hyponatremia, may be associated with adverse outcomes in the general population [7]. Studies on hyponatremia and mortality in community based populations are limited, but in the three population studies that have examined the relationship between hyponatremia and mortality in community based

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subjects, there is evidence that hyponatremia is associated with increased mortality [8–10] and that even a level of sodium concentration in the lower normal range (serum sodium 135–137 mEq/L), a level usually considered benign, is associated with increased mortality [9]. There is a paucity of data on electrolyte disturbance and risk of incident cardiovascular disease in the general population, but two studies have reported that low serum sodium, even within the normal range, is associated with increased stroke risk [11–12], and possibly also to myocardial infarction [9]. Electrolyte disorders are common in the elderly [13] but less is known about the relationship between electrolyte disturbances and incident major CVD events and mortality in the general older population without established CVD. We have examined the association between serum sodium as well as serum potassium and risk of CHD, stroke, CVD mortality and total mortality in a population of older men aged 60–79 years with no history of CVD (CHD, HF or stroke).

Methods

The British Regional Heart Study is a prospective study of cardiovascular disease involving 7735 men aged 40–59 years drawn from one general practice in each of 24 British towns, who were screened between 1978 and 1980 [14]. The population studied was socio-economically representative of British men and consisted almost entirely of white Europeans (>99%). In 1998–2000, all surviving men, now aged 60–79 years, were invited for a 20th year follow-up examination, on which the analyses presented here are based. Ethical approval was obtained from all relevant local research ethics committees. All men completed a mailed questionnaire providing information on their lifestyle and medical history, had a physical examination and provided a fasting blood sample collected using the Sarstedt Monovette system. The samples were frozen and stored at −20 °C on the day of collection and transferred in batches for storage at −70 °C until analysis, carried out after no more than one freeze–thaw cycle. The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (MI), HF or stroke and to bring their medication to the examination session. 4252 men (77% of survivors) attended for the 1998–2000 examination and blood serum samples were available from 4088 men; 4034 men had measurements of sodium. Of these men, 935 men with pre-existing doctor diagnosed CHD (angina or MI), stroke or heart failure were excluded, leaving 3099 men for analyses.

Cardiovascular risk factor measurements at 1998–2000

Details of measurement and classification methods for smoking status, physical activity, body mass index, social class, alcohol intake, blood pressure, blood lipids, alkaline phosphatase and forced expiratory volume in 1 s (FEV_1) in this cohort have been described [15–17]. Mid arm muscle circumference (MAMC) calculated as mid upper arm circumference (MUAC) − 0.3142*(triceps skinfold thickness) was considered an indicator of muscle mass [16,18]. Prevalent diabetes included men with a diagnosis of diabetes or men with fasting blood glucose ≥7 mmol/l. Predicted glomerular filtration rate (eGFR), estimated from serum creatinine using the equation developed by Levey et al. [19] was used as a measure of renal function. C-reactive protein (CRP) was assayed by ultra sensitive nephelometry (Dade Behring, Milton Keynes, UK) [20]. N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined using the Elecsys 2010 electrochemiluminescence method (Roche Diagnostics, Burgess Hill, UK) [21].

Serum sodium

Sodium was measured by an ion selective electrode. A membrane composed of crown ether with a neutral PVC carrier forms a selective membrane for sodium ions, creating an electrical potential as sodium ions traverse the membrane [22]. The electrical potential can be compared to a reference electrode to determine the sodium ion concentration. The between batch imprecision was <2%.

Follow-up

All men have been followed up from initial examination (1978–1980) for cardiovascular morbidity [23] and follow-up has been achieved for 99% of the cohort. In the present analyses, total mortality and morbidity events are based on follow-up from re-screening in 1998–2000 at mean age 60–79 years to June 2010, a mean follow-up period of 11 years (range 10–12). Information on death was collected through the established “tagging” procedures provided by the National Health Service registers. Fatal stroke episodes were those coded on the death certificate to International Classification of Diseases (ICD-9th Revision) 430–438. Non-fatal stroke events were those which produced a neurological deficit that was present for more than 24 h. Fatal CHD events were defined as death with CHD (ICD 9th revision, codes 410–414) as the underlying code. A non-fatal MI was diagnosed according to World Health Organisation criteria [24]. Cardiovascular deaths included all those with ICD-9 codes 390–459. Evidence of non-fatal MI and HF was obtained by ad hoc reports from general practitioners supplemented by biennial reviews of the patients’ practice records (including hospital and clinic correspondence) through to the end of the study period. Outcomes assessed in the current analyses were major CHD (defined as fatal or non-fatal MI) major stroke events (fatal or non-fatal), CVD death and all major CVD events (major CHD events, stroke events or CVD death).

Statistical methods

Cox’s proportional hazards model was used to assess the multivariate-adjusted hazards ratio (relative risk) by levels of serum sodium. Tests for quadratic trends in Fig. 1 were assessed by assigning quantitative values (1–11) for the 11 groups and fitting sodium as a continuous variable rather than as categorical variables and including a quadratic term. In multivariate analyses, smoking (never, long term ex-smokers (>15 years), recent ex-smokers (<15 years) and current smokers), social class (manual vs non manual),