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ORIGINAL RESEARCH ARTICLE

Uric acid predicts mortality and ischaemic stroke in subjects with diastolic dysfunction: the Tromsø Study 1994–2013

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Abstract

Aims To investigate whether serum uric acid predicts adverse outcomes in persons with indices of diastolic dysfunction in a general population.

Methods and results We performed a prospective cohort study among 1460 women and 1480 men from 1994 to 2013. Endpoints were all-cause mortality, incident myocardial infarction, and incident ischaemic stroke. We stratified the analyses by echocardiographic markers of diastolic dysfunction, and uric acid was the independent variable of interest. Hazard ratios (HR) were estimated per 59 μmol/L increase in baseline uric acid. Multivariable adjusted Cox proportional hazards models showed that uric acid predicted all-cause mortality in subjects with E/A ratio <0.75 (HR 1.12, 95% confidence interval [CI] 1.00–1.25) or E/A ratio >1.5 (HR 1.51, 95% CI 1.09–2.09, *P* for interaction between E/A ratio category and uric acid = 0.02). Elevated uric acid increased mortality risk in persons with E-wave deceleration time <140 ms or >220 ms (HR 1.46, 95% CI 1.01–2.12 and HR 1.13, 95% CI 1.02–1.26, respectively; *P* for interaction = 0.04). Furthermore, in participants with isovolumetric relaxation time ≤ 60 ms, mortality risk was higher with increasing uric acid (HR 4.98, 95% CI 2.02–12.26, *P* for interaction = 0.004). Finally, elevated uric acid predicted ischaemic stroke in subjects with severely enlarged left atria (HR 1.62, 95% CI 1.03–2.53, *P* for interaction = 0.047).

Conclusions Increased uric acid was associated with higher all-cause mortality risk in subjects with echocardiographic indices of diastolic dysfunction, and with higher ischaemic stroke risk in persons with severely enlarged left atria.

Keywords Diastolic dysfunction; Echocardiography; Mortality; Ischaemic stroke; Uric acid; Clinical epidemiology

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Introduction

Diastolic dysfunction (DD) is characterised by abnormal cardiac relaxation, stiffness, or filling. It is closely associated with heart failure with preserved ejection fraction (HFpEF), a clinical syndrome where the patient suffers from symptoms and signs of heart failure (HF) and has normal or only mildly reduced ejection fraction.[1] About half of all HF patients have HFpEF.[1] The prevalence of HFpEF in the HF population increases, and the prognosis once hospitalised is on par with that of HF with reduced ejection fraction (HFrEF).[2] Contrary to HFrEF, there is no medical treatment of proven benefit for HFpEF,[1] although a recent study demonstrated a positive effect of exercise and diet on exercise capacity in obese, elderly patients with clinically stable HFpEF.[3] So far medical therapy for HFpEF is mostly symptomatic and consists of treating contributing factors and comorbidities such as hypertension, volume overload, and atrial fibrillation.[1] There is

evidence that DD progresses over time and is a risk factor for the development of HFpEF.[4] DD is commonly asymptomatic and is associated with increased all-cause mortality.[5] Thus, there is a need for more knowledge about possibly modifiable risk factors for adverse outcome in DD.

Elevated uric acid (UA) levels are associated with cardiovascular disease and death. In a previous population-based cohort study, we showed that increased UA was associated with elevated risk for all-cause mortality and ischaemic stroke after 15 and 12 years of follow-up, respectively.[6] In a meta-analysis, hyperuricaemia was associated with high all-cause mortality in HF patients.[7] Furthermore, a recent study demonstrated that hyperuricaemia was associated with increased all-cause mortality in patients who were hospitalised for HFpEF.[8] However, the association between UA and DD remains unclear. Because both DD and UA are associated with increased risk of mortality, and hyperuricaemia is associated with increased mortality in HF, it is of interest to address a possible interaction between UA and DD, not the least because there is effective pharmacological treatment for hyperuricaemia. We investigated the combined associations between UA, markers of DD, and the endpoints incident myocardial infarction, incident ischaemic stroke, and all-cause mortality in a prospective, population-based cohort study with 19 years follow-up.

Methods

Study population

The Tromsø Study is a series of population based prospective surveys, conducted since 1974, with the participation of the inhabitants of the municipality of Tromsø in Northern Norway.[9] The population of the present study is the participants of the Tromsø Study in 1994–95. In this fourth wave, 27 158 men and women attended (77% of eligible subjects). Out of these, all participants aged 55–74 years, as well as smaller, random samples of the other age groups 25–85 years were invited to the more extensive second visit examination, and 7965 subjects attended (75% of eligible subjects). Of those, 7445 persons had their serum UA measured, and 3272 subjects had been randomly selected for echocardiography. Put together, 3068 subjects underwent both UA measurement and echocardiography. We excluded the persons (n = 128) with diabetes at baseline (defined as haemoglobin A1c (HbA1c) ≥6.5%, non-fasting glucose ≥10.0 mmol/L, receiving anti-diabetic treatment or self-reported diabetes). Thus, the final cohort consisted of 1460 women and 1480 men. The University of Tromsø conducted the study in cooperation with The National Health Screening Service. The Regional Committee for Medical and Health Research Ethics approved this study (committee's reference number 2009/2536-3), and all participants gave their informed and written consent to participate. The Tromsø Study complies with the Declaration of Helsinki.

Measurements

The participants provided information on diabetes, smoking habits, physical activity, and current use of medication through a self-administered questionnaire. Blood pressure was recorded in triplicate, and we used the mean of the second and the third measurement. We classified physical activity as active (≥1 h physical activity with prominent perspiration or breathlessness per week) or inactive (all others), and smoking habits as current smokers and non-smokers. We calculated body mass index as weight (kg) / height^2 (m). Blood samples were non-fasting. The analysis of UA was recently described.[10] Creatinine was measured as previously described.[11] We calculated the estimated glomerular filtration rate (eGFR) according to the CKD-EPI formula.[12] Descriptions of measurements of lipids and HbA1c have been published previously.[13]

Echocardiography

Two expert cardiologists and a medical doctor performed all the echocardiography of the survey in 1994–95 using a Vingmed CFM 750 (Vingmed Sound A/S, Horten, Norway), and it was recently described in detail.[14] We indexed left atrial (LA) size by body surface area (BSA) calculated by the Du Bois formula (BSA = [weight {kg} $^{0.425}$ × height {cm} $^{0.725}$] × 0.007184).[14]

Diastolic dysfunction

We used LA size and mitral Doppler measurements as parameters of DD, and the cut-offs were set according to previously published data.[14] An upper limit of E-wave deceleration time (EDT) as a measure of impaired relaxation was added according to guidelines.[15] We set the cut-off of isovolumetric relaxation time (IVRT, the duration of time between the end of aortic ejection and the onset of mitral inflow) in line with guidelines to detect restrictive left ventricular physiology.[15] E/A ratio, the ratio of peak early Doppler mitral flow velocity (E-wave) to peak late Doppler mitral flow velocity (A-wave), was stratified into low (<0.75), normal (0.75–1.5) and high (>1.5). We divided EDT, the deceleration time from peak to end of early Doppler mitral flow, into low (<140 ms), normal (140–220 ms), and high (>220 ms). We stratified LA size into normal (<2.2 cm/m^2), moderately enlarged (2.2–2.79 cm/m^2), and severely enlarged (≥2.8 cm/m^2). IVRT was either reduced (≤60 ms) or normal (>60 ms).

Outcomes

The endpoints were all-cause mortality and first ever fatal or non-fatal myocardial infarction and ischaemic stroke, identified by linkage to the diagnosis registry at the University Hospital of North Norway and the National Causes of Death Registry. An independent endpoint committee evaluated hospital and out-of-hospital journals, autopsy records, and death certificates to adjudicate each myocardial infarction and ischaemic stroke. Information on emigration from the municipality, from Norway, and date of death was obtained from the National Registry of Norway. Endpoint registry is complete through 31 December 2013 (19 years) for all-cause mortality and through 31 December 2012 (18 years) for myocardial infarction and ischaemic stroke. For all-cause mortality data, we censored for emigration from Norway. For myocardial infarction and ischaemic stroke, we censored for migration out of the municipality or Norway, and death from other causes than incident myocardial infarction and incident ischaemic stroke, respectively.

Statistics

The baseline characteristics are given as mean ± SD for the continuous variables or number and percentage of total for the categories. For each of the baseline characteristics, we assessed the Pearson coefficient for the correlation with UA. We used Cox proportional hazards models to investigate the relationship of UA and the echocardiographic indices of DD with the endpoints all-cause mortality, incident myocardial infarction, and incident ischaemic stroke. Covariates were baseline values of sex, age, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, body mass index, current smoking, physical activity, HbA1c, eGFR, and use of antihypertensive medication including diuretics. We tested for the interaction between UA and each echocardiographic marker of DD using two-way cross products between the continuous UA variable and indicator variables of each echocardiographic marker of DD. Missing data were infrequent and random, and therefore we chose not to use imputation methods to account for missing data in this large cohort. We considered a two-sided *P*-value of <0.05 significant. The proportional hazard assumptions were validated by visual inspection of the log minus log survival plots. We did all the analyses with SPSS software version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

Baseline characteristics

Table 1 shows the unadjusted baseline characteristics and Pearson correlation coefficients with UA for the 2940

Table 1 Unadjusted baseline characteristics of study population ($n = 2940$) and Pearson correlation with uric acid

			SD or %	Pearson correlation with UA	*P* for Pearson correlation
Age, years		59.7	±10.4	0.01	0.56
Sex	Men	1480	49.7%	0.46	<0.001
	Women	1460	50.3%		
Systolic blood pressure, mm Hg		144.3	±22.2	0.13	<0.001
Diastolic blood pressure, mm Hg		83.3	±12.6	0.19	<0.001
BMI, kg/m^2		25.9	±3.9	0.32	<0.001
Uric acid μmol/L	Men	359.1	±84.9	—	—
	Women	277.6	±71.7		
Total cholesterol, mmol/L		6.72	±1.28	0.08	<0.001
Triglycerides, mmol/L		1.68	±1.02	0.43	<0.001
HbA1C, %		5.4	±0.4	0.05	0.02
eGFR, mL/min/1.73 m^2		93.1	±13.2	−0.19	<0.001
Daily smoker, *n*		967	32.9%	−0.05	0.01
Use of antihypertensive drugs, *n*		428	14.6%	0.20	<0.001
Use of allopurinol, *n*		4	0.1%	0.04	0.03
Physical activity, *n*		659	22.4%	0.01	0.51
Left ventricular mass, g/m^2	Men	107.0	±27.9	0.22	<0.001
	Women	90.8	±22.7		
Left atrial size, cm/m^2		2.18	±0.32	−0.05	0.01
E/A ratio		1.05	±0.36	−0.06	0.001
E wave deceleration time, ms		200	±43	0.04	0.03
Left ventricular isovolumic relaxation time, ms		104	±20	0.12	<0.001
Left ventricular ejection fraction, %		75.0	±7.8	−0.06	0.004
Left ventricular ejection fraction < 50 %, n		9	0.3%	0.02	0.33

BMI, body mass index; HbA1c, haemoglobin A1c; eGFR, estimated glomerular filtration rate; UA, uric acid.
The Tromsø Study 1994–2013.
The first column in each stratum provides means for the continuous variables and numbers for the categories.

participants. The echocardiographic indices of DD studied in this article correlated weakly with UA, and among the markers, IVRT correlated the strongest with UA.

Events

In our cohort of 2940 persons, a total of 1014 deaths from all causes, 412 first-ever myocardial infarctions, and 271 first-ever ischaemic strokes occurred during follow-up.

Interactions

Results from Cox proportional hazards models with multivariable adjusted hazard ratio (HR) for all-cause mortality, myocardial infarction, and ischaemic stroke, given for each variable in the model, are displayed in *Table 2*. As echocardiographic marker of DD, we present the analysis of E/A ratio. Decreased E/A ratio, but not increased E/A ratio, was associated with increased risk of all-cause mortality, while this DD index was not associated with myocardial infarction or stroke. Elevated UA was associated with increased risk of all-cause mortality and ischaemic stroke, but not risk of myocardial infarction.

In these analyses with the indices of DD, UA interacted significantly with E/A ratio, EDT, and IVRT for the association with all-cause mortality, and with LA size for ischaemic stroke. This led us to stratify the cohort according to the predetermined levels of each of these indices of DD and examine the effect of UA on the risk of outcomes. There was no interaction between sex and echocardiographic markers of DD or UA in these analyses.

Echocardiographic markers of DD modified the associations between UA and the outcomes

Figures 1–4 show the results of multivariable Cox proportional hazards models when the cohort was stratified according to four echocardiographic markers of DD. HRs are per 59 μmol/L (1 mg/dL) UA increase at baseline. Included in the figures is the number subjects and the number of events of the outcome examined in each stratum.

Figure 1 shows that elevated UA was associated with increased risk of all-cause mortality in subjects with E/A ratio <0.75 (HR 1.12, 95% confidence interval [CI] 1.00–1.25, $P = 0.04$) and E/A ratio >1.5 (HR 1.51, 95% CI 1.09–2.09, $P = 0.01$). Subjects with normal E/A ratio had no increased risk of mortality with higher UA (HR 1.03, 95% CI 0.96–1.11, $P = 0.45$); P for interaction between UA and the categorical E/A ratio variable was 0.02.

Both subjects with EDT <140 ms (HR 1.46, 95% CI 1.01–2.12, $P = 0.04$) and EDT >220 ms (HR 1.13, 95% CI 1.02–

Table 2 Multivariable Cox proportional hazard models of risk for all-cause mortality and adverse cardiovascular events

	All-cause mortality			Myocardial infarction			Ischaemic stroke		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Sex (male vs. female)	1.42	[1.21–1.66]	0.000	2.05	[1.60–2.64]	0.000	1.28	[0.94–1.74]	0.121
Age (per year increase)	1.13	[1.11–1.14]	0.000	1.06	[1.04–1.08]	0.000	1.08	[1.06–1.11]	0.000
BMI (per kg/m^2 increase)	0.98	[0.96–1.00]	0.055	1.01	[0.98–1.04]	0.525	0.99	[0.95–1.03]	0.545
Mean systolic blood pressure (per 5 mm Hg increase)	1.01	[0.98–1.03]	0.688	1.04	[1.01–1.08]	0.023	1.04	[1.00–1.09]	0.066
Mean diastolic blood pressure (per 5 mm Hg increase)	1.04	[1.01–1.09]	0.042	1.01	[0.95–1.07]	0.823	1.03	[0.95–1.11]	0.465
Total cholesterol (per mmol/L increase)	0.97	[0.92–1.03]	0.313	1.17	[1.07–1.28]	0.001	0.96	[0.86–1.08]	0.488
Triglycerides (per mmol/L increase)	0.97	[0.90–1.05]	0.503	0.99	[0.88–1.11]	0.841	1.04	[0.91–1.20]	0.538
eGFR (per 10 mL/min/1.73 m^2 increase)	1.02	[0.95–1.09]	0.510	0.91	[0.83–1.00]	0.058	1.05	[0.92–1.21]	0.433
HbA1c (per % increase)	1.26	[1.04–1.52]	0.018	1.21	[0.90–1.62]	0.200	1.11	[0.78–1.60]	0.557
Smoker (yes vs. no)	2.00	[1.74–2.31]	0.000	1.70	[1.37–2.13]	0.000	1.45	[1.09–1.92]	0.011
Physically active (yes vs. no)	0.94	[0.79–1.13]	0.525	0.94	[0.72–1.23]	0.643	0.85	[0.60–1.20]	0.355
Use of antihypertensive medication (yes vs. no)	1.27	[1.07–1.51]	0.005	0.98	[0.75–1.30]	0.914	1.27	[0.92–1.76]	0.154
Uric acid (per 59 μmol/L increase)	1.06	[1.00–1.13]	0.038	1.01	[0.93–1.10]	0.818	1.13	[1.02–1.25]	0.022
E/A ratio (<0.75 vs. 0.75–1.5)	1.31	[1.12–1.52]	0.001	1.10	[0.85–1.42]	0.457	1.09	[0.80–1.48]	0.592
(>1.5 vs. 0.75–1.5)	1.03	[0.73–1.47]	0.852	1.10	[0.67–1.79]	0.707	0.64	[0.30–1.38]	0.254

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1C.
The Tromsø Study 1994–2013.
Covariates: Sex, age, BMI, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, eGFR, HbA1c, current smoking, physical activity, use of antihypertensive medication, uric acid, E/A ratio.

Figure 1 Multivariable Cox proportional hazards model. Hazard ratios per 59 μmol/L uric acid increase for all-cause mortality with low, normal, and high E/A ratio. Covariates: Sex, age, body mass index, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, estimated glomerular filtration rate, haemoglobin A1c, current smoking, physical activity, and use of antihypertensive medication. Abbreviations: e, events. The Tromsø Study 1994–2013.

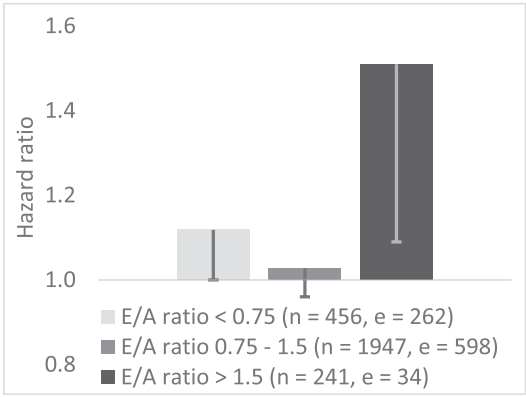


Figure 2 Multivariable Cox proportional hazards model. Hazard ratios per 59 μmol/L uric acid increase for all-cause mortality with low, normal, and high E-wave deceleration time (EDT). Covariates: Sex, age, body mass index, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, estimated glomerular filtration rate, haemoglobin A1c, current smoking, physical activity, and use of antihypertensive medication. Abbreviations: e, events. The Tromsø Study 1994–2013.

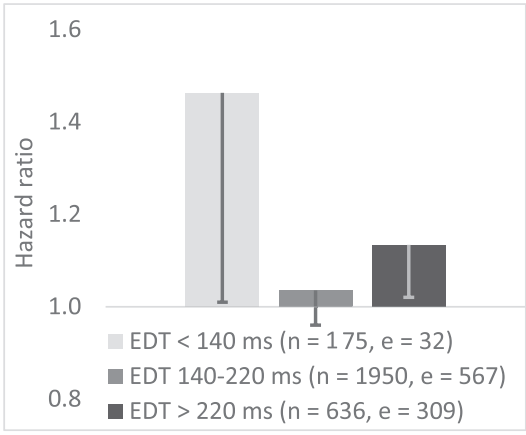


Figure 3 Multivariable Cox proportional hazards model. Hazard ratios per 59 μmol/L uric acid increase for all-cause mortality with low and normal isovolumic relaxation time (IVRT). Covariates: Sex, age, body mass index, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, estimated glomerular filtration rate, haemoglobin A1c, current smoking, physical activity, and use of antihypertensive medication. Abbreviations: e, events. The Tromsø Study 1994–2013.

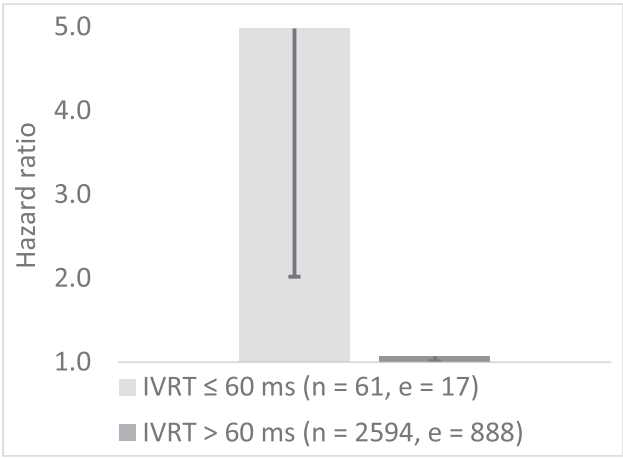
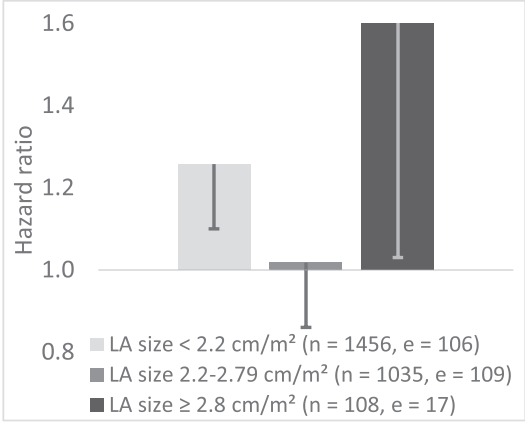


Figure 4 Multivariable Cox proportional hazards model. Hazard ratios per 59 μmol/L uric acid increase for ischaemic stroke with normal, moderately enlarged, and severely enlarged left atria (LA). Covariates: Sex, age, body mass index, mean systolic blood pressure, mean diastolic blood pressure, total cholesterol, triglycerides, estimated glomerular filtration rate, haemoglobin A1c, current smoking, physical activity, and use of antihypertensive medication. Abbreviations: e, events. The Tromsø Study 1994–2013.



1.26, $P = 0.02$) experienced elevated risk of all-cause mortality with increasing UA, as demonstrated in *Figure 2*. Persons with normal EDT did not have increased risk of mortality with higher UA (HR 1.04, 95% CI 0.96–1.11, $P = 0.35$), and P for interaction between UA and the categorical EDT variable was 0.04.

The 61 subjects with IVRT ≤60 ms exhibited a nearly fivefold rate of death with increasing UA (HR 4.98, 95% CI 2.02–12.26, $P < 0.001$), as displayed in *Figure 3*. The subjects with IVRT >60 ms, who make up the rest of the cohort, also had increased risk of death with increasing UA, but at a lower rate (HR 1.07, 95% CI 1.01–1.13, $P = 0.02$), and P for interaction between UA and the categorical IVTR variable was 0.004. There were no significant interactions between UA and the categorical E/A ratio, EDT, or IVRT variables for neither myocardial infarction nor ischaemic stroke.

Persons with LA size ≥2.8 cm/m^2 had significantly higher risk of ischaemic stroke with increasing UA (HR 1.62, 95% CI 1.03–2.53, P = 0.04), as shown in *Figure 4*. The persons with normal LA size also had increased risk of ischaemic stroke with increasing UA, but at a lower rate (HR 1.26, 95% CI 1.10–1.43, P = 0.001). UA was not associated with ischaemic stroke in persons with moderately enlarged LA (HR 1.02, 95% CI 0.86–1.20, P = 0.83), and P for interaction between UA and the categorical LA size variable was 0.047. There were no significant interactions between the LA size variable and UA for the associations with neither all-cause mortality nor myocardial infarction.

Discussion

In this prospective study of 1460 women and 1480 men from the general population with nearly 20 years follow-up, we found that elevated UA predicted all-cause mortality in persons with echocardiographic indices of DD, compared with persons without. Subjects with increased or decreased E/A ratio, increased or decreased EDT, or reduced IVRT all had higher risk of death during follow-up with increasing UA at baseline. In persons with severely enlarged left atria, the risk of ischaemic stroke was higher with elevated UA.

Hypertension

To our knowledge, the present study is the first to demonstrate an association between echocardiographic markers of DD and higher risk of mortality and ischaemic stroke with increasing UA in a general population. Hyperuricaemia is associated with impaired survival in HF patients.[16] Recently, a longitudinal study showed that hyperuricaemia was related to an increased risk of mortality in hospitalised patients with HFpEF.[8] UA is closely associated with hypertension; a meta-analysis reported that higher UA was associated with a statistically significant elevation in incident hypertension.[17] In a recent prospective cohort study, we demonstrated that UA was associated with development of elevated blood pressure in overweight subjects.[10] Hypertension is also closely associated with DD,[5] both being implicated in the development of HFpEF.[1] It is possible that the effect of UA on survival in subjects with signs of DD, as demonstrated in this study, is connected to the presence of hypertension. On the other hand, all multivariable analyses in our study were adjusted for systolic and diastolic blood pressure, as well as current use of blood pressure lowering medication, and therefore additional mechanisms are most likely in play.

Reactive oxygen species

With DD, there is abnormal cardiac relaxation, stiffness, or filling. The mechanisms behind this are not clear. It has been hypothesised that reactive oxygen species (ROS) limit nitric oxide (NO) bioavailability, which in turn may eventually lead to cardiac remodelling and DD, as well as endothelial dysfunction.[18] ROS is a by-product when the enzyme xanthine oxidase (XO) catalyses the reactions of hypoxanthine to xanthine and xanthine to UA.[19] Experimental studies have implicated XO-derived ROS in the pathology of HF, both by demonstrating increased XO activity in the failing heart and by showing that XO inhibition improves survival in animal models of HF.[20] Recently, an experiment showed that male mice fed a western diet (chow rich in fat, sucrose, and high-fructose corn syrup) for 16 weeks developed hyperuricaemia, along with cardiomyocyte hypertrophy, myocardial oxidative stress, and impaired diastolic relaxation.[21] XO inhibition with allopurinol improved all the cardiac abnormalities, and the authors argued that high XO activity, identified as a high UA, was an instigator of DD. In our study, it is possible that UA is a marker of XO activity, and hence oxidative stress that contributes to a deterioration of DD and thus reduces survival. However, a convincing clinical benefit of XO inhibition in HF patients has yet to be demonstrated[22]. To date, no randomised controlled trial has examined XO inhibition or other UA lowering drugs in HFpEF patients or subjects with DD.

Insulin resistance and diabetes

Another possible pathway explaining the association between UA and adverse outcome in subjects with DD may be related to certain degrees of insulin resistance, which may or may not occur with diabetes, and it is an important risk factor for HFrEF and HFpEF.[1] In diabetic cardiomyopathy, DD is an early phenomenon.[23] DD is common in diabetic patients and is associated with the development of HF and increased mortality.[24] We recently showed that UA was associated with elevated fasting glucose in overweight subjects,[10] and UA is epidemiologically associated with the development of both insulin resistance[25] and diabetes.[26] Thus, although participants with diabetes were excluded from the present study, metabolic changes at an earlier stage of the continuum may have played a part in the association between UA and adverse outcomes in persons with DD.

Left atrium size

We found a significant association between UA and ischaemic stroke in participants with severely enlarged LA (≥2.8 cm/m^2). A previous study from our group showed that elevated baseline UA is associated with increased risk of atrial fibrillation,[27] and another study recently demonstrated that LA size ≥2.8 cm/m^2 was significantly associated with increased risk of incident atrial fibrillation.[14] It is conceivable that the

association between severely enlarged LA and risk of ischaemic stroke is mediated through the risk for ischaemic stroke posed by atrial fibrillation. Hyperuricaemia is also associated with endothelial dysfunction[28], and endothelial dysfunction is associated with increased risk of stroke in atrial fibrillation, as shown in one study where raised plasma levels of von Willebrand factor, as a marker of endothelial dysfunction, were predictive of stroke in patients with atrial fibrillation.[29] It is therefore possible that endothelial dysfunction associated with hyperuricaemia could contribute to a prothrombotic state in the appendages of severely enlarged atria and thus is associated with increased risk of ischaemic stroke.

Study strengths and limitations

This study involves a large population-based study with a high attendance rate and long follow-up, and an equal number of men and women, which is a strength when DD is examined. The ability to correct for confounders such as eGFR, traditional cardiovascular risk factors, and the use of antihypertensive medication including diuretics also strengthens the study. Endpoints have been thoroughly validated in each individual through medical records. A shortcoming of this study was that only a single measurement of serum UA was available. The blood samples were not fasting, and this may have affected in particular the triglycerides. The Tromsø Study did not acquire data on tissue Doppler in 1994–95, which could have provided more information on DD, and our data lacked LA volume measurements, so our estimation of LA size was diameter based; this may be additional limitations. The fact that our cohort was homogenous, largely consisting of middle-aged, healthy Caucasians, can be viewed as both a strength and a limitation; the external validity may be reduced while the internal validity is increased

In conclusion, higher baseline UA was a predictor of all-cause mortality in subjects with reduced or increased E/A ratio, reduced or increased EDT, and reduced IVRT. Elevated baseline UA was associated with increased risk of ischaemic stroke in subjects with severely enlarged LA.

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Conflict of interest

None declared.

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