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Kynurenines as predictors of acute coronary events in the Hordaland Health Study☆,☆☆

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ABSTRACT

Background: The kynurenine pathway, the main metabolic route of tryptophan degradation, has been related to inflammatory responses. Some of its metabolites, referred to as kynurenines, have been associated with prevalence of coronary heart disease (CHD) in cross-sectional studies. This prospective study aims to investigate whether increased concentrations of kynurenines are associated with risk of acute coronary events, defined as unstable angina pectoris, acute myocardial infarction, and/or sudden death in community-dwelling elderly.
Methods: The baseline examinations included 2819 individuals aged 71–74 years recruited into the Hordaland Health Study. Participants with known CHD at baseline were excluded from analyses. Baseline plasma concentrations of tryptophan, kynurenine, kynurenic acid, anthranilic acid, 3-hydroxykynurenine, xanthurenic acid, and 3-hydroxyanthranilic acid were measured by LC–MS/MS. During a median follow-up period of 10.8 years, with linkage to acute coronary event endpoints through the CVDNOR project, hazard ratios (HRs) for acute coronary events (n = 376) were estimated using Cox proportional hazard analyses.
Results: After adjustment for established cardiovascular risk factors, HRs (95% CI) comparing the 4th vs 1st quartile were 1.86 (1.19–2.92) for kynurenine and 1.72 (1.19–2.49) for 3-hydroxykynurenine. Tryptophan, kynurenic acid, anthranilic acid, xanthurenic acid and 3-hydroxyanthranilic acid were not associated with acute coronary events.
Conclusions: Kynurenine and 3-hydroxykynurenine were associated with increased risk of acute coronary events in community-dwelling elderly without a known history of CHD. These results suggest the involvement of the kynurenine pathway in the early development of CHD, and their potential usefulness to estimate CHD risk.

1. Introduction

Low grade chronic inflammation contributes to the onset and progression of atherosclerosis and coronary artery disease [1]. Emerging evidence suggests that the kynurenine pathway is essential for the modulation of immune and inflammatory responses [2,3]. During inflammation, the cytokine interferon-γ (IFN-γ) stimulates activity of the rate limiting enzyme of tryptophan catabolism, indoleamine 2,3-dioxygenase (IDO) [4], leading to increased degradation of tryptophan to kynurenine [5]. The resulting increased kynurenine to tryptophan ratio (KTR) is a measure of IFN-γ mediated immune activation and has been associated with risk of cardiovascular events [6].

IFN-γ is a key factor in the pathogenesis of atherosclerosis [7], and experimental studies have indicated up-regulated IDO activity in coronary plaques [8]. In addition, few case control studies have shown decreased plasma tryptophan concentrations and an increased KTR in patients with coronary heart disease (CHD) compared to healthy controls [9], and stronger associations between KTR and the inflammatory marker C-reactive protein in individuals with coronary artery disease

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compared to individuals with normal coronary arteries [10]. In line with this, large prospective studies have revealed strong positive associations between baseline plasma [11,12] and urinary [13] KTR and the incidence of acute coronary events. These studies indicate the role of tryptophan degradation via the kynurenine pathway in the development of cardiovascular disease (CVD) [6].

Kynurenine (Kyn) is metabolized further to other metabolites, collectively referred to as kynurenines [14], including anthranilic acid (AA), kynurenic acid (KA), and 3-hydroxykynurenine (HK). In turn 3-hydroxykynurenine is converted to either 3-hydroxyanthranilic acid (HAA) or xanthurenic acid (XA). Several enzymes in the kynurenine pathway require pyridoxal 5′-phosphate (PLP, the coenzyme form of vitamin B6) or flavin adenine dinucleotide (FAD, the coenzyme form of vitamin B2) as cofactors [15] (Fig. 1). Low plasma vitamin B2 and B6 status impairs enzymatic reactions in this pathway, and thereby also alters concentrations of kynurenines [16].

Several lines of evidence indicate that not only low tryptophan and/or elevated kynurenine concentrations, expressed as high KTR, but also other kynurenines possess immunomodulatory [14], pro- or anti-oxidant [17], and vasoactive [18] properties, which are all important features in the etiology of cardiovascular disease. In the present study, we investigated whether baseline plasma concentrations of a wide panel of kynurenines were associated with acute coronary events among 2819 older individuals without known prior acute coronary events in a community-based prospective Norwegian cohort study.

2. Methods

2.1. Study population

Baseline examinations in the Hordaland Health Study (HUSK) were conducted during 1997–1999 as a collaboration between the National Health Screening Service, the University of Bergen, the University of Oslo, and local health services. Detailed information on study procedures has been published previously [19]. The subjects included in the present study are participants born during 1925–1927 and residing in the city of Bergen or the neighboring suburban municipalities who participated in an earlier study in 1992–93 [20]. The overall attendance rate was 77%, providing a sample of 3328 participants in the age group 70–72 years (1855 women and 1473 men). Participants were followed for hospitalizations and deaths due to CVD from baseline through December 31st 2009 via linkage to the CVDNOR project [21,22] and to the Cause of Death Registry. The study protocol was approved by the Regional Committee for Medical Research Ethics of Western Norway. All participants gave written informed consent at baseline.

Of the 3328 eligible participants, 484 were excluded due to previous hospitalizations with an acute coronary event discharge diagnosis (I20–I21 codes according to ICD-10 version), and 25 because of missing data on kynurenines, leaving 2819 individuals for statistical analyses.

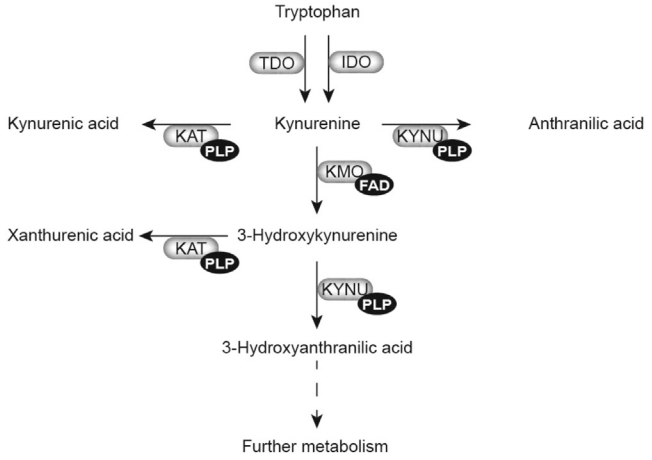

Fig. 1. The kynurenine pathway. Tryptophan is converted to kynurenine either by IDO or TDO. Kynurenine is further metabolized to anthranilic acid, kynurenic acid, 3-hydroxykynurenine. 3-Hydroxykynurenine in turn is converted to either 3-hydroxyanthranilic acid or xanthurenic acid. IDO: indoleamine 2,3-dioxygenase dioxygenase; TDO: tryptophan 2,3-dioxygenase.

2.2. Data collection

Data collection involved a personal invitation sent by mail along with a questionnaire including questions on various health behaviors and personal and family history of diseases (http://www.uib.no/isf/husk). For people who agreed to participate and filled out the questionnaire, a brief medical examination was conducted. Baseline measurements included height, weight, and blood pressure. Body mass index (BMI) was calculated as weight (kg)/height (m^2) and categorized into; 'normal' (BMI < 25), 'overweight' (25 ≤ BMI < 30) and 'obese' (BMI ≥ 30). Smoking was categorized into 'never smokers', 'former smokers', and 'current smokers'.

Participants provided information on medication use. This information was grouped into major classes of medications including antihypertensives, statins, hypoglycemic agents (oral hypoglycemic agents or insulin), and immunosuppressive medications (glucocorticoids and cytostatics). Systolic and diastolic blood pressures are reported as the mean of three consecutive measurements. Hypertension was defined as having a SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg or use of antihypertensive medications. Serum glucose levels in combination with 'time of blood collection since last meal (hours)' were used to define diabetes status and classify participants into: 1) 'no diabetes', 2) prediabetes ('impaired fasting glucose' (IFG; glucose concentrations of 100–125 mg/dL at blood collection ≥ 8 h since last meal) or 'impaired glucose tolerance' (IGT; glucose levels of 140–199 mg/dL at blood collection between 1–7 h since last meal)), or 3) 'diabetes' (glucose levels > 126 mg/dL at blood collection ≥8 h since last meal, glucose levels > 200 mg/dL at blood collection between 1–7 h since last meal, or use of insulin or oral hypoglycemic agents) [23]. Participants reporting the use of insulin or oral hypoglycemic agents were classified in the 'diabetes' category, regardless of blood glucose levels. Hypercholesterolemia was defined as total cholesterol levels ≥ 240 mg/dL or use of statins. Serum creatinine levels served to calculate estimated glomerular filtration rate [24] (eGFR) for men and women separately. Impaired renal function was defined as eGFR < 60 mL/min/1.73 m^2 [24].

2.3. Blood samples and biochemical analyses

Serum total cholesterol and triglycerides were measured at baseline by enzymatic methods using reagents from Boehringer Mannheim, FRG (Roche, Basel, Switzerland). Creatinine was measured colorimetrically using alkaline picrate method with reagents from Roche (Basle, Switzerland). Plasma concentrations of tryptophan, kynurenines, neopterin, and vitamin B2 and B6 vitamers were analyzed by liquid chromatography–tandem mass spectrometry [25] by Bevital A/S (www.bevital.no). Within-day coefficients of variance (CVs) for tryptophan and the kynurenines were 1.8–9.5%, and between-day CVs were 5.0–16.9% [25]. Hs-CRP was determined in serum by an immunoassay based on matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) [26].

2.4. Follow-up time and the study endpoint

Examination day was considered as entry into the study and took place between April 1998 and June 1999. Participants were followed until December 31, 2009. Median (P5–P95) follow-up time was 10.8 (2.3–11.6) years. The study endpoint was a composite of unstable

angina pectoris (UAP; I20 code according to ICD-10), non-fatal or fatal acute myocardial infarction (AMI; I21 code according to ICD-10), or sudden death (R96 or R98 codes according to ICD-10). In case of more than one event in a participant, only the first event was considered and used in the analysis. Information on discharge diagnoses was retrieved from the CVDNOR project which includes all hospitalizations due to CVD from all hospitals in Norway during 1994–2009 (https://cvdnor.b.uib.no) [21,22]. Information on discharge diagnoses before 1994 was obtained from the Cardiovascular Disease Registry Health Region West including all hospitalizations and procedures related to CVD since 1989. Information on deaths was obtained from the Norwegian national Cause of Death Registry. Linkages between baseline variables and endpoints were made possible through the personal identification number, unique to each Norwegian resident.

2.5. Statistical analysis

Characteristics of the study population are presented as percentages or medians (P5–P95). Categorical variables were compared using the χ^2 test. Due to skewed distributions of plasma kynurenines, the non-parametric tests Mann–Whitney U and Kruskal–Wallis tests were applied to compare plasma kynurenines across subgroups of health characteristics.

Hazard ratios (HR) and 95% confidence intervals (95% CI) for risk of acute coronary events comparing the 4th vs 1st quartile and as linear trend across quartiles of kynurenines were estimated by Cox proportional hazard modeling using the SAS PRHEG procedure. Models were tested and plotted based on Schoenfeld residuals [27] to ensure that assumptions of proportional hazards were not violated. For each participant, person-time of follow-up was calculated from baseline until the date of hospitalization for acute coronary events, death, emigration or the end of follow-up (December 31st, 2009), whichever came first. The crude models were adjusted for gender, whereas full models were further adjusted for established cardiovascular risk factors, including diabetes status (no diabetes, IGT or IFG, diabetes), overweight (BMI < 25 kg/m^2 versus BMI ≥ 25 kg/m^2), smoking (never, former, current), hypertension (yes, no), impaired renal function (yes, no), and gender-specific cholesterol quartiles. In addition, linearity of the associations between kynurenines and risk for acute coronary events was investigated by generalized additive regression (GAM) plots based on fully adjusted models. Effect modification by median riboflavin (vitamin B2 marker) and PLP (active vitamin B6 form), median time from blood donation to diagnosis, sex, overweight (BMI < 25 kg/m^2 versus BMI ≥ 25 kg/m^2), and current smoking were investigated by adding the product term of the kynurenines and potential effect modifiers in the model.

In sensitivity analyses, we investigated the associations between kynurenines and acute coronary events when accounting for competing risk events [28,29], including other CHD events such as acute coronary thrombosis not resulting in myocardial infarction (ICD10:I24) and chronic ischemic heart disease (ICD10: I25), and for atherosclerosis related conditions including cerebrovascular diseases (ICD10:I60–I64), peripheral artery disease (ICD10: I73) and congestive heart failure (ICD10:I50). Further, we evaluated whether any of the kynurenines could assign a substantial number of participants into a more correct level of risk by performing continuous net reclassification

Table 1
Characteristics of the study population (n = 2819) at baseline.

	Total population	Men	Women	P for difference
Demography				
Age, years (min–max)	72 (71–74)			
Gender, % male	41.4			
Education				
Less than high school	72.2	63.5	78.7	
High school	10.7	12.7	9.2	
College or university	17.1	23.7	12.1	<.0001
Health				
Smoking				
Never, %	46.3	24.4	61.9	
Ex, %	37.7	57.6	23.4	
Current, %	16.0	17.9	14.7	<.0001
BMI				
<25 kg/m^2	41.4	39.9	42.5	
25–30 kg/m^2	44.5	50.9	39.9	
>30 kg/m^2	14.2	9.3	17.6	<.0001
Hypertension				
Medication, %	10.2	12.0	11.7	0.82
Systolic BP, mm Hg	146 (117–184)	145 (115–180)	146 (118–187)	<.0001
Diabetes status				
Medication, %	3.7	4.5	3.7	0.24
No diabetes, %	94.1	92.2	95.4	
Prediabetes, %	3.8	4.9	3.0	
Diabetes, %	2.2	2.9	1.6	0.003
Hypercholesterolemia				
Yes, %	50.5	38.0	62.9	<.0001
Other medications				
Statins, %	7.8	12.0	12.1	0.91
Immunosuppressive medication, %	7.8	8.9	7.7	0.19
Blood parameters				
Tryptophan, μmol/L	64.7 (44.6–93.2)	67.8 (48.1–96.4)	62.5 (43.4–89.9)	<.0001
Kynurenine, μmol/L	1.69 (1.09–2.59)	1.77 (1.19–2.71)	1.64 (1.05–2.49)	<.0001
Kynurenic acid, nmol/L	50.8 (27.4–91.3)	54.3 (29.4–95.9)	48.0 (26.8–85.2)	<.0001
Anthranilic acid, nmol/L	16.1 (9.78–28.3)	16.4 (9.94–28.5)	15.9 (9.69–28.1)	0.0036
Hydroxy kynurenine, nmol/L	35.3 (20.7–63.2)	36.0 (21.5–62.1)	35.0 (20.4–64.6)	0.0337
Xanthurenic acid, nmol/L	14.9 (6.16–32.6)	16.4 (7.06–34.7)	13.9 (5.79–30.2)	<.0001
Hydroxy anthranilic acid, nmol/L	33.8 (18.1–63.7)	35.4 (19.2–67.9)	32.5 (17.7–59.7)	<.0001

BMI, body mass index (kg/m^2); prediabetes includes impaired fasting glucose and impaired glucose tolerance; concentrations in median (P5–P95).

improvement (NRI > 0) [30]. For the NRI analyses we applied logistic regression models that contained the same variables as the adjusted Cox models.

All statistical tests were 2-tailed and a P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC). R version 3.0.3 for Windows was used to construct GAM curves (packages *survival*), competing risk analyses (packages *crr and cmprsk) and NRI analyses (packages survival, cocr, PredictABEL)* [31].

3. Results

3.1. Population characteristics at baseline

The study population comprised 2819 participants aged 71–74 years, of which 41% were men. The prevalence of current smoking, overweight, hypertension, and (pre)diabetes was 16.0%, 14.2%, 10.2%, and 6.0%, respectively, being generally higher among men than women, except for overweight. Concentrations of all kynurenines were higher among men than women (Table 1).

Concentrations of all kynurenines were highest among individuals with overweight (BMI > 25 kg/m^2), or in those with (pre)diabetes or taking hypoglycemic medication. Kyn, KA, HK, XA, and HAA levels were higher in individuals classified as hypertensive (Table 2).

3.2. Associations between kynurenines and acute coronary events

During a median follow-up time of 10.8 years, 376 individuals were hospitalized for their first acute coronary event, i.e. unstable angina pectoris (UAP), acute myocardial infarction (AMI) or sudden death. Gender adjusted analyses revealed significant positive associations of Kyn, KA, and HK with acute coronary events, with HR (95% CI) comparing the fourth with the first quartile of 2.03 (1.33–3.11) for Kyn, 1.40 (1.01–1.94) for KA, and 1.79 (1.27–2.52) for HK. These associations were slightly attenuated after further adjustment for hypercholesterolemia, kidney function, diabetes status, hypertension, and smoking status, but remained significant for Kyn and HK (Table 3). Further adjustment for CRP, KTR or neopterin did not affect HRs for the individual kynurenines (data not shown). Adjusted General Additive Models (GAM) analyses confirmed positive associations of Kyn below the 25th percentile and of HK throughout the concentration range with acute coronary events (Fig. 2).

When the study population was confined to 2736 individuals without a prior hospitalization for the study endpoint (n = 484), stroke (n = 98), peripheral artery disease (n = 53), or congestive heart failure (n = 61), the associations between kynurenines and risk of acute coronary events were essentially the same as for the entire study population (data not shown). In addition, competing risk analyses showed similar associations between kynurenines and risk of acute coronary events,

Table 2
Median (P5–P95) concentrations of kynurenines across subgroups of common cardiovascular risk factors in 3061 presumptively healthy elderly aged 71–74 years.

	Trp (μmol/L)	Kyn (μmol/L)	KA (nmol/L)	AA (nmol/L)	HK (nmol/L)	XA (nmol/L)	HAA (nmol/L)
Health factors							
BMI[a] (kg/m^2)							
<25 (n = 1167)	63.2 (44.2–91.7)	1.60 (1.05–2.42)	45.6 (25.9–80.8)	15.8 (9.50–27.9)	33.5 (20.0–60.9)	13.6 (5.44–31.0)	31.9 (17.0–59.7)
25–30 (n = 1253)	65.8 (45.8–94.4)	1.74 (1.14–2.66)	53.1 (29.4–93.9)	16.3 (9.96–28.4)	35.9 (21.8–63.2)	15.9 (6.84–32.6)	34.8 (19.6–64.2)
≥30 (n = 399)	65.2 (44.5–92.8)	1.80 (1.16–2.77)	58.1 (29.8–103)	16.6 (9.94–29.4)	39.4 (20.9–69.2)	15.8 (7.16–36.5)	37.2 (19.8–70.9)
P for difference	0.003	<0.001	<0.001	0.004	<0.001	<.0001	<.0001
Smoking							
Never (n = 1264)	64.6 (45.6–94.6)	1.66 (1.09–2.57)	49.8 (28.0–90.2)	16.1 (10.1–29.5)	35.1 (20.6–61.9)	14.7 (6.28–32.3)	33.8 (18.3–62.1)
Ex (n = 1028)	66.2 (45.6–94.1)	1.76 (1.15–2.67)	53.9 (28.1–94.8)	16.8 (10.2–29.9)	36.2 (21.5–65.7)	15.7 (6.73–33.6)	35.2 (19.2–67.4)
Current (n = 438)	62.4 (42.6–88.9)	1.59 (1.05–2.46)	45.9 (24.6–84.4)	14.0 (8.63–24.9)	34.4 (20.2–59.0)	13.3 (4.98–31.9)	30.4 (16.8–57.4)
P for difference	0.0005	0.0026	0.0006	0.2495	0.0075	0.0356	0.0004
Glucose metabolism							
No diabetes (n = 2481)	64.1 (44.2–92.8)	1.68 (1.09–2.57)	50.9 (27.5–90.4)	16.1 (9.82–28.3)	35.2 (20.8–63.8)	14.9 (6.17–32.4)	33.7 (18.1–63.5)
Prediabetes[b] (n = 99)	68.1 (47.0–96.0)	1.78 (1.17–3.12)	49.0 (27.7–108)	16.2 (9.85–27.4)	38.5 (21.8–74.4)	16.0 (5.08–32.9)	35.0 (19.2–60.9)
Diabetes (n = 57)	70.3 (46.3–97.6)	1.82 (1.10–2.82)	58.4 (28.4–111)	17.3 (8.81–32.4)	39.2 (20.2–68.1)	17.5 (9.50–34.2)	43.9 (21.1–78.2)
P for difference	0.0006	0.0052	0.0193	0.0416	0.0015	0.0049	<.0001
Hypercholesterolemia							
No (n = 1396)	67.7 (46.9–94.6)	1.48 (0.97–2.36)	44.2 (24.8–82.6)	14.0 (8.23–25.3)	31.7 (18.4–58.3)	15.8 (6.79–33.8)	33.3 (18.0–61.9)
Yes (n = 1423)	66.0 (45.2–93.9)	1.60 (1.03–2.51)	48.4 (26.7–88.0)	14.8 (8.60–27.2)	33.3 (19.1–58.6)	15.1 (6.25–32.8)	33.5 (17.8–62.8)
P for difference	0.0050	0.5344	0.0439	0.1095	0.0649	0.0900	0.0018
Hypertension							
No (n = 1040)	65.2 (45.5–93.7)	1.66 (1.06–2.61)	47.5 (26.3–87.2)	16.0 (9.90–29.6)	34.7 (20.8–63.3)	14.3 (5.70–31.6)	33.5 (17.7–63.1)
Yes (n = 1779)	64.3 (44.6–93.1)	1.71 (1.10–2.59)	52.2 (28.6–92.7)	16.2 (9.75–27.9)	35.7 (20.7–63.5)	15.1 (6.49–33.0)	34.0 (18.3–63.7)
P for difference	0.2224	0.0435	<.0001	0.2789	0.0329	0.0060	0.0256
Medication							
Hypertension							
No (n = 2533)	64.8 (44.6–93.3)	1.68 (1.08–2.57)	50.1 (27.3–89.5)	16.1 (9.75–28.0)	35.1 (20.7–61.9)	14.7 (6.10–32.4)	33.7 (18.0–63.3)
Yes (n = 286)	63.4 (46.3–90.7)	1.75 (1.17–2.74)	56.7 (30.1–107)	16.7 (10.3–31.0)	37.1 (22.6–68.6)	16.1 (7.00–35.5)	35.0 (19.9–64.5)
P for difference	0.3215	0.0004	<.0001	0.0196	0.0001	0.0080	0.0154
Statins	64.6 (44.7–93.3)	1.68 (1.09–2.57)	50.5 (27.4–90.5)	16.1 (9.80–28.3)	35.2 (20.6–63.6)	14.9 (6.17–32.4)	33.7 (18.0–63.7)
No (n = 2598)	64.6 (44.7–93.3)	1.68 (1.09–2.57)	50.5 (27.4–90.5)	16.1 (9.80–28.3)	35.2 (20.6–63.6)	14.9 (6.17–32.4)	33.7 (18.0–63.7)
Yes (n = 221)	66.6 (45.4–91.1)	1.74 (1.14–2.66)	54.2 (29.1–96.4)	16.7 (9.76–27.9)	35.9 (21.6–62.9)	15.1 (6.00–34.5)	35.6 (19.2–63.3)
P for difference	0.0917	0.0112	0.0083	0.0965	0.3355	0.4645	0.0513
Hypoglycemic	64.6 (44.6–93.1)	1.69 (1.09–2.58)	50.5 (27.3–90.3)	16.1 (9.77–28.1)	35.2 (20.7–63.0)	14.9 (6.12–32.6)	33.6 (18.0–63.3)
No (n = 2716)	64.6 (44.6–93.1)	1.69 (1.09–2.58)	50.5 (27.3–90.3)	16.1 (9.77–28.1)	35.2 (20.7–63.0)	14.9 (6.12–32.6)	33.6 (18.0–63.3)
Yes (n = 103)	66.4 (47.8–96.1)	1.81 (1.25–2.95)	58.4 (31.4–108)	16.5 (10.5–32.4)	39.0 (22.4–74.4)	17.5 (6.92–34.2)	40.3 (23.4–73.4)
P for difference	0.0528	0.0013	0.0001	0.0584	0.0020	0.0040	<.0001
Immunosuppressive	64.7 (44.8–93.2)	1.68 (1.09–2.58)	50.9 (27.4–90.3)	16.1 (9.87–28.5)	35.1 (20.7–61.8)	14.9 (6.10–32.4)	33.7 (18.0–63.7)
No (n = 2589)	64.7 (44.8–93.2)	1.68 (1.09–2.58)	50.9 (27.4–90.3)	16.1 (9.87–28.5)	35.1 (20.7–61.8)	14.9 (6.10–32.4)	33.7 (18.0–63.7)
Yes (n = 221)	64.9 (43.5–94.2)	1.74 (1.10–2.72)	50.2 (27.5–96.0)	15.9 (9.10–27.1)	37.6 (21.6–83.9)	15.3 (6.93–35.6)	35.5 (19.1–60.8)
P for difference	0.4645	0.0955	0.4704	0.0612	0.0025	0.1262	0.1072

[a] BMI, body mass index (kg/m^2).
[b] Prediabetes includes impaired fasting glucose and impaired glucose tolerance.

Table 3
Associations of kynurenines with acute coronary events (composite of UAP, AMI and SD, n = 425) in 3061 presumptively healthy elderly aged 71–74 years with no prior acute coronary events.

Metabolite[1]	Q1	Q2	Q3	Q4	HR/quartile, P for trend
Tryptophan					
Crude[2]	1	0.96 (0.73–1.27)	1.09 (0.82–1.44)	0.89 (0.66–1.19)	0.97 (0.89–1.07), 0.64
Adjusted[3]	1	0.97 (0.73–1.31)	1.08 (0.80–1.46)	0.91 (0.66–1.24)	0.98 (0.89–1.08), 0.72
Kynurenine					
Crude	1	1.90 (1.20–2.99)	1.84 (1.19–2.84)	2.03 (1.33–3.11)	1.16 (1.04–1.29), 0.00
Adjusted	1	1.87 (1.17–2.98)	1.82 (1.16–2.85)	1.86 (1.19–2.92)	1.12 (1.01–1.26), 0.04
Kynurenic acid					
Crude	1	1.18 (0.83–1.69)	1.26 (0.90–1.78)	1.40 (1.01–1.94)	1.11 (1.01–1.22), 0.04
Adjusted	1	1.06 (0.73–1.54)	1.04 (0.73–1.49)	1.11 (0.78–1.58)	1.03 (0.93–1.15), 0.58
Anthranilic acid					
Crude	1	0.89 (0.63–1.27)	0.95 (0.68–1.33)	0.91 (0.66–1.25)	0.98 (0.89–1.08), 0.72
Adjusted	1	0.93 (0.64–1.34)	1.01 (0.71–1.44)	0.90 (0.64–1.28)	0.98 (0.88–1.09), 0.66
Hydroxy kynurenine					
Crude	1	1.22 (0.84–1.78)	1.43 (1.00–2.05)	1.79 (1.27–2.52)	1.21 (1.10–1.34), 0.00
Adjusted	1	1.30 (0.88–1.93)	1.46 (1.00–2.14)	1.72 (1.19–2.49)	1.18 (1.06–1.32), 0.03
Xanthurenic acid					
Crude	1	1.09 (0.81–1.45)	0.92 (0.68–1.24)	1.27 (0.96–1.69)	1.06 (0.97–1.16), 0.21
Adjusted	1	1.03 (0.76–1.40)	0.84 (0.61–1.16)	1.23 (0.90–1.67)	1.05 (0.95–1.16), 0.39
Hydroxy anthranilic acid					
Crude	1	0.93 (0.68–1.26)	1.02 (0.76–1.38)	1.19 (0.90–1.58)	1.07 (0.98–1.17), 0.15
Adjusted	1	1.00 (0.72–1.38)	1.07 (0.77–1.47)	1.17 (0.86–1.61)	1.06 (0.96–1.17), 0.25

[1] The cut-off points for the quartiles of Trp were 56.12, 64.66 and 74.63 μmol/L; for Kyn they were 1.43, 1.69 and 1.99 nmol/L; for HK they were 28.57, 35.28 and 43.64 nmol/L; for KA they were 38.84, 50.77 and 64.75 nmol/L; for XA they were 10.76, 14.92 and 20.49 nmol/L; for AA they were 13.01, 16.13 and, 19.97; and for HAA they were 26.05, 33.83, 43.48 nmol/L.
[2] Crude analyses: adjusted for gender (366 events, 2747 censored).
[3] Adjusted analyses: adjusted for gender, hypercholesterolemia, kidney function (eGFR), smoking, BMI, hypertension, and diabetes (333 events, 2490 censored).

when accounting for 341 CHD events and for 597 atherosclerosis related events during follow-up (data not shown).

Risk classification of acute coronary events was improved when Kyn, HK, or HAA was added to the multivariate model including gender, hypercholesterolemia, kidney function, smoking, overweight, hypertension, and diabetes status. The net reclassification indices (NRI [95% CI]) were 0.09 (0.00–0.18) for Kyn, 0.15 (0.04–0.26) for HK, and 0.12 (0.01–0.23) for HAA.

Finally, we tested whether gender, current smoking, overweight, diabetes status, hypertension, use of immunosuppressive medications, and plasma concentrations of vitamins B2 and B6 modified the associations between kynurenines and the incidence of acute coronary events. Stratified analyses by these health characteristics did not change the most associations. However, the association between Kyn and acute coronary events was significantly stronger among men [HR/quartile (95% CI), P_{trend}: 1.19 (1.01–1.40), 0.04] compared to women [1.05 (0.89–1.23), 0.58] ($P_{interaction}$ = 0.0009). Notably, the association between HK and acute coronary events was significantly stronger among individuals with prediabetes or diabetes [1.98 (1.28–3.08), 0.002] compared to individuals with normal glucose tolerance status [1.13 (1.01–1.27), 0.03] ($P_{interaction}$ = <0.0001). Similarly, XA was stronger associated with acute coronary events among individuals with prediabetes or diabetes [1.40 (0.99–1.99), 0.06] than to those with normal glucose tolerance status [1.02 (0.92–1.34), 0.71] ($P_{interaction}$ = 0.002).

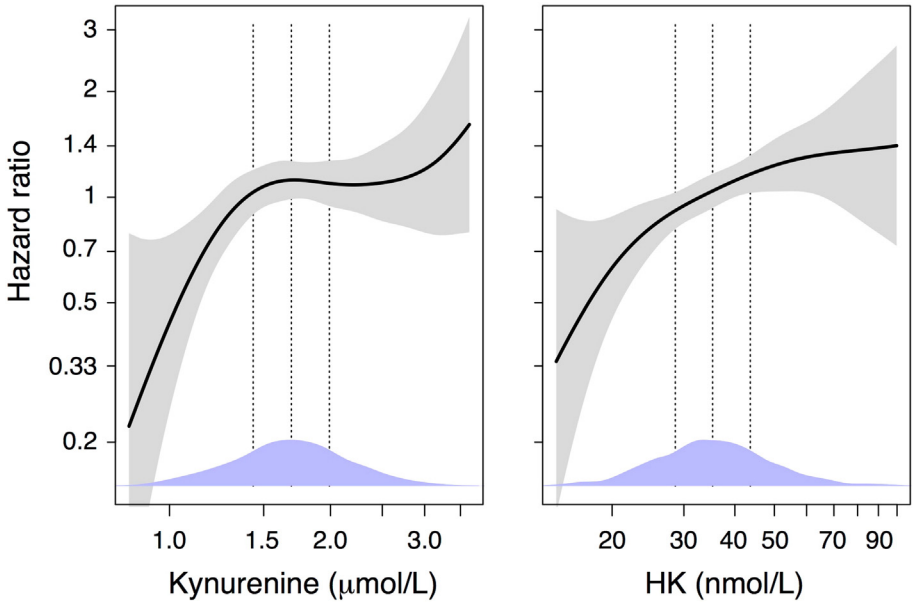

Fig. 2. Associations of Kyn and HK with acute coronary events. Models were constructed by using GAM regression with adjustment for sex, BMI, smoking, physical activity and renal function. The solid lines show HRs and the shaded areas show 95% CIs. Density plots indicate distribution of the parameters, and dotted lines denote the 25th, 50th and 75th percentiles. All the exposures were log-transformed before entering the models.

Finally, the association between Kyn and the study endpoint was borderline significant in those not taking immunosuppressive medications [1.14 (1.00–1.30), 0.06] compared to those who take these medications [1.06 (0.83–1.34), 0.65] ($P_{interaction} < 0.0001$), whereas the association with HK was stronger in those taking immunosuppressing medication [1.42 (1.12–1.79), 0.004] compared to those not taking these medications [1.12 (0.99–1.27), 0.06] ($P_{interaction} = <0.0001$).

4. Discussion

4.1. Principal findings

This prospective cohort study among 2819 community-dwelling elderly without known prior acute coronary events revealed significant positive associations of baseline concentrations of Kyn, KA, and HK with risk of acute coronary events. At baseline, plasma concentrations of kynurenines were generally higher among participants who were overweight, had high blood pressure or (pre)diabetes. Adjustment for these and other established CVD risk factors slightly attenuated the associations of kynurenines with acute coronary events, but the associations remained significant for Kyn and HK.

4.2. Potential mechanisms

The pathogenesis of atherosclerosis involves the stimulation of inflammatory processes by IFN-γ, which activates IDO and TDO, and thereby the degradation of tryptophan to kynurenine. This explains a positive association between KTR and acute coronary events that we previously reported for the HUSK cohort [12]. We now report on an association of Kyn and HK with this endpoint. Kyn and HK are among the kynurenines that showed the strongest relations with markers of cellular immune activation and IDO or TDO activation, neopterin and KTR [32]. But when associations with HK were adjusted for neopterin and KTR in the current study, the association of HK with acute coronary events remained essentially the same. This may reflect the influence of various inflammatory cytokines on different steps of the kynurenine pathway [2], and emphasizes the complexity of the inflammatory processes in atherogenesis [33].

Several kynurenines, including Kyn, KA, AA, HK, and HAA, are endogenous ligands for the transcription factor aryl hydrocarbon receptor, which has been associated with CVD through mediation of cardiotoxicity and vascular inflammation [34]. In addition, high concentrations of HK may be redox-active and thereby have the potential to generate or scavenge reactive oxygen species such as superoxide and hydroxyl radicals [35–37]. Reactive oxygen species play a role in normal physiological processes, but may also be important in the initiation, progression or remission of diseases involving oxidative stress [38], whereby they mediate damage to cell structures [39].

4.3. Inflammation and common CVD risk factors

Emerging evidence from animal and human studies suggest that kynurenines may be related to blood pressure control [18], atherosclerosis or dyslipidemia [40,41], abdominal obesity [42], diabetes [43–46] or insulin resistance [47,48], which are known to cluster in individuals who are prone to develop future cardiovascular events [49]. Interestingly, we observed that plasma concentrations of kynurenines were generally higher in participants with hypertension, overweight, and those with prediabetes or diabetes. Therefore, we included these factors as potential confounders in the regression analyses.

The current body of evidence linking inflammation to these risk factors is based on experimental animal studies, and a few observational human studies. Regarding blood pressure, for instance, a study of mice showed that IDO or Kyn may act as arterial relaxing factors [18]. However, this seems to contradict our observations that kynurenines are associated with hypertension and coronary events. Possibly, kynurenines are produced during inflammation as a feed-back mechanism to counteract vasoconstriction mediated by pro-inflammatory events [6].

Atherosclerosis, as is the main etiological factor for CVD, was inhibited by HAA in rodents [50] via reduced LDL oxidation [51]. Human studies suggested a negative association between KTR and HDL cholesterol [40,41], and a positive association of KTR with LDL cholesterol [40] and triglycerides [40,41]. Further, a positive association between KTR and carotid intima-media thickness has been observed in individuals with advanced atherosclerosis [41,52].

Obesity is a risk factor for CVD. KTR was positively associated with measures of abdominal obesity such as BMI [32,40], waist circumference and waist-to-hip ratio [40]. A recent study revealed that the kynurenine pathway is dysregulated in obese individuals, and affected by other components of the metabolic syndrome [6].

Finally, presence of diabetes accelerates progression of CVD [53]. IFN-γ is not only a key factor in the pathogenesis of atherosclerosis [7], but also stimulates intracellular IDO activity in pancreatic islets, thereby increasing intracellular concentrations of kynurenines [54]. Results from early animal studies suggest that kynurenines are related to insulin resistance [43] and impaired β-cell function [45,55]. A prospective study among patients with stable angina pectoris revealed that plasma kynurenines were generally higher in patients with diabetes compared to those with normal glucose tolerance, and moreover, associations between kynurenines and myocardial infarction were more pronounced in individuals with type 2 diabetes compared to individuals without diabetes [56]. These observations are in agreement with the results of the present study showing increased concentrations of kynurenines in participants with impaired glucose metabolism and stronger associations with cardiovascular events among those with impaired glucose metabolism.

Interestingly, findings from previous animal and human studies were confirmed by a metabolomics study using plasma samples from the Framingham Heart Study and the Malmö Diet and Cancer Study. Strong and consistent positive associations of AA, KA, and Trp with systolic and diastolic blood pressure were observed, a negative association of tryptophan with HDL cholesterol, a strong positive association of KA with BMI, and a strong positive association of plasma tryptophan, KA and AA concentrations with insulin resistance [57]. In conclusion, accumulated evidence suggests a role of increased tryptophan catabolism via the kynurenine pathway in CVD.

4.4. Methodological considerations

None of the participants were lost to follow-up due to linkage via a personal identification number with the CVDNOR project and the Norwegian Cause of Death Registry [58]. Extensive data collection allowed us to adjust statistical analyses for potential confounders, including comorbidities and use of medication. Further, we have observed good stability of most kynurenines stored in plasma as well as a fair to good within-person reproducibility over years [25], which minimized regression dilution bias. However, since only a single blood sample was collected from each participant, we were unable to study the effect of longitudinal changes in kynurenine concentrations on the risk of acute coronary events. Another drawback involves the relatively narrow age range of the study population, which limits generalizability across age groups of the general population.

5. Conclusion

This large prospective study suggests that high plasma concentrations of Kyn and HK are associated with increased risk of acute coronary events in community dwelling older individuals. These findings strengthen current evidence for the involvement of the kynurenine pathway in the early development of CHD, and motivate further studies on the potential usefulness of kynurenines to classify CHD risk.

Conflict of interest

None of the authors have any conflicts of interest.

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