Supplemental Material

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Quantification of serum kynurenine and tryptophan

Collected uremic toxins serum samples were immediately stored at 4°C and aliquoted within 6 hours without additional processing. All CKD-REIN samples were stored deep frozen (-80°C) at the Biobanque de Picardie (BRIF number: BB-0033-00017) and shipped frozen to Paris for analysis. Both teams were blinded for outcome and patients' characteristics. Kynurenine, indoxyl sulfate, p-cresyl sulfate, indole-3-acetic acid and tryptophan fractions were assayed in serum using a validated liquid chromatography tandem mass spectrometry technique, as described previously.[1]

To determine total kynurenine and tryptophan concentrations, 50 µL of serum samples were first precipitated with 340 µL of methanol in the presence of 25 µL of isotope labelled internal standards. After centrifugation for 10 min at 9000 g, the supernatant was evaporated under nitrogen stream and then reconstituted in 80 µL of water.

Free concentrations were determined by ultrafiltration; 150 µL of serum were introduced into an ultra-centrifugal filter of 30 kDa porosity, and then centrifuged at 13300 g for 20 min. Given that kynurenine and tryptophan are mainly bound to albumin (65 kDa, unable to pass through the filter), the residual filtrate contained only the free fraction.

Data collection

Trained clinical research associates collected data from medical records and patient interviews at baseline and then annually for 5 years. We collected patients' characteristics (age, sex, and smoking status) and detailed medical history, including any history of diabetes, hypertension, dyslipidemia, cardiovascular disease, and acute kidney injury. Patients were considered as having a history of cardiovascular disease if they had previous events of coronary heart disease, stroke, peripheral vascular disease, heart failure, dysrhythmia or valvular disease. They were considered as having diabetes if the condition was mentioned in their medical records, if they had serum levels of HbA1c ≥7%, fasting glucose ≥ 7.0 mmol/L, or random glucose ≥ 11.0 mmol/L, or if they used glucose-lowering medications. Likewise, patients were considered as having hypertension if mentioned in their medical records, if they had systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or if they were prescribed antihypertensive medications, and they were considered as having dyslipidemia if it was stated in their medical

records or if they used lipid-lowering medications. Nephrologists or outpatient nurses measured patients' blood pressure, body weight, and height. Body mass index was then calculated as the ratio of weight to height square. All patients were prescribed standard blood and urine tests (as recommended by the French health authorities for routine chronic kidney disease care), which were performed at their usual laboratory at study entry, or at a centralized laboratory for the measurement of serum creatinine, high-sensitivity C-reactive protein, and cystatin C. Blood hemoglobin, serum bicarbonate and albumin, and urine albumin or protein-to-creatinine ratio (ACR) were recorded as well. Estimated glomerular filtration rate was calculated from cystatin C using the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) equation (2009) giving the most accurate and precise estimated glomerular filtration rate for the prediction of cardiovascular risk and mortality,[2] and the ACR was either measured or estimated by an equation based on proteinuria measurements.[3]

Information on medication use was obtained from drug prescriptions during the baseline interview. Patients were asked to bring all their drug prescriptions from the preceding three months to the enrolment visit. The clinical research associates used an electronic case report form (linked to the international Anatomical Therapeutic and Chemical [ATC] thesaurus) to enter standardized ATC codes. Proton pump inhibitors use included omeprazole, esomeprazole, pantoprazole, lansoprazole, or rabeprazole, and diuretic use thiazides, loop diuretics, or distal diuretics. Antidiabetic drugs included the different types of insulin, oral antidiabetic agents (metformin, repaglinide, sulfonylurea, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors) or Glucagon-like peptide-1 receptor agonists. Antihypertensive drugs included beta-blockers, calcium channel blockers, renin-angiotensin system inhibitors, aldosterone inhibitors, diuretics, or others (such as centrally acting agents). Lipid-lowering drugs included statins, fibrates, bile acid sequestrants, ezetimibe, or omega-3 fatty acids.

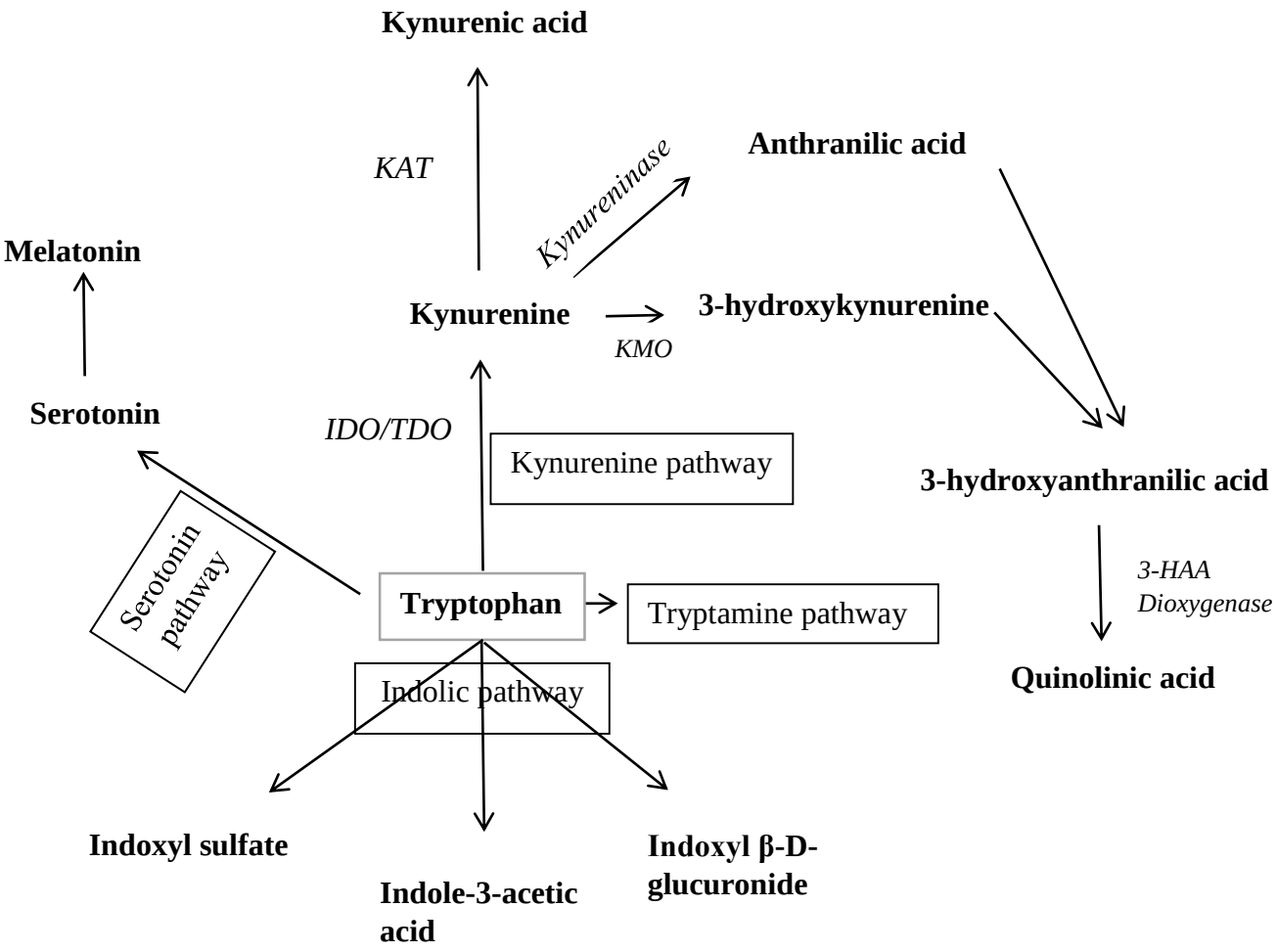
Statistical analysis

The Cox models were adjusted for a set of confounders, which were selected from a directed acyclic graph (DAG), i.e. a diagram of causal pathways summarizing a priori hypothetical causal relationship between variables (Supplemental Figures 3 and 4). This approach allows the selection of optimal set of adjustment factors (i.e. factors associated both with the exposure and the outcome), avoiding adjustment for unnecessary factors, mediators, and colliders.[4] Associations between serum kynurenine and overall cardiovascular risks, all-cause mortality,

cardiovascular and non-cardiovascular mortality risks were adjusted for age at baseline, sex, high-sensitivity C-reactive protein (CRP), urea, diabetes, dyslipidemia, systolic blood pressure, body mass index (BMI), smoking status, baseline eGFR, urine albumin or protein-to-creatinine ratio (ACR), serum free tryptophan, serum free indoxyl sulfate, indol acetic acid and p-Cresyl Sulfate, prescriptions of diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs. We excluded the prescription of diuretics in the adjustment models evaluating the association with atheromatous cardiovascular risk since no previous study found an association between them; and we excluded dyslipidemia and lipid-lowering drugs in the models evaluating the association with non-atheromatous cardiovascular risk. We added serum albumin to the models when evaluating serum free kynurenine given that kynurenine is a protein-bound molecule and any decrease in serum albumin would increase the free fraction of kynurenine. Proton pump inhibitors (PPIs) are known to increase mortality risk, however, given the limited sources of literature confirming a causal link between PPIs and kynurenine and the direction of association between them, a sensitivity analysis compared the results between an adjusted model including PPIs and another one excluding it. We did not find any difference in the results between these two models, therefore PPIs were not considered as a confounding factor and not included in the adjusted models when evaluating mortality outcomes.

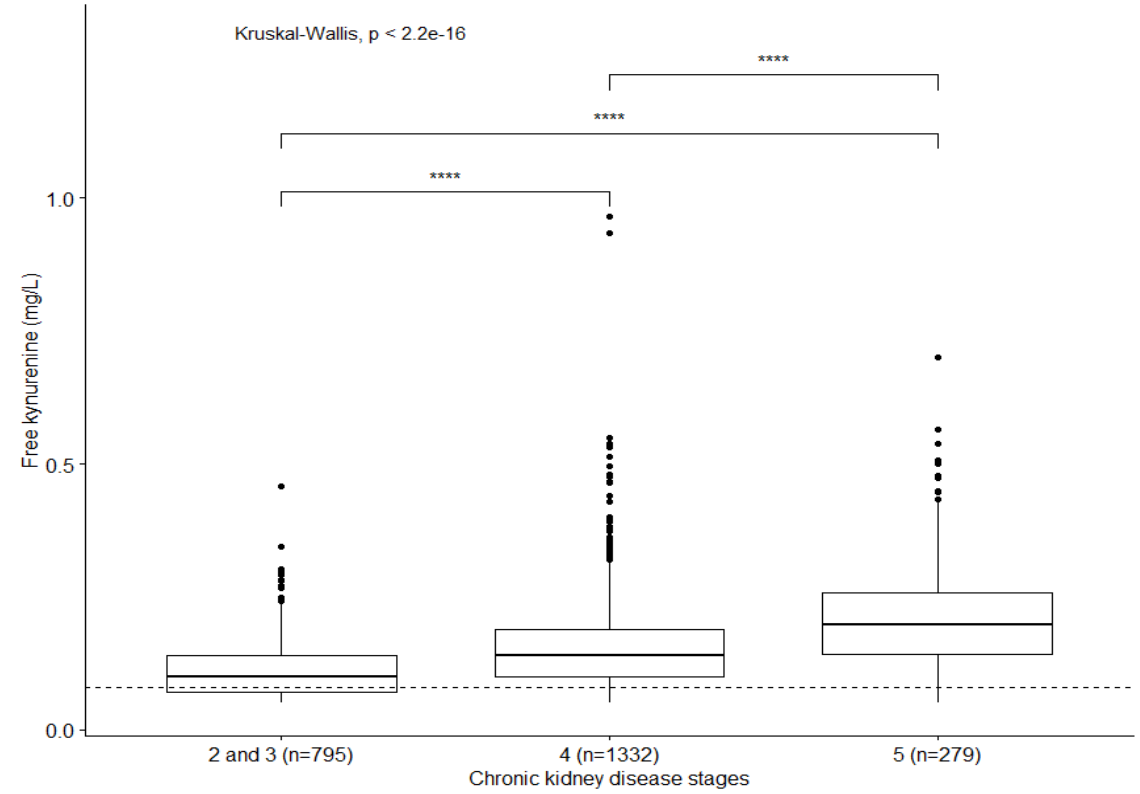
Assuming that data were missing at random, we performed multiple imputation with chained equations (MICE),[5] implemented in the MICE package in R software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria).[6] Given the proportion of missing data, 20 complete datasets were imputed. All covariates present in the Cox models were included in the imputation model. The follow-up time included in the imputation model is the cumulative hazard rate created according to the Nelson-Aalen estimator of the MICE package in R. Fitted Cox models were generated for each dataset, and pooled regression coefficients were obtained using Rubin's rules.

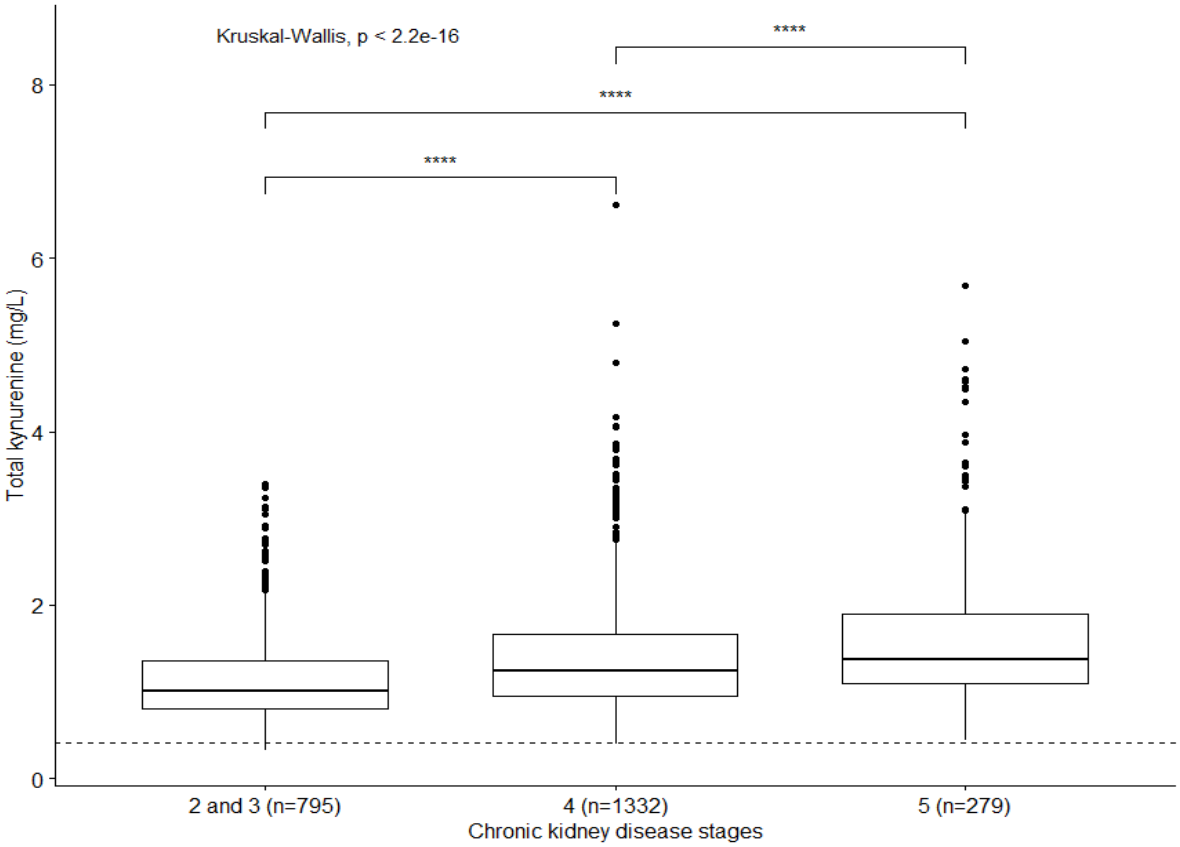
Figure S1. Tryptophan metabolism pathways.



IDO: indoleamine 2,3-dioxygenase; TDO: tryptophan dioxygenase; KAT: kynurenine aminotransferase; KMO: kynurenine monooxygenase; 3-HAA Dioxygenase: 3-hydroxyanthranilic acid dioxygenase.
Adapted from Figure 1 in Sallée et al.[7]

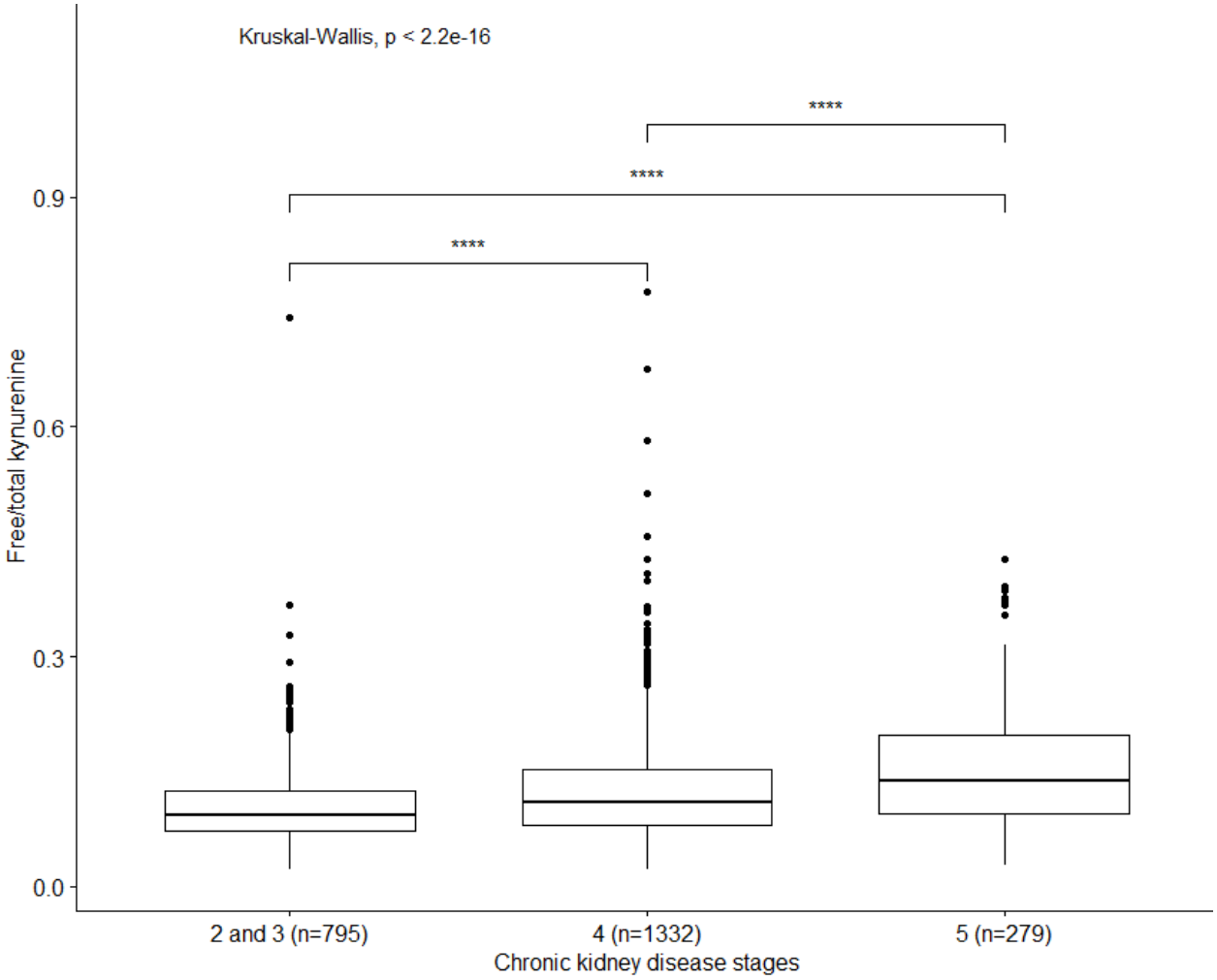
Figure S2. Distribution of kynurenine according to the stages of chronic kidney disease.





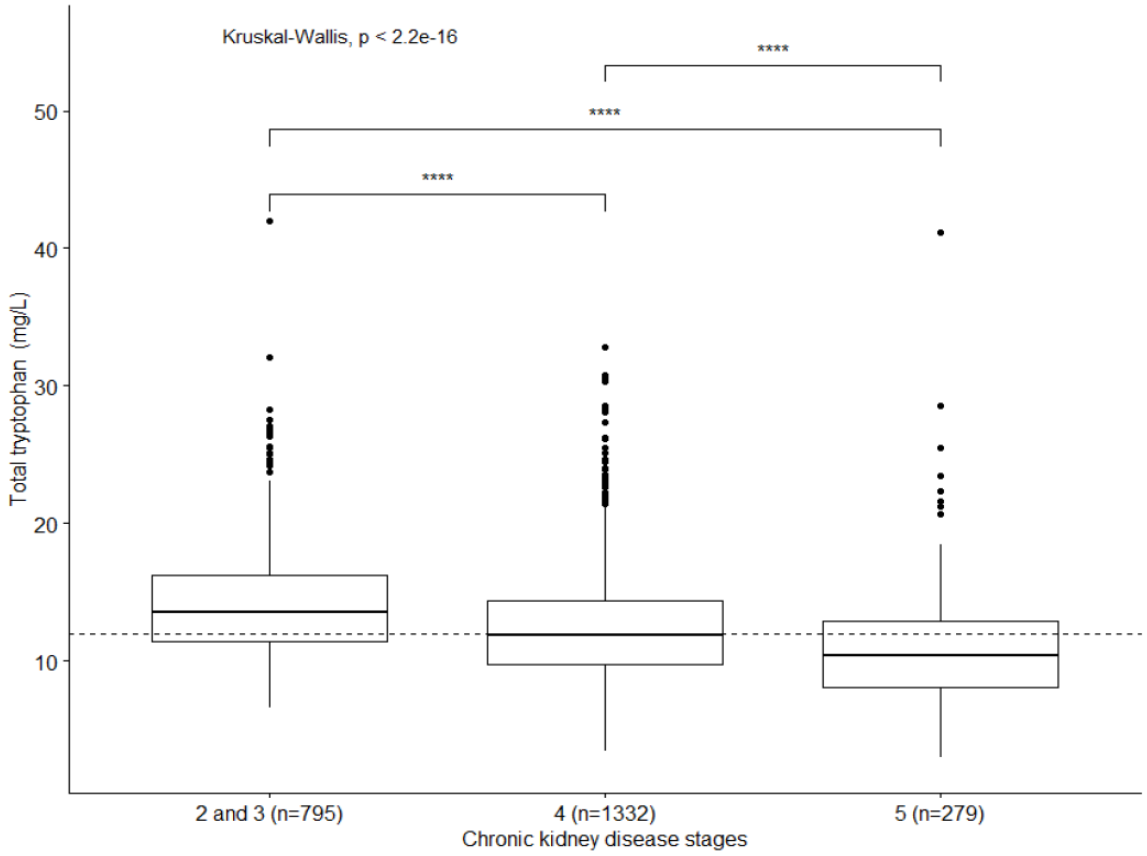
The dotted line indicates the reference value for healthy subjects.
P-values : **** : <0.001.

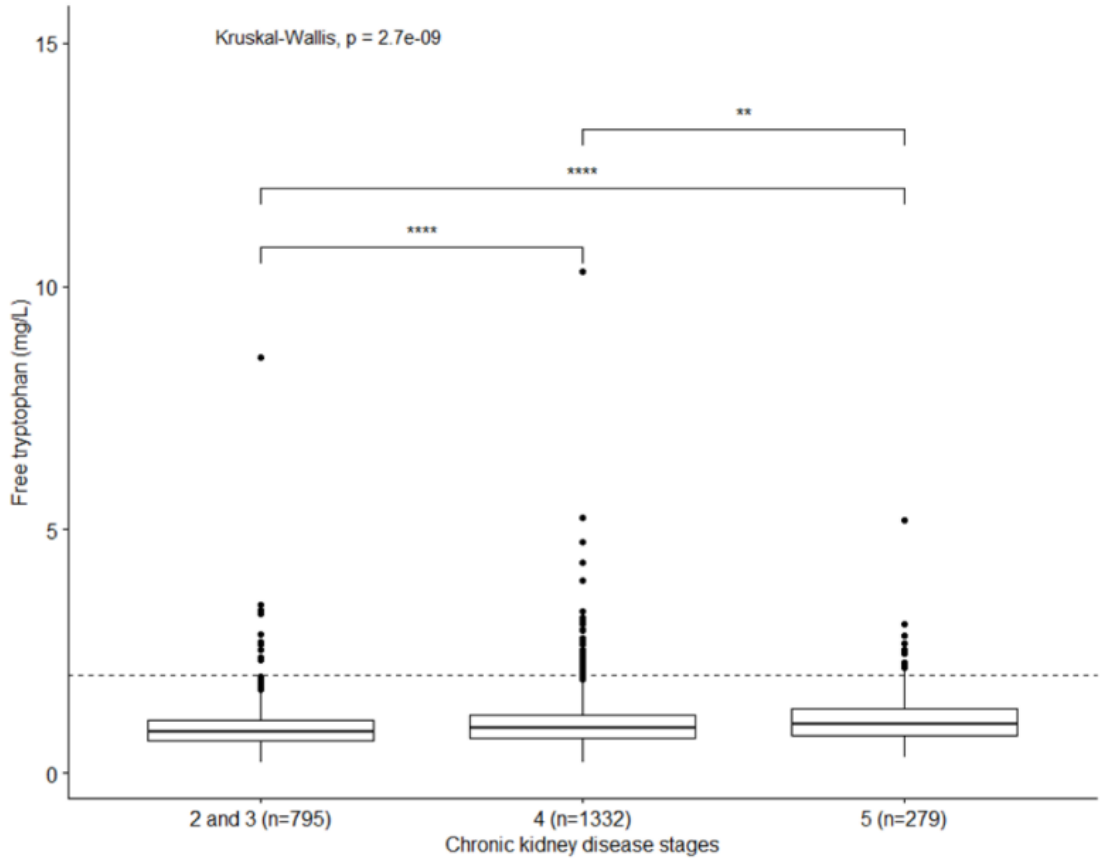
Figure S3. Distribution of free/total kynurenine according to the stages of chronic kidney disease.



P-value : **** : <0.001.

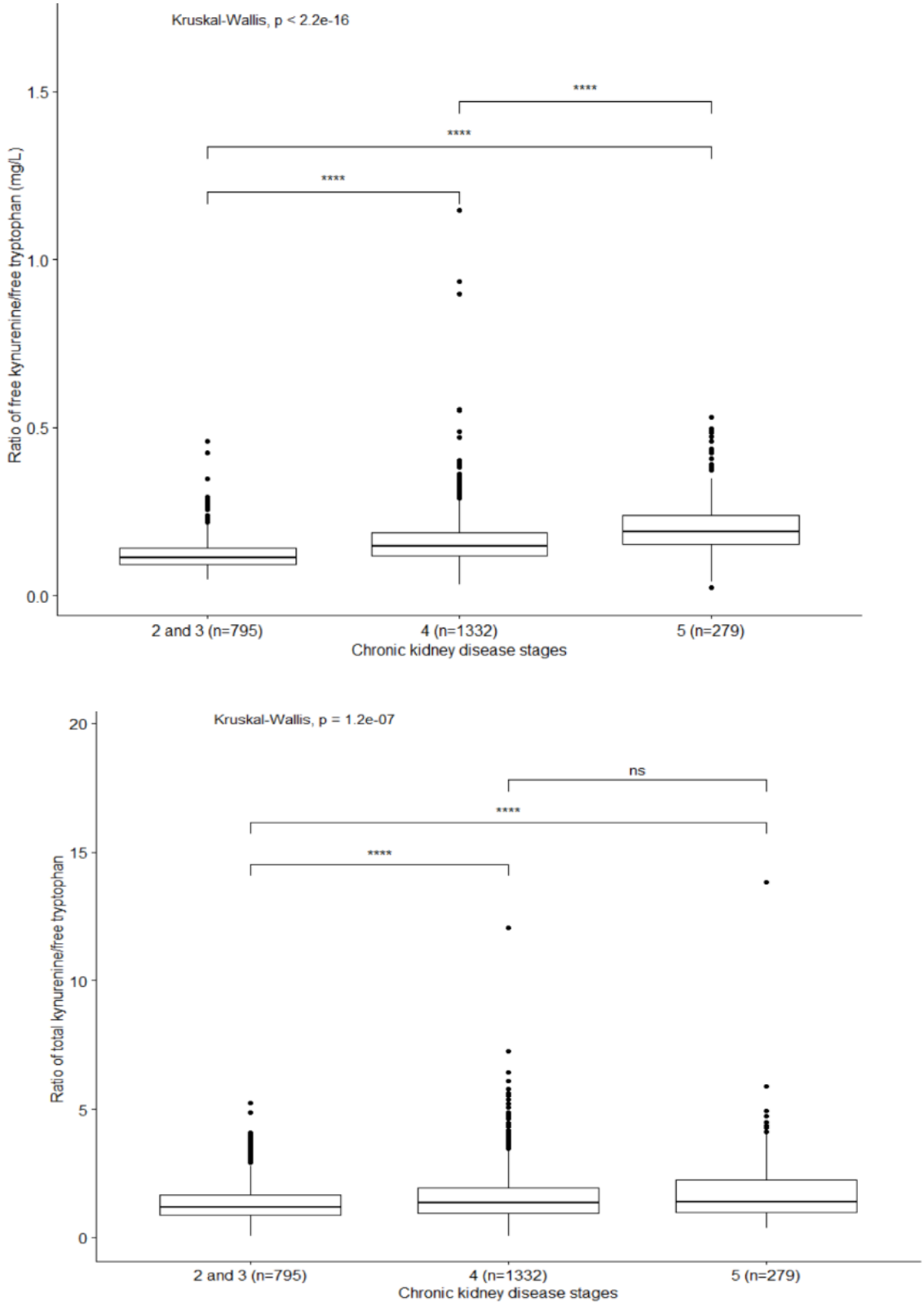
Figure S4. Distribution of tryptophan according to the stages of chronic kidney disease


Kruskal-Wallis, p < 2.2e-16
****
****
****
Total tryptophan (mg/L)
50
40
30
20
10
2 and 3 (n=795)
4 (n=1332)
5 (n=279)
Chronic kidney disease stages


Kruskal-Wallis, p = 2.7e-09
**
****
****
Free tryptophan (mg/L)
15
10
5
0
2 and 3 (n=795)
4 (n=1332)
5 (n=279)
Chronic kidney disease stages

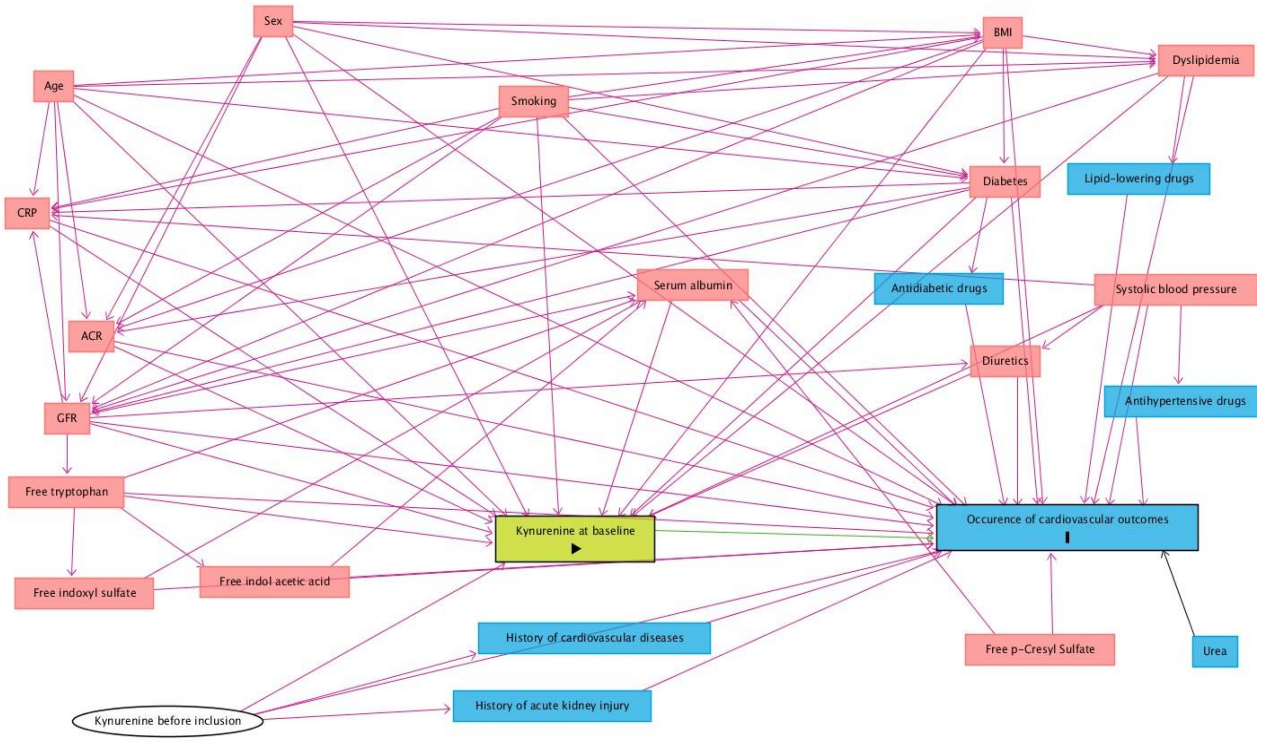
P-values: ** : <0.01 ; **** : <0.001.

Figure S5. Distribution of the ratio kynurenine/tryptophan according to the stages of chronic kidney disease



P-values : ns : non significant ; **** : <0.001.

Figure S6. Directed acyclic graph identifying the minimal sufficient adjustment set for estimating the kynurenine effect on cardiovascular events, atheromatous or not, fatal or not.



ACR : urine albumin-to-creatinine ratio; BMI : body mass index; CRP : C-Reactive Protein ; GFR : glomerular filtration rate.

Legend :

Exposure

Outcome

Risk factor linked to the exposure and outcome

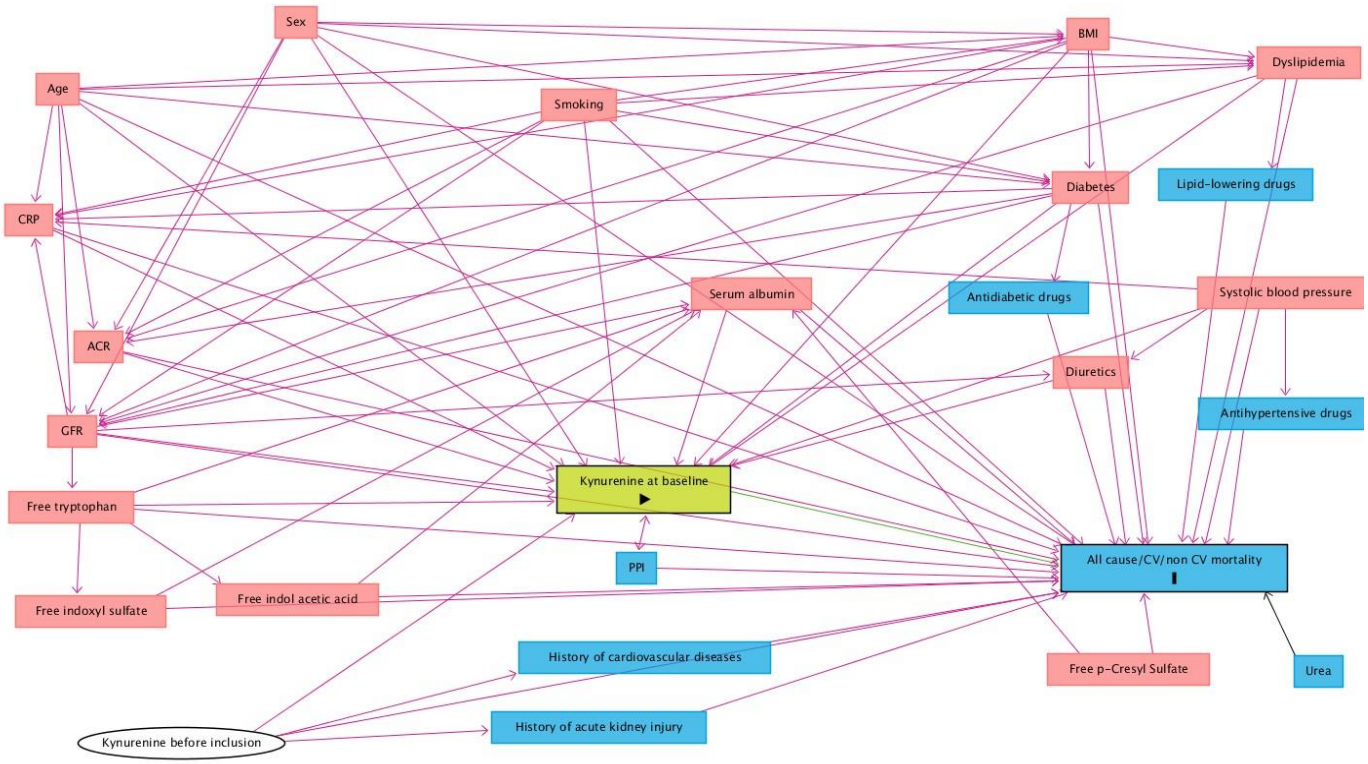
Risk factor linked to the outcome

Unobserved variable

The variables selected from the DAG (Figure S6) are those associated with both exposure (kynurenine) and the endpoint (cardiovascular outcomes, fatal or not), or with the outcome only: age, sex, smoking, albuminuria ratio /creatinuria, glomerular filtration rate, CRP, body mass index, dyslipidemia, diabetes, urea, systolic blood pressure, free tryptophan, free indoxyl sulfate, indol acetic acid and p-Cresyl Sulfate, diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs. We cannot adjust on the history of cardiovascular disease nor the history of acute kidney injury that will be considered as colliders and therefore cannot be included in the model in order to avoid biased results. The prescription of diuretics are not selected in the adjustment models evaluating the association with atheromatous

cardiovascular risk; and dyslipidemia and lipid-lowering drugs in the models evaluating the association with non-atheromatous cardiovascular risk. Serum albumin is selected for the models evaluating serum free kynurenine.

Figure S7. Directed acyclic graph identifying the minimal sufficient adjustment set for estimating the kynurenine effect on all cause/ cardiovascular /non cardiovascular mortality.



ACR : urine albumin-to-creatinine ratio; BMI : body mass index; CRP : C-Reactive Protein ; CV : cardiovascula; GFR : glomerular filtration rate; PPI: proton pump inhibitors.

Legend :

Exposure

Outcome

Risk factor linked to the exposure and outcome

Risk factor linked to the outcome

Unobserved variable

The variables retained from the DAG (Figure S7) are those associated with both exposure (kynurenine) and the endpoint (all-cause/CV/non CV mortality), or with the outcome only: age, sex, smoking, albuminuria ratio /creatinuria, glomerular filtration rate, CRP, body mass index, dyslipidemia, diabetes, urea, systolic blood pressure, free tryptophan, free indoxyl sulfate, indol acetic acid and p-Cresyl Sulfate, diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs. Concerning PPIs, and given that we have no sources of literature confirming the causal link with kynurenine and in which direction the association exists, a sensitivity analysis will be necessary to compare the results of a model

excluding this factor and another one including it. We cannot adjust on the history of cardiovascular disease nor the history of acute kidney injury that will be considered as colliders and therefore cannot be included in the model in order to avoid biased results. Serum albumin is selected for the models evaluating serum free kynurenine.

Table S1. Characteristics of the study population according to the tertiles of serum total kynurenine

Characteristics	Total	Tertiles of serum total kynurenine (mg/L)			P-value [2]	Imputed data
	N = 2406[1]	<0.99 (n=799)[1]	[0.99-1.4) (n=804) [1]	>=1.4 (n=803) [1]		
Age at baseline (years)	68 [60-76]	68 [60-75]	68 [59-76]	69 [62-76]	0.09	0%
Men	66%	65%	66%	66%	0.9	0%
eGFR at baseline (ml/min/1.73m^2)	24.7 [18.4-33.1]	29 [22-38]	24 [17-32]	22 [17-28]	**<0.0001**	0%
Albumin- or protein-to-creatinine ratio (mg/g)	104 [21-491]	77 [18-382]	113 [22-546]	135 [28-566]	**<0.0001**	11.5%
History of acute kidney injury	23%	22%	23%	25%	0.6	7.2%
Smoking status Never-smoker Current smoker Former smoker	 40.5% 12.5% 47%	 41% 15% 44%	 38% 12% 50%	 42% 9.9% 48%	**0.01**	 0.6%
Systolic blood pressure (mmHg)	140 [128-153]	139 [129-154]	139 [127-151]	140 [130-154]	0.1	0.5%
Diabetes	41%	39%	43%	42%	0.2	0.2%
Dyslipidemia	74%	73%	73%	74%	0.8	0.4%
History of cardiovascular disease	52%	49%	53%	55%	0.06	0.5%
Serum bicarbonate (mmol/L)	25 [23-27]	25 [23-27]	25 [23-27]	25 [22.6-27]	0.1	8.8%
Serum albumin (g/L)	40.4 [38-43]	40.3 [37.9-43]	40.6 [38-43]	40.4 (37.7-43]	0.6	14.5%
Hemoglobin (g/dL)	13 [11.8-14.2]	13.1[11.95-14.3]	13 [11.8-14.1]	12.9 [11.8-14.1]	0.1	0.9%
High-sensitivity C-reactive protein (mg/L)	2.4 [1.1-5.1]	2.1 [0.9-4.5]	2.2 [1.1-4.9]	2.7 [1.2-5.8]	**<0.0001**	5.4%

Body mass index (kg/m²)	27.9 [24.7-31.7]	27.1 [24.2-30.9]	28.1 [24.7-32]	28.4 [25.3-32.3]	**<0.0001**	1.9%
PPI prescription at baseline	32%	32%	32%	34%	0.6	0.2%
Diuretics prescription at baseline	52%	48%	53%	56%	**0.004**	0.3%
Antihypertensive drugs prescription at baseline	2243 (94%)	729 (92%)	748 (94%)	766 (96%)	**0.006**	0.3%
Lipid-lowering drugs prescription at baseline	1520 (63%)	489 (61%)	502 (63%)	529 (66%)	0.2	0.3%
Antidiabetic drugs prescription at baseline	820 (34%)	255 (32%)	296 (37%)	269 (34%)	0.1	0.3%
Free tryptophan (mg/L)	0.91 [0.7-1.17]	0.85 [0.66-1.08]	0.94 [0.72-1.23]	0.96 [0.76-1.25]	**<0.0001**	0%
Total tryptophan (mg/L)	12.3 [10-14.8]	10.7 [8.8-12.9]	12 [10.1-14.1]	14.4 [11.9-17.6]	**<0.0001**	0%
Total kynurenine	1.19 [0.91-1.6]	0.8 [0.7-0.9]	1.18[1.08-1.3]	1.8[1.6-2.2]		0%
Free kynurenine	0.13 [0.09-0.18]	0.09 [0.07-0.12]	0.13[0.1-0.19]	0.16[0.1-0.2]	**<0.0001**	0%

[1] Median [Q1-Q3]; %

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

eGFR: estimated glomerular filtration rate; PPI: proton pump inhibitor.

Table S2. Hazard ratio for fatal and nonfatal cardiovascular events, according to the baseline serum total kynurenine level (mg/L).

	Total kynurenine (mg/L)
Unadjusted HR [95% CI] – p-value	1.5 [1.3, 1.7] -- **<0.001**
Adjusted HR[1] [95% CI] – p-value	1.2 [1.05, 1.4] – **0.01**
Adjusted HR[2] [95% CI] – p-value	1.2 [1.05, 1.4] – **0.01**
Adjusted HR[3] [95% CI] – p-value	1.2 [1.05, 1.4] -- **0.01**

[1]Model adjusted for age at baseline, sex, high-sensitivity C-reactive protein, urea, diabetes, dyslipidemia, body mass index, smoking status, baseline estimated glomerular filtration rate, urine albumin- or protein-to-creatinine ratio, systolic blood pressure, prescriptions of diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs.

[2] 1+serum free tryptophan.

[3] 1+ serum free indoxyl sulfate, indole-3-acetic acid and p-Cresyl Sulfate.

Table S3. Hazard ratio for atheromatous cardiovascular events, according to the baseline serum total kynurenine level (mg/L).

	Total kynurenine (mg/L)
Unadjusted HR [95% CI] – p-value	1.5 [1.2, 1.8] – **0.0003**
Adjusted HR[1] [95% CI] – p-value	1.3 [1.04, 1.64] – **0.02** 1.15 [1.01, 1.3] – **0.03**
Adjusted HR[2] [95% CI] – p-value	1.3 [1.04, 1.6] – **0.02**
Adjusted HR[3] [95% CI] – p-value	1.29 [1.03, 1.6] – **0.02**

[1]Model adjusted for age at baseline, sex, high-sensitivity C-reactive protein, urea, diabetes, dyslipidemia, body mass index, smoking status, baseline estimated glomerular filtration rate, urine albumin- or protein-to-creatinine ratio, systolic blood pressure, prescriptions of antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs.

[2] 1+serum free tryptophan.

[3] 1+ serum free indoxyl sulfate, indole-3-acetic acid and p-Cresyl Sulfate.

Table S4. Hazard ratio for non-atheromatous cardiovascular events, according to the baseline serum total kynurenine level (mg/L).

	Total kynurenine (mg/L)
Unadjusted HR [95% CI] – p-value	1.7 [1.4, 1.9] -- **<0.001**
Adjusted HR[1] [95% CI] – p-value	1.21 [1.006 , 1.46] – **0.04**
Adjusted HR[2] [95% CI] – p-value	1.21 [1.009 , 1.46] –**0.04**
Adjusted HR[3] [95% CI] – p-value	1.2 [1.01, 1.46] – **0.03**

[1]Model adjusted for age at baseline, sex, high-sensitivity C-reactive protein, urea, diabetes, body mass index, smoking status, baseline estimated glomerular filtration rate, urine albumin- or protein-to-creatinine ratio, systolic blood pressure, prescriptions of diuretics, antihypertensive drugs, and antidiabetic drugs.

[2] 1+serum free tryptophan.

[3] 1+ serum free indoxyl sulfate, indol-3-acetic acid and p-Cresyl Sulfate.

Table S5. Hazard ratio for all-cause mortality, according to the baseline serum total kynurenine level (mg/L).

	Total kynurenine (mg/L)
Unadjusted HR [95% CI] – p-value	1.4 [1.1, 1.6] -- **0.0009**
Adjusted HR[1] [95% CI] – p-value	1.04 [0.9, 1.3] – 0.7
Adjusted HR[2] [95% CI] – p-value	1.04 [0.9, 1.3] – 0.7
Adjusted HR[3] [95% CI] – p-value	1.04 [0.9, 1.3] – 0.6

[1]Model adjusted for age at baseline, sex, high-sensitivity C-reactive protein, urea, diabetes, dyslipidemia, body mass index, smoking status, baseline estimated glomerular filtration rate, urine albumin- or protein-to-creatinine ratio, systolic blood pressure, prescriptions of diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs.

[2] 1+serum free tryptophan.

[3] 1+ serum free indoxyl sulfate, indol-3-acetic acid and p-Cresyl Sulfate.

Table S6. Hazard ratio for non-cardiovascular mortality, according to the baseline serum total kynurenine level (mg/L).

	Total kynurenine (mg/L)
Unadjusted HR [95% CI] – p-value	1.3 [1.07, 1.7] – **0.008**
Adjusted HR[1] [95% CI] – p-value	1.01 [0.8, 1.3] – 0.9
Adjusted HR[2] [95% CI] – p-value	1.01 [0.8, 1.3] – 0.9
Adjusted HR[3] [95% CI] – p-value	1.009 [0.8, 1.3] – 0.9

[1]Model adjusted for age at baseline, sex, high-sensitivity C-reactive protein, urea, diabetes, dyslipidemia, body mass index, smoking status, baseline estimated glomerular filtration rate, urine albumin- or protein-to-creatinine ratio, systolic blood pressure, prescriptions of diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs.

[2] 1+serum free tryptophan.

[3] 1+ serum free indoxyl sulfate, indol-3-acetic acid and p-Cresyl Sulfate.

Table S7. Hazard ratio for cardiovascular mortality, according to the baseline serum total kynurenine level (mg/L).

	Total kynurenine (mg/L)
Unadjusted HR [95% CI] – p-value	1.5 [1.05, 2.04] – **0.02**
Adjusted HR[1] [95% CI] – p-value	1.16 [0.8, 1.7] – 0.4
Adjusted HR[2] [95% CI] – p-value	1.16 [0.8, 1.7] – 0.4
Adjusted HR[3] [95% CI] – p-value	1.17 [0.8, 1.7] – 0.4

[1]Model adjusted for age at baseline, sex, high-sensitivity C-reactive protein, urea, diabetes, dyslipidemia, body mass index, smoking status, baseline estimated glomerular filtration rate, urine albumin- or protein-to-creatinine ratio, systolic blood pressure, prescriptions of diuretics, antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs.

[2] 1+serum free tryptophan.

[3] 1+ serum free indoxyl sulfate, indol-3-acetic acid and p-Cresyl Sulfate.

List of biological resources centers

The authors would like to thank the teams of all the biological resources centers that participated in the CKD-REIN project:

- Biobanque de Picardie, CRB du Centre Hospitalier Universitaire Amiens Picardie, 1 Rond-Point du Pr Christian Cabrol, 80054 Amiens Cedex 1 (BRIF number: BB-0033-00017)
- NeuroBioTec, CRB des Hospices Civils de Lyon Groupement Hospitalier Est, Hôpital Neurologique, 59 Boulevard Pinel, 69677 Bron Cedex (BRIF number: BB-0033-00046)
- Centre de ressources biologiques du Centre Hospitalier Universitaire de Nantes Hôtel Dieu, Institut de biologie, 9, quai Moncousu, 44093 Nantes Cedex 1 (BRIF number: BB-0033-00040)
- Centre de ressources biologiques du Centre Hospitalier Universitaire Grenoble Alpes, Boulevard de la Chantourne, CS 10217, 38700 La Tronche (BRIF number: BB-0033-00069)
- Centre de ressources biologiques du Centre Hospitalier Régional Universitaire de Nancy, Hôpitaux de Brabois, Bâtiment Recherche Rue du Morvan, 54500 Vandoeuvre-les-Nancy (BRIF number: BB-0033-00035)

- Servicer de Néphrologie, Centre Hospitalier de Perpignan, 20 Avenue du Languedoc, 66046 Perpignan Cedex 9
- Plateforme de Ressources Biologiques, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94000 Créteil (BRIF number: BB-0033-00021)
- CIC-1435, Centre d'Investigation Clinique Plurithématique, Centre Hospitalier Universitaire de Limoges, 2 Avenue Martin Luther King, 87042 Limoges Cedex
- Plateforme de Ressources Biologiques de l'Hôpital européen Georges-Pompidou, 20-40 rue Leblanc, 75015 Paris (BRIF number: BB-0033-00063)
- Etablissement Français du sang Hauts de France – Normandie, Site de Bois-Guillaume 609, chemin de la Bretèque, 76235 Bois-Guillaume
- Etablissement Français du sang Nouvelle Aquitaine, site Pellegrin, Place Amélie Raba Léon, CS 21010, 33075 Bordeaux Cedex
- Etablissement Français du sang Hauts de France – Normandie, Site de Loos-Eurasanté, Avenue Pierre Mauroy, Parc Eurasante Epi-de Soil, 59120 Loos
- Etablissement Français du sang Ile de France, Site Avicenne, Hopital Avicenne porte 8, 125 route de Stalingrad, 93009 Bobigny
- Etablissement Français du sang Occitanie, Site de Toulouse, 75 rue de Lisieux, 31300 Toulouse
- Etablissement Français du sang Grand-Est, Site de Colmar, 6 rue du Hohnack, 68025 Colmar Cedex
- Etablissement Français du sang Grand-Est, Site de Metz, 6 rue des Dames de Metz, 57000 Metz
- Etablissement Français du sang PACA-Corse, Site de Marseille, 149, boulevard Baille, 13392 Marseille Cedex 05

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