Brain, Behavior, and Immunity 75 (2019) 155–162

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

The kynurenine pathway and cognitive performance in community-dwelling older adults. The Hordaland Health Study

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ARTICLE INFO

Keywords:
Hordaland Health Study
Kynurenines
Inflammation
Cognition
Tryptophan metabolism
Kendrick Object Learning Test
Controlled Oral Word Association Test

ABSTRACT

Introduction: Tryptophan, its downstream metabolites in the kynurenine pathway and neopterin have been associated with inflammation and dementia. We aimed to study the associations between plasma levels of these metabolites and cognitive function in community-dwelling, older adults.

Methods: This cross-sectional study included 2174 participants aged 70–72 years of the community-based Hordaland Health Study. Tryptophan, kynurenine, neopterin and eight downstream kynurenines were measured in plasma. Kendrick Object Learning Test (KOLT), Digit Symbol Test (DST) and the Controlled Oral Word Association Test (COWAT) were all outcomes in standardized Zellner's regression. The Wald test of a composite linear hypothesis of an association with each metabolite was adjusted by the Bonferroni method. Age, body mass index, C-reactive protein, depressive symptoms, diabetes, education, glomerular filtration rate, hypertension, previous myocardial infarction, prior stroke, pyridoxal 5′phosphate, sex and smoking were considered as potential confounders.

Results: Higher levels of the kynurenine-to-tryptophan ratio (KTR) and neopterin were significantly associated with poorer, overall cognitive performance ($p < 0.002$). Specifically, KTR was negatively associated with KOLT ($\beta -0.08$, $p = 0.001$) and COWAT ($\beta -0.08$, $p = 0.001$), but not with DST ($\beta -0.03$, $p = 0.160$). This pattern was also seen for neopterin (KOLT: $\beta -0.07$; $p = 0.001$; COWAT: $\beta -0.06$, $p = 0.010$; DST: $\beta -0.01$, $p = 0.800$). The associations were not confounded by the examined variables. No significant associations were found between the eight downstream kynurenines and cognition.

Conclusion: Higher KTR and neopterin levels, biomarkers of cellular immune activation, were associated with reduced cognitive performance, implying an association between the innate immune system, memory, and language.

1. Introduction

Tryptophan (TRP), an essential amino acid, is degraded primarily through the kynurenine pathway (KP, Fig. 1) which generates metabolites collectively referred to as the kynurenines (Chen and Guillemin, 2009). TRP and the kynurenines have been related to cognitive impairment (Baran et al., 1999), cardiovascular disease (Sulo et al., 2013; Zuo et al., 2016), renal function (Theofylaktopoulou et al., 2013), inflammation, obesity, diabetes and psychiatric disorders (Cervenka et al., 2017). However, a relationship between the kynurenines and

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https://doi.org/10.1016/j.bbi.2018.10.003
Received 30 May 2018; Received in revised form 17 September 2018; Accepted 23 October 2018
Available online 25 October 2018
0889-1591/

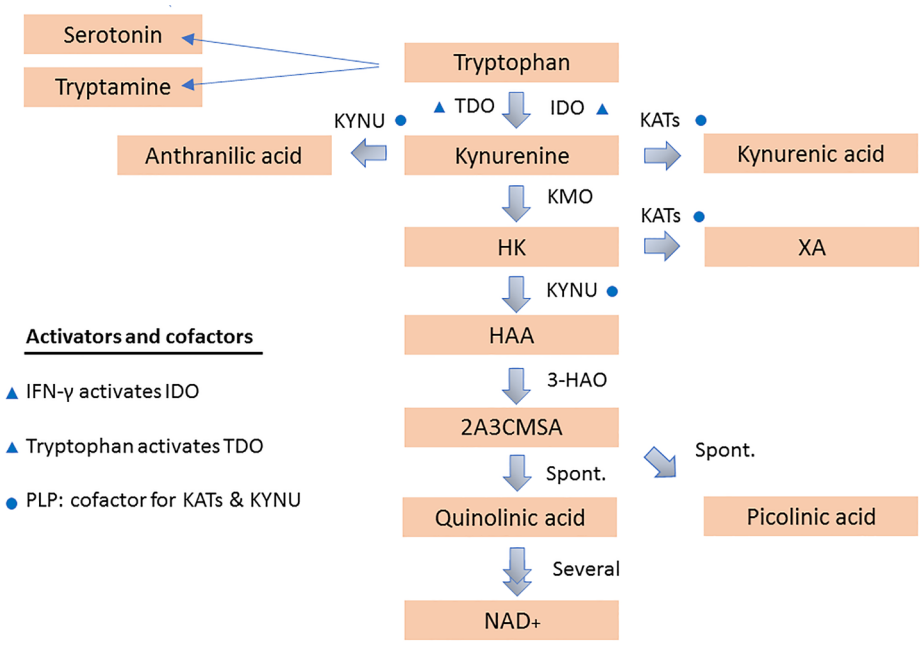

Fig. 1. The kynurenine pathway. TDO and IDO converts tryptophan to kynurenine. HK is converted to 3-hydroxyanthranilic acid (HAA) by kynureninase (KYNU), and subsequently to quinolinic acid (QA), catalyzed by quinolinate phosphoribosyl transferase. QA is converted to nicotinamide adenosine dinucleotide (NAD), the final product of the pathway. Anthranilic acid is produced from KYN by KYNU. Kynurenine aminotransferases (KATs) generate KA from KYN and xanthurenic acid (XA) from HK. Picolinic acid is produced by spontaneous conversion of HAA. Both KYNU and KATs have pyridoxal 5′-phosphate (PLP) as a cofactor (Chen and Guillemin, 2009). HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; 3-HAO, 3-hydroxyanthranilic acid 3, 4-dioxygenase; IDO, indoleamine 2, 3-dioxygenase; KATs, kynurenine aminotransferases; KMO, kynurenine monooxygenase; KTR, kynurenine-tryptophan ratio; NAD^+, nicotine adenine dinucleotide; Spont, spontaneous; TDO, tryptophan 2, 3-dioxygenase.

cognitive function in a community-dwelling cohort has not been established.

Reduced levels of circulating TRP and several kynurenines have been found in persons with dementia compared to controls (Giil et al., 2017), while elevated levels of anthranilic acid (AA), a derivative of kynurenine (KYN), has been linked to dementia in a prospective study (Chouraki et al., 2017). In cognitively healthy persons, elevated levels of inflammatory mediators are linked to poor cognitive performance (Smith et al., 2012). The kynurenines are closely linked to the innate immune system and have immune regulatory actions (Hwu et al., 2000). During an inflammatory state, cytokines stimulate the activity and expression of indoleamine 2, 3-dioxygenase (IDO), which converts TRP to KYN, mostly in monocytes. This leads to reduced TRP and an increase in downstream kynurenines, especially KYN (Capuron et al., 2011). The most important activator of IDO is interferon-γ (IFN-γ), which also activates GTP-cyclohydrolase I (GTP-CH), the rate-limiting enzyme in the biosynthesis of neopterin, which is a pteridine produced by monocytes during inflammation (Wirleitner et al., 2002). Increased levels of neopterin have been linked to dementia (Parker et al., 2013).

IDO is also expressed in the brain and may have importance in the relationship between systemic inflammation and cognitive impairment (Comim et al., 2017). Inflammation activates IDO and may increase levels of neurotoxic kynurenine metabolites in the brain with potential harmful effects on the hippocampus (Lim et al., 2013; Schwarcz and Kohler, 1983). Further, TRP and KYN pass the blood-brain barrier (BBB) (Fukui et al., 1991; Smith et al., 1987) and are key substrates for the brain's synthesis of serotonin and kynurenines (Chen and Guillemin, 2009).

Our aim was to study the relationship between circulating levels of TRP, kynurenines, and neopterin with cognitive test performance in a community-based cohort of adults aged 70–72 years, The Hordaland Health Study (HUSK).

2. Methods

2.1. Study participants

Study participants were included from HUSK, conducted in Hordaland County, Western Norway (http://husk-en.w.uib.no). Details of the recruitment procedures in both the main study and the cognitive sub-study have been described previously (Nurk et al., 2007). Briefly, from the source cohort, 2841 participants born in 1925–27, living in Bergen and three surrounding municipalities, were invited by letter to participate in HUSK during 1997 to 1999. Of these, 2197 participants (77.3%) were included in the sub-study on cognitive function and of these, 2174 had available blood samples and were included in the present study. The presence of disease was not an exclusion criterion in this population-based cohort. The self-reported prevalence of hypertension was 32.8%, previous myocardial infarction 10.6%, diabetes 6.7%, and prior stroke 4.7% (Table 1). The Regional Committee for Medical and Health Research Ethics approved the study protocol (REC number: 2016/2208) and all participants provided signed informed consent.

2.2. Measurement of metabolites

Non-fasting blood samples were collected at baseline, and aliquots of EDTA plasma samples were stored at −80 °C until analysis. TRP, eight kynurenines (KYN, AA, kynurenic acid (KA), 3-hydroxykynurenine (HK), 3-hydroxyanthranilic acid (HAA), xanthurenic acid (XA), picolinic acid (PIC), quinolinic acid (QA)), pyridoxal 5′ phosphate (PLP), neopterin and cotinine were measured using liquid chromatography-tandem mass spectrometry (Midttun et al., 2009). In general, the kynurenine metabolites remain stable under long-term cryopreservation. TRP, KYN, KA, XA, PIC and QA remain stable. Under non-optimal preanalytical handling or storage, HK and HAA may decrease, while AA may increase (Hustad et al., 2012). However, all these three markers were within their normal concentration range in our study (Midttun et al., 2017). The ratio between kynurenine and tryptophan was calculated as KYN (μM)/TRP (μM) * 100. The limit of detection was 0.4 μmol/L for TRP, while for neopterin and the kynurenines, limits of detection ranged from 0.5 nmol/L to 7 nmol/L. Within-day and between-day coefficients of variation were 3.0–9.5% and 5.7–16.9%, respectively.

Plasma high-sensitivity C-reactive protein (CRP) level was determined using an immune-MALDI (matrix-assisted laser desorption/ionization) mass spectrometry method (Meyer and Ueland, 2014). For CRP, the limit of detection was 0.2 μg/L, and within-day and between-day coefficients of variation were 5.5–8.4% and 7.0–11.7%, respectively. All biochemical analyses were performed in the laboratory of Bevital AS (http://bevital.no).

Table 1
Demographic and clinical characteristics.

Variable	Statistic
Demographics and general health	
Age, years, median [range]	71 [70–72]
Women, %	55.2
Education, %	
< 7 years of Primary School	7.3
7–10 years of Primary School	31.6
1–2 years of High School	30.2
3 years of High School	11.9
College/University	19.0
Diabetes, %	6.7
Current smoking[a], %	17.8
eGFR, mL/min/1.73 m^2, mean [SD]	71.7 [15.7]
BMI, mean [SD]	26.1 [3.9]
Hypertension, %	32.8
Stroke, %	4.7
MI, %	10.6
Depressive symptoms, %	8.8
Antidepressants[b], %	4.3
NSAIDs[c], %	5.9
Cognitive test scores	
KOLT score, mean [SD]	35 [8.1]
COWAT score, mean [SD]	15 [5.5]
DST score mean [SD]	10 [4.2]
Metabolite levels	
TRP, µmol/L, median [IQR]	67.8 [17.5]
KYN, µmol/L, median [IQR]	1.72 [0.50]
KA, nmol/L, median [IQR]	54.8 [25.2]
AA, nmol/L, median [IQR]	16.0 [7.20]
XA, nmol/L, median [IQR]	16.4 [10.0]
HK, nmol/L, median [IQR]	36.1 [15.5]
HAA, nmol/L, median [IQR]	35.0 [17.0]
PIC, nmol/L, median [IQR]	49.4 [28.1]
QA, nmol/L, median [IQR]	462 [2 2 6]
Neopt, nmol/L, median [IQR]	8.70 [3.30]
PLP, nmol/L, median [IQR]	49.1 [44.5]
KTR, µmol/L/ µmol/L*100, median [IQR]	2.50 [0.70]
KA/QA, nmol/L/nmol/l*100, median [IQR]	11.87 [5.55]

[a] Plasma cotinine level ≥ 10 nmol/l.
[b] ATC-classification system, NX5 and N06A: selective serotonin and norepinephrine reuptake inhibitors. Tricyclic and tetracyclic antidepressants.
[c] ATC-registry groups M01A and N02B. AA, anthranilic acid; BMI, body mass index; COWAT, Controlled Oral Word Association Test; DST, Digit Symbol Test; eGFR, estimated glomerular filtration rate; HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; IQR, inter-quartile range; KA, kynurenic acid; KA/QA, kynurenic acid-quinolinic acid ratio; KOLT, Kendrick Object Learning test; KTR, kynurenine-tryptophan ratio; KYN, kynurenine; MI, previous myocardial infarction; Neopt, neopterin; NSAIDs, non-steroidal anti-inflammatory drugs; PIC, piconilic acid; PLP, pyridoxal 5′phosphate; QA, quinolinic acid; TRP, tryptophan; XA, xanthurenic acid.

2.3. Testing of cognitive function

We identified ceiling effects in both a brief version of the Mini-Mental Status Examination and Block-Design (supplementary materials, Figure S1). This implies that the true level of cognitive function has not been accurately measured in the participants who reached the ceiling effects. Further, the Trail Making Test A displayed a log-normal distribution with a bimodal trend. These cognitive tests were therefore considered unsuitable as measurements of cognitive function.

The following normally distributed tests, which indicates an appropriate difficulty level with a centralized mean, were selected to describe cognitive function: Kendrick Object Learning Test (KOLT), the Controlled Oral Word Association Test (COWAT), and the Digit Symbol Test (DST) (Nurk et al., 2007). Briefly, KOLT measures immediate recall and requires participants to observe picture charts, before telling the examiner what they observed (Kendrick, 1985). DST evaluates executive function and is performed by completing a coding table that consists of the numbers 1–9 and symbols. Participants are instructed to fill in blank squares with the symbol that is paired with the digit displayed above the square (Wechsler, 1981). Lastly, COWAT encourages participants to write as many words as possible beginning with a given letter in 60 s and is considered a measure of language, memory, and executive function (Benton A, 1989). Thus, the cognitive domains of memory, language, and executive function were examined in this study.

2.4. Potential confounders

Age, gender and educational attainment (Ngandu et al., 2007) were adjusted for. Cardiovascular disease (Zuo et al., 2016), diabetes (Stone and Darlington, 2002) and stroke (Darlington et al., 2007) have been associated with both kynurenines and cognitive performance (Biessels et al., 2008; Stampfer, 2006; Tatemichi et al., 1994). Similarly, a high body mass index (BMI) is associated with higher levels of kynurenines (Mangge et al., 2014) and poor cognition (Cournot et al., 2006). PLP is a coenzyme in the kynurenine pathway and associated with inflammation and cognitive function (Kennedy, 2016). Renal function determines kynurenine levels (Pawlak et al., 2002) and poor renal function is associated with cognitive dysfunction (Seliger et al., 2004). The same applies to smoking (Anstey et al., 2007). Thus, estimated glomerular filtration rate (Modification of Diet in Renal Disease equation) (Levey et al., 2006) and current smoking (plasma cotinine ≥ 10 nmol/L) were adjusted for in our analyses (Seccareccia et al., 2003).

Kynurenine levels are higher in major depression and TRP levels is lower (Myint et al., 2007). Furthermore, depression is associated with poor cognitive performance (Biringer et al., 2005). We aimed to establish whether kynurenines were associated with depressive symptoms in this population-based sample. To this purpose, we applied the Hospital Anxiety and Depression Scale (HADS) and defined a score of ≥8 as an indicator of mild depressive symptoms, in accordance with Stern et al. (Stern, 2014). HADS questionnaires with one or two missing answers on the items examining depressive symptoms were imputed as the mode of the other answers (N = 122). A total of 234 participants who underwent cognitive testing did not answer the HADS questionnaire. To further characterize if TRP and kynurenines were related to depressive symptoms in this study, we used antidepressant agents as a surrogate marker. Anti-depressive medications were categorized according to the 1997 ATC-classification system and included all agents under N06A (selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants) and NX5 (selective norepinephrine reuptake inhibitors). Further, we investigated if the use of non-steroidal anti-inflammatory drugs (NSAIDs) were associated with kynurenine levels. If so, these would be included in the multivariate models. NSAIDs were defined by the 1997 ATC-registry groups M01A and N02B.

Finally, CRP is of special interest, as it is one of the most frequent measures of inflammation reported as a negative determinant of cognitive performance. Innate immune activation is expected to increase both CRP levels, and the levels of several kynurenines downstream of TRP (Kuo et al., 2005; Zuo et al., 2016). We thus evaluated associations between TRP, kynurenines and CRP, and adjusted any significant findings for CRP levels.

2.5. Statistics

Prior to multivariable analysis, metabolites were transformed according to Tukey's ladder of Powers (Tukey, 1977). The purpose was to linearize relationships by achieving approximately normal distributions, as assessed by histograms and quantile-quantile plots. KYN was transformed by an inverse transformation, QA and KTR as the inverse of the square root and KA, XA, PIC, the KA/QA ratio, PLP and neopterin by log transformations. CRP was transformed by a Box-Cox transformation (Box and Cox, 1964). To compare effect sizes across the scales that arose from the use of transformations, all continuous covariates and

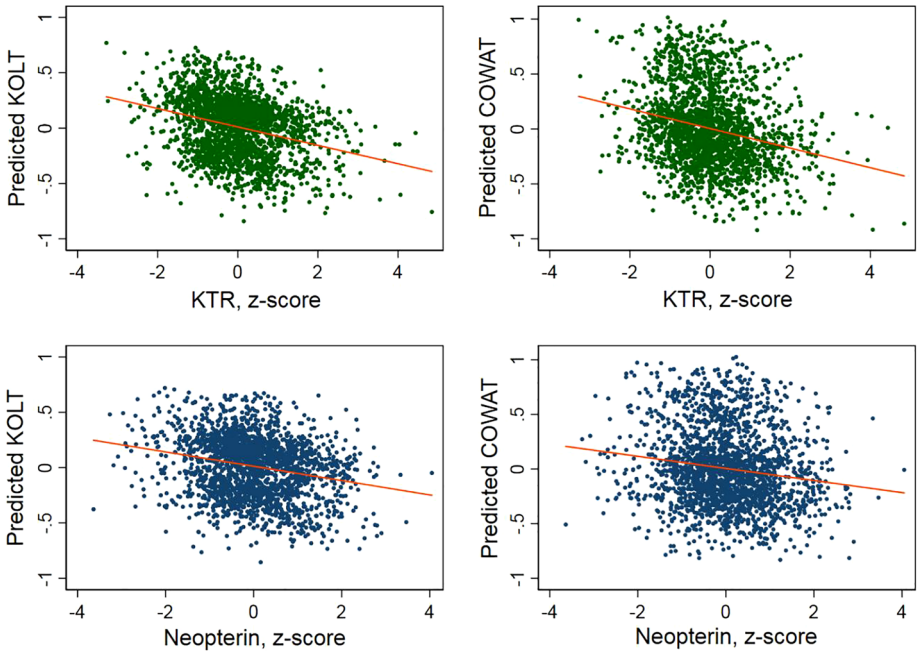

Fig. 2. Cognitive tests and markers of immune activation. Predicted results from Zellner's regression, adjusted for age, sex, body mass index, educational level, estimated glomerular filtration rate, current smoking, diabetes, hypertension, previous myocardial infarction, prior stroke, and pyridoxal 5′ phosphate as covariates. COWAT, Controlled Oral Word Association Test; KOLT, Kendrick Object Learning Test; KTR, kynurenine-tryptophan ratio.

outcomes were scaled to z-scores. Logistic- and linear regressions were used to determine associations between potential confounders, kynurenines and outcomes.

The cognitive tests were positively correlated (supplementary materials, Figure S2) and potentially not independent outcome variables. We first identified a highly significant Breusch-Pagan test (Breusch and Pagan, 1979), which indicates correlated residuals from separate linear regressions. Therefore, we decided to assess the associations between all cognitive tests and each metabolite by Zellner's seemingly unrelated regression (SUR), which estimates a set of *m* linear regressions with correlated error terms (Jahanshad et al., 2015). We used the two-step estimation procedure. After initial analysis with age, gender, body mass index, education (in years), GFR, current smoking, diabetes, previous myocardial infarction, prior stroke and PLP, additional confounders associated with TRP, kynurenines or neopterin, were adjusted.

It is impractical to formulate a hypothesis about which exact cognitive test is related to which metabolite. Therefore, we tested the joint significance of the association between each metabolite and "cognition", represented by the three cognitive outcomes in SUR. In order to test the joint significance, we applied the Wald test on a composite linear hypothesis (Cameron, 2009), composed of the three hypotheses of association between the metabolite and the three cognitive tests. The joint significance ($\alpha = 0.05$) threshold was adjusted for the number of hypotheses tested, according to the Bonferroni method (Chen et al., 2017). All statistical analyses were conducted using Stata (version 15, Stata Corp, College Station, Texas, USA).

3. Results

3.1. Participant characteristics

A total of 2174 participants (55.2% women), aged 70–72 years with cognitive tests and available blood samples are included in the analysis. The mean scores and standard deviations (SD) of KOLT, DST, and COWAT were 35 (SD: 8.1), 10 (SD: 4.2) and 15 (SD: 5.5), respectively. KOLT, DST, and COWAT were approximately normally distributed within the population (supplementary materials, Figure S2). Nineteen percent of the study participants went to college or university (Table 1). There were no major differences in the plasma concentrations of kynurenines between the subgroups completing cognitive testing and the HADS questionnaire.

3.2. Kynurenines and cognitive performance

KTR and neopterin were significantly inversely associated with cognitive performance measured by KOLT (memory) and COWAT (language) (Fig. 2), while no such associations were seen with DST (executive function) (Table 2). KTR showed the strongest association with cognitive performance (Table 2). Further, PLP was significantly associated with DST (β 0.069, p = 0.001), but did not act as a confounder.

3.3. Kynurenines and potential confounders

3.3.1. Depressive symptoms and antidepressant agents

TRP, KTR, the kynurenines, the KA/QA ratio and neopterin were not associated with depressive symptoms or antidepressant agents (Table 3). Thus, depression was not considered as a potential confounder for the relationship between kynurenines and cognition.

3.3.2. Non-steroidal anti-inflammatory drugs

Six percent of the participants reported use of NSAIDs (Table 1). NSAIDs showed an association with TRP, KYN and KTR (Table 3), but did not confound our results (Table 4).

3.3.3. C-reactive protein

CRP was associated with KYN, HK, HAA, QA, KTR, the KA/QA ratio and neopterin (Table 3). After adjusting the SUR model for CRP, it did not act as a confounder (Table 4).

4. Discussion

We studied cognition in relation to neopterin, tryptophan, and the kynurenines in a community sample of older adults and found that elevated levels of both KTR and neopterin were associated with lower performance in the cognitive domains of memory and language. KTR showed the strongest association.

Our study included 2174 persons (55.2% women) aged 70–72 years recruited from a population of home-dwelling older adults. In comparison, other studies that have investigated the relationship between the kynurenines, neopterin and cognitive function, have been based on small patient groups with specific diseases. Higher levels of neopterin and kynurenines were related to lower cognitive performance post-

Table 2
Cognitive performance and individual metabolites (N = 2174).[a]

	KOLT Memory			COWAT Language			DST Executive function			Wald test[d]	
Association of each metabolite with three cognitive tests											
	β	SE	p	β	SE	p	β	SE	p	X^2	p[c]
TRP	0.047	0.022	0.03	0.043	0.022	0.05	0.050	0.021	0.02	9.2	0.027
KYN[b]	-0.021	0.024	0.4	-0.030	0.024	0.2	0.026	0.023	0.3	4.6	0.2
KYN2[b]	-0.061	0.021	0.003	-0.021	0.020	0.3	-0.044	0.020	0.03	11.3	0.01*
KA	0.022	0.026	0.4	-0.011	0.025	0.7	0.034	0.024	0.2	3.1	0.38
AA	0.003	0.022	0.9	0.014	0.021	0.5	0.003	0.021	0.9	0.42	0.94
XA	0.049	0.023	0.03	0.024	0.023	0.3	0.047	0.022	0.03	7.3	0.06
HK	-0.002	0.242	0.9	-0.009	0.024	0.7	0.026	0.023	0.3	1.8	0.6
HAA	0.032	0.023	0.2	0.013	0.023	0.6	0.043	0.022	0.05	4.7	0.2
PIC	0.031	0.022	0.2	0.005	0.021	0.2	0.005	0.021	0.8	2.0	0.6
QA	-0.007	0.024	0.8	-0.050	0.024	0.04	0.034	0.023	0.1	9.0	0.03
KTR	-0.084	0.024	0.001	-0.077	0.024	0.001	-0.032	0.023	0.16	17.7	< 0.001*
Neopt	-0.074	0.023	0.001	-0.056	0.022	0.01	-0.007	0.022	0.8	14.6	0.002*
KA/QA	0.022	0.021	0.3	0.028	0.021	0.2	-0.003	0.021	0.9	2.8	0.43
Association between KTR and three cognitive tests, with covariates											
	β	SE	p	β	SE	p	β	SE	p	X^2	p
Age											
71	-0.024	0.050	0.6	0.072	0.049	0.1	-0.040	0.048	0.4	4.3	0.2
72	-0.050	0.050	0.3	0.072	0.049	0.1	-0.062	0.048	0.2	6.8	0.1
Female	0.408	0.044	< 0.001	0.072	0.043	0.1	0.085	0.042	0.05	85.6	< 0.001
GFR	-0.061	0.024	0.01	-0.067	0.024	0.005	-0.033	0.023	0.2	11.5	0.01
Edu	0.150	0.022	< 0.001	0.340	0.022	< 0.001	0.402	0.021	< 0.001	486.7	< 0.001
Smoke	-0.021	0.050	0.7	-0.016	0.049	0.8	-0.061	0.048	0.2	1.8	0.6
Dia	-0.103	0.086	0.2	-0.206	0.084	0.01	-0.090	0.082	0.3	6.8	0.08
BMI	-0.001	0.006	0.8	-0.005	0.005	0.4	0.001	0.005	0.8	0.92	0.8
HT	-0.045	0.046	0.3	-0.014	0.045	0.8	-0.049	0.044	0.3	1.5	0.7
MI	-0.123	0.069	0.07	-0.051	0.067	0.4	-0.022	0.066	0.7	3.4	0.3
Stroke	-0.246	0.098	0.01	-0.208	0.097	0.03	-0.091	0.095	0.3	8.7	0.03
PLP	-0.003	0.022	0.9	0.032	0.021	0.1	0.069	0.021	0.001	13.1	0.005
KTR	-0.084	0.024	0.001	-0.077	0.024	0.001	-0.032	0.023	0.16	17.7	< 0.001*

[a] Zellner's seemingly unrelated regression, estimated for each metabolite with age, BMI, dia, edu, GFR, MI, sex, smoking, hypertension, MI, stroke and PLP as covariates.
[b] The association between KOLT and KYN was non-linear. A second degree orthogonal polynomial gave a good fit.
[c] The significance threshold for 12 tests is 0.0042, according to the Bonferroni method, indicated by *.
[d] Test of the joint significance of the association between each metabolite and three cognitive outcomes. AA, anthranilic acid; BMI, body mass index; COWAT, Controlled Oral Word Association Test; Dia, diabetes; DST, Digit Symbol Test; Edu, education; GFR, glomerular filtration rate; HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; HT, hypertension; KA, kynurenic acid; KA/QA, kynurenic acid-quinolinic acid ratio; KOLT, Kendrick Object Learning Test; KYN, kynurenine; KYN2, 2nd degree orthogonal polynomial of KYN; KTR, kynurenine-tryptophan ratio; MI, previous myocardial infarction; Neopt, neopterin; p, p-value; PIC, picolinic acid; PLP, pyridoxal 5′phosphate; QA, quinolinic acid; SE, standard error; Smoker, current smoking; Stroke, prior stroke; TRP, tryptophan; X^2, chi-squared; XA, xanthurenic acid; β, standardized regression coefficient.

operatively amongst patients who had undergone cardiac bypass surgery (N = 28, mean age of 60.2 years, 11% women), and major non-cardiac thoracic surgery (N = 28, mean age of 67.6 years, 32% women) (Forrest et al., 2011). Additionally, a study of patients with stage IV renal failure (N = 27, mean age of 76.4 years, 33% women), suggested that rising levels of neopterin and KYN were associated with lower cognitive performance (Karu et al., 2016). Further, neopterin was associated with progression of cognitive deficits in patients with Alzheimer's disease (Blasko et al., 2007; Leblhuber et al., 1999). Previous studies have shown that acute TRP depletion may impair episodic memory, and suggest a role of the serotonergic system in cognitive function (Mendelsohn et al., 2009). Our results support that the kynurenine pathway may be relevant for cognitive function.

There is evidence of an association between peripheral pro-inflammatory mediators, such as tumor necrosis factor-α, Il-6, and CRP, and reduced cognitive performance in healthy humans (Economos et al., 2013; Schram et al., 2007; Teunissen et al., 2003; Wichmann et al., 2014; Yaffe et al., 2003). Therefore, the kynurenines could rather be indirect markers of their underlying activators, which are mainly related to inflammation. We did not identify confounding from CRP in our data, but a more comprehensive assessment of inflammation would have been informative.

In this study, nine percent of the participants had depressive symptoms (HADS score > = 8), but we found no association with TRP or kynurenine levels. Although an association between kynurenines and major depression has been described, our study is not comparable and does not generalize to major depressive disorder. First, HADS is not a diagnostic test of depression (Cosco et al., 2012; Myint et al., 2007). Second, patients with major depression are less likely to participate as study volunteers (Hughes-Morley et al., 2015). Finally, participants with depressive symptoms and patients using antidepressants likely represent a heterogeneous group, as antidepressant agents have broad indications, for example for treating anxiety and sleeping disturbances in the elderly (Noordam et al., 2015). Here, depressive symptoms were mainly of interest as potential confounders.

PLP, the active form of vitamin B6, was associated with DST but did not act as a confounder in our study. Our findings are in line with studies indicating both a detrimental effect on cognition from PLP deficiency. Vitamin B6 is actively transported over the BBB and is a rate-limiting cofactor in the synthesis of neurotransmitters such as dopamine and serotonin (Kennedy, 2016). Circulating PLP levels are lower in individuals with inflammation compared to healthy subjects (Ueland et al., 2017), and has been proposed to contribute to cognitive decline (Kennedy, 2016). Intervention studies administering vitamin B6

Table 3
Evaluating potential confounders. Association with exposure [a].

	Depressive symptoms [b]		Anti-depressants [b]		NSAIDs [b]		C-reactive protein [c]	
	OR	p	OR	p	OR	p	β	p
TRP	1.01	0.9	0.91	0.4	0.65	< 0.001	-0.02	0.3
KYN	0.94	0.5	1.16	0.3	0.74	0.003	0.19	< 0.001
KA	0.88	0.2	0.89	0.4	0.96	0.7	0.04	0.2
AA	0.89	0.2	0.98	0.9	1.2	0.1	0.06	0.003
XA	0.93	0.4	0.80	0.1	0.93	0.4	-0.04	0.05
HK	1.10	0.3	1.06	0.7	1.00	0.9	0.17	< 0.001
HAA	0.97	0.7	1.11	0.4	0.93	0.5	0.15	< 0.001
PIC	0.98	0.8	0.87	0.2	1.02	0.9	-0.02	0.3
QA	0.98	0.8	1.07	0.6	1.02	0.82	0.24	< 0.001
KTR	0.94	0.5	1.27	0.1	1.29	0.01	1.21	< 0.001
Neopt	1.09	0.3	1.20	0.1	1.03	0.74	0.18	< 0.001
KA/QA	0.94	0.4	0.88	0.3	0.95	0.6	-0.15	< 0.001

Note. 252/2869 had depressive symptoms, 141/3319 used anti-depressants, and 196/3319 used NSAIDs.
[a] All models adjusted for age, body mass index, current smoking, diabetes, educational level, glomerular filtration rate, hypertension, previous myocardial infarction, prior stroke, pyridoxal 5′ phosphate and sex.
[b] Logistic regression.
[c] Linear regression. AA, anthranilic acid; HAA, hydroxyanthranilic acid; HK, hydroxykynurenine; KA, kynurenic acid; KA/QA, kynurenic acid-quinonilic acid ratio; KTR, kynurenine-tryptophan ratio; KYN, kynurenine; Neopt, neopterin; OR, odds ratio; p, p-value; PIC, picolinic acid; QA, quinonilic acid; TRP, tryptophan; X^2, chi-squared; XA, xanthurenic acid; β, standardized regression coefficient.

Table 4
Cognitive performance and individual metabolites. Adjusted models (N = 2174).[a]

	KOLT Memory			COWAT Language			DST Executive function			Wald test[b]	
Model 1: Unadjusted model											
	β	SE	p	β	SE	p	β	SE	p	X^2	p
KTR	-0.084	0.024	0.001	-0.077	0.024	0.001	-0.032	0.023	0.2	17.7	< 0.001
Neopt	-0.074	0.023	0.001	-0.056	0.022	0.01	-0.007	0.022	0.8	14.6	0.002
Model 2: Adjustment for C-reactive protein											
KTR	-0.078	0.025	0.002	-0.081	0.025	0.001	-0.040	0.024	0.1	16.1	0.001
Neopt	-0.071	0.024	0.003	-0.052	0.023	0.02	-0.011	0.022	0.6	11.7	0.008
Model 3: Adjustment for non-steroidal anti-inflammatory drugs											
KTR	-0.082	0.024	0.001	-0.079	0.024	0.001	-0.032	0.023	0.2	17.8	< 0.001
Neopt	-0.074	0.022	0.001	-0.055	0.022	0.01	-0.007	0.022	0.7	14.5	0.002

Note. 196 out of 3319 participants used non-steroidal anti-inflammatory drugs.
[a] Zellner's seemingly unrelated regression, estimated for each metabolite with age, sex, body mass index, educational level, glomerular filtration rate, current smoking, diabetes, hypertension, previous myocardial infarction, prior stroke, pyridoxal 5′ phosphate as covariates and either CRP (Model 2) or NSAIDs (Model 3).
[b] Test of the joint significance of association between each metabolite and all three cognitive outcomes. Neopt, neopterin; KTR, kynurenine-tryptophan ratio; p, p-value; SE, standard error; X^2, chi-squared; β, standardized regression coefficient.

supplementation for age-related memory decline has shown some encouraging trends (Deijen et al., 1992). However, given the involvement of PLP in a wide range of biological processes, it remains to be determined if PLP plays an active role in cognitive performance.

Our rationale for using the KTR was that it provides a better measure of IDO activity than the individual metabolites, particularly when KTR correlates with inflammatory markers, such as neopterin (Schrocksnadel et al., 2006). The rate-limiting enzymes in kynurenine and neopterin biosynthesis, IDO and GTP-CH respectively, are both induced by IFN-γ. The absence of IFN-γ is associated with improvements in neurogenesis, synaptic plasticity, and performance in hippocampus-dependent tasks in mice (Monteiro et al., 2016). Experimental studies have implicated IDO in inflammation-associated cognitive dysfunction (Chen and Guillemin, 2009; Comim et al., 2017; Heisler and O'Connor, 2015; Yu et al., 2015).

Experimental studies support a neuroexcitatory role of QA in the brain, and a neuroprotective role of KA. The hippocampus has been reported to be particularly susceptible to the neurotoxic effects of QA (Schwarcz and Kohler, 1983). KA, on the other hand, is considered neuroprotective (Leib et al., 1996). We did not find evidence to support that the ratio between these metabolites (KA/QA) in peripheral blood was related to cognitive function. However, QA and KA cross the BBB poorly (Fukui et al., 1991), and therefore measurement in the cerebrospinal fluid will be needed to settle this issue.

An important question in studies such as ours is to what extent, if any, peripheral inflammation relates to neuroinflammation. Blood-borne cytokines can enter the brain by transport systems at the BBB (Varatharaj and Galea, 2017) and immune cells enter the brain under physiological conditions, though at a much lower rate than in other organs (Takeshita and Ransohoff, 2012). TRP and KYN are themselves transported to the brain and are precursors of both brain serotonin (Young and Leyton, 2002) and kynurenines (Chen and Guillemin, 2009). In microglia, KYN is a precursor for QA, which could activate the N-methyl-D-aspartate receptor (NMDAR) (Ganong and Cotman, 1986). Thus, high plasma KTR may be related to cognitive function as a marker of inflammation, serotonin depletion and NMDAR activation in the brain, but this must be investigated in future studies.

Strengths of this study include a large sample size of 2174 persons, a

relatively high response rate among the participants, and similar age of the participants (70–72 years), which limits the impact of age itself on metabolites and cognition. The main limitations are the constraints of cross-sectional studies. This involves difficulties in ascertaining the direction of associations between predictors and outcomes and the potential for unmeasured confounders. Cognitive domains are not mutually exclusive, which can make interpretation challenging (Malek-Ahmadi et al., 2011). Further, non-fasting blood samples is a limitation, and measurements of the kynurenines in the cerebrospinal fluid would have been informative. Longitudinal studies are needed to further delineate these associations.

In summary, we found that KTR and neopterin, biomarkers of cellular immune activation, were associated with a lower cognitive function in the domains of memory and language in a sample of community-dwelling older adults. The findings add support for a role of the innate immune system in cognitive function.

Acknowledgements

We wish to thank all the study participants, staff and researchers in HUSK. The study was funded by the Norwegian Health Association, Dementia Research Program (contract number: 7349). We are grateful for their support and their continuous work for patients, caregivers, and scientists. The funding source had no role in the study design, data gathering or interpretation of the results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2018.10.003.

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