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RESEARCH ARTICLE

Kynurenine pathway metabolite alterations in Down syndrome and Alzheimer's disease

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Abstract

INTRODUCTION: Down syndrome (DS) is a genetic disorder that leads to intellectual disability and accelerated aging, increasing the risk of Alzheimer's disease (AD). The pathophysiology of AD and DS is multifactorial, involving amyloid precursor protein overexpression, neuroinflammation, and oxidative stress. This study investigates kynurenine pathway metabolites in elderly individuals with DS (with/without cognitive decline), AD, and cognitively healthy controls to clarify their roles in these pathogeneses.

METHODS: A cross-sectional study was conducted involving DS, AD, and healthy participants. Plasma levels of tryptophan, kynurenine, 3-hydroxykynurenine, anthranilic acid, 3-hydroxyanthranilic acid, and quinolinic acid were analyzed by Liquid Chromatography coupled with Tandem Mass spectrometry (LC-MS/MS) methodology.

RESULTS: Elevated kynurenine and other neuroprotective metabolites were found in DS individuals without cognitive decline, while significant differences in neurotoxic metabolites were observed between groups.

DISCUSSION: Our findings suggest a link between kynurenine pathway dysregulation and cognitive decline, indicating alterations in DS and AD.

KEYWORDS
Alzheimer's disease, cognitive decline, Down syndrome, kynurenine pathway, plasma biomarkers

Highlights

- There are altered kynurenine pathway metabolites in Down syndrome and Alzheimer's disease.
- Elevated neuroprotective metabolites are found in Down syndrome without cognitive decline.
- Significant differences in neurotoxic metabolites among study groups were analyzed.

- There is a potential link between kynurenine pathway dysregulation and cognitive decline.
- The study provides insights into metabolic changes in aging and neurodegeneration.

1 | BACKGROUND

Down syndrome (DS), also known as trisomy 21 (T21), is a human genetic disorder caused by an extra copy of chromosome 21. This chromosome, also referred to as HSA21, is responsible for encoding more than 215 proteins and at least 187 noncoding RNAs.[1] Because most of these genes have not yet been thoroughly characterized, it is not possible to fully establish all the alterations that they may cause.[2,3]

DS is not only associated with intellectual disability but also with a group of clinical manifestations of "accelerated aging,"[4] such as Alzheimer's disease (AD), for example. It is well known that the gene responsible for encoding amyloid precursor protein (APP) is located on chromosome 21. The triplication of chromosome 21 can lead to an increase in *APP* expression and a subsequent rise in amyloid beta (Aβ) deposition.[5,6] However, the complex pathophysiology of AD in DS extends beyond Aβ accumulation.

Neuroinflammation, oxidative stress, and mitochondrial dysfunction are recognized as key factors in neurodegeneration.[6] Recently, the kynurenine (KYN) pathway has been identified as a pivotal contributor to both neuroinflammation and neurodegeneration in a range of neurological disorders.[6] This pathway generates a range of neuroactive metabolites; some of have neuroprotective properties (e.g., kynurenic acid [KYNA]), whereas others possess neurotoxic properties, for example, quinolinic acid (QUIN).[7,8] An imbalance in these metabolites may significantly impact disease progression.

Tryptophan (TRP), an essential amino acid that cannot be synthesized by the human body, is required for protein synthesis and serves as a precursor to serotonin and melatonin. However, the primary metabolic pathway of TRP is the KYN pathway, particularly under inflammatory conditions. In this pathway, TRP is metabolized by the enzyme tryptophan-2,3-dioxygenase (TDO) in the liver or by indoleamine-2,3-dioxygenase (IDO) in the brain, resulting in the synthesis of KYN, which is subsequently catabolized to KYNA by the enzyme kynurenine aminotransferase or to nicotinamide adenine dinucleotide by kynurenine 3-monooxygenase.[7]

Alternatively, KYN can be metabolized to anthranilic acid (AA) and 3-hydroxykynurenine (3-HK) by the enzymes kynureninase and kynurenine-3-monooxygenase, respectively. These organic compounds can then be metabolized to 3-hydroxyanthranilic acid (3-HAA), which is eventually converted to aminocarboxymuconic hemialdehyde (ACMA). ACMA is subsequently converted to QUIN, a neurotoxin. Alternatively, ACMA, with the enzyme 2-amino-3-carboxymuconate-semialdehyde decarboxylase, can generate picolinic acid, a neuroprotective metabolite.[7–9]

It is noteworthy that the end products of TRP catabolism are known to influence the mechanisms of aging, a neurodegenerative condition. The role of KYNA, as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and QUIN, as an NMDA receptor agonist, can be highlighted. The KYN pathway is also one of the largest sources of nicotinamide adenine dinucleotide, an important cofactor for cellular respiration, ATP synthesis, DNA repair, and regulation of gene transcription.[7,10,11] In fact, early mitochondrial dysfunction has been observed at the embryonic stages of DS.[12,13]

In addition to the *APP* gene, there is growing evidence that two other genes located on chromosome 21, interferon alpha and beta receptor subunits 1 and 2 (*IFNAR1* and *IFNAR2*), play an important role in the pathogenesis of DS. These genes encode the two subunits of the receptor for type I interferons (IFN-I), a group of potent antiviral and pro-inflammatory cytokines. In AD, IFN-I can promote toxic consequences, such as synapse loss and microglial activation, in addition to inflammation. In these inflammatory states, increased IDO activity leads to a decrease in the synthesis of serotonin and melatonin, which can trigger neuropsychiatric disorders. Furthermore, depletion of TRP leads to a reduction in protein synthesis and promotes tissue atrophy.[14]

Because AD and DS share several common features, and inflammation is present in both conditions, the objective of this study was to examine the behavior of different metabolites in the KYN pathway, specifically TRP, KYN, 3-HK, AA, 3-HAA, and QUIN. To this end, we examined these metabolites in plasma samples from elderly individuals with DS, both with and without cognitive decline, individuals with established AD, and a cognitively healthy (CH) group.

2 | METHODS

2.1 | Study design and participants

We conducted a cross-sectional study, consisting of 31 participants with DS, 21 with AD, defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-V) and 26 CHe individuals. All participants were recruited from the Aging and Down Syndrome Outpatient Clinic of the Laboratory of Neuroscience (LIM-27; Faculdade de Medicina, Universidade de São Paulo [FMUSP], Brazil). Written informed consent was obtained from the participants or their legally authorized representatives.

The study was approved by the Research Ethics Committee of FMUSP (REC; no. 66092117.0.1001.0068) and adhered to the ethical standards for medical research in humans as outlined in the Declaration of Helsinki.

RESEARCH IN CONTEXT

1. **Systematic review**: Many of the degenerative changes observed in individuals with Down syndrome have been associated with the amyloidogenesis process and free radicals, and more recently with the dysfunctional kynurenine pathway.
2. **Interpretation**: Our findings show elevated concentrations of neurotoxic metabolites of the kynurenine pathway in Down syndrome participants with cognitive decline similar to the dementia process of Alzheimer's disease, but not in Down syndrome without cognitive decline.
3. **Future directions**: Because there is a relationship between metabolites in the kynurenine pathway and the progression of AD and DS, more studies using plasma and cerebrospinal fluid are necessary for confirmation of these metabolites as potential biomarkers for these diseases.

2.2 | Clinical and cognitive assessment

Participants were clinically examined by a geriatric psychiatrist, a neurologist, and a geriatrician, and were assessed according to DSM-V, which was used as the reference for diagnosing mental health conditions. All DS participants had trisomy 21 (or T21) confirmed by karyotype.

The clinical variables were assessed using the Brazilian version of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) interview.[15,16] The CAMDEX schedule includes the Cambridge Cognitive Test (CAMCOG), a brief cognitive assessment battery that evaluates several neuropsychological domains, namely: memory (recent/remote recall; learning ability), orientation, language (comprehension; expression), attention, calculation, praxis, abstract thinking, and perception. An adapted version for participants with DS was also used (CAMCOG-DS).[17]

The cognitive diagnosis was stratified into: (1) no cognitive decline and (2) with cognitive decline. Therefore, the groups were categorized as follows: (1) CH individuals (young, CHy; elderly, CHe), (2) DS no cognitive decline (DSnCD), (3) DS with cognitive decline (DSwCD), and (4) AD. Demographic variables and clinical characteristics are presented in Table 1.

2.3 | Blood sample collection

Peripheral blood samples were collected from all participants in the fasting state (8–12 h of fasting) using sterile needles with adapters designed for vacuum blood collection tubes containing ethylenediaminetetraacetic acid (EDTA), through venipuncture. Plasma was separated by centrifugation at 1.500 × *g* for 15 min at 4°C and stored in aliquots at −80°C until analysis.

2.4 | Analysis of kynurenine pathway metabolites

The extraction method was based on the principle of protein precipitation: the sample was combined with deionized water containing 2% formic acid and a deuterated internal standard d4-KYN (PI). Chilled methanol (protein precipitation solution) was then added, the samples were vortexed, and subsequently centrifuged at 4°C for 10 min at 16.000 × *g*. The supernatant was collected and transferred to a new tube, and the solvent completely evaporated under vacuum. The pellet was then resuspended in the mobile phase, and 5 µL was injected into the Liquid Chromatography coupled with tandem Mass Spectrometry (LC-MS/MS)system (LC-MS/MS 8050, Shimadzu, Japan).

The chromatographic conditions used to separate, identify, and quantify the metabolites were as follows: mobile phase flow rate of 0.3 mL/min, column temperature at 30°C, mobile phase A consisting of 0.1% formic acid, and mobile phase B consisting of acetonitrile with 0.1% formic acid. The gradient program was as follows: 0–1 min at 5% B, 1–2 min at 20% B, 2–3 min at 30% B, 3.5 min at 40% B, 5–8 min at 80% B, and 10–15 min for column reconditioning. The total chromatographic run time was 15 min.

Using the Real-Time Analysis–Lab Solutions software (Shimadzu), the following analytical conditions were established: Electrospray Ionization (ESI) in positive multiple reaction monitoring (MRM) mode, capillary voltage of 4 kV, cone potential of 10 kV, desolvation temperature of 300°C, desolvation gas flow at 10 L/min, and cone gas flow at 10 L/min. The collision energy for each analyte was individually optimized to obtain both the qualifier and quantifier ions, ensuring a low signal-to-noise ratio and higher intensity. The analytical parameters for identifying each of the compounds are presented in Table 2.

For data integration and subsequent quantification, linear standard curves for each analyte were constructed (Figure S1). A deuterated internal standard was implemented to correct the retention time and verify the efficiency of our extraction method. In addition, we analyzed the matrix effect and the signal/noise of plasma. Quantification was obtained by calculating the ratio of the analyte and internal standard peak area. The calibration curve for TRP and KYN ranged from 50 to 1000 ng/mL, whereas for the other metabolites analyzed the range was 5 to 50 ng/mL.

2.5 | Statistical analysis

Statistical analysis were performed using SPSS v.22 (Chicago, IL, USA). Normality was assessed using the Shapiro–Wilk test, and parametric or nonparametric tests were applied accordingly. Categorical variables were analyzed using Pearson's chi-square test, whereas numerical variables were analyzed using one-way analysis of variance (ANOVA) or Kruskal–Wallis tests, followed by the Steel–Dwass–Critchlow–Fligner post hoc test, as appropriate. The level of significance was set at $p \leq .05$.

TABLE 1 Demographic variables and clinical characteristics.

	CHe $n = 26$	DSnCD $n = 22$	DSwCD $n = 9$	AD $n = 21$	p-value
Age (Years)	66.92 ± 8.09	35.45 ± 10.25	41.89 ± 12.26	73.95 ± 8.82	0.001[a]
Sex (M/F)	10/16	14/8	4/5	6/15	0.207[b]
Camcog	89.65 ± 7.70	55.96 ± 22.02[c]	30.61 ± 17.98[c]	52.80 ± 20.36	< 0.001[a]

Note: The data were shown as mean ± standard deviation (SD) and median.
Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; CAMCOG, Cambridge Cognitive Assessment. ;CHe, cognitively healthy elderly; DSnCD, Down syndrome no cognitive decline; DSwCD, Down syndrome with cognitive decline; F, female; M, male.
[a]One-way ANOVA.
[b]Pearson's chi-square test.
[c]CAMCOG-DS.

TABLE 2 Parameters of analysis conditions for mass spectrometry.

Metabolite	Precursorion (*m/z*)	Production (*m/z*)	Time (min)	Collision energy
TRP	204.95	188.10 146.10	3.0–3.5	−11 −18
KYN	208.90	192.20 146.10	2.5–3.0	−11 −18
3-HK	225.00	162.10 208.10	1.0–1.5	−9 −20
AA	138.25	120.20 64.95	3.9–4.0	−20 −43
3-HAA	153.95	136.10 108.05	2.9–3.3	−15 −26
QUIN	167.95	150.00 94.05	1.0–1.5	−14 −26

Abbreviations: 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hidroxikinurenine; AA, anthranilic acid; KYN, kynurenine; *m/z*, mass-to-charge ratio.; QUIN, quinolinic acid; TRP, tryptophan.

3 | RESULTS

In this study, the CHe group was selected as the control group, based on the metabolite profiles observed in both the CHy and CHe groups, as presented in Tables S1 and S2. Table 3 and Figure 1 demonstrate the results of the KYN pathway among the CHe, DSnCD, DSwCD, and AD groups.

Upon analyzing the metabolites of the KYN pathway in the comparison between the CHe and DSnCD groups, the Kruskal–Wallis test followed by the Steel–Dwass–Critchlow–Fligner post hoc test revealed that the concentrations of TRP, AA, 3-HAA, and QUIN were similar between the two groups ($p \geq 0.05$). KYN and 3-HK levels were significantly elevated in the DSnCD group compared to the CHe group ($p = 0.002$ and $p < 0.001$, respectively), indicating a notable alteration in the KYN pathway metabolites in individuals with DS, which may reflect underlying biochemical changes specific to this population.

The Kruskal–Wallis test, followed by the Steel–Dwass–Critchlow–Fligner post hoc test, revealed a significant reduction in the levels of neuroprotective metabolites—specifically TRP, 3-HK, and AA—in the DSwCD group compared to the DSnCD group, with p-values of $p < 0.001$, $p < 0.001$, and $p = 0.026$, respectively. This observed decrease in neuroprotective metabolites within the DSwCD group mirrors the pattern seen in the AD group, where similar reductions in TRP ($p < 0.001$) and KYN ($p < 0.001$) were detected. However, although a decrease in AA was also observed in the AD group, this did not reach statistical significance ($p = 0.074$), suggesting a potential difference in the regulation or modulation of neuroprotective pathways between these two groups.

Regarding neurotoxic metabolites, our analysis revealed a marked increase in the levels of 3-HAA, specifically in the AD group compared to the CHe ($p < 0.001$), DSnCD ($p < 0.001$), and DSwCD ($p < 0.001$) groups. This suggests that 3-HAA may play a prominent role in the neurotoxic process associated with AD.

Conversely, QUIN, another well-known neurotoxic metabolite, was significantly decreased in both the DSwCD and AD groups when compared to the CHe group, with p-values of $p < 0.001$ and $p = 0.026$, respectively. Furthermore, when comparing the DSwCD group to the DSnCD group, we observed a further significant reduction in QUIN levels ($p = 0.001$), suggesting a progressive modulation of this neurotoxic metabolite as the disease severity increases.

4 | DISCUSSION

The primary objective of this study was to investigate potential differences in the metabolic profile of the KYN pathway in four distinct groups: individuals with DS, subdivided into those with cognitive decline and those without; individuals diagnosed with AD; and CHe.

AD is the most prevalent form of dementia, and DS is the primary genetic risk factor for early-onset AD. Individuals with DS often exhibit the hallmark neurodegenerative features associated with AD at a much earlier age. This accelerated onset of AD in DS is attributed predominantly to the trisomy of chromosome 21. Recent studies have indicated that alterations in chromosomal structure resulting from the additional copy of chromosome 21, in conjunction with epigenetic modifications, may lead to changes in gene expression that extend beyond those associated with chromosome 21 itself. As a result, several other significant pathophysiological changes are shared by both conditions, including chronic low-grade inflammation, mitochondrial dysfunction, impaired autophagy, lysosomal dysfunction, and oxidative stress.[18]

TABLE 3 Kynurenine pathway metabolite levels.

Metabolite	CHe *n* = 26	DSnCD *n* = 22	DSwCD *n* = 9	AD *n* = 21	*p-value*
TRP	51,640 ± 21,110	56,840 ± 23,290	27,100 ± 10,930	29,760 ± 20,510	< 0.001
KYN	643.50 ± 375.90	837.30 ± 316.90	769.40 ± 621.90	424.10 ± 297.80	< 0.001
3-HK	6.89 ± 3.40	8.58 ± 1.98	6.45 ± 1.25	5.33 ± 1.38	< 0.001
AA	42,0300 ± 20,3200	39,5400 ± 11,4300	30,4600 ± 46,610	33,7200 ± 18,0200	
3-HAA	7.29 ± 1.31	6.84 ± 0.175	6.63 ± 0.03	7.59 ± 1.04	< 0.001
QUIN	11.71 ± 5.95	9.30 ± 1.60	7.96 ± 0.57	9.17 ± 1.66	< 0.001

Note: Metabolite levels are in ng/mL. The data were shown as mean ± SD. For all analyses, the Kruskal–Wallis test was applied.
Abbreviations: 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hidroxikinurenine; AA, anthranilic acid; AD, Alzheimer's disease; CHe, cognitively healthy elderly; DSnCD, Down syndrome no cognitive decline; DSwCD, Down syndrome with cognitive decline; KYN, kynurenine; QUIN, quinolinic acid; TRP, tryptophan.

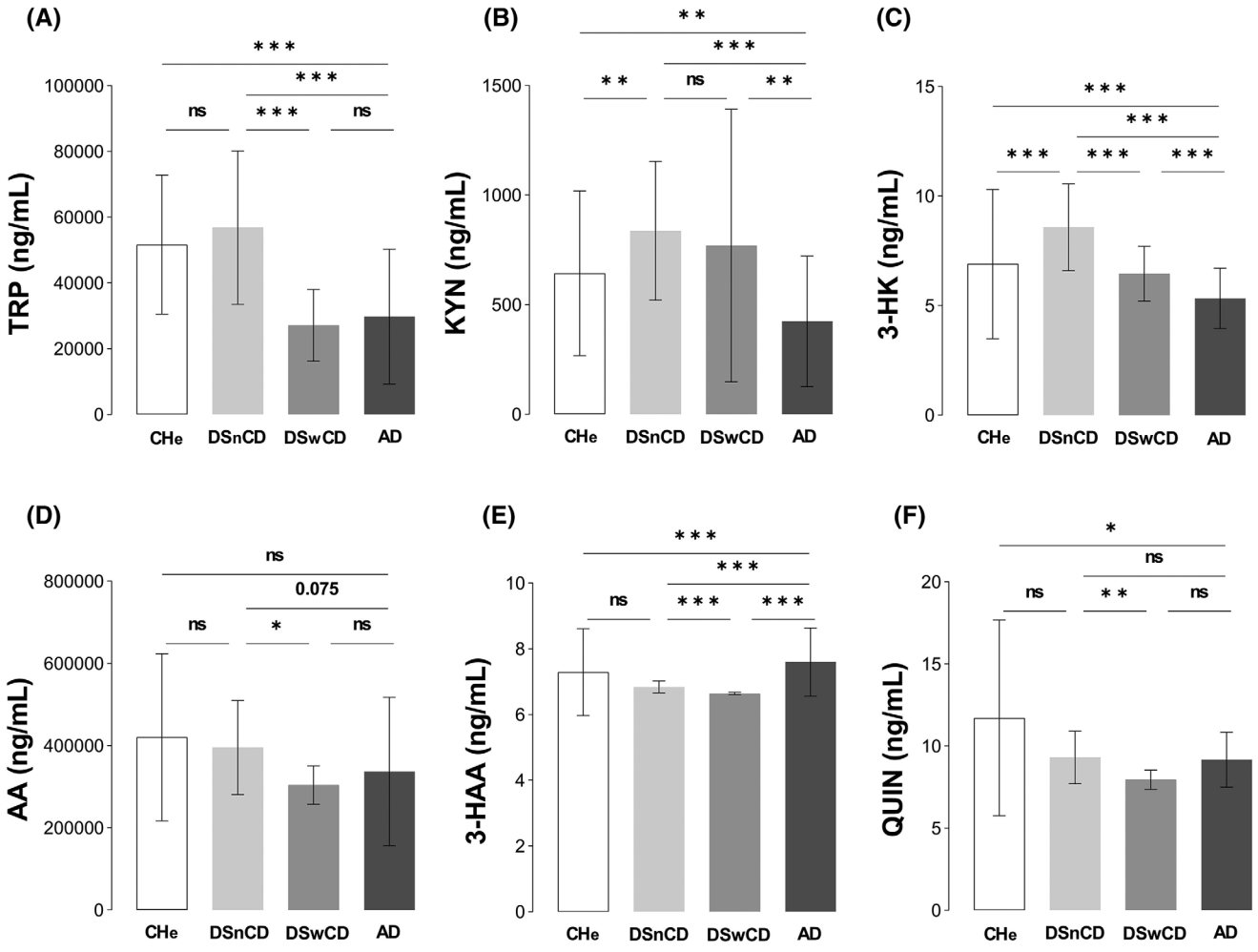

FIGURE 1 Plasma metabolites of the kynurenine pathway. Metabolite levels are in ng/mL. The data were shown as mean ± SD. For all analyses, the Kruskal–Wallis test was applied. Nonsignificant $p > .05$; $^{*}p \leq .05$; $^{**}p \leq .01$; $^{***}p \leq .001$. 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hidroxikinurenine; AA, anthranilic acid; AD, Alzheimer's disease; CHe, cognitively healthy elderly; DSnCD, Down syndrome no cognitive decline; DSwCD, Down syndrome with cognitive decline; KYN, kynurenine; QUIN, quinolinic acid; TRP, tryptophan.

Notably, both inflammatory mediators and oxidative damage have been shown to stimulate the expression of the enzyme IDO, which plays a pivotal role in the catabolism of TRP into kynurenine KYN. The activation of the KYN pathway results in the generation of several bioactive metabolites. Among these, KYN and its downstream metabolite, KYNA, have been shown to activate the aryl hydrocarbon receptor (AhR), a key transcription factor involved in regulating both innate and adaptive immune responses. This activation of AhR contributes to the establishment of an immunosuppressive environment within the context of inflammation.[14]

We observed elevated levels of TRP, KYN, and their neuroprotective metabolites exclusively in individuals with DS who exhibited no cognitive impairment (DSnCD), which supports previous studies that highlight the activation of IDO and consequently, the KYN pathway.[14] Conversely, our findings revealed no significant differences in the neurotoxic metabolites, specifically 3-HAA and QUIN, when compared to controls in individuals with DSnCD. In contrast, Powers et al. (2019) reported increased levels of QUIN in individuals with DS compared to euploid controls.[19] However, a critical bias must be considered a notable limitation of their study: they combined two cohorts of individuals with DS, with mean ages of 8.1 years (cohort 1) and 28.7 years (cohort 2), for comparative analyzes. Moreover, their euploid control groups consisted primarily of younger individuals—given the progeroid nature of DS,[2,20] which often leads to an accelerated aging process; our control group consisted of euploid elderly individuals (mean age 66.92 ± 8.09 years) as well as individuals diagnosed with AD. This comparison was essential to ensure that age-related factors that may influence the KYN pathway were appropriately controlled for. In this study, when we compared two healthy euploid control cohorts—one consisting of cognitively healthy young individuals (CHy; mean age = 29.94 ± 7.03) and the other of cognitively healthy elderly individuals (CHe; mean age = 66.92 ± 8.09)—we observed that age alone could activate the KYN pathway (Figure S2).

Upon examining the DSwCD group, we found an upregulation of metabolite levels compared to the control group, similar to the profile observed in the AD group, affecting both neuroprotective and neurotoxic metabolites. The discrepancy in the KYN pathway between the two DS subgroups may suggest that not all individuals with DS inevitably develop dementia, challenging assertions made by some authors.[21–23] In fact, certain studies have highlighted the notable heterogeneity in comorbidities associated with DS. Although it is established that every individual with trisomy 21 exhibits brain pathology related to that seen in AD (such as Aβ deposition and neurofibrillary tangles), it remains uncertain when, or if, these individuals will progress to a state of dementia. This interindividual variability may be attributed to modifier genes influencing the genetic background of DS individuals.[2]

A significant limitation in interpreting our results is the absence of data regarding the inflammatory profiles of the subjects. Given that chronic inflammation is prevalent in DS and that inflammatory cytokines can activate the KYN pathway,[24–27] it remains unclear whether the inflammatory profiles differ between groups with and without cognitive decline, and how these differences may uniquely influence the KYN pathway in these individuals. In addition, other physiological systems, such as the endocrine and hematopoietic systems, as well as intermediary metabolism of carbohydrates, lipids, and proteins, may also contribute to changes in the enzyme systems involved in the KYN pathway.[11] Finally, conducting additional studies with larger sample sizes would significantly improve the reliability of the findings, enabling more robust conclusions to be drawn and ensuring that the observed effects are applicable to a broader range of populations and settings.

In conclusion, our findings suggest that the KYN pathway is significantly altered in both DS and AD. Furthermore, to the best of our knowledge, this is the first study to investigate the KYN pathway in elderly individuals with DS, categorized according to their cognitive status.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Written Informed Consent was provided by all human subjects in accordance with the institutional review board-approved protocol. The data will be provided upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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