

Does Exercise Influence Kynurenine/Tryptophan Metabolism and Psychological Outcomes in Persons With Age-Related Diseases? A Systematic Review

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ABSTRACT

BACKGROUND: The kynurenine (KYN) pathway has been implicated in many diseases associated with inflammation and aging (“inflammaging”). Targeting the kynurenine pathway to modify disease outcomes has been trialled pharmacologically, but the evidence of non-pharmacological means (ie, exercise) remains unclear.

OBJECTIVE: We aim to assess the evidence of the effects of exercise on the kynurenine pathway and psychological outcomes.

METHODS: Under Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, a systematic literature search was performed in MEDLINE, EMBASE, EMCARE, and the Cochrane Central Registry of Controlled Trials. The main outcomes were changes in kynurenine pathway metabolite levels and psychological outcomes.

RESULTS: Six studies were analyzed (total n=379) with exercise demonstrating significant concomitant effects on kynurenine pathway metabolite levels and associated psychological outcomes in domains of somatization, anxiety, and depression.

CONCLUSION: Exercise has significant concomitant effect on kynurenine pathway metabolite levels and psychological outcomes. However, clear limitations exist in determining if the changes in the kynurenine pathway can fully explain the changes in psychological outcomes, or whether different diseases and exercise interventions act as confounding factors.

KEYWORDS: Kynurenine, tryptophan, inflammation, aging, exercise, mental health, psychological outcomes, systematic review

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Introduction

Aging is a process that every human goes through; our population is indeed living longer, with the median lifespan generally increasing.^{1,2} Despite its universal nature, the exact mechanisms of aging remain incompletely understood. One leading explanation,³ however, explores the possibility that aging is associated with, or is a result of, continuous inflammatory insult throughout life. These inflammatory changes are associated with a number of diseases, including cardiovascular,⁴ neurological,^{5,6} and musculoskeletal diseases,⁷ and cancer.⁸ Interestingly, while these diseases are generally called “age-related,” it seems likely that inflammatory changes start early and the accumulation of changes leads to disease progression. Nonetheless, given that each of these diseases have been shown to be age-related,^{9–12} it is worth exploring possible mechanisms of this “inflammaging”¹³ process.

Inflammation is a highly complex process involving mediators^{14,15} with multiple effects on physiological and pathological processes. There are many pathways to explore that may be studied for potential therapeutic intervention.^{3,16} One pathway

of recent interest linked to both inflammation and aging¹³ is the kynurenine pathway of tryptophan degradation. The kynurenine pathway is involved in many physiological processes; well-known examples include tryptophan as the precursor for serotonin, an important neuroactive mediator,¹⁷ and the role of gut microbiota in tryptophan metabolism.¹⁸ It is becoming known that imbalances in tryptophan metabolism and the associated kynurenine pathway are involved in the process of aging and the progression of age-related diseases.¹⁹ The kynurenine pathway has been implicated in many age-related disease categories including cardiovascular (eg, coronary artery disease),²⁰ neurological (eg, Alzheimer’s disease, depression, schizophrenia),^{21–23} musculoskeletal (ie, osteoporosis),²⁴ and cancer.^{25,26}

There are various consequences of changes in the kynurenine pathway; for example, changes in serum levels of kynurenine, an intermediate metabolite of this pathway, have been shown to correlate with symptom severity in patients with Parkinson’s disease.²⁷ Some studies have even gone so far as to investigate individual metabolites, such as indoleamine



Table 1. Search strategy developed for database search using ovid interface.

#	SEARCHES	RESULTS	SEARCH TYPE
1	Kynurenine/	10769	Advanced
2	Exp tryptophan/or 5-hydroxytryptophan/	99866	Advanced
3	Exp ortho-Aminobenzoates/	34258	Advanced
4	Kynurenic Acid/	6582	Advanced
5	Exp Picolinic Acids/	4520	Advanced
6	Exp quinolinic acids/or quinolinic acid/	5536	Advanced
7	3-Hydroxyanthranilic Acid/	1131	Advanced
8	Indoleamine-Pyrrole 2,3,-Dioxygenase/	9968	Advanced
9	Kynurenine 3-Monooxygenase/	713	Advanced
10	Tryptophan Oxygenase/	4467	Advanced
11	(Kynurenine* or tryptophan* or 5-hydroxytryptophan* or anthranilic* or ortho-Aminobenzoates or "kynurenic acid*" or "picolinic acid*" or "quinolinic acid*" or 3-hydroxykynurenine* or "3-hydroxyanthranilic acid*" or "indoleamine 2,3-dioxygenase" or "ido" or "ido1" or "kmo" or "tdo").mp.	202516	Advanced
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	220912	Advanced
13	Exp Exercise/	738719	Advanced
14	(Exercis* or sports or physical activit* or walking or swimming or running or cycling or jogging).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2201371	Advanced
15	13 or 14	2216392	Advanced
16	12 and 15	3647	Advanced
17	16 and (((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial. ab. or groups.ab.) not (exp animals/ not humans.sh.))	360	Advanced

2,3-dioxygenase (IDO), and their relation to cancer-related fatigue.²⁸ Thus, there seems to be potential to target discrete elements of the pathway for therapeutic benefit in patients with age-related diseases, and there are many pharmacological treatments under current investigation to target the kynurenine pathway in different disease states.²⁵

In addition to pharmacological treatment, however, one must consider non-pharmacological interventions (ie, lifestyle) for disease. Of particular interest is exercise and its effect on the kynurenine pathway. As a lack of physical activity is increasingly common,²⁹ and linked to many chronic diseases associated with inflammaging,³⁰ exercise is an intervention worthy of consideration. However, exercise is an intervention that is highly variable in terms of frequency, intensity, time, and type.³¹ It is especially important to distinguish between acute and chronic exercise bouts when considering the effects of exercise on the kynurenine pathway. It is known that both acute and chronic exercise alters cellular immune function in general.^{32,33} However, 2 reviews^{34,35} have suggested acute exercise may produce different kynurenine pathway outcomes than chronic exercise. The potential mechanism for these inflammatory pathway changes may involve accumulation of changes due to repetitive bouts of acute exercise.³⁴ While

acute exercise does result in significant changes in cellular immunity (eg, white blood cell proportions), these changes tend to be temporary; in chronic exercise, however, these changes are not temporary,³² as there are likely long-term adaptations of the immune system in response to such continuous exercise.

Therefore, the aims of this review were to assess the evidence of the effects of exercise on the kynurenine pathway and psychological outcomes in age-related disease.

Methods

This review was registered at PROSPERO (University of York) with registration number CRD42020204035 and conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Search strategy

A systematic literature search was performed in MEDLINE, EMBASE, EMCARE, and the Cochrane Central Registry of Controlled Trials, from the first available date of the database to September 2020. The search strategy created and executed is shown in Table 1.

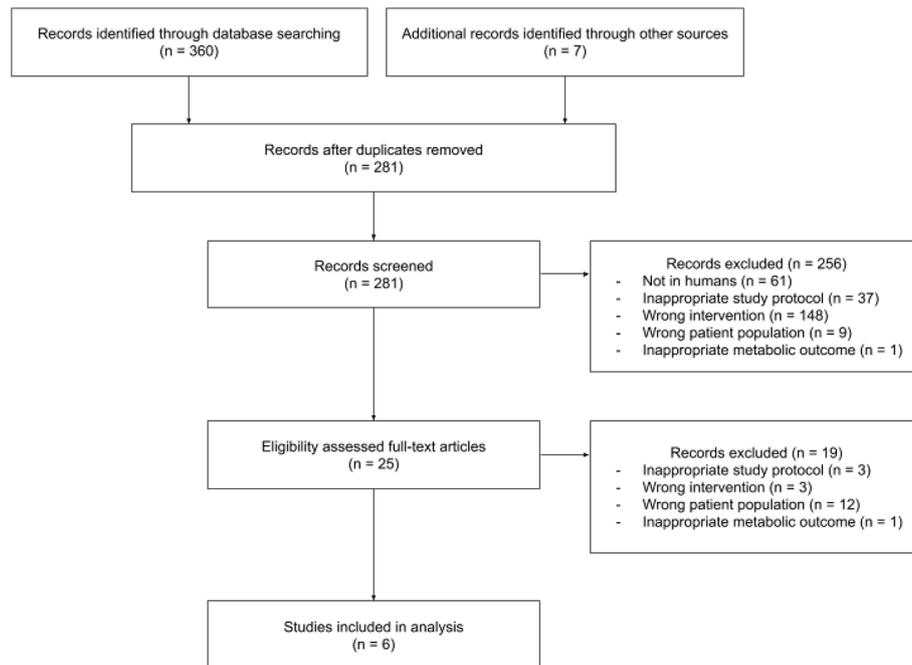


Figure 1. PRISMA flowchart.

Inclusion and exclusion criteria

COVIDENCE was used for reference importing, title and abstract screening, and full text review.

Inclusion criteria:

- Experimental trials or randomized controlled trials comparing exercise intervention with placebo/baseline exercise control in persons with known age-related disease.
- Age-related disease can include, but are not limited to, cardiovascular, neurological, or oncological disease.
- Exercise can include, but is not limited to, aerobic, resistance, mixed, high-intensity interval training, passive, certain forms/sports of exercise (running/jogging, swimming).
- Physiological/metabolic outcomes can include, but are not limited to, kynurenine pathway measures of activity (eg, kynurenine/tryptophan ratio), kynurenine pathway metabolites (eg, kynurenic acid), inflammatory markers (eg, IL-1, neopterin).
- If psychological outcomes are present, these can include, but are not limited to, quality of life, symptom burden/relief, mood.

Exclusion criteria:

- Reviews of primary studies.
- Non-human studies, which can include, but are not limited to, animals (eg, mice), cell culture lines, bacteria.
- Persons without current age-related disease or risk factors for age-related disease.
- Studies in which exercise was not compared against a valid control group, for example, both groups exercising,

but the intervention was actually a protein supplement versus placebo.

Studies were screened by 2 reviewers (AL, CH), and studies without consensus were given a final decision by a third reviewer (GD).

Data extraction

COVIDENCE and Google Sheets were used to compile study data and assess risk of bias in studies. Risk of bias was assessed using either Cochrane RoB 2.0³⁶ or ROBINS-I.³⁷ Bias was assessed in 2 rounds: first round separately by AL and CH, second round for consensus.

Results

Included studies

The search strategy identified 360 studies (see Figure 1). Bibliographic search outside the database search identified 7 studies. Eighty-six duplicates were removed.

Table 2 provides a summary of studies and their effects of intervention on the kynurenine pathway. Included disease pathologies included cardiovascular (diabetes), cancer (pancreatic, breast, gastroesophageal), neurological disease (stroke), psychiatric disease (major depressive disorder, dysthymia, somatization syndrome).

Risk of bias assessment

Herrstedt et al⁴¹ was at “critical” (ROBINS-I) risk of bias, owing to the use of an ill-described and unsupervised control group with no record-keeping of types of exercise in the control group,

Table 2. Included study characteristics.

STUDY	STUDY DESIGN	BLINDING	RISK OF BIAS	N	SAMPLE POPULATION, INCLUSION/ EXCLUSION CRITERIA	SAMPLE AGE	INTERVENTION ARMS	MEASUREMENT PROTOCOL	DURATION	OUTCOMES
Acute exercise studies										
Mudry et al. ³⁶	Non-randomized experimental study	Unknown	Moderate	24	Normal glucose tolerance (NGT) or type 2 diabetes Inclusion NGT or T2DM Exclusion Insulin treatment Blood pressure >160/95 Cardiovascular disease Smoking status Physical impairment	NGT: 59 ± 2 T2DM: 58 ± 2	1. NGT: Acute exercise bout on cycle ergometer—5 min warmup (50% power output at RER 1.0 as determined during VC2 max test), then 30 min continuous exercise (workload to reach 85% max heart rate) 2. T2DM: As above	Samples obtained: Plasma, muscle biopsies Timing "EXERCISE" time period: "Immediately" after exercise "RECOVERY" time period: After 3 hours of quiet rest in sitting position Sample storage Plasma: Stored at -40°C until analysis Muscle biopsies: Immediately frozen in liquid nitrogen	1 session (35 min)	mRNA: KAT1, KAT2, KAT3, KAT4, PGC1a1, PPARa, PPARd Serum concentration: TRP, Kynurenine, KYNA, neuroprotective ratio Group response to intervention, difference BETWEEN NGT and T2DM groups Significant: KAT1, KAT2, PPARa Non-significant: KAT3, KAT4, PGC1a1, PPARd, TRP, KYNA, Kynurenine, neuroprotective ratio Group response to intervention (vs pre-intervention), both NGT and T2DM groups Significant decrease: KAT4, TRP, Kynurenine Significant increase: PGC-1a1, KYNA, neuroprotective ratio Non-significant: KAT1, KAT2, PPARa, PPARd Covariates BMI: Positive correlation with Kynurenine
Chronic exercise studies										
Baek et al. ³⁹	Non-randomized experimental study	Unknown	Moderate	40	Post-stroke + MDD, dysthymia Inclusion MDD, dysthymia, DSM-IV diagnostic criteria MMSE ≥23 Walk 10 m unassisted ≥6 months since onset of stroke Exclusion Cognitive problems: dementia, aphasia, dysarthria Other mental health problems Acute musculoskeletal problems Previously/currently on antidepressants (eg, SSRIs) pre-stroke	CCT: 57.2 ± 10.8 CON: 58.7 ± 9.7	1. Circuit class training (CCT), 1 session, 3×/week, 80 min gradual task-oriented CCT + 30 min general physical therapy. 2. Control (CON), 1 session, 3×/week, 80 min stretching and weight-bearing + 30 min general physical therapy.	Samples obtained: Blood Timing "Immediately" after exercise at each time period (day 1/ the start; weeks 2, 4, 6, 8) Sample storage: Stored at -82°C until analysis	8 weeks	BCAAs f-TRP f-TRP/BCAAs ratio BDI CCT BCAAs: Significant decrease over time immediately after start of exercise (but not between 6 and 8 weeks). f-TRP: Significant increase throughout 8 weeks; no significant differences between 1 and 2 weeks, 6 and 8 weeks. f-TRP/BCAAs ratios: Significant increase over time. BDI: Significant decrease in final week. CON All parameters, no significant difference over time or between pre and post-intervention. CCT vs CON, post-intervention BCAAs: Significantly lower f-TRP, f-TRP/BCAAs ratio: Significantly higher

(Continued)

Table 2. (Continued)

STUDY	STUDY DESIGN	BLINDING	RISK OF BIAS	N	SAMPLE POPULATION, INCLUSION/ EXCLUSION CRITERIA	SAMPLE AGE	INTERVENTION ARMS	MEASUREMENT PROTOCOL	DURATION	OUTCOMES
Hennings et al ⁴⁰	Non-randomized experimental study	Unknown	High	113	<p>Patients with MDD, or somatization syndrome (referred to as "SSI-8/SSI-8 group")</p> <p>Inclusion MDD group: MDD diagnosis (presumably as per DSM) SSI-8 group: ≥ 6 (men) or ≥ 8 (women) persistent and medically unexplained bodily symptoms</p> <p>Exclusion MDD group: ≤ 3 medically unexplained bodily symptoms SSI-8 group: MDD diagnosis Current delusional disorders Alcohol or substance abuse or dependence Persistent medical illnesses that could affect immune status (autoimmune diseases, severe chronic viral infection) Ongoing psychotherapy Medical illnesses Injuries in the last 2 weeks and medication with opiates</p>	<p>MDD: 32.08 ± 12.25 Somatization: 33.81 ± 14.29 Control: 36.44 ± 13.28</p>	<p>MDD, SSI-8, Control—patients in each group underwent 1 of the 2 below interventions: 1. 1 week increased exercise, then 3 weeks normal exercise, then 1 week reduced activity 2. (Reverse of 1.) 1 week reduced activity, then 3 weeks normal exercise, then 1 week increased exercise</p>	<p>Samples obtained: Blood Timing 8:00 AM at baseline, after "active" and "passive" weeks Sample storage Stored at -80°C until analysis</p>	5 weeks	<p>Depressive symptoms (BDI) Somatoform symptoms (SOMS7) IL-6 Neopterin TRP Kynurenine 5-hydroxyindoleacetic acid</p> <p>Covariates Antidepressant medication, male/female, physical activity level (FKKA)</p> <p>Depressive symptoms (BDI) MDD, SSI-8, control Significant time, group, effects; trend of significant group \times time interaction Significant decrease active/passive conditions vs baseline Trend toward decrease ($P < .10$) active vs passive condition in MDD/SSI-8 groups Significantly higher in MDD vs SSI-8 group, MDD/SSI-8 vs control group, at baseline, and active/passive conditions Active condition: more significant decrease in MDD vs SSI-8 group; unchanged for control group</p> <p>Somatoform symptoms (SOMS7) MDD, SSI-8, control Significant time, group effects; trend of significant group \times time interaction Significant decrease active vs passive condition, passive condition vs baseline in MDD/SSI-8 groups Trend toward difference ($P < .10$) between active vs passive condition in MDD/SSI-8 groups vs control at baseline, and active/passive conditions (ie, between groups, at same exercise condition) Significant decrease in SSI-8 group after passive/active condition, no significant difference in MDD and control groups</p> <p>Biological parameters No significant effects on group differences or effects of exercise interventions for: IL-6, neopterin, 5-HIAA, TRP Kynurenine: Significant group effect (MANCOVA) Major depression vs control group: Kynurenine (significantly lower) SSI-8 group vs MDD/control groups: Kynurenine (no significant difference, but values between MDD vs control groups)</p> <p>Covariates: Antidepressant medication associated with: BDI (higher), IL-6 (higher), neopterin (higher) Female vs male associated with: BDI (higher), SOMS7 (higher), TRP (lower) Physical activity level: 5-HIAA (higher)</p>

(Continued)

Table 2. (Continued)

STUDY	STUDY DESIGN	BLINDING	RISK OF BIAS	N	SAMPLE POPULATION, INCLUSION/ EXCLUSION CRITERIA	SAMPLE AGE	INTERVENTION ARMS	MEASUREMENT PROTOCOL	DURATION	OUTCOMES
Herrstedt et al ⁴¹	Non-randomized experimental study (secondary analysis)	Open-label	Critical	50	<p>Patients with stage I-III gastroesophageal junction (GEJ) adenocarcinoma</p> <p>Inclusion GEJ adenocarcinoma diagnosis stage I-III Scheduled to start standard neoadjuvant treatment</p> <p>Exclusion Patients <18 or >80 yo Deemed inoperable following multidisciplinary medical conference Pregnancy Presence of any other known malignancy requiring active treatment Deemed ineligible for neo adjuvant treatment WHO performance status >1 Physical/mental disabilities precluding physical testing and/or exercise Inability to read/ understand Danish</p>	<p>Exercise: 63.8 ± 8.0 Control: 65.4 ± 6.9</p>	<p>1. Exercise. On average: 2x/week, 30-45min on stationary bike, then resistance training. 2. Control. Allowed to participate in any standard hospital-based or community-based exercise programs.</p>	<p>Samples obtained: Blood, muscle biopsies Timing Blood: Pre- and post-intervention (week 12, before tumour resection). No exact time after exercise specified.* Muscle biopsies: Pre- and post-intervention (week 12, before tumour resection). No exact time after exercise specified. *4 patients in the exercise group: "immediately" after one of the planned training sessions.</p>	12 weeks	<p>Depression and anxiety scores (HADS) TRP Kynurenine KYNA 3-hydroxykynurenine (HK) HK/Kynurenine ratio KMO (gene expression) Xanthurenic acid 3-hydroxyanthranilic acid Anthranilic acid Quinolinic acid Neopterin TNFa IL-6 (serum) IL-6 (gene expression) IL-10 Watt_max Leg press</p> <p>Exercise (pre vs. post-exercise) HADS depression: Significant decrease HADS anxiety: Significant decrease TRP: Significant decrease Kynurenine, KYNA: No significant difference HK, HK/Kynurenine: No significant difference Xanthurenic acid, 3-hydroxyanthranilic acid: No significant difference Anthranilic acid: Significant increase Quinolinic acid: No significant increase Neopterin, TNF-a, IL-6, IL-10: No significant difference Watt_max, leg press: Significant increase</p> <p>Control (pre vs. post-exercise) HADS depression: No significant difference HADS anxiety: Significant decrease TRP: Significant decrease Kynurenine, KYNA: No significant difference HK, HK/Kynurenine ratio: Significant increase Xanthurenic acid, 3-hydroxyanthranilic acid: No significant difference Anthranilic acid: Significant increase Quinolinic acid: Significant increase Neopterin, TNFa, IL-6, IL-10: No significant difference</p> <p>Post-exercise KMO (gene expression): Significant increase in exercise versus control group IL-6 (gene expression): No significant difference</p>

(Continued)

Table 2. (Continued)

STUDY	STUDY DESIGN	BLINDING	RISK OF BIAS	N	SAMPLE POPULATION, INCLUSION/EXCLUSION CRITERIA	SAMPLE AGE	INTERVENTION ARMS	MEASUREMENT PROTOCOL	DURATION	OUTCOMES
Pal et al ⁴²	Randomized controlled trial (secondary analysis)	Open-label	High	32	<p>Pancreatic cancer</p> <p>Inclusion Resectable or non-resectable pancreatic cancer (stage I-IV) ≥ 18yo Sufficient German skills</p> <p>Exclusion Patients <18 or >80yo Deemed inoperable following multidisciplinary medical conference Pregnancy Presence of any other known malignancy requiring active treatment Deemed ineligible for neo adjuvant treatment WHO performance status >1 Physical/mental disabilities precluding physical testing and/or exercise Inability to read/understand Danish</p>	<p>Supervised: 61.1 \pm 5.8</p> <p>Home-based: 59.3 \pm 9.86</p> <p>Control: 61.3 \pm 10.5</p>	<p>1. Supervised resistance training. Weight machines, 60%-80% of maximum (1-RM)</p> <p>2. Home-based resistance training. Unsupervised, given exercise manual. Resistance was their own body weight and/or resistance bands, intensity 14-16 on Berg Scale of Perceived Exertion</p> <p>3. Control. No exercise.</p>	<p>Samples obtained: Blood Timing Baseline (t0), after 3 months (t1), after 6 months (t2). No exact time after exercise specified. Sample storage Stored at -80°C until analysis</p>	6 months	<p>Kynurenine TRP Kynurenine/TRP ratio IL-6</p> <p>Kynurenine Significant group x time interaction Significant time effect Potential difference between supervised and home-based at 6 months Significant increase over time within home-based at 0 to 3 months, and 3 to 6 months</p> <p>TRP No significant group x time interaction Significant time effect Tendency for difference ($P = .05$) between supervised and home-based at 6 months No significant difference over time</p> <p>Kynurenine/TRP ratio Significant group x time interaction Significant time effect Significant difference between supervised and home-based at 6 months Significant increase over time within home-based at 0 to 3 months, and 3 to 6 months</p> <p>IL-6 No significant group x time interaction Almost significant ($P = .06$) significant time effect Significant time effect from 0 to 3 months for home-based, supervised, control</p> <p>Control group Kynurenine, TRP, Kynurenine/TRP ratio over time: No significant difference IL-6: Significant time effect from 0 to 3 months</p>

(Continued)

Table 2. (Continued)

STUDY	STUDY DESIGN	BLINDING	RISK OF BIAS	N	SAMPLE POPULATION, INCLUSION/ EXCLUSION CRITERIA	SAMPLE AGE	INTERVENTION ARMS	MEASUREMENT PROTOCOL	DURATION	OUTCOMES
Zimmer et al. ³	Randomized controlled trial (secondary analysis); breast cancer (intervention vs. control) Observational: breast cancer (intervention + control) versus healthy (intervention)	Single (outcomes assessor)	Unclear/ some concerns (Cochrane RoB 2.0) Moderate (ROBINS-I)	120	Breast cancer Inclusion >18yo Breast cancer patients (intervention + control); Breast cancer (stage 0-3) Healthy (intervention); Healthy, comparable age Exclusion Breast cancer patients: anything preventing exercise, including If received adjuvant or neo-adjuvant chemotherapy Acute infectious disease Severe cardiac/respiratory disease Healthy anything preventing exercise, including: Previous cancer Chronic internal disease Orthopedic impairment	Breast cancer + intervention: 57.3 ± 8.8 Breast cancer + control: 56.7 ± 9.0 Healthy + intervention: 53.1 ± 10.0	1. Breast cancer + intervention: 60 min sessions, 2x/ week, 1 to 3 sets, 60%-80% of maximum (1-RM), 1-min rest between sets, 8 different exercises for major upper/lower muscle groups. Weight progressively increased. 2. Breast cancer + control: 60min sessions, 2x / week. Progressive muscle relaxation, no aerobic or resistance components.	Samples obtained: Blood, urine Timing: At rest Baseline (t0), after 6 weeks (t1)*, after 12 weeks (t2). No exact time after exercise specified. *In the breast cancer groups, there was also 6-week radiotherapy treatment.	12 weeks	TRP Kynurenine QUINA Kynurenine/TRP ratio KYN/A/Kynurenine ratio QUINA/KYNA ratio Resistance training: Breast cancer (intervention + control groups) versus healthy (intervention) TRP, Kynurenine, KYNA, Kynurenine/TRP, (ANCOVA) QUINA: Significant time effect (ANCOVA, post-hoc), significant group x time interaction (ANCOVA), significant increase at 6 months (post-hoc) QUINA/KYNA ratio: Significant time effect (ANCOVA, post-hoc), significant increase over time (post-hoc), significant group x time interaction (ANCOVA), significant increase at 6 months (post-hoc) Resistance training: Breast cancer (intervention vs. control group) TRP: Significant time effect (ANCOVA), no significant difference over time (post-hoc) Kynurenine: Significant group x time interaction (ANCOVA), significant decrease from baseline to 3 months for intervention group, significant increase from baseline to 6 months for control group, significant difference between groups at 3 months and 6 months Kynurenine/TRP ratio: Significant group x time interaction (ANCOVA); significant increase from baseline to 3 months, 3 months to 6 months in control group (post-hoc); no significant difference over time in intervention group (post-hoc) KYNA/Kynurenine ratio: Significant time effect (ANCOVA); significant decrease from baseline to 6 months in control group (post-hoc); no significant difference over time in intervention group (post-hoc) QUINA, QUINA, QUINA/KYNA ratio: No significant time effect or group x time interaction (ANCOVA)

Abbreviations:

-Biochemical: BCAAs, branched chain amino acids; f-TRP, free-tryptophan; KMO, kynurenine 3-monooxygenase; Kynurenine, kynurenine; KYNA, kynurenic acid; QUINA, quinolinic acid; TRP, tryptophan.
-Psychiatric: BDI, Beck Depression Inventory; HADS, Hospital Anxiety and Depression Scale; MDD, major depressive disorder; SSI-8, Somatoform Symptom Index-8; SOMS7, Screening for Somatoform Disorders 7.

missing outcome data with a high proportion of non-adherence, and omission of one data set deemed of sufficient importance.

Pal et al⁴² was at “high” (Cochrane RoB 2.0) risk of bias, owing to randomization that actually started using living distance as a condition (introduces confounders), missing outcome data likely to differ between intervention arms, and different supervision levels between intervention arms.

Hennings et al⁴⁰ was at “high” (Cochrane RoB 2.0) risk of bias, owing to the use of many self-reported questionnaires (including a demographics questionnaire and self-reported food intake log) in outcomes measures.

Zimmer et al⁴³ was evaluated using both the Cochrane RoB 2.0 tool for the randomized controlled trial portion comparing breast cancer intervention and control groups, and the ROBINS-I tool for the observational study comparing breast cancer (intervention + control) versus healthy intervention groups. Zimmer et al⁴³ was at “unclear/some concerns” (Cochrane RoB 2.0) risk of bias, owing to the lack of information of how the 24 healthy volunteers were allocated for inclusion in the study (eg, was it the first 24 who volunteered, or 24 randomly assigned from a larger volunteer pool). Zimmer et al⁴³ was at “moderate” (ROBINS-I) risk of bias, owing to possible confounders such as radiotherapy and different stages/types of breast cancer; however, the study did measure baseline differences and made clear the limitations of these confounders.

Mudry et al³⁸ was at “moderate” (ROBINS-I) risk of bias, owing to the single-intervention arm treatment design with possible confounders unaccounted for. However, the exclusion criteria were adequately defined to exclude most confounders of diabetes comorbidities.

Baek et al³⁹ was at “moderate” (ROBINS-I) risk of bias, owing to the confounders that could not be eliminated due to matching for physical demographics. However, the exclusion criteria were adequately defined to exclude most confounders (eg, overlapping psychiatric conditions) of post-stroke depression.

Discussion

In this review, we considered the current evidence of exercise and its effects on the kynurenine pathway concomitantly with psychological outcomes. In particular, this review included studies with patients with known chronic/age-related diseases (and healthy controls, where appropriate). See Table 2 for all outcome data discussed.

Our findings suggest exercise has significant effects on multiple parts of the kynurenine pathway²⁵ from the start (tryptophan), to quinolinic acid—the precursor to the NAD⁺ pathway, and other branch pathways such as that leading to anthranilic acid. However, mixed results were found. Table 2 contains all biochemical outcome data; as there were numerous measurements and comparisons made, the discussion on biochemical outcomes will focus on broader comparisons.

Comparing post-exercise versus pre-exercise within the same group (ie, not vs healthy controls), for example, serum

tryptophan could have significantly decreased,³⁸ increased,^{39,41} or showed no significant difference.^{40,42,43} Each study implemented different exercise programs (eg, aerobic, resistance, mixed), making it hard to predict differential biochemical effects. With the lack of studies on this topic, it becomes more challenging to ascertain the true direction of change in certain kynurenine pathway metabolites.

Comparing post-exercise versus pre-exercise between groups (ie, diseased vs healthy controls), for example, serum tryptophan (as compared previously), could have been significantly higher,³⁹ or showed no statistically significant difference^{38,40,42,43}; Herrstedt et al⁴¹ made no intergroup comparison. Post-exercise intergroup differences may suggest a different pre-exercise baseline, as was the case in Zimmer et al⁴³ (significantly higher kynurenine/TRP ratio in breast cancer patients vs healthy controls), or a true effect of exercise producing a differential kynurenine pathway outcome (ie, a significant group \times time interaction as was the case with kynurenine in Pal et al.⁴²)

While there are extensive comparisons made between post-exercise versus pre-exercise, another comparison alluded to in the Introduction section is the acute versus chronic exercise conditions. Only one study (Mudry et al³⁸) qualifies as acute exercise, as this was a single session of cycle ergometry with no other follow-up exercise interventions. Importantly, Mudry et al³⁸ reported that in response to acute exercise in both groups (normal glucose tolerance, type 2 diabetes), there was a significant decrease in serum tryptophan and kynurenine, and a significant increase in kynurenic acid. However, for chronic exercise studies included in our review, the post-exercise versus pre-exercise results were mixed. Serum tryptophan increased,³⁹ decreased,⁴¹ or showed no significant difference;⁴⁰ Pal et al⁴² and Zimmer et al⁴³ did not report on the direction of change for serum tryptophan, but noted a significant time effect post versus pre-exercise. Serum kynurenine showed no significant difference^{40,41}; Pal et al⁴² and Zimmer et al⁴³ did not report on the direction of change for serum kynurenine, but noted a significant time effects post versus pre-exercise. Serum kynurenic acid showed no significant difference;⁴¹ Zimmer et al⁴³ did not report on the direction of change for serum kynurenic acid, but noted a significant time effects post versus pre-exercise. These mixed results, while difficult to directly compare to the acute exercise study by Mudry et al,³⁸ do not rule out the suggestion that there may be differential activation of the kynurenine pathway between acute and chronic exercise.³⁴

Further complicating the discussion of acute versus chronic exercise is the importance of obtaining the sample at the correct time, especially for measuring inflammatory-associated pathways.⁴⁴ Ideally, to measure the acute/short-term effects of an intervention, a measurement should be taken immediately after the intervention is completed. In the acute exercise study by Mudry et al,³⁸ the samples for serum metabolite analysis were appropriately obtained “immediately” after both exercise (“EXERCISE” time period) and a 3-hour sitting period

(“RECOVERY” time period). The immediate sampling ensures that the measurements accurately reflect the acute effects of exercise on the kynurenine pathway. The sampling after the 3-hour sitting period is useful to compare to both exercise and baseline and show there is measurable change before and after exercise. For chronic exercise, however, the measurement process must be done more carefully. After any exercise bout, there will be short-term changes (eg, inflammatory⁴⁵) relative to pre-exercise. Thus, it is important not to sample too quickly after the exercise bout, even though it may be session number 10 out of 20 total sessions, since the goal is to measure change over all multiple or all 20 sessions, rather than just the single session. The chronic exercise studies had variable measurement protocols, with samples being obtained either “immediately” after exercise³⁹ or during some unspecified time after exercise.^{40–43} One study⁴⁴—while not specifically about the kynurenine pathway—has suggested 2 cut-off points for acute exercise: up to 4 hours post-exercise for measuring inflammatory-associated outcomes; 24 hours post-exercise is not useful. This seems to suggest that to study chronic exercise effects, samples should be taken after 24 hours post-exercise. However, given all the chronic exercise studies in our review did not provide any evidence of such a rigorous sampling time period, there may be considerable difficulty in interpreting results. Future studies must not only account for the exercise intervention and outcomes themselves, but also the measurement and sampling thereof.

While all studies measured markers of the kynurenine pathway (and other inflammatory markers), only 3 studies (Baek et al,³⁹ Hennings et al,⁴⁰ Herrstedt et al⁴¹) measured psychological outcomes. In this review, the included studies measured 3 psychological domains: somatization, anxiety, depression. Baek et al³⁹ and Hennings et al⁴⁰ reported on depressive symptoms using the Beck Depression Inventory (BDI)⁴⁶ score, and Hennings et al⁴⁰ reported on somatoform symptoms using the Screening for Somatoform Symptoms-7 (SOMS-7)⁴⁷ score. Herrstedt et al⁴¹ reported on depressive and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS).⁴⁸

In Baek et al,³⁹ depressive symptoms were significantly decreased in the final week of exercise (vs first day). In Hennings et al⁴⁰ depressive and somatoform symptoms were significantly decreased in all groups when considering post- versus pre-exercise. In Herrstedt et al,⁴¹ there was a significant decrease in HADS depression and anxiety scores when considering post- versus pre-exercise. Notably, in Hennings et al,⁴⁰ there was a significant decrease in depressive and somatoform symptoms in the control group (post- vs pre-exercise) with no known psychiatric conditions; there was a trend of significant group \times time interaction that may have justified a “stronger effect” in the groups with major depression and somatization, but for reasons unknown (eg, small sample size), this finding was not conclusive. Similarly, in Herrstedt et al,⁴¹ there was a significant decrease in HADS depression (but not anxiety), in the control group (post- vs pre-exercise). Baek et al,³⁹ however, reported no

significant difference in depressive symptoms post-exercise in the control group. A possible explanation, as noted in Herrstedt et al⁴¹ may be the effect of supervision of the exercise program, rather than the exercise itself, on depressive symptoms; this may apply to somatoform and anxiety symptoms as well. While studies could remove the supervision element from exercise, for example, home-based exercise programs (Pal et al⁴²) there is a trade-off of lower adherence/proper implementation of the program. Therefore, we note that for psychological outcomes, higher-powered studies with appropriate supervision levels are necessary to justify that exercise has a more pronounced effect on psychological outcomes in patients with psychiatric conditions, versus healthy controls.

Clinically, pharmacological modulation of the kynurenine pathway has proven challenging. Many drugs targeting the kynurenine pathway are under investigation.²⁵ However, studies on pharmacological intervention have stalled,⁴⁹ revealed appreciable amounts of side effects,⁵⁰ or have been demonstrated to be ineffective or have failed.⁵¹ In addition, these drugs are likely to be for very specific use cases, for example, breast cancer, and may not be cost-effective. Exercise, however, can be implemented in more populations and is likely to be more cost-effective. As mentioned earlier, it is no surprise that pharmacological approaches will almost always carry the risk of side effects.⁵² Given that many chronic diseases will still require pharmacological approaches, it is useful to know that exercise may attenuate these side effects^{53,54} that have a significant impact on people with chronic disease.

Some limitations of this review include the small number of studies, sample size, intervention variation, and the confounder of exercise itself. Among the small number of studies available for analysis, 3 (Herrstedt et al,⁴¹ Pal et al,⁴² Zimmer et al⁴³) were actually analyses of data obtained in previous clinical trials. This introduces elements of bias, and for our review, particularly unmeasured confounding⁵⁵ for temporally distant outcomes, and reporting of secondary analyses without mentioning of uncertainty.⁵⁶ As mentioned earlier, the controversy of acute versus chronic exercise resulting in differential kynurenine pathway activation, and the need to obtain samples within an appropriate time period, must not be understated. Given only the acute exercise study (Mudry et al³⁸) obtained samples within an appropriate time period, while the chronic exercise studies did not provide evidence of appropriate measurement protocols, it is not possible to conclude if long-term exercise has a long-term effect on the kynurenine pathway, and thus outcomes for age-related disease.

Small sample size, while convenient and cost-effective, presents problems. In Pal et al,⁴² 65 patients were eligible for the study, but only 32 were included for analysis due to blood sample quantity requirements. There are 2 important points to consider here: (1) future studies must measure exercise effects on the kynurenine pathway as a primary outcome (vs leaving the duty to a secondary investigator and analysis) and (2) when the sample size is already small and further decreased, the

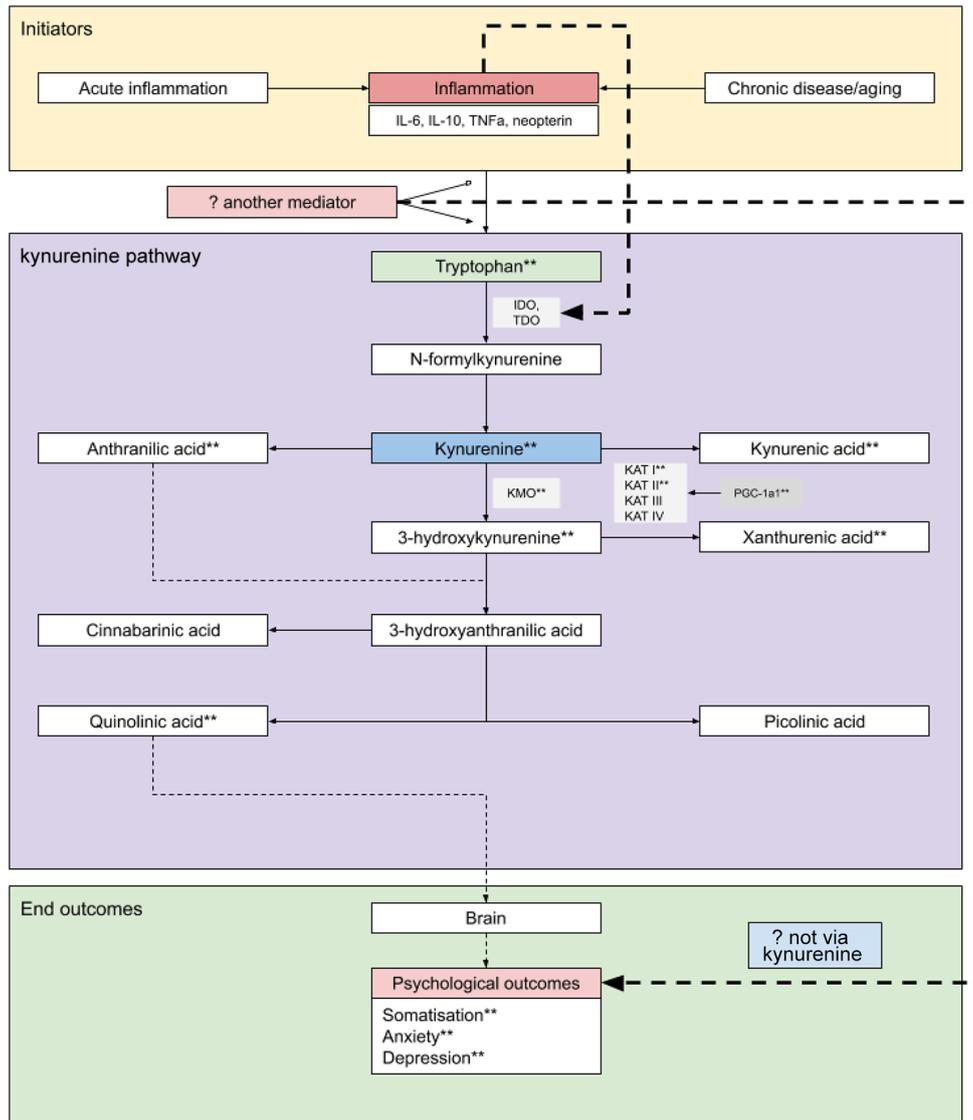


Figure 2. Schematic of kynurenine pathway and effects of exercise on kynurenine pathway elements and end outcomes. However, this is not exhaustive. Abbreviations: IDO, indoleamine-2,3-dioxygenase; KAT, kynurenine aminotransferase; KMO, kynurenine-3-monooxygenase; kynurenine, kynurenine; TDO, tryptophan-2,3-dioxygenase. **Exercise found to have a significant effect, in included studies of this review.

difference in absolute number (ie, number of participants) of outcomes makes it difficult to determine whether the effect is due to the intervention or simply chance.⁵⁷

Either a limitation in theory or a fortunate element in practice, “exercise” is highly variable. Most exercise studies create reproducible and objectively-measured regimens. However, unlike pharmacological interventions, it is inherently difficult to tailor specific exercise interventions with variable populations. Though most, if not all, of the studies included in this review reported significant results post- versus pre-exercise, or significant differences post-exercise between chronically ill and healthy/other groups, the studies have inherent variations between exercise and control groups that are hard to measure. In the case of Herrstedt et al,⁴¹ the referenced study design’s control group was actually allowed to participate in any standard hospital/community-based exercise programs; while this may be interpreted as a loosely-defined control group that

introduces too many confounding factors (which may have been prevented had all participant exercise programs in the control group been recorded), it may represent a new way to compare highly-structured exercise programs with exercise programs available in the community. Of course, we cannot overstate the importance of defining the methods pre-intervention and robust data collection of the exercise regimen (frequency, intensity, time, and type).³¹ Without this data, outcomes comparisons between studies is invalid, if not nearly impossible. Future investigators may wish to make such similar comparisons, implement and record a set number of exercise programs to participants in one control group, and collect and analyse data in a pooled/unpooled setting all in one study. This would increase the number of exercise program comparisons, without introducing extra cost/time burden of designing multiple studies.

Perhaps the most pressing limitation, however, is the complexity of the relationships associated with the kynurenine

pathway (see Figure 2). All our included studies reported significant effects of exercise on the kynurenine pathway, that is, evidence does exist for at least a unidirectional relationship between exercise and the kynurenine pathway. Only Hennings et al⁴⁰ and Herrstedt et al⁴¹ measured psychological outcomes. However, it is widely known that exercise produces benefits on the measured mental health outcomes in our included studies: depressive symptoms,⁵⁸ somatoform symptoms,⁵⁹ anxiety symptoms.⁶⁰ Thus, the current evidence is unclear whether exercise affects psychological outcomes through the kynurenine pathway, or through some other mediator (see Figure 2), for example, supervision,³⁵ some other inflammatory pathway (eg, TNF α ²²).

We recommend that a future study be constructed with multiple intervention/control arms to elucidate these relationships backed up by robust evidence: multiple arms including kynurenine pathway pharmacological intervention (with placebo control) and exercise intervention (including “non-exercise” control), with outcomes including kynurenine pathway metabolites and psychological outcomes. Differences between kynurenine pathway pharmacological interventions and exercise interventions could then be assessed to determine if psychological outcomes are due to kynurenine pathway modulation or other confounders present during exercise interventions.

Conclusion

There are few studies investigating the effects of exercise on the kynurenine pathway and/or psychological outcomes associated with the kynurenine pathway. Of the studies that have been performed, it is easier to find studies performed in healthy volunteers^{34,61,62} without documented age-related disease versus studies conducted in people with age-related disease. In addition, this review did not explore other age-related diseases, particularly high-burden ones such as cardiovascular disease⁶³ and osteoporosis.⁶⁴ Currently, there are few reviews^{34,35,65} on the effects of exercise on the kynurenine pathway and potential mechanisms. Importantly, one review⁶⁵ mentions the possibility that long-term exercise interventions may only have measurable effects if age-related disease is present. Thus, further studies and reviews, particularly with a “prolonged duration” element (age-related disease and exercise intervention), are needed to establish a guideline for a combination²² of lifestyle modification and pharmacological treatment that can be prescribed for diseases of inflammaging.

Author Contributions

AL - first investigator, paper writing

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SV - assistance with following: data analysis/interpretation, risk of bias assessment

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