MEDICAL UNIVERSITY OF GDAŃSK

Faculty of Health Sciences with the Institute of Maritime and Tropical Medicine

DOCTORAL THESIS

Effects of Omega-3 fatty acids supplementation on stress-induced changes to kynurenine metabolism and mood in physically active and inactive males

Wpływ suplementacji kwasami omega-3 na indukowany stresem nastrój i metabolizm kinureniny u mężczyzn aktywnych i nieaktywnych fizycznie

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I. Publications forming a cumulative PhD thesis

1st publication

Bidzan-Wiącek, M., Tomczyk, M., Błażek, M., Mika, A., Antosiewicz, J. (2024). No effects of Omega-3 supplementation on kynurenine pathway, inflammation, depressive symptoms, and stress response in males: a placebo-controlled trial. *Nutrients*, *16*(21), 3744. https://doi.org/10.3390/nu16213744

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3rd publication

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II. List of abbreviations used in this PhD thesis

3-HAA	3-hydroxyanthranilic acid
3-HK	3-hydroxykynurenine
DASS-21	Depression, anxiety and stress scale - 21 items
DHA	Docosahexaenoic acid
EA	Energetic arousal
EPA	Eicosapentaenoic acid
GC–MS	Gas chromatography-mass spectrometry
HT	Hedonic tone
IDO	Indoleamine 2,3-dioxygenase
IFOS	International fish oil standards
IL-10	Interleukin 10
IL-6R alpha	Interleukin 6 receptor alpha
KAT	Kynurenine aminotransferase
KYN	Kynurenine
KYNA	Kynurenic acid
LC-MS-MS	Liquid chromatography with tandem mass spectrometry
MVPA	Moderate-to-vigorous physical activity
n-3 PUFA	Omega-3 polyunsaturated fatty acids
n-6 PUFA	Omega-6 polyunsaturated fatty acids
PA	Picolinic acid
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator alpha
QA	Quinolinic acid

TA	Tense arousal
TNF RI	Tumor necrosis factor receptor 1
TNF	Tumour necrosis factor
Trp	Tryptophan
TSST	Trier social stress test
UMACL	UWIST Mood Adjective Check List
WHO	World Health Organization
XA	Xanthurenic acid

III. Funding

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IV. Summary

The typical Western diet has shifted towards a greater intake of omega-6 polyunsaturated fatty acids (*n*-6 PUFAs) at the expense of intake of omega-3 fatty acids (*n*-3 PUFAs). Considering the proinflammatory functions of *n*-6 PUFAs, this type of diet can increase inflammation in the body. This is particularly alarming considering the negative health consequences associated with inflammation. Apart from physical symptoms, inflammation of the brain can also cause behavioural and mood disturbances, including low mood. Meanwhile, studies have demonstrated the anti-inflammatory properties of *n*-3 PUFA supplementation. In particular, the *n*-3 PUFA *Docosahexaenoic Acid* (DHA), has been reported to be effective at reducing inflammation. Numerous studies have been conducted on the effects of the anti-inflammatory properties of *n*-3 PUFAs on mood. However, the results from these studies are not consistent. Meanwhile, inflammation seems to be only one of the triggers of negative affect and low mood. Mood disturbances seem to be additionally mediated by psychosocial stress. For example, data from animal models have shown that different types of psychosocial stress may enhance changes in the brain resembling those observed in depressed patients. The biological mechanism that might explain the role of inflammation and psychosocial stress in mood disturbances is kynurenine (KYN) metabolism, which seems to change in response to psychosocial stress and inflammatory factors. Meanwhile, a recent animal study has suggested that physical activity protects from stress-induced mood disturbances. Specifically, the increased activity of peroxisome proliferator-activated receptor-gamma coactivator alpha (PGC-1α) in skeletal muscle, which is activated during endurance-type activity, was found to mediate resilience to stress-induced depressive behaviour.

The purpose of the current study was to explore the effect of *n*-3 PUFA supplementation on mood and stress-induced changes to mood. Furthermore, a potential biological mechanism involved in the relationship between psychosocial stress and mood – KYN metabolism – was assessed. Finally, based on the findings that PGC-1α overexpression in skeletal muscle might protect against stress-induced depressed mood, the study compared two groups of participants: Physically Active and Physically Inactive men.

This is the first controlled trial to investigate the effect of *n*-3 PUFA supplementation on the KYN pathway and mood as well as the effect of supplementation on the KYN pathway and mood following the induction of stress. The main observation from this placebo-controlled experiment is that *n*-3 PUFA supplementation in the Physically Active group of men had a beneficial effect on KYN metabolites. Specifically, it increased concentrations of picolinic acid (PA) – an endogenous metabolite of tryptophan with neuroprotective abilities. Higher concentrations of PA were not found among Physically Inactive men or among Physically Active men who supplemented placebo. This suggests a moderating effect of physical activity on the relationship between the KYN pathway and the fatty acid profile. Moreover, the study indicated that *n*-3 PUFA levels ameliorated inflammatory markers in Physically Inactive men. Meanwhile, there was no effect of *n*-3 PUFA supplementation on mood and depressive symptoms in Physically Inactive men. The study found no evidence that increased *n*-3 PUFA levels in Physically Active or Inactive men using *n*-3 PUFA supplements has any benefit on mood, or mood following the induction of stress. While depressive symptoms were not assessed in Physically Active men, the systematic review and meta-analysis suggest that the beneficial effect of physical activity might depend on the level of physical activity, with moderate level of physical activity being most beneficial for

alleviating depressive symptoms. The Physically Active men group involved participants engaged in high level of physical activity training, which might explain the non-significant effect of physical activity on mood.

Keywords: *n*-3 PUFA, Omega-3 fatty acids, kynurenine metabolism, depressive symptoms, mood, physical activity

V. Summary in Polish

Zwiększone spożycie kwasów omega-6 (*n*-6 PUFA) kosztem kwasów omega-3 (*n*-3 PUFA) jest typowe dla diety społeczeństw zachodnich. Z uwagi na prozapalne działanie *n*-6 PUFA tego rodzaju dieta może nasilać stany zapalne w organizmie, co pociąga dalsze niekorzystne konsekwencje zdrowotne. Konsekwencją stanów zapalnych, oprócz objawów fizycznych, mogą być również stany obniżonego nastroju. Jednocześnie, jak wskazują badania, suplementacja *n*-3 PUFA może wywierać efekt przeciwzapalny. Szczególnie skuteczny w redukcji stanu zapalnego wydaje się jeden z kwasów tłuszczowych *n*-3 PUFA, kwas dokozaheksaenowy (DHA). Wyniki badań empirycznych nad skutecznością *n*-3 PUFA na nastrój nie przyniosły, jak dotąd, jednoznacznych ustaleń. Przyczyną może być brak uwzględnienia wieloczynnikowej genezy zaburzeń nastroju. Jako przykład można wskazać mediującą rolę stresu psychospołecznego w stanach depresyjnych. Badania na zwierzętach wskazują, że stres psychospołeczny może pogłębiać zmiany degeneracyjne w mózgu podobne do tych, które obserwuje się u pacjentów z depresją. Wzrost stężenia kinureniny (KYN) we krwi indukowany stanem zapalnym lub stresem psychologicznym może być potencjalnym mechanizmem biologicznym wyjaśniającym wpływ tych czynników na nastrój. Jednocześnie, ostatnie badania na modelach zwierzęcych sugerują, że aktywność fizyczna ma działanie protekcyjne wobec zaburzeń nastroju indukowanych stresem. Trening wytrzymałościowy poprzez wzrost ekspresji białka koaktywator 1α receptora γ aktywowanego przez proliferatory peroksysomów (PGC-1α) oraz aminotransferazy kinureniny (KAT) w mięśniach szkieletowych wpływają na metabolizm kinureniny, co w konsekwencji pozytywnie wpływa na nastrój.

Celem projektu była ocena efektywności suplementacji *n*-3 PUFA na nastrój oraz nastrój po indukcji stresu. Dodatkowo zbadany został metabolizm KYN w celu oceny biologicznych mechanizmów odpowiedzialnych za związek stresu psychospołecznego i nastroju. Uwzględniając potencjalne właściwości ochronne zwiększonej aktywności czynnika transkrypcyjnego PGC-1α w mięśniach szkieletowych na obniżony nastrój, w badaniu porównane zostały dwie grupy badanych: mężczyźni aktywni i nieaktywni fizycznie. Jest to pierwsze badanie na ludziach oceniające jednocześnie wpływ

suplementacji *n*-3 PUFA, stresu psychospołecznego i aktywności fizycznej na nastrój oraz metabolizm kinureniny.

Kluczowym wynikiem obecnych badań jest korzystny wpływ suplementacji *n*-3 PUFA w połączeniu z aktywnością fizyczną na metabolizm KYN. U mężczyzn aktywnych fizycznie suplementujących *n*-3 PUFA zaobserowowano zwiększone stężenie kwasu pikolinowego - metabolitu tryptofanu z udokumentowanym pozytywnym wpływem na funkcjonowanie mózgu. Zwiększonego stężenia kwasu pikolinowego nie zauważono w grupie mężczyzn nieaktywnych fizycznie suplementujących *n*-3 PUFA, ani w grupie mężczyzn aktywnych fizycznie suplementujących placebo. Sugeruje to o moderującym wpływie aktywności fizycznej na zależność między metabolizmem kinureniny, a poziomem *n*-3 PUFA. Z przeprowadzanych badań wynika również, że u zdrowych dorosłych mężczyzn niektywnych fizycznie suplementacja *n*-3 PUFA przynosi ochronne korzyści zdrowotne związane ze stanem zapalnym. Wbrew przewidywaniom, zarówno u mężczyzn aktywnych, jak i nieaktywnych fizycznie wysokie stężenia *n*-3 PUFA nie miały wpływu na nastrój oraz nastrój po indukcji stresu. U mężczyzn niekaktywnych fizycznie suplementacja *n*-3 PUFA nie miała również wpływu na symptomy depresyjne. Pomimo, że w badaniu nie oceniono wpływu suplementacji *n*-3 PUFA na symptomy depresyjne u mężczyzn aktywnych fizycznie, przeprowadzony przegląd systematyczny i meta-analiza sugerują, że intensywność aktywności fizycznej może być istotnym mediatorem w zależności między aktywnością fizyczną, a nastrojem. W badanej grupie intensywność była wysoka, stąd potencjalnie nie wykazano korzyści płynących z aktywności fizycznej na nastrój.

Słowa kluczowe: *n*-3 PUFAs, kwasy tłuszczowe Omega-3, metabolizm kinureniny, symptomy depresyjne, nastrój, aktywność fizyczna

CHAPTER 1: INTRODUCTION

Background and the State of the Art

Depressive disorders affect approximately 280 million people worldwide (Institute of Health Metrics and Evaluation, n.d.) and are a major cause of global health burden (GBD, 2019; Mental Disorders Collaborators, 2022).

Inflammation and Depressive Symptoms

Increased inflammation and heightened physiological stress reactivity have been associated with the pathophysiology of mood disorders. Peripheral blood elevations of proinflammatory cytokines, including tumour necrosis factor (TNF) alpha and interleukin 6 (IL-6), are some of the most reliable biomarkers of increased inflammation in patients with depressive symptoms (Haroon et al., 2012). Cytokines can cross the blood brain barrier and affect central neural function, which may promote depressive symptoms and low mood (Beurel, Toups, & Nemeroff, 2020; Bhatt et al., 2023). The role of proinflammatory cytokines in depressive symptoms is supported by prospective studies, which have shown that acute administration of proinflammatory cytokines can trigger depressive symptoms (Dantzer & Kelley, 2007; Felger & Lotrich, 2013).

Links between Stress, Inflammation, and Depressive Symptoms

Meanwhile, animal models have shown that exposure to stressors facilitates the expression of proinflammatory cytokines and promotes depressive-like behaviour (Norman et al., 2010). Physiological responses to acute stressors can vary widely among individuals experiencing the same stressor (Turner et al., 2020), and reactivity to

stressors can be a predictor of depressive symptoms (Felsten, 2004). The biological mechanism that may explain the link between reactivity to psychological stressors and depressive symptoms is altered hypothalamic–pituitary–adrenal (HPA) activity (Malhi & Mann, 2018). In healthy individuals, psychological stress activates a HPA response causing the central nervous system to release cortisol. This is followed by a 'stress recovery' phase in which cortisol returns to baseline levels. A meta-analysis on the association between depression and cortisol responses to psychosocial stressors showed that while patients with major depressive disorder show similar baseline cortisol levels to healthy controls (before being exposed to a psychological stressor), patients with major depressive disorder have significantly higher cortisol levels during the recovery period (over 25 min after being exposed to a psychological stressor; Burke et al., 2005). While an adaptive stress response is flexible and short-lived, patients with major depressive disorder seem to have blunted stress reactivity and impaired recovery from acute stressors (Burke et al., 2005). An exaggerated prolonged response to acute stressors may facilitate higher increase of proinflammatory cytokines.

Kynurenine Pathway

The underlying biological mechanisms via which pro-inflammatory cytokines and stress can affect neurogenesis is through alterations of the kynurenine (KYN) pathway. The KYN pathway is one of the two major enzymatic pathways of tryptophan (Trp) catabolism. Trp can either be converted into serotonin, a neurotransmitter involved in mood, anxiety, and cognition, or it can be metabolised through the KYN pathway. In humans, about 95% of the total Trp is metabolized through the KYN pathway, with participation of indoleamine 2,3-dioxygenase (IDO), which catabolizes the conversion

of Trp into KYN (Myint & Kim, 2003). KYN can then be metabolised in two ways. In the neuroprotective branch, KYN is transformed into kynurenic acid (KYNA) by kynurenine aminotransferase (KAT). KYNA can have some major health benefits, including antioxidant, anti-inflammatory, and neuroprotective properties. The expression of KAT is enhanced via peroxisome proliferator-activated receptor-gamma coactivator alpha (PGC-1α) – a transcriptional coactivator in skeletal muscles, which is activated when adaptation to endurance exercise occurs (*Fig.* 1). Hence, endurance exercise leads to higher KAT activity in skeletal muscles and may in turn enhance KYNA levels. In the neurotoxic branch, KYN is accumulated in the central nervous system and forms other neurotoxic metabolites, such as 3-hydroxykynurenine (3-HK) and quinolinic acid (QA). Unlike KYNA, KYN can also cross the blood-brain barrier. KYN formation from Trp seems to be activated by psychological or physiological stress as well as directly by inflammatory cytokines, which can stimulate the activity of IDO and can in turn lead to over-activation of the KYN pathway (Miura et al., 2008; Tanaka et al., 2021). Peripheral Trp conversion to KYN under proinflammatory conditions and under stress conditions has been linked to neuroinflammation and may contribute to depressed mood (Schwarcz et al., 2012). Increased levels of KYN, 3-HK, and QA can lead to depressive symptoms (Wichers et al., 2005).

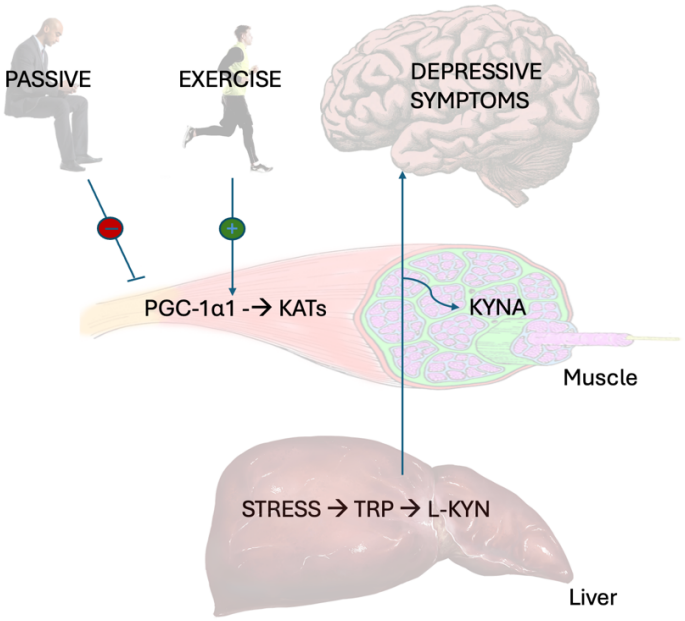

Fig. 1. Skeletal Muscle PGC-1α1 Modulates Kynurenine Metabolism and Mediates Resilience to Stress-Induced Depression

Adapted from: Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression by Agudelo, L. Z., Femenía, T., Orhan, F., Porsmyr-Palmertz, M., Goiny, M., Martinez-Redondo, V., ... & Ruas, J. L, 2014, *Cell, 159*(1), 33-45, Graphical abstract.

Physical Activity

The benefit of physical activity for alleviating depressive symptoms is generally accepted (Singh et al., 2023). Physically active individuals regularly performing endurance exercise have higher KAT activity in skeletal muscles (Schlittler et al., 2016) – KAT are the enzymes responsible for the transformation of KYN into KYNA. Considering the neuroprotective effects of KYNA, exercise-induced PGC-1α expression in skeletal muscles might protect against the stress-induced neurobiological mechanisms of depressed mood. There is evidence that physical activity improves mental health, including depressive symptoms. A cross-sectional and prospective study of 32,392 Europeans across a four-year follow-up showed that physical activity is

negatively associated with depressive symptoms and predicts lower depression scores four years later (Marques et al., 2020). A recent meta-analysis with meta-regression of 41 randomized controlled trials demonstrated large effects of exercise interventions on depressive symptoms (Heissel et al., 2023). The authors concluded that moderate exercise is an evidence-based option in the treatment of depression and depressive symptoms. Based on animal models, it seems that skeletal muscle PGC-1α modulates the KYN pathway, which mediates resilience to stress-induced depression (Agudelo et al., 2014).

N-3 PUFAs

Omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) may reduce the risk of depressive symptoms by regulating inflammation and stress-responsive systems (Ginty & Conklin, 2012; Kavyani et al., 2022). Specifically, higher levels of *n*-3 PUFAs may inhibit proinflammatory cytokine release during psychological stress exposure. A randomized, controlled trial showed that daily supplementation of 2.5 grams of *n*-3 PUFAs – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – reduced overall cortisol and IL-6 throughout the stressor (Madison et al., 2021). It was suggested that *n*-3 PUFA supplementation alters the damaging effects of stress and may thus reduce the risk of depression.

N-3 PUFAs have anti-inflammatory properties and are suggested to positively influence brain functioning (Delpech et al., 2015; Rangel-Huerta et al., 2012). Numerous studies have been conducted on the effects of the anti-inflammatory properties of *n*-3 PUFAs on mood. While there is evidence for higher plasma *n*-3 PUFAs being

associated with improved mood and lowered depressive symptoms (Liao, 2019; Wolters et al., 2021), a number of randomized controlled trials have showed limited effects of *n*-3 PUFA supplementation on mood, either as a main effect or in interaction with other variables such as stress in healthy individuals (Giles et al., 2015; Okereke et al., 2021). Inconsistent results on the effect of *n*-3 PUFA supplementation on mood may be due to the insufficient quality of evidence. Studies in this area have often implemented supplementation protocols shorter than 3 months – this length of time is crucial to achieve a significant increase of one of the *n*-3 PUFAs, DHA, in human blood cells (Giles et al., 2015). Furthermore, the quality of evidence from studies on the effect of *n*-3 PUFA supplementation on depressive symptoms is often insufficient. For example, 25% out of 25 studies included in the meta-analysis on the effects of *n*-3 PUFA supplementation on depressive disorder had a high risk of bias (Wolters et al., 2021). Further funnel plot inspection confirmed that the results from those studies may be biased.

Gender Differences

Overall, controlled intervention trials addressing the causal nature of the effect of *n*-3 PUFAs on mood, inflammation, and stress-responsive systems are scarce, and results from the limited number of studies available are divergent. When studying the biological mechanisms of depressive symptoms, it is crucial to consider possible gender differences. Inflammatory responses differ between males and females – responses in females have been shown to be more pronounced than in males (Klein & Flanagan, 2016). Gender differences in inflammatory responses seem to also apply to the peripheral immune system in patients with depression. One cross-sectional study found

that serum levels of IL-6 and TNF-α were higher in depressed females than depressed males (Birur et al., 2017). This suggests that the association between proinflammatory cytokines and depressive symptoms is possibly gender-specific, and hence males and females need to be studied individually.

Current Study

The purpose of the current study was to explore the effect of *n*-3 PUFA supplementation on KYN metabolism and mood, and the effects on KYN metabolism and mood after the induction of an acute, psychological stress. While previous studies suggest that peripheral Trp conversion is mediated by endurance exercise and can influence stress response depressive symptoms, the evidence is based mainly on animal models. Hence, this will be the first study where the combined effects of *n*-3 PUFA supplementation and endurance exercise on KYN will be assessed. In the current study, participants were administered *n*-3 PUFA supplementation or placebo over 12 weeks. *N*-3 PUFA supplementation in this study aimed to reduce inflammation. The *n*-3 PUFA supplementation was controlled by investigating serum concentration and percentage content of *n*-3 PUFAs (*n*-3 PUFA index). Serum concentrations of KYN pathway metabolites were investigated – including KYN, KYNA, QA, xanthurenic acid (XA), picolinic acid (PA), 3-hydroxykynurenine, and 3-hydroxyanthranilic acid (3-HAA). The anti-inflammatory markers assessed were: interleukin 6 receptor alpha (IL-6R alpha), interleukin 10 (IL-10), glycoprotein 130 (gp130), and tumor necrosis factor receptor 1 (TNF R1). The stress response in participants was experimentally induced by conducting a stress manipulation task. Finally, based on the findings that exercise-induced PGC-1α expression in skeletal muscles might protect against stress-induced

neurobiological mechanisms of depressed mood, the study compared two groups of participants: Physically Inactive and Physically Active males, who potentially have higher KAT activity in skeletal muscles. This study design allowed the investigation of the effect of endurance training on KYN metabolism, inflammation, and mood. Considering the consistent rise in the consumed levels of *n*-6 PUFAs at the expense of *n*-3 PUFAs as well as a more sedentary lifestyle and higher experienced stress in Western countries, this study may have significant potential for therapeutic application and expand our understanding of the mechanisms of how supplementation and exercise can influence mood.

This PhD thesis is composed of three scientific articles published in peer-reviewed open-access scientific journals. Two of these publications are original research studies and one is a systematic review and meta-analysis.

Aims

Original Study (Publications 1 and 2)

- To control *n*-3 PUFA supplementation by investigating serum concentration and percentage content of *n*-3 PUFAs to assess whether participants complied with the supplementation protocol.
- To determine the impact of three months of supplementation with *n*-3 PUFAs on changes in KYN metabolism in Physically Active and Inactive males.
- To determine the impact of three months of supplementation with *n*-3 PUFAs on anti-inflammatory markers (IL-10, gp130, IL-6R alpha, TNF R1) in Physically

Inactive males and a pro-inflammatory marker (IL-6) in Physically Active males.

- To determine the impact of three months of supplementation with *n*-3 PUFAs on mood and depressive symptoms in Physically Inactive males.
- To determine the impact of a stress manipulation test on KYN metabolism after *n*-3 PUFA supplementation in Physically Active and Inactive males.
- To determine the impact of a stress manipulation test on mood after *n*-3 PUFA supplementation in Physically Active and Inactive males.

Systematic Review and Meta-analysis (Publication 3)

- To assess the relationship between physical activity and depressive symptoms in males.
- To assess the relationship between physical activity intensity (low, moderate, high) and depressive symptoms in males.

Materials and Methods

Original Study

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee for Research Projects at the University of Gdańsk (protocol number 44/2020; date of approval: 20 August 2020). Informed consent was obtained from all participants involved in the study. This study was registered at ClinicalTrials.gov with identifier NCT05520437 (14/07/2021 first trial registration).

Study Group

This was an interventional study that recruited Physically Inactive men (N = 51; Omega-3 group: n = 27; Placebo group: n = 24) and Physically Active men (amateur long-distance runners; N = 40; Omega-3 group: n = 20; Placebo group: n = 20). Participants classified as Physically Inactive did not meet the World Health Organization recommendations of at least 150 minutes of moderate to vigurous physical activity (MVPA) per week (Bull et al., 2020). Table 1 provides a description of inclusion and exclusion criteria for the two study groups. Participants were instructed to take *n*-3 PUFAs or placebo over 12 weeks. Additionally, during the course of the study, Physically Active males underwent structured progressive endurance training supervised by a track and field coach. From the 51 Physically Inactive men enrolled in the study, four participants dropped out (two from the experimental group and two from the control group). From the 40 Physically Active men enrolled in the study, 14 participants were not included in the final analysis (6 from the experimental group and

8 from the control group), either due to sickness or injury, insufficient training sessions, or other reasons (Tomczyk et al., 2022). As a result, 47 Physically Inactive males (Omega-3 group: *n* = 25; Placebo group: *n* = 22) and 26 Physically Active males (Omega-3 + TRAIN group: *n* = 14; Placebo + TRAIN group: *n* = 12) were included in the final analyses (Table 2). In Publication 1 the whole sample of Physically Inactive males was included. In Publication 2, the whole sample of Physically Active males was included and 11 participants from the Physically Inactive males were chosen through random sampling.

Table 1. Inclusion and Exclusion Criteria for the two study groups (Physically Inactive men and Physically Active men)

Study group	Physically Inactive men	Physically Active men
Inclusion criteria	age between 23 and 52 years MVPA < 150 min/week	age between 29 and 42 years amateur long-distance runners completion of an official 10 km running competition within 37– 57 min consent to carry out only the training courses included in the program and to keep diet as constant as possible during the experimental period
Exclusion criteria	DSM-5 psychiatric disorders other than depression and anxiety, neurological disorders, chronic illnesses, and any other illnesses that could interfere with the study, vigorous physical activity or moderate physical activity over 120 min per week, and use of dietary supplements containing *n*-3 PUFAs or anti-inflammatory drugs	neurological disorders, chronic illnesses, and any other illnesses that could interfere with the study, cigarette smoking, use of dietary supplements containing *n*-3 PUFAs or any other prescribed medications

Table 2. Sample characteristics

Sample Characteristics	Physically Inactive males		Physically Active males	
	Omega-3 (n = 25)	Placebo (n = 22)	Omega-3 + TRAIN (n = 14)	Placebo + TRAIN (n = 12)
	M ± *SD*	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*
Age [years]	36 ± 5	37 ± 7	37 ± 3	37 ± 4
Body mass [kg]	92 ± 14	87 ± 16	76 ± 11	78 ± 8

Procedure

During the first stage of the study, before supplementation, blood samples were collected in Physically Active and Physically Inactive males. Mood and depressive symptoms were also assessed in Physically Inactive males with the UWIST Mood Adjective Check List (UMACL) and the Depression, Anxiety and Stress Scale – 21 Items (DASS-21) respectively. Additionally, Physically Active males participated in an exercise performance test on a treadmill – a graded exercise test to exhaustion. Participants in Omega-3 groups received *n*-3 PUFA supplements (NAMEDSPORT) in the form of softgels over a period of 12 weeks. The supplement is certified by the International Fish Oil Standards™ (IFOS™) Program. The daily dose contained a total of 3,276 mg of Omega 3 (4,000 mg of fish oil of which: EPA 2,234 mg; DHA 916 mg). Participants in the Placebo groups received a placebo in the form of MCT oil capsules with no effect on the hypothesized outcomes. Additionally, Physically Active males

underwent twelve weeks of structured progressive endurance training supervised by a track and field coach (TRAIN).

During the second stage of the study, after 12 weeks of supplementation (combined with endurance training in the Physically Active group), blood samples were collected and mood was assessed. Depressive symptoms were also assessed in Physically Inactive males. Additionally, Physically Active males participated in an exercise performance test. This was followed by inducing a stress response in both groups of participants with a validated stress manipulation test – the Trier Social Stress Test (TSST). Immediately after the stress manipulation test and one hour after stress manipulation test, blood samples were drawn and mood was reassessed in both Physically Active and Physically Inactive males. *Fig*. 2 presents the stages of the study.

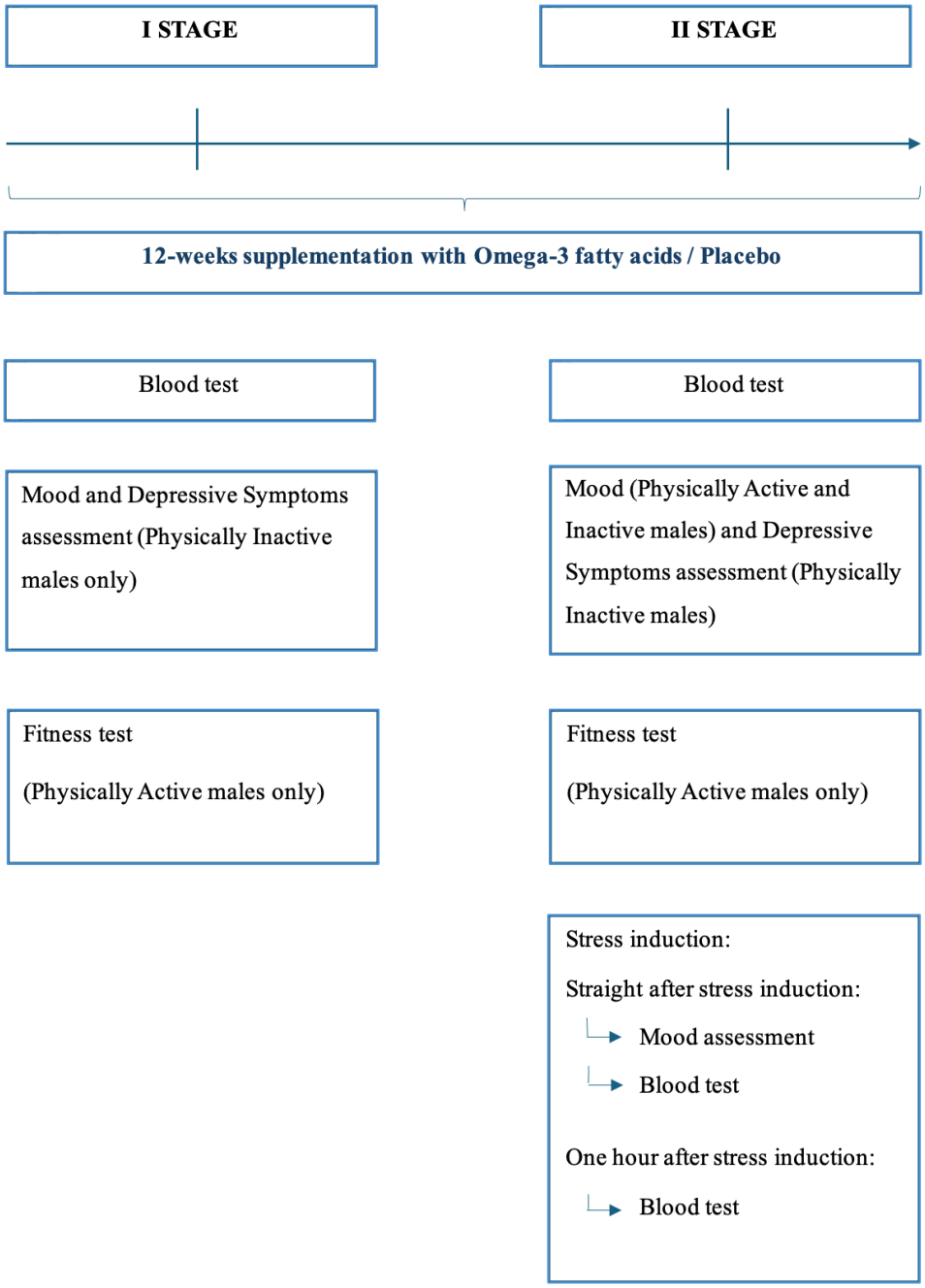

Fig. 2. Stages of the study

Methods

Biochemical analysis – EPA and DHA. Gas chromatography–mass spectrometry (GC–MS) was used to identify the percentage share and concentration of EPA and DHA

in serum. The method is described in detail in Publication 1 under the *Methods* section.

Assessment of Inflammation Markers. Thermo Fisher Scientific Elisa Analyzer (Thermo Fisher Scientific Waltham, MA, USA) and enzyme-linked immunosorbent assay kits (DRG International, Inc., Springfield, NJ, USA) were used to analyse inflammation markers – IL-6R alpha, IL-10, TNF RI, and gp130. Plasma concentrations of IL-6 was measured using sandwich ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol (catalog no. HS600B).

Biochemical analysis – KYN metabolism. Liquid chromatography with tandem mass spectrometry (LC-MS-MS) was used to determine plasma concentrations of metabolites of KYN metabolism - KYN, KYNA, QA, XA, PA, 3-HK, and 3-HAA. The method is described in detail in Article 1. under the *Methods* section.

Supplements. The Namedsport Omega 3 Double Plus (Namedsport, Lombardy, Italy) dietary supplement was used in the study (3,276 mg/day including 2,234 mg EPA; 916 mg DHA). Now Foods Medium Chain Triglyceride (MCT) oil was used as a placebo (4,000 mg/day).

Mood Assessment. The Polish adaptation of the UWIST Mood Adjective Check List (UMACL; Matthews, Jones, & Chamberlain, 1990) was used to assess mood (Goryńska, 2005). The questionnaire comprises a list of 29 adjectives. Participants rate on a scale of 1 to 4 the extent to which their present mood corresponds to each of the adjectives. The final score is represented by the three dimensions: energetic arousal (EA), tense arousal

(TA), and hedonic tone (HT). A high score for EA corresponds to being restful, energetic, and vigorous; a high score for TA corresponds to being stressed, anxious, or tense; and a high score for HT is associated with being cheerful, satisfied, and happy. The Polish adaptation of the UMACL is reliable and valid, with Cronbach's alpha for the individual subscales between 0.79 and 0.92 (Goryńska, 2005).

Assessment of Depressive Symptoms. The Polish adaptation of the Depression, Anxiety and Stress Scale – 21 Items (DASS-21; Lee, 2019) was used to assess depressive symptoms (Makara-Studzińska et al., 2022). DASS-21 measures the emotional states of depression, anxiety, and stress (for each of the subscales, the minimum score is 10 and the maximum score is 42, with higher scores representing higher levels of the emotional states). The Polish version of the DASS-21 is reliable and valid. The Cronbach's alpha for the overall score is 0.93 and Cronbach's alpha for the individual subscales is between 0.80 and 0.86 (Zawislak et al., 2020).

Stress Manipulation Test. The Trier Social Stress Test (TSST) was used to induce a stress response in participants (Kirschbaum, Pirke & Hellhammer, 1993). The TSST is a three-stage psychosocial stress task conducted in front of a panel of ex-perimenters. It includes (i) a 3 min preparation period, (ii) a 5 min public speaking task, and (iii) a 5 min metal arithmetic task. During the preparation period participants were asked to make an interview-style presentation, which they then presented. In the mental arithmetic task, participants were asked to sequentially subtract the number 7 from a 4 -digit number. If the participants made a mistake, the interviewer asked them to start over. The TSST is a reliable method for inducing psychosocial stress, with Cronbach's alpha = 0.83 (Giles et al., 2014).

Statystical analysis - Publication 1

For every studied outcome variable, a two-way mixed models ANOVA with group (Omega-3/Placebo), time (before/after supplementation), and the group x time interaction as fixed effects and participant as random effect was performed. Additionally, for variables measured before and after the stress task, similar two-way mixed models ANOVA (with time effects before, after, and 1 h after stress task) was performed.

Results - Publication 1

Fatty Acids Profile

Significant group-by-time interactions were found for percentage share and concentration of EPA and DHA in serum (*Fig.* 3). Post hoc comparisons revealed significantly higher percentage share and concentration of EPA and DHA in serum values at t1 (after supplementation) in comparison to t0 (before supplementation) for the Omega-3 group but not for the Placebo group.

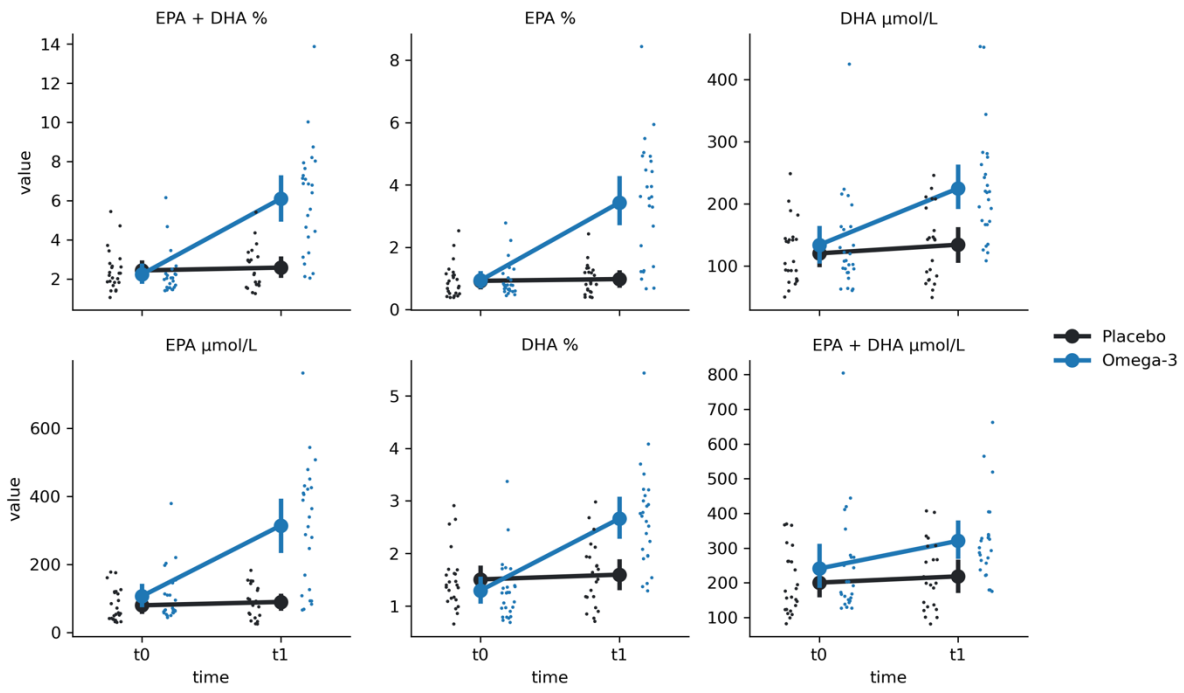

Fig. 3. Distributions of the group x time interaction effect on the fatty acids profiles in the Placebo (black) and Omega-3 (blue) groups at times t0 (before supplementation) and t1 (after supplementation). Large points represent mean values, with error bars representing a 95% confidence intervalaround the mean value. Small points represent single observations

Depressive Symptoms and Mood Measures

For DASS, there were no significant group-by-time interactions (all *p*-values > 0.05), suggesting that *n*-3 PUFA supplementation had no effect on DASS outcomes. For UMACL HT, a significant group-by-time interaction ($F(1, 49) = 6.50$, $p = 0.014$) was found. Post hoc tests indicated that there was an increase in scores from t0 to t1 in the Placebo group (Mt0 = 30.83 ± 6.38, Mt1 = 34.38 ± 4.69; $t = -4.00$; $p < 0.001$) but not in the Omega-3 group (Mt0 = 31.56 ± 4.25, Mt1 = 32.0 ± 4.93; $t = -0.53$, $p = 0.60$). No significant differences were found for other UMACL subscales ($p > 0.05$).

KYN Pathway

No significant group-by-time interactions were found (all *p*-values > 0.05) for KYN metabolites.

Inflammation Markers

Significant group-by-time interactions were found for inflammation markers (GP 130, IL-6R alpha, and TNF RI) (*Fig. 4*). Post hoc tests revealed significantly higher values of TNF RI, GP 130, and IL-6R alpha at t1 compared to t0 in the Omega-3 group.

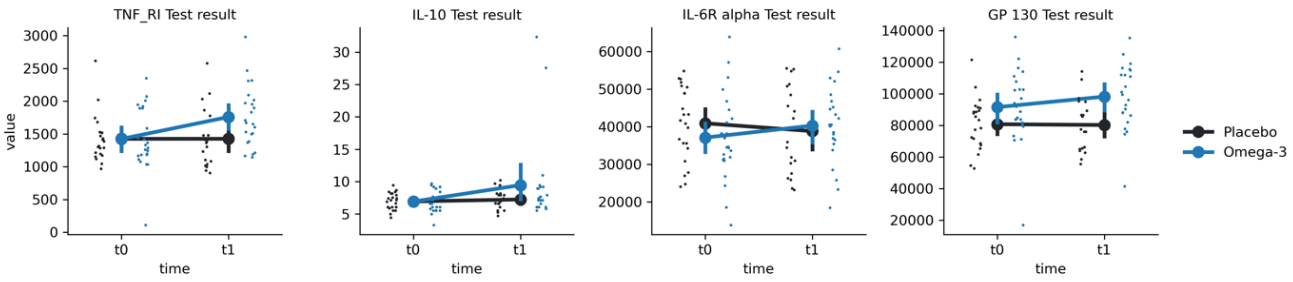

Fig. 4. Distributions of the group x time interaction effect on inflammation markers in the Placebo (black) and Omega-3 (blue) groups at times t0 (before supplementation) and t1 (after supplementation). Large points represent mean values, with error bars representing a 95% confidence interval around the mean value. Small points represent single observations.

Stress Induction

No significant group-by-time interactions of stress induction on any of the KYN metabolites (all *p*-values > 0.05) were found. Similarly, no effects of stress induction on UMACL outcomes (all *p*-values > 0.05) were found.

Statystical analysis - Publication 2

Separate two-way repeated measures analyses of variance (rANOVA) were used with group (Omega-3/Placebo) and time (before supplementation (t0), after supplementation (t1)). To estimate interaction effect sizes, partial eta squared (ηp2) was computed with $\eta p2 \geq 0.01$ indicating small, ≥ 0.059 medium and ≥ 0.138 large effects.

Results - Publication 2

Fatty Acids Profile

Significant group-by-time interactions were found for percentage share and concentration of EPA and DHA in red blood cells and plasma (Table 3). Post hoc comparisons revealed significantly higher percentage share and concentration of EPA and DHA values at t1 (after supplementation) in comparison to t0 (before supplementation) for the Omega-3 + TRAIN group but not for the Placebo + TRAIN group.

	Omega-3 + TRAIN (n=14)			**Placebo + TRAIN (n=12)**			**rANOVA**
	t0	t1	Δ (CI)	t0	t1	Δ (CI)	Group x time
DHA (% in red blood cells)	4.68±1.03	6.69±0.76*	2.01 (1.66;2.35)	4.42±1.11	4.68±1.01	0.2 (-0.28;0.68)	**<0.01**
EPA (% in red blood cells)	1.11±0.39	4.88±1.11*	3.77 (3.14;4.41)	1.16±0.3	1.18±0.44	-0.01 (-0.28;0.26)	**<0.01**
DHA (% in plasma)	2.38±0.5	4.01±0.5*	1.64 (1.32;1.96)	2.18±0.69	2.2±0.78	-0.09 (-0.59;0.4)	**<0.01**
EPA (% in plasma)	1.17±0.51	5.15±1.53*	3.94 (3.05;4.83)	1.19±0.38	1.04±0.46	-0.21 (-0.61;0.2)	**<0.01**
DHA + EPA (% in red blood cells)	5.79±1.35	11.57±1.7*	5.78 (4.9;6.66)	5.67±1.37	5.86±1.39	0.19 (-0.5;0.88)	**<0.01**
DHA + EPA (% in plasma)	3.59±0.97	9.16±1.97*	5.58 (4.43;6.73)	3.38±0.97	3.08±1.14	-0.3 (-1.16;0.56)	**<0.01**

Note: values are presented as mean ± SD; EPA - eicosapentaenoic acid; DHA - docosahexaenoic acid

Table 3. EPA, DHA and their sum as a percentage of total fatty acids in red blood cells and plasma. Values are presented as mean ± SD; EPA—eicosapentaenoic acid; DHA—

docosahexaenoic acid. Δ—t1 to t0 changes; CI—confidence interval of changes; rANOVA—repeated measurement analysis of variance*- statistically significant difference compared to t0; $p < 0.05$. Data are presented as mean ± SD *statistically significant difference in groups (Δ) with a trend of higher percentages in the Omega-3 + TRAIN group and lower percentages in the Placebo + TRAIN group.

KYN Pathway

A significant group-by-time interaction was found for 3-HK ($p = 0.01$; ηp2 = 0.22), where post hoc comparisons indicated a significant increase in the Omega-3 group, with no change in the Placebo group (Table 4). A significant group-by-time interaction was also found for PA, where a significant increase was noticed in Omega-3 + TRAIN group but not the Placebo + TRAIN group.

	Omega-3 + TRAIN (n=14)			**Placebo + TRAIN (n=12)**			**rANOVA p (η_p^2)**
	t0	t1	Δ (CI)	T0	t1	Δ (CI)	T x G
3-HK [ng/mL]	4.73±1.33	5.09±1.73*	0.36 (0.06;0.67)	4.54 ± 0.71	4.32 ± 0.5	-0.22 (-0.56;0.15)	**0.01 (0.22)**
PA [ng/mL]	4.5±1.72	5.8±1.81*	1.3 (0.83;1.76)	5.12 ± 1.47	5.31 ± 1.58	0.23 (-0.45;0.91)	**0.01 (0.26)**

Table 4. The effect of *n*-3 PUFA supplementation combined with 12-week structured running training on plasma Trp metabolite concentrations in Physically Active participants.
The table only includes statistically significant group x time interactions.

Mood Measures: before and after stress induction

The scores on the three dimensions of the Mood Adjective Check List scale were not significantly different before and after stress induction (all *p*-values > 0.05)

To see full results, please refer to the *Results* sections in Publications 1 and 2.

Systematic Review and Meta-analysis (Publication 3)

The systematic review and meta-analysis was registered in the International *Prospective Register of Systematic Reviews* (PROSPERO) number CRD42023417219. The systematic review and meta-analysis was conducted in accordance with the guidelines outlined by PRISMA 2020 (Page et al., 2021).

Inclusion and Exclusion Criteria

The systematic review and meta-analysis included: 1) cross-sectional and cohort studies that included 2) male participants aged 18 years or older, 3) assessed depressive symptoms with validated screening measures, 4) assessed the participants' levels of physical activity, and 5) were published in peer-reviewed journals. Excluded papers included 1) studies without primary data, 2) data from poster presentations and conferences, and 3) studies that recruited participants with physical and mental disorders (other than depressive symptoms).

Search Strategy

An electronic search of Medline, Web of Science, and Pubmed from January 1, 2003 to February 20, 2023. The search used relevant terms relating to physical activity (e.g., physical activit*, exercis*) and depressive symptoms (e.g., depress* symptoms, depression). After removing duplicates, the titles and abstracts identified with the search terms were analysed by two independent reviewers who applied the eligibility criteria and generated a final list of included articles (*Fig. 5*).

The method is described in detail in Publication 3 under the *Methods* section

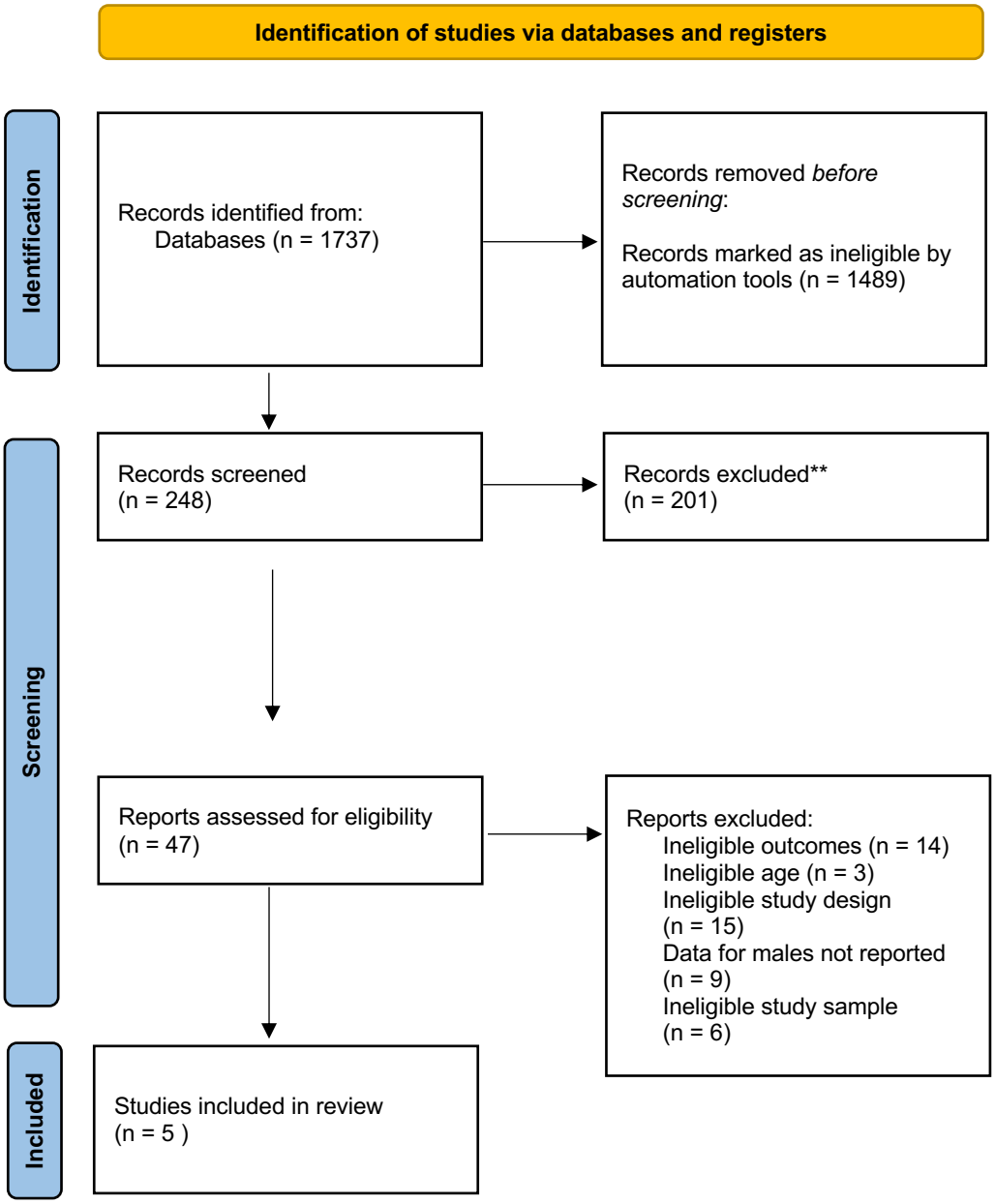

Fig. 5. Flowchart of study selection. Flowchart adapted from the PRISMA 2020 statement

Study quality assessment

To identify the risk of bias *Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies* (Institute, 2017) was used.

Statistical Analysis

Odds ratios and their respective confidence intervals were extracted from eligible studies and analysed using random-effects meta-analytic models. Three models were constructed, comparing groups with either low, moderate, or high levels of physical activity, with no physical activity as a reference.

The method is described in detail in Publication 3 under the *Methods* section.

Results

A random effects meta-analytic model of pooled data from 5 studies that incorporated measures of moderate physical activity predicted an odds ratio estimate of 0.68 (95 % C.I. 0.50–0.93). The model estimate indicated that medium physical activity has a statistically significant effect on depressive symptoms (Est. -0.38; SE = 0.11; t(4) = −3.41; $p < 0.001$) (*Fig.* 6). Additionally, the Chi^2 test indicated substantial heterogeneity between the included studies (Q(4) = 20.36; $p < 0.001$; $tau^2 = 0.05$, tau^2 SE = 0.04; I^2 = 80.3 %).

Random effects meta-analytic models that incorporated measures of low physical activity and high physical activty predicted odds ratio estimates of 0.79 (95 % C.I. 0.52–1.20) and 0.78 (95 % C.I. 0.47–1.30) respectively. The models indicated that low physical activity and high physical activity do not have a statistically significant effect on depressive symptoms. Additionally, the Chi^2 test indicated substantial heterogeneity between the included studies.

To see full results, please refer to the *Results* section in Publication 3.

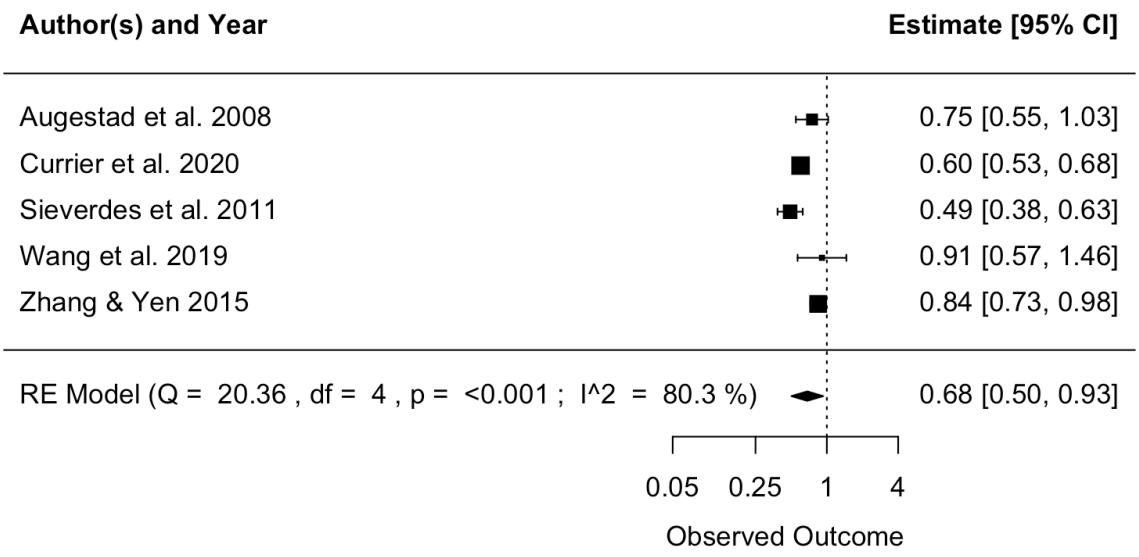

Fig. 6. Meta-analysis of studies on the effect of moderate physical activity on depressive symptoms.

CHAPTER 2: SCIENTIFIC ARTICLES

No Effects of Omega-3 Supplementation on Kynurenine Pathway, Inflammation, Depressive Symptoms, and Stress Response in Males: A Placebo-Controlled Trial

Authors: Monika Bidzan-Wiącek, Maja Tomczyk, Magdalena Błażek, Adriana Mike, Jędrzej Antosiewicz

Journal: Nutrients

Date of publication: 31.10.2024

Key findings

- A significant group-by-time interaction was found for the following inflammation markers: gp130 ($p = 0.011$), IL-6R alpha ($p = 0.003$), and TNF RI ($p = 0.002$).
- No significant group-by-time interactions were found for depressive symptoms or mood, except for HT ($p = 0.014$).
- No significant group-by-time interactions were found for KYN metabolites and stress-induced changes to the KYN metabolites and mood following a laboratory stressor.
- Overall, increasing *n*-3 PUFA levels in healthy males ameliorated inflammatory markers but did not ameliorate KYN metabolism, depressive symptoms, or mood; increasing *n*-3 PUFA levels did not ameliorate KYN metabolism or mood after stress induction.

Author contribution

Monika Bidzan-Wiącek: conceptualization, methodology, investigation, project administration, funding acquisition, writing of the original draft, review and editing

Maja Tomczyk: methodology, investigation, review and editing

Jędrzej Antosiewicz: conceptualization, methodology, review and editing

Magdalena Błażek: methodology, review and editing

Adriana Mika: investigation

Omega-3 fatty acid supplementation affects tryptophan metabolism during a 12-week endurance training in amateur runners: a randomized controlled trial

Authors: *Tomczyk, M., *Bidzan-Wiącek, M., Kortas, J. A., Kochanowicz, M., Jost, Z., Fisk, H. L., Calder, P. C. & Antosiewicz, J

* contributed equally

Journal: Scientific Reports

Nature Portfolio

Date of publication: January 2024

Key findings

- We found that *n*-3 PUFA supplementation accompanied by endurance training led to increased plasma concentrations of picolinic acid (PA), a neuroprotective KYN metabolite, and the neurotoxic 3-HK.
- Concentrations of 3-HK and PA significantly increased only in the Physically Active Omega-3 group ($p = 0.01$) but not in the Physically Active Placebo group or either Physically Inactive group.
- The ratio of neurotoxic KYN+3HK to neuroprotective XA+PA decreased, which indicated beneficial effects of the intervention
- No changes in mood or IL-6 concentrations were observed in either group.
- Supplementation with *n*-3 PUFAs during endurance training has beneficial effects on KYN neuroprotective metabolites.

Author contribution

Maja Tomczyk and Monika Bidzan-Wiącek contributed equally to the publication

(Autorki Maja Tomczyk i Monika Bidzan-Wiącek miały taki sam wkład do publikacji)

Monika Bidzan-Wiącek: conceptualization, methodology, investigation, funding acquisition, writing of the original draft, review & editing

Maja Tomczyk: conceptualization, methodology, investigation, funding acquisition, project administration, writing of the original draft, review & editing

Jędrzej Antosiewicz: conceptualization, methodology, writing of the original draft, review & editing

Zbigniew Jost: methodology, investigation, writing of the original draft, review & editing

Magdalena Kochanowicz: methodology, writing of the original draft, review & editing

Jakub Kortas: methodology, writing of the original draft, review & editing

Helena Fisk: methodology, writing of the original draft, review & editing

Philip Calder: methodology, writing of the original draft, review & editing

The relationship between physical activity and depressive symptoms in males: A systematic review and meta-analysis

Authors: Monika Bidzan-Wiącek, Magdalena Błażek, Jędrzej Antosiewicz

Journal: Acta Psychologica

Elsevier

Date of publication: January 2024

Key findings

- Results indicated significant effects of moderate physical activity on depressive symptoms (OR = 0.68; 95% CI: 0.50–0.93).
- No effect of low and high physical activity on depressive symptoms was found.
- High heterogeneity between the studies should be considered when interpreting the results.

Author contribution

Monika Bidzan-Wiącek: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing of the original draft, Review & editing

Magdalena Błażek: Supervision

Jędrzej Antosiewicz: Funding acquisition, Supervision

CHAPTER 3: DISCUSSION

This PhD thesis is composed of three scientific articles published in peer-reviewed open-access scientific journals. Below, I present the main findings from the study.

- *N*-3 PUFA supplementation improved anti-inflammatory markers in Physically Inactive men.
- *N*-3 PUFA supplementation had no effect on any KYN metabolites among a group of Physically Inactive males.
- *N*-3 PUFA supplementation had a beneficial effect on KYN metabolites among Physically Active males. *N*-3 PUFA supplementation accompanied by endurance training led to increased plasma concentrations of a neuroprotective KYN metabolite, PA, and the neurotoxic 3-HK.
- The ratio of neurotoxic KYN+3HK to neuroprotective XA+PA decreased, which indicated beneficial effects of the intervention.
- *N*-3 PUFA supplementation had no effect on mood and depressive symptoms in Physically Inactive males except for Hedonic Tone.
- *N*-3 PUFA supplementation had no effect on mood or KYN metabolism after stress induction in either Physically Active or Physically Inactive males.
- The systematic review and meta-analysis indicated that the intensity of physical activity may be important when considering mood

Main Findings

Original Study (Publications 1 and 2)

Publication 1 investigated only Physically Inactive men, while Publication 2 investigated both Physically Active men and a random sample of Physically Inactive men (Table 2). Publication 1 showed that *n* -3 PUFA supplementation had no effect on

any KYN metabolites among a group of Physically Inactive men. Publication 2 showed that *n*-3 PUFA supplementation in Physically Active men had a beneficial effect on KYN metabolites. Specifically, 12 weeks of *n*-3 PUFA supplementation accompanied by endurance training increased plasma concentrations of PA. PA is a KYN metabolite, which – similarly to KYN, 3-HK, and xanthurenic acid (XA) – can penetrate the blood-brain barrier and has been reported to possess a wide range of neuroprotective properties as well as to modulate the immune system (Guillemin et al., 2001). Consequently, a significant increase in PA in amateur runners who supplemented *n*-3 PUFAs seems to be a marker of an adaptive response to exercise. At the same time, a statistically significant increase in 3-HK was observed among Physically Active men who supplemented *n*-3 PUFAs. Meanwhile, the ratio of neurotoxic KYN+3HK to neuroprotective XA+PA decreased. Although 3-HK is a neurotoxic KYN metabolite, it can further be converted to either PA or QA. In Physically Active men who supplemented *n*-3 PUFAs, despite a significant increase of PA, the levels of quinolinic acid (QA) remained stable. It seems that exercise-induced coactivator PGC-1α in Physically Active participants who supplemented *n*-3 PUFAs might have favoured the conversion of 3-HK to the neuroprotective PA over the neurotoxic QA and hence the PA plasma levels were increased in this group. Furthermore, among Physically Active men who supplemented *n*-3 PUFAs, although not statistically significant, there was a large Group x Time interaction for KYNA and a medium Group x Time interaction for XA. Both KYNA and XA are neuroprotective KYN metabolites, which form from KYN and 3-HK respectively under coactivator PGC-1α, which is activated when adaptation to endurance training occurs (*Fig. 1*). Consequently, endurance exercise together with *n*-3 PUFA supplementation seems to be beneficial for KYN metabolism.

Neither Physically Inactive men who supplemented *n*-3 PUFAs or placebo nor Physically Active men who supplemented placebo had significant changes to KYN metabolites. This suggests a moderating effect of physical activity on the relationship between the KYN pathway and the fatty acid profile. Moreover, the study indicated that *n*-3 PUFA levels improved majority of anti-inflammatory markers in Physically Inactive men but did not ammeliorate a pro-inflammatory cytokine IL-6 in Physically Active men. Non-significant changes in serum IL-6 in Physically Active group may be explained by adequate IL-6 levels in this group before the supplementation. Additionally, there was no effect of *n*-3 PUFA supplementation on mood (except for HT) and depressive symptoms in Physically Inactive males. The study found no evidence that increasing *n*-3 PUFA levels in Physically Active and Inactive males using *n*-3 PUFA supplements has any benefit for mood following stress induction. While depressive symptoms were not assessed in Physically Active men, the systematic review and meta-analysis suggested that the beneficial effect of physical activity on depressive symptoms might be dependent on the intensity of the physical activity. The study group in the controlled trial involved participants engaged in high intensity physical activity, which might explain the non-significant effect of physical activity on mood. Alternatively, a longer protocol should have been implemented in order to observe a change in mood (Raeder et al., 2007).

Systematic Review and Meta-analysis (Publication 3)

This is the first meta-analysis to assess the relationship between physical activity and depressive symptoms in healthy males that takes into consideration the intensity of the physical activity. This study suggests that the intensity of physical activity seems to be

crucial for ameliorating depressive symptoms. The meta-analysis indicated significant effects of moderate physical activity on depressive symptoms. Meanwhile, no effect of low or high physical activity on depressive symptoms was found.

Strengths and Limitations of the Conducted Studies

Original Study (Publications 1 and 2)

The many strengths of this placebo-controlled trial include the 12-week supplementation period – the time crucial to achieve a significant increase of DHA, one of the *n*-3 PUFAs, in human blood cells. To ensure construct validity, the supplement chosen in this study is certified by the International Fish Oil Standards™ (IFOS™) Program. Plasma EPA and DHA concentrations were also measured to investigate whether *n*-3 PUFA supplementation was successful. In addition, all psychological tools applied in this study are valid and reliable.

Some limitations of the study include the methodological limitations of the materials used. Firstly, stress was only induced at one time point. The reasoning behind inducing stress only at one time point was based on the familiarity of the laboratory stressor. Stress induction before and after the intervention would require applying the same procedures, and hence the stressor could have been perceived as being less stressful at the second time point (Allen et al., 2017). Considering that each participant completed the acute laboratory stressor only at one time point (i.e., after the intervention), the results were not adjusted for baseline reactivity. Consequently, the results did not account for potential interindividual variability.

Furthermore, the duration of the study seems adequate to achieve a significant change in serum concentrations of KYN metabolites, *n*-3 PUFA derivatives, and inflammatory markers. However, it seems that in order to observe a change in mood and depressive symptoms, a longer protocol should have been implemented (Raeder et al., 2007). Moreover, although the UMACL can be used as a repeated measure, it may not be sensitive to minor mood changes (Goryńska, 2005). Full discussion of the study's strengths and limitations is included in Publications 1 and 2 in the *Limitations* subsections of the *Discussion* sections.

Systematic Review and Meta-analysis (Publication 3)

This is the first meta-analysis to assess the relationship between physical activity and depressive symptoms in healthy males that takes into consideration the intensity of the physical activity. The meta-analysis yielded a total of 13,763 males. The selection of cross-sectional studies in this meta-analysis has a number of advantages over a randomized controlled trial (RCT). Although RCTs may show a clear cause–effect relationship between the outcomes, participants may be less representative due to the methodological design and inclusion criteria. Firstly, RCTs studying the effect of physical activity on depressive symptoms recruit participants who are willing to take part in the standardized exercise regime. Secondly, recruited participants are willing and motivated to participate in the study, which can be a concern when studying depressive symptoms, which by nature can result in social withdrawal. The cross-sectional design of the study on the other hand allows observing the relationship between the variables without interfering with them. Consequently, the cross-sectional study design could have yielded relatively representative data.

However, it is important to consider limitations when drawing conclusions from this meta-analysis. When interpreting the results, the relatively low number of studies and the high heterogeneity of the selected studies needs to be considered. Funnel plot analysis for all three models (between 80.3% and 93.6% for the moderate physical activity model and high physical activity model, respectively) indicated that a substantial number of studies with relatively low SE estimates had a relatively high variance in observed outcome. High heterogeneity of the included studies can stem from: different participant characteristics; non-unified measures of depressive symptoms and physical activity levels; different studies using different methodologies; and different cultural backgrounds. Moreover, sensitivity analysis revealed that one study (Wang et al., 2019) might have impacted the overall findings. Finally, classification of low, medium and high physical activity might have differed between the studies. The results therefore need to be interpreted with caution. A full discussion of the study's limitations is included in Publication 3 in the *Discussion* section (5.2 Limitations).

Implications

Overall, it seems that the clinical usefulness of *n*-3 PUFA supplementation in healthy males for improving mood is questionable. The Academy of Nutrition and Dietetics recommends at least 500 mg/day of EPA and DHA for adults (Vannice & Rasmussen, 2014). The health benefits promoted include mental health. Our findings suggest that daily *n*-3 PUFA supplementation alone may not have any clinical usefulness for improving mood in a non-clinical group of males without a diagnosis of major

depressive disorder. Yet, it is successful in ameliorating inflammation markers, which can be beneficial for overall health.

The findings from meta-analysis highlight the importance of medium-intensity physical activity on depressive symptoms and the findings from the original study highlight the importance of endurance physical activity combined with *n*-3 PUFA supplementation on the KYN pathway. *N*-3 PUFA supplementation alone in healthy, Physically Inactive males did not improve the KYN pathway. Given the relatively low level of physical activity among Polish men, with 41% of Polish men claiming to participate in sports or recreational activity (Główny Urząd Statystyczny, 2022), it seems that over half of Polish males may be disadvantaged in terms of a potentially higher risk of inflammation, neurotoxic KYN metabolites, and depressive symptoms.

Meanwhile, it seems that the intensity of physical activity is an important moderator of the relationship between physical activity and depressive symptoms. Various levels of intensity of physical activity were not included in the original study as all participants were involved in a high intensity physical activity. Study 3 indicated that moderate physical activity seems to be the most beneficial for depressive symptoms. Meanwhile, high physical activity has not been shown to improve mood. In fact, some studies included in the meta-analysis indicate a negative effect of high physical activity on mood.

Conclusions

The main observation from the placebo-controlled experiment is that elevating *n*-3 PUFA levels had no effect on any KYN metabolites among a group of physically inactive men, however *n*-3 PUFA supplementation had a beneficial effect on KYN metabolites among Physically Active males. Specifically, the study found that *n*-3 PUFA supplementation accompanied by endurance training leads to increased plasma concentrations of the neuroprotective metabolite picolinic acid. This suggests a moderating effect of physical activity on the relationship between the KYN pathway and the fatty acid profile.

Moreover, elevating *n*-3 PUFA levels ameliorates inflammatory markers among healthy, physically inactive males. The study did not indicate a beneficial effect of *n*-3 PUFA supplementation on mood. While depressive symptoms were not assessed in the original study, the systematic review and meta-analysis suggested that when considering the effect of physical activity on depressive symptoms, it may be important to consider the intensity of the physical activity. Based on the meta-analysis, it can be expected that participants with a 'medium' intensity of physical activity might have yielded different results on mood, with a more beneficial effect of *n*-3 PUFA supplementation on mood.

Overall, it seems that the clinical usefulness of *n*-3 PUFA supplementation in healthy males to improve mood is questionable. When drawing conclusions from this study, it is crucial to consider the study group. The study group consisted of healthy males with no diagnosis of major depressive disorder. Thus, the study investigated changes in mood and depressive symptoms in healthy males.

Future research on *n*-3 PUFA supplementation should consider the intensity of physical activity. It can be speculated that moderate physical activity together with *n*-3 PUFA supplementation could have a beneficial effect on both KYN metabolism and mood.

VI. References

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VII. Other scientific articles and monographs

I. Scientific articles

Bidzan L., Jurek P., Olech M., Bidzan-Wiącek M., Bidzan-Bluma I., & Bidzan M. (2023) Somatic comorbidity and the progression of cognitive impairment. *Frontiers in Aging Neuroscience,15,*1219449. doi:10.3389/fnagi.2023.1219449

Impact Factor: 4.1; MEiN scoring: 100

Bidzan L., Piasecki T., Bidzan-Wiącek M. (2023). *Rokowanie* w *zaburzeniach depresyjnych* wieku podeszłego w oparciu o badanie prospektywne. *Geriatria, 17*(2), 53-60.

MEiN scoring: 20

Mueller-Haugk, S., Bidzan-Bluma, I., Bidzan-Wiącek, M., Bulathwatta, D. T., & Stueck, M. (2023). Anxiety and coping during COVID-19. Investigation of anxiety management types in a German and Polish sample. *Health Psychology Report, 11*(4), 282–294. https://doi.org/10.5114/hpr/171884

Impact Factor: 2.2; MEiN scoring: 40

Bidzan, L., Shan, A., Piasecki, T., Bidzan-Wiącek, M., & Grabowski, J. (2022). Depressive disorder in old age: an early report of a 6-month prospective study. *Geriatria, 16*(2), 69-74.

MEiN scoring: 20

Bidzan, M., & Bidzan, L. (2020). Masa ciała a zaburzenia czynności poznawczych [Body weight and cognitive impairment.] *Neuropsychiatria Neuropsychologia* [*Neuropsychiatry and Neuropsychology*], *15*(1), 51-59.

Impact Factor: 0.4; MEiN scoring: 40

Bidzan-Bluma, I., Bidzan, M., Jurek, P., Bidzan, L., Knietzsch, J., Stueck, M., & Bidzan, M. (2020). A Polish and German population study of quality of life, well-being, and life satisfaction in older adults during the COVID-19 pandemic. *Frontiers in Psychiatry*, *11*, 585813. https://doi.org/10.3389/fpsyt.2020.585813

Impact Factor: 3.2; MEiN scoring: 140

Article cited 234 times since being published.

Bidzan, M., Bidzan-Bluma, I., Szulman-Wardal, A., Stueck, M., & Bidzan, M. (2020). Does self-efficacy and emotional control protect hospital staff from COVID-19 anxiety and PTSD symptoms? Psychological functioning of hospital staff after the announcement of COVID-19 coronavirus pandemic. *Frontiers in Psychology*, *11*, 552583. https://doi.org/10.3389/fpsyg.2020.552583

Impact Factor: 2.6; MEiN scoring: 70

Article cited 65 times since being published.

Dymecka, J., Bidzan-Bluma, I., Bidzan, M., Borucka-Kotwica, A., Atroszko, P., & Bidzan, M. (2020). Validity and reliability of the Polish adaptation of the Health-Related Hardiness Scale–the first confirmatory factor analysis results for a commonly used scale. *Health Psychology Report*, *8*(3), 248-262.

Impact Factor: 2.2; MEiN scoring: 40

Bidzan, M., Yousaf, O., Lipowski, M., & Lipowska, M. (2018). How health-related behaviors predict body-esteem in men. American journal of men's health, 12(6), 1901-1907. doi:10.1177/1557988318801634

Impact Factor: 2.4; MEiN scoring: 70

Bidzan, M. (2017). Biological bases of dissociative amnesia. *Acta Neuropsychologica, 15*(1), 1-11. doi:10.5604/12321966.123319

Impact Factor: 1.0; MEiN scoring: 70

II. Monographs

Bidzan M., Jurek P., Bidzan-Wiącek M., Bidzan-Bluma I., Szulman-Wardal A. (2022). Zadowolenie odbiorców z usług medycznych: uwarunkowania, konsekwencje i diagnoza. Difin, ISBN 978-83-8270-059-6

MEiN scoring: 80

Impact Factor (IF) total score: 18.1

MEiN total score: 690

Total Impact Factor and Total MEiN scoring does not include articles from the doctoral thesis

VIII. APPENDICES

Appendix 1

NARODOWE CENTRUM NAUKI

DOW.420.119.63.2019 Kraków, dnia 18-05-2020

DECYZJA
DYREKTORA NARODOWEGO CENTRUM NAUKI
Nr DEC-2019/35/N/NZ7/03757

Na podstawie art. 33 ust. 1 w związku z art. 27 ust. 3 ustawy z dnia 30 kwietnia 2010 r. o Narodowym Centrum Nauki (t.j. Dz.U. z 2019 r. poz. 1384) po rozpatrzeniu wniosku o finansowanie projektu badawczego o nr rejestracyjnym 2019/35/N/NZ7/03757 złożonego w ramach konkursu PRELUDIUM 18 na projekty badawcze

przyznaję

podmiotowi:

Gdański Uniwersytet Medyczny,

środki finansowe w wysokości: **190 800 zł** (słownie: sto dziewięćdziesiąt tysięcy osiemset zł),

na realizację projektu badawczego

pt. **Wpływ suplementacji kwasami omega-3 na indukowany stresem nastrój i metabolizm kinureniny u mężczyzn aktywnych i nieaktywnych fizycznie**,

który realizować będzie Gdański Uniwersytet Medyczny, Wydział Nauk o Zdrowiu z Oddziałem Pielęgniarstwa i Instytutem Medycyny Morskiej i Tropikalnej.

Kierownikiem projektu będzie Pan/i **mgr Monika Mariola Bidzan - będący/a wnioskodawcą,**

z zastrzeżeniem dopełnienia następującej czynności: przedłożenia w formie elektronicznej, projektu umowy o realizację i finansowanie projektu badawczego podpisanego kwalifikowanym podpisem elektronicznym w standardzie PAdES przez osobę/y umocowaną/e do podpisywania umów w imieniu podmiotu wskazanego we wniosku jako podmiot realizujący oraz kierownika projektu badawczego.

Projekt umowy należy przesłać w formie elektronicznej na adres Elektronicznej Skrzynki Podawczej Narodowego Centrum Nauki: /ncn/SkrytkaESP w terminie 2 miesięcy od dnia doręczenia niniejszej decyzji wnioskodawcy.

Niedotrzymanie ww. terminu skutkować będzie odmową podpisania umowy przez Narodowe Centrum Nauki oraz uchyleniem niniejszej decyzji w trybie art. 162 § 2 ustawy z dnia 14 czerwca 1960 r. Kodeks postępowania administracyjnego (t.j. Dz.U. z 2020 r. poz. 256).

Projekt umowy o realizację i finansowanie projektu badawczego wraz z załącznikami dostępny jest w systemie ZSUN/OSF (Zintegrowany System Usług dla Nauki/Obsługa Strumieni Finansowania) na stronie www.osf.opi.org.pl.

Środki finansowe zostały przyznane z zastrzeżeniem niewydatkowania przez adresata niniejszej decyzji kosztów uznanych przez Zespół Ekspertów za niekwalifikowalne. Wykaz kosztów uznanych za niekwalifikowane znajduje się w uzasadnieniu oceny wniosku w systemie

Appendix 2

Co-author statements

No Effects of Omega-3 Supplementation on Kynurenine Pathway, Inflammation, Depressive Symptoms, and Stress Response in Males: A Placebo-Controlled Trial

Authors: Monika Bidzan-Wiącek, Maja Tomczyk, Magdalena Błażek, Adriana Mike, Jędrzej Antosiewicz

Journal: Nutrients

Date of publication: 31.10.2024

Gdańsk, 5.12.2024

dr hab. Magdalena Błażek, prof. uczelni
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. 'No Effects of Omega-3 Supplementation on Kynurenine Pathway, Inflammation, Depressive Symptoms, and Stress Response in Males: A Placebo-Controlled Trial' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: wkład w opracowanie metodologii oraz wkład w przygotowanie ostatecznej wersji tekstu do publikacji.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Monikę Bidzan-Wiącek jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład mgr Moniki Bidzan-Wiącek przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Magdalena Błażek
.....
(podpis współautora)

Gdańsk, 6.12.2024

dr Maja Tomczyk
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. 'No Effects of Omega-3 Supplementation on Kynurenine Pathway, Inflammation, Depressive Symptoms, and Stress Response in Males: A Placebo-Controlled Trial' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: wkład w opracowanie metodologii, wkład w przeprowadzenie badania, wkład w przygotowanie ostatecznej wersji tekstu do publikacji.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Monikę Bidzan-Wiącek jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład mgr Moniki Bidzan-Wiącek przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Maja Tomczyk
.....
(podpis współautora)

Gdańsk, 4.12.2024

dr hab. Adriana Mika, prof. uczelni
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. 'No Effects of Omega-3 Supplementation on Kynurenine Pathway, Inflammation, Depressive Symptoms, and Stress Response in Males: A Placebo-Controlled Trial' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: wkład w przeprowadzenie badania.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Monikę Bidzan-Wiącek jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład mgr Moniki Bidzan-Wiącek przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Adriana Mika

.....

(podpis współautora)

Gdańsk . dnia.....

Prof. Jerzy Leszek Kulczycki

(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. 'No Effects of Omega-3 Supplementation on Kynurenine Pathway, Inflammation, Depressive Symptoms, and Stress Response in Males: A Placebo-Controlled Trial' oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to: wkład w opracowanie koncepcji i metodologii oraz wkład w przygotowanie ostatecznej wersji tekstu do publikacji.

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez mgr Monikę Bidzan-Wiącek jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład mgr Moniki Bidzan-Wiącek przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Jerzy Kulczycki

(podpis współautora)

Omega-3 fatty acid supplementation affects tryptophan metabolism during a 12-week endurance training in amateur runners: a randomized controlled trial

Authors: *Tomczyk, M., *Bidzan-Wiącek, M., Kortas, J. A., Kochanowicz, M., Jost, Z., Fisk, H. L., Calder, P. C. & Antosiewicz, J

* contributed equally

Journal: Scientific Reports

Nature Portfolio

Date of publication: January 2024

Gdańsk, 4.12.2024

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład mgr Moniki Bidzan-Wiącek przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Magdalena Kochanowicz

(podpis współautora)

Gdańsk, 6.12.2024

dr Maja Tomczyk
(tytuł zawodowy, imię i nazwisko)

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.....

(podpis współautora)

Gdańsk . dnia.....

Prof. Jerzy Ambrożewicz
(tytuł zawodowy, imię i nazwisko)

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Jerzy Ambrożewicz
(podpis współautora)

Gdańsk, 4.12.2024

Prof Philip Calder

(Name, Surname, Title)

Co-author Statement

As a co-author of the article 'Omega-3 fatty acid supplementation affects tryptophan metabolism during a 12-week endurance training in amateur runners: a randomized controlled trial' I hereby declare that my own contribution to the creation of the article is: contribution to the methodology of the study, and writing of the original draft, review & editing.

At the same time, I declare that mgr Monika Bidzan-Wiącek has contributed to the publication and has significantly contributed to the following: conceptualization, methodology, investigation as well as preparation and interpretation of the results of the study.

I agree for the publication to be submitted by mgr Monika Bidzan-Wiącek as a part forming a cumulative PhD thesis.

.....

(co-author signature)

P.C. Calder

Gdańsk, 4.12.2024

dr hab. Jakub Kortas, prof. AWFiS
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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Jakub Antoni Kortas
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(podpis współautora)

Gdańsk, 4.12.2024

Dr Helena Fisk

(Name, Surname, Title)

Co-author Statement

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(co-author signature)

Gdańsk, 5.12.2024

dr Zbigniew Jost
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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.....
(podpis współautora)

The relationship between physical activity and depressive symptoms in males: A systematic review and meta-analysis

Authors: Monika Bidzan-Wiącek, Magdalena Błażek, Jędrzej Antosiewicz

Journal: Acta Psychologica

Elsevier

Date of publication: January 2024

Gdańsk . dnia.....

Dr hab. Tadeusz Antoniewicz
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. 'The relationship between physical activity and depressive symptoms in males: A systematic review and meta-analysis'
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Tadeusz Antoniewicz
.....
(podpis współautora)

Gdańsk, 5.12.2024

dr hab. Magdalena Błażek, prof. uczelni
(tytuł zawodowy, imię i nazwisko)

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Magdalena Błażek
(podpis współautora)