Basal myokine levels are associated with quality of life and depressed mood in older adults

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Abstract
In an aging society, late-life depression has become an increasing problem. There is evidence that physical activity ameliorates depressive symptoms and increases the quality of life (QoL). However, the underlying mechanisms are still poorly understood. Myokines are molecules secreted in response to muscle contraction. Some of them can cross the blood-brain barrier, making them promising candidates for mediating the beneficial effects of physical activity on mood. The present study aims to compare circulating myokine levels to depression/QoL in older athletes and controls. 55 athletes, 57 controls >59 years were enrolled. The assessment included ergometry, magnetic resonance imaging, blood withdrawal, and neuropsychological testing. Serum interleukin-6 (IL-6), irisin, brain-derived neurotrophic factor (BDNF), kynurenine, and cathepsin B were analyzed and compared to surrogates of depression and quality of life. Athletes presented with higher levels of Cathepsin B. Among controls, all myokines but irisin were associated with age. Also, among controls, kynurenine and IL-6 correlated inversely with specific dimensions of quality of life questionnaires, and IL-6 further with depressive symptoms and decreased physical performance. No such associations could be found among athletes. Irisin levels were inversely associated with mild depression and low-grade white matter-lesions in the brain and predicted impaired QoL. The circulating levels of several myokines/muscle activity-related factors appear to be associated with depressive symptoms and impaired QoL among older adults. However, in athletes, some of these connections seem ameliorated, suggesting additional stressors (as f.e. age) or a different pathomechanism among athletes.

KEYWORDS
athletes, late-life depression, MRI, myokines, physical activity
1 INTRODUCTION

It is well established that continual physical activity goes along with a better quality of life (Batmyagmar et al., 2019; Boldt et al., 2018; Sillanpää et al., 2012) and less depressive symptoms (Archer et al., 2014; Haslacher et al., 2015a). This effect is mainly seen in older adults (Sjösten & Kivelä, 2006), who might suffer from depression or report poor quality of life often due to various comorbidities. The mechanisms by which muscle activity influences brain physiology are still poorly understood. During the last years, several compounds termed “myokines” were identified that might mediate the beneficial effects of physical activity (Pedersen, 2019). During physical activity, these myokines and muscle-activity-related factors are secreted into the blood circulation and eventually cross the blood-brain-barrier. In return, this activity-related secretion acts on their basal levels (Janikowska et al., 2020; Moon et al., 2016). Therefore, it could be hypothesized that circulating levels of those compounds might serve as a surrogate for depressive symptoms and quality of life.

As stated above, physical activity has been shown to positively affect depressive symptoms and reduced quality of life. For instance, sedentary older adult report significantly higher levels of anxiety and depression and reduced quality of life when compared to physically active individuals (de Oliveira et al., 2019). This holds for various intensities of physical activity, as, for example, Yoga interventions (Noradetchanunt et al., 2017), flexibility exercise (Byeon, 2019) or marathon sports (Batmyagmar et al., 2019). There are several hypotheses regarding the pathogenesis of depression, including the monoamine hypothesis, the vascular depression hypothesis, and the cytokine hypothesis (Khalaf et al., 2015; Marathe et al., 2018). Especially late-life depression is often accompanied by structural changes in the central nervous system, as, for example, by gliosis, which presents as white matter lesions in MRI, which most likely result from cerebrovascular disease and increased inflammation (Khalaf et al., 2015). Especially the cytokine and the vascular hypotheses offer a target for circulating messenger and effector molecules, whose concentration and/or composition could be mediated by physical activity.

In this regard, previous mechanistic research has identified several molecular that are affected by muscle activity. Some of them are regulated by PGC1α, whose expression is induced by physical activity (Pedersen, 2019). In murine muscles, overexpression of PGC1α enhances the expression of fibronectin type III domain-containing protein 5 (FNDC5). FNDC5 then increases plasma irisin levels, which might overcome the blood-brain barrier, stimulating BDNF (Brain-derived neurotrophic factor) expression within the central nervous system (Bostrom et al., 2012).

Indeed, an association between physical activity and circulating irisin levels was also reported for humans (Wrann, 2015). Above that, PGC1α upregulates kynurenine aminotransferase, an enzyme that produces kynurenic acid from kynurenine (KYN) generated in the tryptophan metabolism (Muller & Schwarz, 2007; Schwarcz et al., 2012). KYN is a neurotoxin that induces neuronal apoptosis and inflammation. Hence, dysregulations of the KYN metabolism are associated with depression (Claes et al., 2011; Myint & Kim, 2014). The conversion to kynurenic acid prevents the molecule from crossing the blood-brain barrier (Schwarz et al., 2012). Moreover, PGC1α levels are inversely correlated with Interleukin-6 (IL-6) concentrations (Handschin et al., 2007).

Although it is better known as a cytokine, IL-6 was one of the first molecules defined as a myokine (Pedersen & Febbraio, 2008). IL-6 is not only produced by macrophages but also expressed in myoblasts, and it can be secreted by muscle cells without activating the pro-inflammatory pathway (Bartoccioni et al., 1994; De Rossi et al., 2000). Whether the cytokine develops a pro- or anti-inflammatory character mainly depends on the environment and whether IL-6 is expressed acutely or chronically (Pedersen & Febbraio, 2008). Hence, acute IL-6 expression seen in athletes goes along with low basal levels of inflammatory cytokines during resting periods (Janikowska et al., 2020). As the inflammation hypothesis of late-life depression suggests, an imbalance between pro- and anti-inflammatory signals impairs neurotoxins’ clearance and reduces neuron density (Alexopoulos, 2019). Indeed, patients with major depression exhibit higher circulating IL-6 levels than healthy controls, and IL-6 levels decrease in response to treatment (Goldsmith et al., 2016; Jin et al., 2020).

Physical activity-induced upregulation of PGC1α is also accompanied by a rise in Cathepsin B (CTSB) levels (Karlsson et al., 2019), although a causal relationship between those molecules has not yet been established. CTSB is a protein belonging to the family of lysosomal cysteine proteases, which can be detected at high levels in various types of human cancer (Aggarwal & Sloane, 2014). However, it could be shown for mice, rhesus monkeys, and humans that CTSB is increased by physical activity. CTSB induces BDNF expression, and it is not surprising that CTSB concentrations were associated with better fitness and hippocampus-dependent memory function (Moon et al., 2016).

Together, there is increasing evidence that physical activity’s beneficial effect on depressive symptoms and quality of life might be at least partially attributable to so-called myokine action. For this, myokines and muscle-activity-related factors might be distributed by the bloodstream and pass the blood-brain-barrier. As a consequence, the peripheral concentrations of these molecules might be
associated, whether causal or not, with depressive symptoms and reduced quality of life. The effect sizes, however, might be low to medium, as most of these mediators are not produced by the contracting muscle alone, but by various cells and tissues and their function varies with their place of action. Irisin has been found in non-small cell lung cancer cells and stromal fibroblasts (Nowinska et al., 2019), Kynurenine aminotransferases, for instance, are expressed in the central nervous system as well (Song et al., 2018), however, intrathecally produced kynurenic acid is unlikely to affect circulating kynurenine levels. Kynurenine itself can be produced by the skin as well (Sheipouri et al., 2012). CTSB is not only produced in response to muscle activity, but for instance also by macrophages during perineural invasion (Bakst et al., 2017), cartilage cells (Zwicky et al., 2002), by various types of cancer, where high CTSB expression often goes along with a less favorable prognosis (Chan et al., 2010; Ozeki et al., 1993; Ruan et al., 2016), and by microglia in the central nervous system (Ni et al., 2019). Regarding IL-6, for example, it might not be expected that athletes feature higher basal levels. In contrast, it can be hypothesized that microinflammation during the marathon might induce anti-inflammatory pathways as a counter-regulatory response, by which basal circulating IL-6 levels are kept low (Janikowska et al., 2020), which is also supported by the short half-life of the cytokine. A relevant part of peripherally measurable BDNF origins from platelets (Hochstrasser et al., 2013; Türck & Frizzo, 2015), which impairs the interpretation of serum BDNF levels. These could rather reflect a BDNF secretion capacity than the values actually present in the central nervous system. However, molecules acting as myokines might not only be secreted by tissues other than muscle, but also dependent on physiological states. One potential confounder is age, as the peripheral levels of several myokines change with advanced age (de Bie et al., 2016; Ferrucci et al., 2005; Refaey et al., 2017; Ruan et al., 2019; Wei et al., 1992; Wyczałkowska-Tomasik & Pączek, 2012). Moreover, the amount of adipose tissue might influence the levels of cytokines (Carey et al., 2004), and must, therefore, be considered when interpreting the results.

As stated above, at least part of the circulating levels might be attributable to muscle activity, and it cannot be excluded that circulating levels might serve as surrogate markers for muscle-brain interaction. The present study, therefore, aims to investigate whether basal concentrations of myokines or muscle-activity-related factors (IL-6, CTSB, KYN, irisin, and BDNF) i) are differently associated with lifestyle- and physiological characteristics among athletes and controls, and if in either of the groups these circulating myokine levels are useful for predicting ii) reduced quality of life or iii) depressive symptoms, and associated features in imaging data of the central nervous system, respectively.

2  METHOD

2.1  Study design and participants

This study follows a retrospective, exploratory cross-sectional design, and reverts to the cohorts of the Vienna Marathon Trial (Batmyagmar et al., 2019; Winker et al., 2010), which were prospectively enrolled in 2009. Back then, 63 older marathon athletes and 73 control participants, who did not differ in terms of sex, age, and education, were screened. Of those, 56 athletes and 58 controls met all inclusion criteria (inclusion criteria: [a] participation in one of the three listed marathons during the preceding two years, [b] weekly amount of training ≥ 2 hr, [c] at least in the 60th year of life [age ≥ 59]; exclusion criteria: [a] present or past exposure to neurotoxic substances, [b] not German as a native language, [c] diseases that markedly affect CNS functions: cerebrovascular stroke, brain tumor, depression, Alzheimer's disease, multiple sclerosis, Parkinson's disease, etc., [d] manifest cardiovascular disease, [e] chronic alcoholism, [f] unwillingness to give informed consent). Of 55 athletes and 57 controls, biomaterial was available to quantify myokines and muscle-activity-related factors (IL-6:1 missing data point because of insufficient material). Those were included in the present analysis.

In brief, the examinations started between 10:00 and 10:30 a.m. to minimize circadian variability. After the recording of biographic and biometric data and medical history, participants underwent a medical check-up performed by a specialist in internal medicine. Subsequently, blood was drawn for routine analyses and part of which was sent to the MedUni Wien Biobank, as described below. Then, physical performance was assessed by ergometry. After this, participants were asked to complete neuropsychological test batteries and questionnaires (Winker et al., 2010).

2.2  Neuropsychological assessment and imaging

Depressive symptoms were assessed by the Beck Depression Inventory (Beck et al., 1961) and the Geriatric Depression Scale (Alexopoulos et al., 1993). Reductions in Quality of Life (QoL) perception were screened using the WHO-5 Well-being-index (Heun et al., 2001). Domain-specific impairments in different QoL dimensions were queried using the SF-36 clinical questionnaire (Larson, 1997). Lifestyle specifics were assessed using the Personal Lifestyle Questionnaire (PLQ) with 24 items (Brown et al., 1983). Each of the items had to be rated from 0 (never) to 3 (nearly always), or indicated whether it was not applicable (e.g., monthly breast examination). An experienced clinical psychologist evaluated all tests.
Magnetic resonance imaging was performed on a Siemens Symphony 1.5 T (Siemens, Erlangen, Germany) using a standard head coil (29). The protocol included the following: (a) axial FLAIR (fluid-attenuated inversion recovery): TR 696 msec, TE 24 msec, 5 mm slice thickness, distance factor 20%, FOV (field of view) 183 × 230, number of slices 20, resolution 256 × 224. (b) axial T2* flash 2d: TR 477, TE 12 msec, 5 mm slice thickness, distance factor 20%, FOV 183 × 210, number of slices 20, resolution 448 × 512. (c) axial T1 TSE (turbo spin-echo sequence) TR 477 msec, TE 12 msec, 5 mm slice thickness, distance factor 20%, FOV 196 × 210, number of slices 20, resolution 228 × 256. (d) coronal T2 TSE: TR 4,480 msec, TE 94 msec, high resolution (perpendicular to the hippocampus), 2 mm slice thickness, distance factor 20%, FOV 186 × 230, number of slices 24, resolution 198 × 256. (e) coronal 3D MPRAGE: TR 1,420 msec, TE 3.2 msec, slice thickness (partition) 3 mm, FOV 178 × 260 number of slices 36, resolution 316 × 512. The images were used in conjunction with a board-certified radiologist to manually rate the white matter lesions as “not present,” “isolated lesions,” or “pronounced changes.”

2.3 | Physical performance test

Ergometry was supervised by trained medical personnel. Individual working capacity was calculated as a percentage of the predicted (=100% workload) Watt value (derived from the tabulation, standardized for sex, age, and body surface (Böhm et al., 1978)). Briefly, the workload was increased every two minutes in steps of 25 W, beginning with 25 W and going on until the point of exhaustion on an Ergometrics 900 (Ergoline GmbH, Bitz, Germany). The individual physical working capacity (PWC) was expressed as the individual maximal power (Wattmax) in percent of a reference value (Wattref): PWCind = 100 × Wattmax/Wattref (Böhm et al., 1978).

2.4 | Laboratory analyses

At the time of inclusion, blood was drawn and submitted to the MedUni Wien Biobank, a central facility at the Medical University of Vienna specialized in the processing and storage of human biomaterial (Haslacher et al., 2018). There, blood serum was prepared and stored at median temperatures <−70°C until analysis.

BDNF was quantified in 2010 from frozen sera through enzyme-linked immunosorbsorbent assays (ELISA) purchased from Ray Biotech Inc. (Norcross, USA) as described earlier (Winker et al., 2010). All other parameters were measured in 2020 from banked sera. IL-6 was quantified with Roche Elecsys® IL-6 electrochemiluminescence on a Cobas e602 analyzer immunoassays (Roche, Rotkreuz, Switzerland) at the Department of Laboratory Medicine, Medical University of Vienna, in a certified (ISO 9001:2015) and accredited (ISO 15189:2012) environment. KYN was quantified using a commercially available, CE/IVD-marked competitive ELISA kit (IDK® Kynurenine K7728, Immundiagnostik, Bensheim, Germany). ELISAs measured CTSB (Human Cathepsin B ELISA kit ab119584, Abcam, Cambridge, UK) and irisin (competitive Irisin ELISA RAG018R, BioVendor, Brno, Czech Republic). ELISAs were performed in single determinations after the tests’ intra-assay variability was verified in duplicates. Due to a considerable between-assay variability for CTSB and irisin, which hampered the comparison of results derived from different ELISA plates, measurement results were z-standardized assay-wise, and only z-standardized values were compared. To ensure comparability, both athletes and control samples were applied on each assay plate, and overall results were interpreted together with assay-wise results. This approach was not necessary for CE-marked tests (kynurenine, IL-6) and BDNF, as for the latter already available data from previous analyses were used.

2.5 | Statistical analyses

Continuous data are presented as median (interquartile range) and categorical data as counts (percentages). As stated above, z-standardized values of CTSB and irisin were calculated assay-wise and were included in the calculations instead of the resulting concentrations. Mann-Whitney U tests compared differences in myokine levels and other continuous data between athletes and controls. Differences in myokine levels between two dichotomous factors (e.g., group and BDNF category) were assessed by 2 × 2 ANOVA. Since variables did not meet the normality assumption required for analyses of variances, ANOVA was performed on ranks instead of actual numbers as suggested by Brownie and Boos (1994). Pearson’s χ2 tests assessed differences in categorical variables. Predictive values were evaluated by binary logistic regression models (odds ratios are given ± 95% confidence intervals [95%CI]) and areas under the receiver-operating-characteristic (ROC)-curves (AUC, given ± 95%CI) were interpreted. All calculations were performed using MedCalc v19.4.1 (MedCalc Software Ltd, Ostend, Belgium), graphs were drawn with GraphPad Prism 8.4.2 (GraphPad, La Jolla, USA). p values <.05 were considered statistically significant. Due to the exploratory nature of the study, no correction of p values for multiple testing was performed.

3 | RESULTS

3.1 | Cohort characteristics

Baseline characteristics of 55 athletes and 57 control participants are listed in Table 1. As intended, controls and
| TABLE 1 Baseline characteristics of athletes and controls |
|----------------------------------------------------------|
| **Athletes (n = 55)** | **Controls (n = 57)** | **p value** |
| **Biometry and physical performance** | | |
| Age, years | 66 [62–68] | 66 [63–69] | U = 1,510.0; p = .737 |
| Female Sex [%] | 5 (9%) | 6 (11%) | $\chi^2 = 0.065; p = .800$ |
| Education, years | 9 [8–13] | 10 [8–16] | U = 1,441.0; p = .444 |
| Training intensity [hr/week] | 7.0 [95%CI 5.8–8.2] | | |
| Year of first marathon (examination in 2009) | 1991 (1985–1998) | | |
| Year of best marathon | 1999 (1992–2003) | | |
| Best completion time | | | |
| Marathon (N = 45) | 3:30 (3:12–3:55) | | |
| Half-marathon (N = 4) | Range: 1:30–2:03 | | |
| Bicycle marathon (N = 5) | Range: 1:00–1:55\* | | |
| Triathlon (N = 1) | Not specified | | |
| Ergometer performance [W] | 200 [175–238]\*↑ | 150 [123–175]\*↓ | U = 446.5; p < .0001 |
| Ergometer performance [%] | 152 [128–169]\*↑ | 99 [85–115]\*↓ | U = 245.5; p < .0001 |
| BMI, kg/m² | 23.3 [22.4–25.0]\*↓ | 26.2 [24.6–29.3]\*↑ | U = 651.0; p < .0001 |
| **Neuropsychological diagnostics** | | |
| BDI | 3 [1–7]\*↓ | 7 [5–10]\*↑ | U = 896.5; p < .0001 |
| GDS | 0 [0–1]\*↓ | 1 [0–3]\*↑ | U = 1,191.0; p = .017 |
| WHO-5 Well-being index | 20 [18–22]\*↑ | 19 [16–20]\*↓ | U = 1,091.5; p < .0001 |
| SF-36 General Health Perception | 82 [72–95]\*↑ | 72 [58–87]\*↓ | U = 1,091.5; p < .0001 |
| SF-36 Physical functioning | 100 [95–100]\*↑ | 90 [80–96]\*↓ | U = 700.0, p < .0001 |
| SF-36 Physical role function | 100 [100–100]\*↑ | 100 [50–100]\*↓ | U = 1,114.5, p = .0002 |
| SF-36 Bodily pain | 100 [84–100]\*↑ | 84 [62–100]\*↓ | U = 1,098.5, p = .004 |
| SF-36 Vitality | 80 [73–90]\*↑ | 70 [60–80]\*↓ | U = 930.5, p = .0003 |
| SF-36 Emotional well-being | 84 [80–88] | 80 [72–89] | U = 1,298.0, p = .153 |
| SF-36 Emotional role functioning | 100 [100–100]\*↑ | 100 [83–100]\*↓ | U = 1,253.0, p = .008 |
| SF-36 Social functioning | 100 [100–100]\*↑ | 100 [75–100]\*↓ | U = 1,128.0, p = .003 |
| **Lifestyle (PLQ), 4-point-rating from never (0) to nearly always (3)** | | |
| Annual medical examination | 3 (2–3) | 3 (2–3) | U = 1,566.5, p = .994 |
| Meeting with friends | 2 (2–2) | 2 (2–3) | U = 1,524.5, p = .920 |
| Regular meals | 3 (2–3) | 3 (2–3) | U = 1,566.5, p = .994 |
| Uses security belt in car | 3 (3–3) | 3 (3–3) | U = 1,459.5, p = .159 |
| Balanced nutrition | 3 (2–3)\*↑ | 3 (2–3)\*↓ | U = 1,214.0, p = .027 |
| Conversations about personal matters | 2 (1–3) | 2 (1–2½) | U = 1,436.0, p = .885 |
| Drink and drive | 0 (0–0)\*↓ | 0 (0–1)\*↑ | U = 1,297.5, p = .049 |
| Emergency phone numbers | 2 (1–3) | 2 (1–3) | U = 1,414.0, p = .653 |
| Sufficient sleep | 3 (2–3) | 3 (2–3) | U = 1,479.5, p = .684 |
| Personal fitness program | 3 (3–3)\*↑ | 1 (1–2)\*↓ | U = 428.0, p < .0001 |
| Climb 5 stairs or walk 1.5 km/day | 3 (3–3)\*↑ | 2 (1–3)\*↓ | U = 834.0, p < .0001 |
| Adhere to speed limit when driving | 3 (2–3) | 3 (2–3) | U = 1,373.0, p = .434 |
| Daily consumption of cigarettes | 0 (0–0) | 0 (0–0) | U = 1,428.5, p = .054 |
| Adding salt to prepared food | 0 (0–1)\*↓ | 1 (0–1)\*↑ | U = 1,157.7, p = .008 |
| Daily relaxing (15–20 min) | 2 (2–3) | 2 (2–3) | U = 1,448.5, p = .459 |
| Daily alcohol consumption | 1 (0–1) | 1 (0–1) | U = 1,480.0, p = .574 |

(Continues)
Athletes did not differ in age, sex, and education years. Athletes presented with considerably higher physical performance and a lower BMI. In terms of psychological test systems, athletes yielded more favorable scores in both BDI and GDS and the WHO-5 questionnaire and all SF-36 dimensions except for emotional well-being. When comparing lifestyle habits between athletes and controls, it turned out that both groups differ in terms of physical activity and diet (items “Personal fitness program,” “Climb 5 stairs or walk 1.5 km /day,” “3 times sports per week,” and “Maintain weight within desirable limits,” “Balanced nutrition,” “Adding salt to prepared food”). Beyond these expected differences, athletes reported more time for physical intimacy ($p = .014$) and had a slightly stricter attitude toward not to drive after drinking alcohol ($p = .049$). However, there were no other significant differences concerning health promotion, relaxation, safety, and substance use.

### 3.2 Association of basal myokines levels with biometric data in athletes and controls

Basal levels were measured in blood samples taken late in the morning and stored at $\leq -70{^\circ}C$ until analysis. As stated above, levels of CTSB and irisin were $z$-standardized assay-wise to reduce inter-assay variability. A comparison between athletes and controls is presented in Table 2. In brief, basal levels of IL-6, KYN, BDNF, or irisin ($z$-standardized) did not differ between athletes and controls, whereas $z$-standardized CTSB was significantly higher in athletes (Hodges-Lehmann median difference of $z$ values $= 0.6$ [95% CI: 0.3–0.9], $p = .004$).

Among athletes, CTSB levels were negatively associated with BMI ($\rho = -0.397$, $p = .003$). However, controlling for BMI in an ANOVA on CTSB ranks did not affect the fact that CTSB was higher in athletes than in controls (mean rank difference: $16.6$, $p = .011$).

### Table 1 (Continued)

| Basal myokine levels | Athletes ($n = 55$) | Controls ($n = 57$) | Difference |
|----------------------|---------------------|---------------------|------------|
| IL-6 [pg/ml]         | 0.75 [0.75–2.46]    | 1.54 [1.75–2.78]    | $U = 1,477.0; p = .694$ |
| Kynurenine [µmol/L]  | 2.8 [2.4–3.2]       | 2.8 [2.3–3.9]       | $U = 1,564.5; p = .986$ |
| BDNF [ng/ml]         | 16.9 [12.4–24.8]    | 16.0 [8.4–23.6]     | $U = 1,409.5; p = .358$ |
| Cathepsin [B z-score]| 0.11 [−0.29–1.02]   | −0.46 [−0.87–0.06]  | $U = 962.5; p < .001$ |
| Irisin [z-score]     | −0.13 [−0.86–0.33]  | −0.02 [−0.63–0.65]  | $U = 1,359.0; p = .225$ |

Note: Continuous data are given as medians (interquartile ranges) and compared by Mann-Whitney tests. Bold values indicate significant differences between the values given in columns two and three: median (interquartile range) or counts (percentage). Column four: test statistics (Mann-Whitney-U) and p-value.

*3 data points missing.

### Table 2 Basal myokine/muscle-activity-related factors in athletes and controls

| Basal myokine/muscle-activity-related factors | Athletes ($n = 55$) | Controls ($n = 57$) | Difference |
|---------------------------------------------|---------------------|---------------------|------------|
| 3 times sports per week                     | 3 (3–3)↑            | 1 (1–2½)↓           | $U = 429.0, p < .0001$ |
| Time for physical intimacy                  | 2 (1½–3)↑           | 2 (1–2)↓            | $U = 1,119.5, p = .014$ |
| Limit caffeine intake to 3 cups/day         | 1 (0–3)             | 1 (½–3)             | $U = 1,503.5, p = .828$ |
| Smoking in bed                              | 0 (0–0)             | 0 (0–0)             | $U = 1,485.0, p = .317$ |
| Annual dental checkup                       | 3 (3–3)             | 3 (2–3)             | $U = 1,427.5, p = .283$ |
| Monthly breast examination                  | 1 (1–3), $N = 5$    | 1½ (¾–2), $N = 6$  | $U = 12.0, p = .561$ |
| Maintain weight within desirable limits     | 3 (3–3)↑            | 2 (2–3)↓            | $U = 920.5, p < .0001$ |
| Avoiding alcohol when taking medication     | 3 (3–3)             | 3 (2–3)             | $U = 1,405.5, p = .273$ |

Note: For more than 5 data points, continuous data are given as medians (interquartile ranges) and compared by Mann-Whitney tests. Bold values indicate significant differences between the values given in columns two and three: median (interquartile range) or counts (percentage). Column four: test statistics (Mann-Whitney-U) and p-value.

Abbreviation: PLQ, Personal Lifestyle Questionnaire.
Several correlations between myokines or muscle activity-induced factors became apparent within groups (athletes/controls). In this regard, all myokines/muscle activity-induced factors but BDNF were rising with age (Table 3). Moreover, higher IL-6 levels were associated with significantly worse absolute physical performance (\( \rho = -0.432, p = .008 \)) and higher BMI (\( \rho = 0.435, p = .001 \)), again only in controls (athletes: \( p = .167, p = .224 \)). In contrast, there was in athletes a trend for an inverse correlation between KYN and BDNF (\( \rho = -0.254, p = .062 \)), which was in-turn trend-wise positively associated with training intensity [hr/week] (\( \rho = 0.263, p = .053 \)). However, there was no such correlation among controls.

Hence, it appears as if in athletes, levels of most assessed myokines and muscle-activity-related factors might be uncoupled from other physiological characteristics, like f.e. age, and physical performance. In contrast, there was a weak and statistically non-significant relationship between the weekly amount of training and serum BDNF levels and a non-significant inverse association between serum BDNF and the neurotoxin KYN that could be seen only in athletes, which moreover presented with comparatively higher levels of CTSB. In the next steps, we aimed to assess whether basal myokine levels are also related to depressive symptoms and quality of life in either group.

### 3.3 Basal myokine levels and quality of life in athletes and controls

Among controls, significant inverse correlations between KYN levels and the subscales general health perception (\( \rho = -0.300, p = .023 \)), bodily pain (\( \rho = -0.272, p = .041 \)), vitality (\( \rho = -0.398, p = .002 \)), as well as a trend-wise correlation with the subscale physical functioning (\( \rho = -0.255, p = .056 \)) of the SF-36 appeared. Physical functioning (\( \rho = -0.365, p = .005 \)) and vitality (\( \rho = -0.273, p = .040 \)) correlated with basal IL-6 levels as well. Moreover, basal IL-6 levels were negatively associated with the WHO-5 questionnaire (\( \rho = -0.287, p = .300 \)). A correlogram is shown in Figure 1.

When compiling a binary logistic regression model for the appearance of suspicious WHO-5 Well-being scores \( \leq 12.5 \) (50%), irisin turned out as a significant predictor (\( p = .018 \)). Results from regression analyses are summarized in Table 4.

Basal myokine levels, depressive symptoms, and associated MRI features in athletes and controls.

IL-6 levels were associated with quantitative scores of the Geriatric Depression Scale (\( \rho = 0.297, p = .025 \)) in controls. Among athletes, no such correlation could be found. When comparing irisin levels between athletes and controls with BDI scores above or below 10, which are considered suspicious, BDI scores \( \geq 10 (F = 4.050, df_1 = 1, df_2 = 108, p = .047) \) and whether individuals were athletes or controls (\( F = 5.101, p = .026 \)) presented with a significant main effect regarding circulating irisin concentrations (Figure 2).

A binary logistic regression model providing group assignment (athletes/controls), z-standardized irisin and CTSB, as well as IL-6-, KYN- and BDNF levels, yielded statistical significance \( (\chi^2 = 14.165, df = 6, p = .028) \). Within the model, only group assignment presented as a significant predictor.

(odds ratio 0.262 [95% CI: 0.085–0.806], \( p = .019 \) for athletes). However, the resulting predictive capability of the model including the myokines (ROC-AUC = 0.737 ± 0.057, \( p < .0001 \), Figure 3) was significantly greater than that derived from predicting suspicious BDI scores by group assignment alone (difference between areas = 0.095 ± 0.044, \( p = .033 \)).

Regarding associations with structural changes within the central nervous system, irisin levels were significantly predicted by the presence of white matter lesions in MRI \( (F = 10.438, df_1 = 2, df_2 = 105, p < .001) \). In detail, irisin levels were significantly lower in individuals with isolated gliosis compared to both individuals with no white matter lesions \( (p <.001) \) and pronounced gliosis (\( p = .010 \)), see Figure 2. The inclusion of age, BMI or HbA1c, as a surrogate of insulin resistance, as covariates did not significantly affect this relationship (\( p = .302, p = .236 \)).

### Table 3 Basal myokine/muscle-activity-related factors and their correlation with age

| Correlation with age | Athletes | Controls | Difference in \( \rho \) |
|----------------------|----------|----------|----------------------|
| IL-6 [pg/ml] \( \rho = 0.181, p = .189 \) & \( \rho = 0.380, p = .004 \) & \( Z = -1.11, p = .266 \) |
| Kynurenine [µmol/L] \( \rho = 0.197, p = .150 \) & \( \rho = 0.362, p = .006 \) & \( Z = -0.94, p = .355 \) |
| BDNF [ng/ml] \( p = 0.039, p = .776 \) & \( \rho = -0.105, p = .439 \) & \( Z = 0.743, p = .457 \) |
| Cathepsin [B z-score] \( \rho = -0.227, p = .96 \) & \( \rho = 0.327, p = .013 \) & \( Z = -2.94, p = .003 \) |
| Irisin [z-score] \( \rho = -0.109, p = .429 \) & \( \rho = 0.331, p = .012 \) & \( Z = -2.33, p = .020 \) |

Note: The column “Difference in \( \rho \)” indicates whether Spearman’s \( \rho \) are significantly different between groups. Bold values indicate statistically significant Spearman’s \( \rho \).
DISCUSSION

Physical activity is associated with an improved quality of life and fewer depressive symptoms. For this reason, exercise programs are among the accepted therapeutic approaches today, also for older adults. There is evidence that crosstalk between the skeletal muscle and the brain mediates at least part of physical activity’s positive effect on mood and mental health. However, the specific mechanisms and factors involved in this crosstalk are still not fully understood.

FIGURE 1

Correlogram of Spearman’s rank correlations between myokines/muscle-activity-related factors and Quality of Life (WHO-5 Well-being index; SF-36 domains General health perception, GH; Emotional role functioning, ER; Physical functioning, PF; Physical role functioning, PR; Bodily pain, BP; Emotional well-being, EW; Social functioning, SF; Vitality, V) or Depression scales (Beck Depression Inventory, BDI; Geriatric Depression Scale, GDS). The correlogram is divided by a grey border: the bottom-left-sided values were derived from athletes, the top-right-sided values from control individuals. For correlations including myokine levels, cell colors indicate the extent and the direction of the correlation (with the minimum observed ρ in blue and the maximum observed ρ in red). p values are presented below the Spearman’s ρ in italic letters, correlation coefficients with p < .05 are highlighted by bold letters.

TABLE 4

Prediction of suspicious BDI and WHO−5 scores by group status (athlete/control) and myokine concentrations

Note: Nagelkerke’s R² is given for the model including all predictors, as well as for a model including only the significant predictor. Bold values indicate statistically significant omnibus tests or regression coefficients.
The present study confirmed that basal levels of some molecules that are either themselves considered "myokines" or are modified by myokines, namely KYN, IL-6, and irisin, are associated with impairments of quality of life or depressed mood. However, this association appeared to be disrupted in athletes, suggesting a more complex regulatory mechanism in athletes that affects basal circulating myokine levels.

4.1 Irisin predicts surrogates of depression and reduced quality of life

Low z-standardized irisin levels were associated with suspicious BDI scores (≥10) at baseline (preferably in athletes than in controls), and presented as significant predictors of reduced well-being, indicated by WHO-5 scores < 50%. This is in-line with the literature. Han et al. (2019) reported significantly lower serum irisin levels among patients with coronary heart disease (CHD) and add-on depression when compared to CHD patients without depression or healthy controls. Furthermore, COPD patients with disturbed mood presented with lower circulating irisin in a study by Papp et al. (2017). Moreover, it was described that irisin levels predicted the incidence of post-stroke depression assessed six months after study inclusion (Tu et al., 2018). In contrast, a study enrolling 98 obese women could not find any differences in irisin levels between patients with low and high depressiveness (Hofmann et al., 2016). However, those patients were morbidly obese (mean BMI = 49.2 kg/m²) and suffered various comorbidities.

The found connection between irisin and suspicious BDI levels was accompanied by an association between baseline irisin and (low-grade) white matter lesions (p < .001). According to the vascular depression hypothesis, the accumulation of gliosis could be a key driver of late-life depression (Herrmann et al., 2008; Krishnan et al., 2004). One of the potential mechanisms, by which irisin could be linked to white matter lesions, might be insulin resistance, which is associated with both increased with matter hyperintensities (Schur et al., 2015) and decreased irisin levels (Perakakis et al., 2017). However, this hypothesis could not be confirmed by our data, as BMI and HbA1c-levels did not significantly moderate the association between the MRI findings and rank-scaled, z-standardized irisin, neither were they correlated with z-standardized irisin levels in either of the groups (p > .05). Moreover, it needs to be further investigated why irisin was not linearly associated with white matter lesions, since only isolated lesions predicted decreased irisin levels, but not pronounced gliosis.

However, when predicting suspicious BDI levels by circulating levels of myokines/muscle-activity-related factors and group assignment (athletes/controls), the latter presented, indeed, as the strongest and solely significant predictor. Nevertheless, the model including the myokines significantly outperformed a model containing only the group status (p = .033). It is meanwhile well established that an individuals’ lifestyle must be taken into account when interpreting biomarkers. Physical activity, for example, affects various biomarkers and laboratory results, inter alia, by changes in...
blood volume, altered basal metabolism, and increased cellular turnover (Haslacher et al., 2015a, 2015b, 2017; Sanchis-Gomar & Lippi, 2014). Myokines seem to follow this line, as their potential as biomarkers might be affected by physical activity.

4.2 KYN and IL-6 are associated with depressive symptoms and reduced quality of life among controls

The same holds for kynurenine and IL-6, which were significantly associated with several dimensions of the SF-36 in controls, but not in athletes. IL-6 correlated further with the WHO Quality of Life score ($\rho = -0.287, p = .030$), as well as with the Geriatric Depression Scale ($\rho = 0.297, p = .025$). The connection between IL-6 and depression is well established (Goldsmith et al., 2016; Jin et al., 2020). Regarding the change in plasma KYN levels in depression, the literature is ambiguous. Whereas some report lower KYN concentrations (Colle et al., 2020; Pompili et al., 2019), others found no association between KYN levels and major depressive disorder (Bradley et al., 2015).

In a recent meta-analysis, however, it was shown that therapeutic immune activation by IFN$\alpha$, which often induces depressive symptoms, for example, in patients with chronic Hepatitis C, was accompanied by a rise in peripheral KYN levels, suggesting a connection between KYN and the inflammatory pathogenesis of depression (Charlotte Hunt et al., 2020).

Among athletes, however, this association between circulating KYN- or IL-6 levels and mood states was disturbed. A possible association between myokines and quality of life/depression could be masked among athletes by the comparatively lower interindividual variability in the respective scores, which may have affected the correlation analyses. Moreover, physical activity may induce downstream-reactions that have not been monitored in this study. Su et al. showed that KYN injections induced depression-like behavior in non-exercising, but not in exercising mice, which presented with overexpression of kynurenine aminotransferase III, which enhances KYN metabolism (Su et al., 2020). However, these findings imply that circulating myokines might have a limited predictive value regarding depressive symptoms and impaired quality of life among athletes, except for irisin levels.

4.3 CTSB is higher in athletes

We could show that CTSB concentrations were significantly higher in athletes than in controls ($U = 962.5, p <.05$). This molecule is a lysosomal cysteine protease that plays a variety of different roles, for instance, in tumor growth (Aggarwal & Sloane, 2014) and cell death (de Castro et al., 2016), whereby only some of them are considered beneficial. Above that, it has been demonstrated that CTSB is expressed and secreted by murine skeletal muscle in response to activity. This increase in CTSB levels led to an overexpression of the neuronal growth factor BDNF and doublecortin within the murine hippocampus, as well as to an improved outcome in the water maze test, suggesting a neuroprotective role for CTSB (Moon et al., 2016). In contrast to our findings, De la Rosa et al. (2019) reported a decrease in both CTSB and BDNF levels in amateur athletes in a dose-dependent manner concerning the weekly training intensity. However, De la Rosa et al. (2019) recruited a heterogeneous sample of athletes in terms of age and sport disciplines, including veteran amateur rugby players and young individuals practicing tennis and taekwondo. The control group consisted of people who reported exercising less than 150 min per week. It has been shown before that IL-6 facilitates CTSB expression in monocytes in tumor tissue, suggesting a potential connection between physical activity-induced IL-6 levels and CTSB. In fact, due to its short half-life, IL-6 may have dropped below the detection limit within a short period of time after a training session, whereas CTSB would still be detectable due to its markedly higher biological half-life of $\sim 14$ hr (Katunuma, 2010). Except for CTSB, we found no other myokine/muscle activity-related factor to be different between athletes and controls. As stated above, it must be kept in mind that those factors are not solely produced by the contracting muscle, but also by other tissues. Therefore, the circulating amount might not be fully attributable to physical activity. This is especially true for IL-6, for which adipose tissue is a major source, explaining the association between IL-6 and BMI/reduced physical performance among controls.

4.4 Myokine levels increase with age in controls

KYN, CTSB, irisin, and IL-6 significantly increased with age among controls nearly to the same extend ($\rho \sim 0.35$), but not in athletes. This is in line with the literature, describing increasing levels of both plasma and cerebrospinal fluid irisin (Ruan et al., 2019), of IL-6 (Ferrucci et al., 2005; Wei et al., 1992), KYN (de Bie et al., 2016; Refaey et al., 2017), and CTSB (Wyczalkowska-Tomasik & Pączek, 2012). It is most likely the pro-inflammatory shift in the metabolism of older adults, mainly due to increased oxidative stress that shifts the balance between neurotoxin and neuroprotective mediators in favor of the neurotoxic pathway (de Bie et al., 2016; Maggio et al., 2006). Moreover, in controls, higher IL-6 levels were associated with impaired physical performance ($\rho = -0.432$, $p = .008$) and BMI ($\rho = 0.435$, $p = .001$), reemphasizing the connection between inflammation and physical capacities.
Especially the connection between IL-6 and BMI is well established, as adipose tissue is considered one of the main sources of circulating IL-6 (Carey et al., 2004). In athletes, an inverse correlation between the neurotransmitter KYN and the neurotrophin BDNF emerged, however, without statistical significance ($\rho = -0.254, p = .062$). BDNF, again, showed a trend for being positively associated with training intensity [hr/week] ($\rho = 0.263, p = .053$).

Limitations were the sample size, which was too low to yield statistically significant results regarding the association between KYN, BDNF, and training intensity among athletes. Moreover, the necessity to transform CTSB and irisin levels due to considerable inter-assay-variability might decrease statistical power. Above that, the share of female participants was too low to be able to make statements with regard to sex. Finally, it might be considered a limitation that the included individuals do not represent a random sample of older marathoners, which could impair generalizability.

In conclusion, circulating myokines/muscle activity-related factors like KYN and irisin and the multifunctional cytokine/myokine IL-6 are associated with depressive symptoms among older adults, as data from our control cohort suggest. However, several of these associations appear to be diminished among athletes. It can only be speculated what might be the reason for this, however, it could be due to a shift of the balances in favor of anti-inflammatory mediators, a more significant influence of other factors, as f.e. age, or small effect size for any of the parameters which might be masked by the small inter-assay variability in the athletes’ quality of life scores. Hence, circulating myokine levels might be promising candidates to quantify the inflammatory component of depressive symptoms, but with limited applicability among athletes.

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AUTHOR CONTRIBUTIONS

Patrick Mucher: Conceptualization; Formal analysis; Investigation; Writing-original draft. Delgerdalai Batmyagmar: Investigation; Writing-review & editing. Thomas Perkmann: Investigation; Writing-review & editing. Manuela Repl: Investigation; Writing-review & editing. Astrid Radakovics: Investigation; Writing-review & editing. Elisabeth Ponocny-Seliger: Investigation; Methodology; Writing-review & editing. Ina Lukas: Investigation; Methodology; Writing-review & editing. Monika Fritzer-Szekeres: Investigation; Resources; Writing-review & editing. Johann Lehrner: Conceptualization; Investigation; Writing-review & editing. Thomas Knogler: Methodology; Writing-review & editing. Dimiter Tscholakoff: Investigation; Writing-review & editing. Martina Fondi: Conceptualization; Writing-review & editing. Oswald Wagner: Conceptualization; Resources; Supervision; Writing-review & editing. Robert Winker: Conceptualization; Investigation; Methodology; Supervision; Writing-review & editing. Helmut Haslacher: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing-original draft.

ETHICS STATEMENT

The initial trial (EK 401/2005, ClinicalTrials.gov NCT01045031), which included obtaining written informed consent and the present study (EK 2149/2019), were reviewed and approved by the ethics committee of the Medical University of Vienna. The approved research protocol (in German language) was uploaded to https://www.researchgate.net/publication/344237384_Myokinkonzentration_bei_alteren_MarathonathletInnen_Expose_zur_Masterarbeit?_sg%5B0%5D=BT5wlyYhyhMH9OVtibRjQ7z- vnB9mONK866HDFrPP6wx9Qglh0CPqi_7f0oTnSqi_inpMMwALX8fU-Vtq2WQ7p4lSkWb9biNLbH_EV.adKrLEHEqyoqUA7M1V717wFhtS81W3IxPU2UluSZy96cqi4-eRpiGjJK2xQOEkbJWQwKA59HojwtKmOnwmg.

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REFERENCES

Aggarwal, N., & Sloane, B. F. (2014). Cathepsin B: Multiple roles in cancer. Proteomics Clinical Applications, 8, 427–437. https://doi.org/10.1002/prca.201300105
Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. Translational Psychiatry, 9, 188. https://doi.org/10.1038/s41398-019-0514-6
Alexopoulos, G. S., Young, R. C., & Meyers, B. S. (1993). Geriatric depression: Age of onset and dementia. Biological Psychiatry, 34, 141–145. https://doi.org/10.1016/0006-3223(93)90383-o
Archer, T., Josefsson, T., & Lindwall, M. (2014). Effects of physical exercise on depressive symptoms and biomarkers in depression. CNS & Neurological Disorders: Drug Targets, 13, 1640–1653. https://doi.org/10.2174/1871527313666141130203245
Bakst, R. L., Xiong, H., Chen, C.-H., Deborde, S., Lyubchik, A., Zhou, Y., He, S., McNamara, W., Lee, S.-Y., Olson, O. C., Leiner, I. M.,
Marcadis, A. R., Keith, J. W., Al-Ahmadie, H. A., Katabi, N., Gil, Z., Vakiani, E., Joyce, J. A., Pamer, E., & Wong, R. J. (2017). Inflammatory monocytes promote perineural invasion via CCL2-mediated recruitment and cathepsin B expression. *Cancer Research, 77*, 6400–6414. https://doi.org/10.1158/0008-5472.CAN-17-1612

Bartoccioni, E., Michaelis, D., & Hohlfeld, R. (1994). Constitutive and cytokine-induced production of interleukin-6 by human myoblasts. *Immunology Letters, 42*, 135–138. https://doi.org/10.1016/0165-2478(94)90076-0

Batmyagmar, D., Kundi, M., Ponocny-Seliger, E., Lukas, I., Lehrner, J., Haslacher, H., & Winker, R. (2019). High intensity endurance training is associated with better quality of life, but not with improved cognitive functions in elderly marathon runners. *Scientific Reports, 9*, 4629. https://doi.org/10.1038/s41598-019-41010-w

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004

Böhm, H., Bürklen, R., Dienstl, F., Ehrenböck, G., Gaul, W., Herberger, E., Kiss, E., Kubicek, F., Kühn, P., & Kummer, F. (1978). Empfehlungen für eine standardisierte Ergometrie. *Österr Ärzteztg, 33*, 333–344.

Boldt, P., Knechtle, B., Nikolaidis, P., Lechleitner, C., Wirmitzer, G., Leitzmann, C., Rosemann, T., & Wirtzfeld, K. (2018). Quality of life of female and male vegetarian and vegan endurance runners compared to omnivores - results from the NURMI study (step 2). *Journal of the International Society of Sports Nutrition, 15*, 33. https://doi.org/10.1186/s12970-018-0237-8

Bostrom, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., Rabsch, K. A., Boström, E. A., Choi, J. H., Long, J. Z., Kajimura, S., Zingaretti, M. C., Vind, B. F., Tu, H., Cinti, S., Hojlund, K., Gyg, S. P., & Spiegelman, B. M. (2012). A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature, 481*, 463–468. https://doi.org/10.1038/nature10777

Bradley, K. A., Case, J. A., Khan, O., Ricart, T., Hanna, A., Alonso, C. M., & Gabbay, V. (2015). The role of the kynurenine pathway in suicidality in adolescent major depressive disorder. *Psychiatry Research, 227*, 206–212. https://doi.org/10.1016/j.psychres.2015.03.031

Brown, N., Muhlenkamp, A., Fox, L., & Osborn, M. (1983). The relationship among health beliefs, health values, and health promotion activity. *Western Journal of Nursing Research, 5*, 155–163. https://doi.org/10.1177/019394598300500205.

Brownie, C., & Boos, D. D. (1994). Type I error robustness of ANOVA and ANOVA on ranks when the number of treatments is large. *Biometrics, 542–549*. https://doi.org/10.2307/2533399.

Byeon, H. (2019). Relationship between physical activity level and depression of elderly people living alone. *International Journal of Environmental Research and Public Health, 16*(20), 4051. https://doi.org/10.3390/ijerph16204051

Carey, A. L., Bruce, C. R., Sacchetti, M., Anderson, M. J., Olsen, D. B., Saltin, B., Hawley, J. A., & Feubbraio, M. A. (2004). Interleukin-6 and tumor necrosis factor-alpha are not increased in patients with Type 2 diabetes: Evidence that plasma interleukin-6 is related to fat mass and not insulin responsiveness. *Diabetologia, 47*, 1029–1037. https://doi.org/10.1007/s00125-004-1403-x

Chan, A. T., Baba, Y., Shima, K., Nosho, K., Chung, D. C., Hung, K. E., Mahmood, U., Madden, K., Poss, K., Ranieri, A., Shue, D., Kucherlapati, R., Fuchs, C. S., & Ogino, S. (2010). Cathepsin B expression and survival in colon cancer: Implications for molecular detection of neoplasia. *Cancer Epidemiology, Biomarkers & Prevention, 19*, 2777–2785. https://doi.org/10.1158/1055-9965.EPI-10-0529

Charlotte Hunt, B. S., e Cordeiro, T. M., Robert, S., de Dios, C., Leal, V. A. C., Soares, J. C., Robert, D., Antonio, T., & Sudhakar, S. (2020). Effect of immune activation on the kynurenine pathway and depression symptoms—A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 118*, 514–523. https://doi.org/10.1016/j.neubiorev.2020.08.010

Claes, S., Myint, A. M., Domschke, K., Del-Favero, J., Entrich, K., Engelborghs, S., De Deyn, P., Mueller, N., Baune, B., & Rothermundt, M. (2011). The kynurenine pathway in major depression: Haplotype analysis of three related functional candidate genes. *Psychiatry Research, 188*, 355–360. https://doi.org/10.1016/j.psychres.2011.03.012

Colle, R., Masson, P., Verstuyft, C., Fève, B., Werner, E., Bourrier-Neyret, C., Walther, B., David, D. J., Boniface, B., Falissard, B., Chanson, P., Corruble, E., & Becquemont, L. (2020). Peripheral tryptophan, serotonin, kynurenine, and their metabolites in major depression: A case-control study. *Psychiatry and Clinical Neurosciences, 74*, 112–117. https://doi.org/10.1111/pcn.12944

de Bie, J., Guest, J., Guillemin, G. J., & Grant, R. (2016). Central kynurenine pathway shift with age in women. *Journal of Neurochemistry, 136*, 995–1003. https://doi.org/10.1111/jnc.13496

de Castro, M. A. G., Bunt, G., & Wouters, F. S. (2016). Cathepsin B launches an apoptotic exit effort upon cell death-associated disruption of lysosomes. *Cell Death Discovery, 2*, 16012. https://doi.org/10.1038/cddiscovery.2016.12

De la Rosa, A., Solana, E., Corpas, R., Bartres-Faz, D., Pallas, M., Vina, J., Sanfeliu, C., & Gomez-Cabrera, M. C. (2019). Long-term exercise training improves memory in middle-aged men and modulates peripheral levels of BDNF and Cathepsin B. *Scientific Reports, 9*, 3337. https://doi.org/10.1038/s41598-019-40040-8

de Oliveira, L., Souza, E. C., Rodrigues, R. A. S., Fett, C. A., & Piva, A. B. (2019). The effects of physical activity on anxiety, depression, and quality of life in elderly people living in the community. *Trends Psychiatry Psychother, 41*, 36–42. https://doi.org/10.1590/2237-6089-2017-0129

De Rossi, M., Bernasconi, P., Baggi, F., de Waal Malefyt, R., & Mantegazza, R. (2000). Cytokines and chemokines are both expressed by human myoblasts: Possible relevance for the immune pathogenesis of muscle inflammation. *International Immunology, 12*, 1329–1335. https://doi.org/10.1093/intimm/12.9.1329

Ferrucci, L., Corsi, A., Lauretani, F., Bandinelli, S., Bartali, B., Taub, D. D., Guralnik, J. M., & Longo, D. L. (2005). The origins of age-related proinflammatory state. *Blood, 105*, 2294–2299. https://doi.org/10.1182/blood-2004-07-2599

Goldsmith, D. R., Rapaport, M. H., & Miller, B. J. (2016). A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Molecular Psychiatry, 21*, 1696–1709. https://doi.org/10.1038/mp.2016.3

Han, W., Zhang, C., Wang, H., Yang, M., Guo, Y., Li, G., Zhang, H., Wang, C., Chen, D., Geng, C., & Jiang, P. (2019). Alterations of irisin, adropin, preptin and BDNF concentrations in coronary heart disease patients comorbid with depression. *Annals of Translational Medicine, 7*, 298. https://doi.org/10.21037/atm.2019.05.77.

Handschin, C., Chin, S., Li, P., Liu, F., Maratos-Flier, E., Lebrasseur, N. K., Yan, Z., & Spiegelman, B. M. (2007). Skeletal muscle fiber-type switching, exercise intolerance, and myopathy in PGC-1alpha
mammal-specific knock-out animals. *Journal of Biological Chemistry*, 282, 30014–30021. https://doi.org/10.1074/jbc.M704817200

Haslacher, H., Gerner, M., Hofer, P., Jurkwitsch, A., Hainfellner, J., Kain, R., Wagner, O. F., & Perkmann, T. (2018). Usage data and scientific impact of the prospectively established fluid bioresources at the hospital-based meduni wien biobank. *Biopreserv Biobank*, 16, 477–482. https://doi.org/10.1089/bio.2018.0032

Haslacher, H., Michlmayr, M., Batmyagmar, D., Perkmann, T., Ponocny-Seliger, E., Scheichenberger, V., Pilger, A., Dal-Bianco, P., Lehrner, J., Pezawas, L., Wagner, O., & Winker, R. (2015a). Physical exercise counteracts genetic susceptibility to depression. *Neuropsychobiology*, 71, 168–175. https://doi.org/10.1159/000381350

Haslacher, H., Michlmayr, M., Batmyagmar, D., Perkmann, T., Ponocny-Seliger, E., Scheichenberger, V., Scherzer, T. M., Nistler, S., Pilger, A., Dal-Bianco, P., Lehrner, J., Pezawas, L., Wagner, O. F., & Winker, R. (2015b). rs6295 [C]-Allele protects against depressive mood in elderly endurance athletes. *Journal of Sport and Exercise Psychology*, 37, 637–645. https://doi.org/10.1123/jsep.2015-0111

Haslacher, H., Ratzinger, F., Perkmann, T., Batmyagmar, D., Nistler, S., Scherzer, T. M., Ponocny-Seliger, E., Pilger, A., Gerner, M., Scheichenberger, V., Kundi, M., Endler, G., Wagner, O. F., & Winker, R. (2017). A combination of routine blood analytes predicts fitness decrement in elderly endurance athletes. *PLoS One*, 12, e0177174. https://doi.org/10.1371/journal.pone.0177174

Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery and Psychiatry*, 79, 575–584. https://doi.org/10.1136/jnnp.2007.124651

Heun, R., Bonsignore, M., Barkow, K., & Jessen, F. (2001). Validity of the five-item WHO Well-Being Index (WHO-5) in an elderly population. *European Archives of Psychiatry and Clinical Neuroscience*, 251, 27–31. https://doi.org/10.1007/BF03035123

Hochstrasser, T., Ehrlich, D., Sperner-Unterweger, B., & Humpel, C. (2013). Antidepressants and anti-inflammatory drugs differentially reduce the release of NGF and BDNF from rat platelets. *Pharmacopsychiatry*, 46, 29–34. https://doi.org/10.1055/s-0032-1314843

Hofmann, T., Elbelt, U., Ahnis, A., Obbarius, A., Rose, M., Klapp, B. F., & Stengel, A. (2016). The exercise-induced myokine irisin does not show an association with depressiveness, anxiety and perceived stress in obese women. *Journal of Human Physiology and Pharmacology*, 37, 204–211. https://doi.org/10.1016/j.jad.2020.08.024

Jin, K., Lu, J., Yu, Z., Shen, Z., Li, H., Mou, T., Xu, Y., & Huang, M. (2020). Linking peripheral IL-6, IL-1β and hypocretin-1 with cognitive impairment from major depression. *Journal of Affective Disorders*, 277, 204–211. https://doi.org/10.1016/j.jad.2020.08.024

Karlsson, L., González-Alvarado, M. N., Metallée, R., Blomgren, K., Börjesson, M., & Kuhn, H. G. (2019). Constitutive PGC-1α overexpression in skeletal muscle does not protect from age-dependent decline in neurogenesis. *Scientific Reports*, 9, 12320. https://doi.org/10.1038/s41598-019-48795-w

Katunuma, N. (2010). Posttranslational processing and modification of cathepsins and cystatins. *Journal of Signal Transduction*, 2010, 375345. https://doi.org/10.1155/2010/375345

Khalaf, A., Edelman, K., Tudorascu, D., Andreescu, C., Reynolds, C. F., & Aizenstein, H. (2015). White matter hyperintensity accumulation during treatment of late-life depression. *Neuropsychopharmacology*, 40, 3027–3035. https://doi.org/10.1038/npp.2015.158

Krishnan, K. R., Taylor, W. D., McQuoid, D. R., MacFall, J. R., Payne, M. E., Provenzale, J. M., & Steffens, D. C. (2004). Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biological Psychiatry*, 55, 390–397. https://doi.org/10.1016/j.biopsych.2003.08.014

Larson, J. S. (1997). The MOS-36 item short form health survey. A Conceptual Analysis. *Evaluation & the Health Professions*, 20, 14–27. https://doi.org/10.1016/0163-2787(97)0200102

Maggio, M., Guralnik, J. M., Longo, D. L., & Ferrucci, L. (2006). Interleukin-6 in aging and chronic disease: A magnificent pathway. *Journals of Gerontology. Series A*, 61, 575–584. https://doi.org/10.1093/gerona/61.6.575

Marathe, S. V., D’Almeida, P. L., Virmani, G., Bathini, P., & Alberi, L. (2018). Effects of monoamines and antidepressants on astrocyte physiology: implications for monoamine hypothesis of depression. *Journal of Experimental Neuroscience*, 12, 1179069518789149. https://doi.org/10.1177/1179069518789149

Marland, A. L., Gianaros, P. J., Abramowitch, S. M., Manuck, S. B., & Hariri, A. R. (2008). Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biological Psychiatry*, 64, 484–490. https://doi.org/10.1016/j.biopsych.2008.04.016

Moon, H. Y., Becke, A., Berron, D., Becker, B., Sah, N., Benoni, G., Janke, E., Lubejko, S. T., Greig, N. H., Mattison, J. A., Duzel, E., & van Praag, H. (2016). Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metabolism*, 24, 332–340. https://doi.org/10.1016/j.cmet.2016.05.025

Muller, N., & Schwarz, M. J. (2007). The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. *Molecular Psychiatry*, 12, 988–1000. https://doi.org/10.1038/sj.mp.4002006

Myint, A. M., & Kim, Y. K. (2014). Network beyond IDO in psychiatric disorders: Revisiting neurodegeneration hypothesis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 48, 304–313. https://doi.org/10.1016/j.pnpbp.2013.08.008

Ni, J., Wu, Z., Stoka, V., Meng, J., Hayushi, Y., Peters, C., Qing, H., Turk, V., & Nakanishi, H. (2019). Increased expression and altered subcellular distribution of cathepsin B in microglia induce cognitive impairment through oxidative stress and inflammatory response in mice. *Aging Cell*, e12856. https://doi.org/10.1111/ace1.2856

Noradechanunt, C., Worsley, A., & Groeller, H. (2017). Thai Yoga improves physical function and well-being in older adults: A randomised controlled trial. *Journal of Science and Medicine in Sport*, 20, 494–501. https://doi.org/10.1016/j.jsams.2016.10.007

Nowinska, K., Jablonska, K., Pawelczyk, K., Piotrowska, A., Partynska, A., Gomulkiewicz, A., Ciesielska, U., Katnik, E., Grzegorzka, J., Glatzel-Plucinska, N., Ratajczak-Wielgomas, K., Podhorska-Okolow, M., & Dziegel, P. (2019). Expression of Irisin/FNDC5 in cancer cells and stromal fibroblasts of non-small cell lung cancer. *Cancers*, 11, 1538. https://doi.org/10.3390/cancers11101538

Ozeki, Y., Takishima, K., Takagi, K., Aida, S., Tamai, S., Mamiya, G., & Ogata, T. (1993). Immunohistochemical analysis of cathepsin B expression in human lung adenocarcinoma: The role in cancer progression. *Japanese Journal of Cancer Research*, 84, 972–975. https://doi.org/10.1111/j.1349-7006.1993.tb00187.x

Papp, C., Pak, K., Erdei, T., Juhasz, B., Seres, I., Szentpeteri, A., Kardos, L., Szilasi, M., Gesztesy, R., & Zsuga, J. (2017). Alteration
of the irisin-brain-derived neurotrophic factor axis contributes to disturbance of mood in COPD patients. *International Journal of Chronic Obstructive Pulmonary Disease*, 12, 2023–2033. https://doi.org/10.2147/copd.S135701

Pedersen, B. K. (2019). Physical activity and muscle-brain crosstalk. *Nature Reviews Endocrinology*, 15, 383–392. https://doi.org/10.1038/s41574-019-0174-x

Pedersen, B. K., & Febbraio, M. A. (2008). Muscle as an endocrine organ: Focus on muscle-derived interleukin-6. *Physiological Reviews*, 88, 1379–1406. https://doi.org/10.1152/physrev.90100.2007

Perakis, N., Triantafyllou, G. A., Fernández-Real, J. M., Park, K. H., Heinonen, J., & Haakinen, K. (2012). Decreased level of irisin, a skeletal muscle cell-derived myokine, is associated with post-stroke depression in the ischemic stroke population. *Journal of Neuroinflammation*, 15, 133. https://doi.org/10.1186/s12974-018-1177-6

Türck, P., & Frizzo, M. E. (2015). Riluzole stimulates BDNF release from human platelets. *Biomed Research International*, 2015, 189307. https://doi.org/10.1155/2015/189307

Wei, J., Xu, H., Davies, J. L., & Hemmings, G. P. (1992). Increase of plasma IL-6 concentration with age in healthy subjects. *Life Sciences*, 51, 1953–1956. https://doi.org/10.1016/0024-3205(92)90112-3

Winker, R., Lukas, I., Perkmann, T., Haslacher, H., Ponocny, E., Lehrner, J., Tscholakoff, D., & Dal-Bianco, P. (2010). Cognitive function in elderly marathon runners: Cross-sectional data from the marathon trial (APSOEM). *Wiener Klinische Wochenschrift*, 122, 704–716. https://doi.org/10.1007/s00508-010-1485-z

Wranne, C. D. (2015). FNDC5/irisin - their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. *Brain Plasticity*, 1, 55–61. https://doi.org/10.3233/bpl-150019

Wyczalkowska-Tomasik, A., & Paczek, L. (2012). Cathepsin B and L activity in the serum during the human aging process: Cathepsin B and L in aging. *Archives of Gerontology and Geriatrics*, 55, 735–738. https://doi.org/10.1016/j.archger.2012.05.007

Zwicky, R., Müntener, K., Goldring, M. B., & Baici, A. (2002). Cathepsin B expression and down-regulation by gene silencing and antisense DNA in human chondrocytes. *The Biochemical Journal*, 367, 209–217. https://doi.org/10.1042/BJ20020210

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