Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Irisin

Evidence Summary

Preclinical evidence for neuroprotection is compelling. Irisin levels are increased or decreased in humans depending on various age-related conditions. No studies have tested irisin as an intervention in humans.

Neuroprotective Benefit: CSF irisin is increased with age, decreased in AD, and correlate with cognitive function, CSF BDNF, and CSF Aβ42 levels. Blood irisin is decreased in vascular dementia and PD, and unchanged in AD. Some sex differences exist.

Aging and related health concerns: In humans, both higher and lower circulating irisin levels have been associated with disease and mortality. No studies have tested irisin as an intervention in humans. Preclinical studies generally show protective benefits.

Safety: No studies have tested irisin as a therapy in humans. Levels are increased or decreased depending on different age-related conditions, so safety as a therapy is not yet clear. As a natural circulating hormone/myokine, it is likely safe at physiological levels.

Availability: Not available; research grade only	**Dose**: Not established. In mice, doses have ranged from 10-500 µg/kg via i.v. or i.p.	**Chemical formula:** N/A **MW**: 12 kDa (undergoes glycosylation and dimerization, so the apparent molecular weight is likely higher, ~39-48 kDa)
Half life: less than 1 hour	**BBB**: It is not clear whether irisin penetrates the BBB, but peripheral FNDC5/irisin can affect brain FNDC5/irisin levels. Irisin is also locally induced in the hippocampus.	
Clinical trials: none	**Observational studies**: Irisin has been studied in numerous meta-analyses (including thousands of people total) as a serum or plasma biomarker.	

What is it?

Irisin was discovered in 2012 for its role in stimulating adipocyte browning, energy expenditure, and thermogenesis by enhancing mitochondrial uncoupling protein 1 (UCP1) expression (Bostrom et al., 2012). Since then, irisin has been shown to have wider ranging effects on many tissues to regulate energy metabolism, such as promoting glucose and lipid uptake by skeletal muscles and increasing glucose and lipid metabolism in the liver (Pignataro et al., 2021).

Irisin is a 112-amino-acid hormone/myokine that is proteolytically cleaved from the membrane protein fibronectin type III domain containing protein 5 (FNDC5; 212 amino acids) in skeletal muscle cells prior to being secreted into the blood circulation. This cleavage is regulated by the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), and both PGC-1α and FNDC5 are induced by exercise training. Once cleaved, irisin is secreted by skeletal and cardiac muscle cells (Askari H et al., 2018). Irisin binds to the integrin αV/β5 receptor (Kim et al., 2023). Irisin exerts its biological effects via MAPK, AMPK, PI3K/AKT, STAT3, and cAMP/PKA/CREB signaling pathways. Irisin is also an upstream mediator of BDNF expression (Wrann et al., 2013).

Beyond skeletal and cardiac muscles, irisin/FNDC5 is also highly expressed in the brain. Irisin has been studied most extensively as a biomarker. It has not been used as a treatment in humans, but its role in neuroprotection has been studied in numerous preclinical models (e.g., Lourenco et al., 2019).

Neuroprotective Benefit: CSF irisin is increased with age, decreased in AD, and correlate with cognitive function, CSF BDNF, and CSF Aβ42 levels. Blood irisin is decreased in vascular dementia and PD, and unchanged in AD. Some sex differences exist.

Types of evidence:

- 0 clinical trials
- 11 observational studies examining CSF/blood levels of irisin
- 1 study of FNDC5 single nucleotide polymorphism (SNP) and its relationship with brain metabolism and Alzheimer's-related biomarkers
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There have not been any studies in humans that have tested irisin as an intervention for preventing dementia or cognitive decline. However, several studies have probed whether circulating levels of irisin or genetic variations of FNDC5 are associated with cognitive function.

In 21 middle-aged and older adults who underwent high-intensity interval training (30 minutes) and moderate-intensity continuous exercise (30 minutes), working memory accuracy rates were significantly increased only after the moderate-intensity continuous exercise intervention (Tsai et al., 2021). However, both types of exercise improved reaction time and increased event-related potential P3 amplitudes. Circulating irisin levels increased significantly with high-intensity interval training (pre- vs. post-intervention: 622.23 ± 151.81 ng/mL vs. 674.32 ± 150.08 ng/mL; p=0.003). With moderate-intensity continuous exercise, irisin levels approached statistical significance when pre- and post-intervention levels were compared (pre- vs. post-intervention: 629.77.19 ± 111.76 ng/mL vs. 657.81 ± 113.25 ng/mL; p=0.076). Serum BDNF levels were significantly increased after both types of exercise. Changes in irisin and BDNF levels were not correlated with changes in neurocognitive performance, with the exception of a correlation between irisin levels and reaction times with moderate-intensity continuous exercise.

In 26 endurance athletes and 10 sedentary men, cognitive scores (measured by MSSE and Isaac's Set Test of Verbal Fluency) and irisin levels were higher in endurance athletes than sedentary individuals (Belviranli et al., 2016). Irisin levels in were 3.25 ± 0.70, 6.16 ± 0.99, and 6.58 ± 1.09 µg/mL in the sedentary, orienteers, and pentathletes, respectively. Irisin levels were inversely correlated with body fat and positively correlated with cognitive function (MMSE, Isaac's Set Test) and BDNF levels ($p<0.05$ for all; *see scatterplots*).

In a pilot human study of stroke patients, CSF irisin levels were lower than those from control subjects (Jin et al., 2021). CSF irisin levels in control subjects, stroke patients at acute stage, and stroke patients after recovery were 3.92 ± 0.23 ng/ml, 2.12 ± 0.25 ng/ml, and 2.83 ± 0.29 ng/ml, respectively. In stroke patients, there was a positive correlation between CSF irisin levels and cognitive function (measured by MoCA).

In a randomized controlled study of 44 elderly women with mild cognitive impairment, the effects of physical training (8 weeks of aerobic training), mental training (computer gaming), and the combination of physical and mental training were tested against control (Damirchi et al., 2018). The study found that the combination of physical and mental training slightly elevated irisin levels compared to baseline, but not compared to the control group. Other interventions did not have significant changes in irisin levels compared to baseline.

In a human postmortem study, subjects older than 90 years old had a trend for a lower hippocampal expression of FNDC5 than individuals ranging from 77 to 89 years old (z-score mean difference: −0.32; $p=0.06$) (Lourenco et al., 2022). Although the expression of FNDC5 was not significantly different across Alzheimer's pathology staging, there was a trend for an inverse correlation between FNDC5 expression and brain Aβ42 levels (Spearman $r=0.29$; $p=0.09$) and between FNDC5 expression and brain Aβ42/Aβ40 ratio (Spearman $r=0.31$; $p=0.07$). Also, subjects with high tau pathology had a trend for reduced FNDC5 expression in the hippocampus (Braak I-II: 0.005 ± 0.14; Braak III-VI: −0.35 ± 0.11; $p=0.06$). Lower FNDC5 expression was associated with higher AT8-positive labeling reflecting pSer202/Thr205 tau-positive neurofibrillary inclusions (Spearman $r=-0.40$; $p=0.01$). FNDC5 z-scores also showed a trend for an inverse association with p-tau181 immunoreactivity in the hippocampus (Pearson $r=-0.30$; $p=0.07$).

In 240 cognitively unimpaired elderly people from the ADNI cohort, having the FNDC5 rs1746661(T) minor allele was associated with a regional reduction in glucose metabolism ([18F]FDG-PET) in brain regions important for cognitive/executive function (e.g., superior frontal gyrus and the inferior occipital gyrus) as well as in other regions (nucleus accumens, postcentral gyrus and parietal lobe white matter

tracts) and increased brain Aβ PET load (Lima-Filho et al., 2023). In 485 cognitive impaired elderly people from the ADNI cohort, reduced brain glucose metabolism (measured by [18F]FDG-PET) was observed compared to cognitively unimpaired patients, but there were no differences between rs1746661(T) carriers vs non-carriers. In cognitively impaired elderly people, [18F]florbetapir PET retention was significantly higher compared to unimpaired people, indicating higher Aβ deposition, and rs1746661(T) carriers had significantly higher Aβ PET SUVR than non-carriers. Thus, this SNP appears to be associated with Aβ accumulation in cognitively impaired individuals.

There were no differences in cognition or levels of CSF Aβ42, phosphorylated tau, or total tau between FNDC5 rs1746661(T) allele carriers and non-carriers (Lima-Filho et al., 2023). There were also no significant differences in age, sex, or APOE4 status between rs1746661(T) allele carriers and non-carriers. FNDC5 transcript counts were similar between rs1746661(T) allele carrier and non-carrier groups, suggesting that this allele does not significantly alter FNDC5 mRNA levels. Because this study was cross-sectional, it was not designed to determine causality of the SNP on brain glucose metabolism or Alzheimer's-related pathology. Also, since FNDC5 is expressed both in the brain and in peripheral tissues, future studies are needed to establish whether the differences in brain metabolism in SNP carriers originate from the brain or periphery.

Human research to suggest benefits to patients with dementia:

There have not been any studies in humans that have tested irisin as an intervention for dementia. However, several studies have probed whether circulating levels of irisin might be associated with mild cognitive impairment or dementia.

In a postmortem study of brains from 26 controls, 14 mild cognitive impairment, 14 Alzheimer's disease, and 13 Lewy body dementia, CSF and hippocampal levels of irisin were significantly reduced in late-stage Alzheimer's patients compared to age-matched early Alzheimer's patients, people with mild cognitive impairment, or cognitively normal subjects (Lourenco et al., 2019). Lewy body dementia patients also had reduced CSF levels of irisin. In contrast, no significant changes were seen in plasma levels of irisin in Alzheimer's or Lewy body dementia patients compared to non-demented controls.

CSF irisin levels positively correlated with age in non-demented controls, but not in Alzheimer's patients (Lourenco et al., 2019).

In an observational study of 14 Alzheimer's patients and 25 non-demented controls, CSF irisin levels positively correlated with cognitive function (MMSE score), CSF BDNF, and CSF Aβ42, but not with CSF total tau (Lourenco et al., 2020). Higher irisin levels correlating with higher CSF Aβ42 suggests that there is less Aβ42 deposition in the brain.

In an observational study of 40 Alzheimer's patients and 20 age-matched healthy controls, serum irisin levels were slightly elevated in Alzheimer's patients with agitation/aggression (by 10.0%, $p<0.05$), which correlated with the duration of agitation/aggression ($r=0.74$; $p<0.03$)(Conti et al., 2019). However, serum irisin (and BDNF) levels were unchanged when considering the whole sample of Alzheimer's patients compared to age-matched controls. Serum irisin levels failed to correlate with sex, age, disease duration, Neuropsychiatric Inventory-10 scores, MMSE scores, or medication use (AChEi or memantine).

In a study of 35 Alzheimer's patients, 49 mild cognitive impairment, and 23 cognitively normal people, higher plasma irisin levels correlated with better cognition only in people without Alzheimer's disease (Kim et al., 2022). Plasma irisin was measured from blood collected in the morning after an overnight fast, to minimize variability. In a correlation analysis of cognitively normal and mild cognitive impairment individuals, plasma irisin levels positively correlated with memory ($p=0.030$), language ($p=0.044$), executive function ($p=0.041$), and the total CERAD-K ($p=0.039$). In people with Alzheimer's disease, this correlation was not significant, and showed an inverse association with attention in one of the statistical models ($p=0.023$). Also, higher levels of irisin in Alzheimer's patients correlated with smaller hippocampal, superior temporal, and inferior frontal volumes. The authors speculated that these findings suggest the possibility of "irisin resistance", or a compensatory increase in irisin levels with neurodegeneration. These correlations were not modified by the presence of type 2 diabetes. Plasma irisin levels (log ng/mL) were 0.97 ± 0.13, 0.73 ± 0.07, 0.64 ± 0.09, for cognitively normal, mild cognitive impairment, and Alzheimer's disease, respectively ($p=0.057$). People with Alzheimer's disease tended to have fewer years of education, higher depression scores, and a higher proportion of APOE4 carriers. However, metabolic indices (fasting glucose, HbA1c, and HOMA-IR) were not different across cognitive states. Exercise frequency (days/week) were 3.13 ± 0.62, 1.96 ± 0.40, and 1.88 ± 0.43, for cognitively normal, mild cognitive impairment, and Alzheimer's disease, respectively ($p=0.176$). Exercise frequency was not correlated with the plasma irisin levels in the overall cohort or within cognitive subgroups. Because this study was a cross-sectional study with irisin levels taken at a single timepoint, correlations do not translate to causality.

In a cross-sectional study of 82 Alzheimer's patients, 44 mild cognitive impairment, and 20 people with subjective memory complaint, CSF irisin was significantly lower in Alzheimer's patients ($p<0.0001$), with

lower levels observed in female patients (Dicarlo et al., 2024). No significant differences were observed in male patients. There were no significant differences across Alzheimer's disease, mild cognitive impairment, and subjective memory complaints in plasma irisin levels.

CSF irisin positively correlated with CSF Aβ42 in both female (r=0.379, p<0.001) and male (r=0.262, p<0.05) subjects, as well as the overall cohort (r=0.331, p=0.0001 in all subjects)(Dicarlo et al., 2024). This correlation remained significant when corrected for sex, sex and age, and sex, age, and CDR. No correlations were observed between CSF irisin and p-tau in the total patient population, female patients, or male patients (p>0.05 for all). There was a significant inverse correlation between CSF irisin and a cognition/function measure, CDR-SB (higher score indicates greater impairment; r = -0.234, p < 0.05), only in female patients. Because this study was a cross-sectional study with biomarker assessments taken at a single timepoint, these findings cannot determine causality. Primary analyses were corrected for multiple comparisons, but exploratory analyses were not.

Vascular dementia is the second prevalent subtype of dementia after Alzheimer's disease, and accounts for about 15-20% of dementia cases. In a study of 105 vascular dementia patients and 82 controls, serum irisin levels were significantly lower in vascular dementia patients (79.37 ± 8.74 ng/ml) compared to the control group (127.80 ± 11.15 ng/ml; p<0.001)(Zhang et al., 2021). Serum irisin was measured from blood collected within 24 hours of admission in a fasting state. Serum irisin levels in vascular dementia patients were inversely correlated with age (r=−0.231, p<0.001), BMI (r=−0.159, p<0.001), systolic blood pressure (r=−0.254, p<0.001), diastolic blood pressure (r=−0.217, p<0.001), total cholesterol (r=−0.322, p=0.013), triglycerides (r=−0.283, p<0.001), LDL-c (r=−0.195, p<0.001), and fasting blood glucose (r=−0.170, p<0.001), and positively correlated with HDL-c (r=0.272, p<0.001) and cognitive scores (MoCA; r=0.316, p<0.001). There was no significant correlation between serum irisin and homocysteine in patients with vascular dementia.

In a study of 100 Parkinson's disease patients and 70 healthy people, plasma levels of α-syn and irisin in patients with Parkinson's disease gradually increased and decreased, respectively, with the progression of the disease (Shi et al., 2024). Plasma irisin was measured from blood collected between 7:30-8:30am after an overnight fast, to minimize variability. Plasma irisin levels were significantly lower in Parkinson's patients than in the healthy controls (238.61 ± 39.08 pg/ml vs. 251.77 ± 31.77 pg/ml, p=0.021). When the Parkinson's patients were divided into early-stage (n=58) and middle-to-late-stage (n=42), plasma irisin levels in early-stage Parkinson's patients were lower than those in healthy controls (p=0.037), and plasma irisin levels in middle-to-late-stage Parkinson's patients were lower than those in early-stage (p=0.016). There was an inverse correlation between plasma α-syn and irisin levels in patients with

Parkinson's disease (r=−0.605, p<0.001). Plasma irisin levels were inversely correlated with Unified Parkinson's Disease Rating Scale (UPDRS)-III scores (r=-0.524, p<0.001) and positively correlated with Montreal Cognitive Assessment (MoCA) scores (r=0.327, p=0.001). Based on DOPA PET/MRI data, in Parkinson's disease patients with high irisin levels, striatal/occipital lobe uptake ratios of the ipsilateral and contralateral (to the affected limb) caudate nucleus and anterior and posterior putamen were significantly greater than those with low irisin levels.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

One of the first studies to report neuroprotective actions of irisin was in a 2013 Cell Metabolism paper (Wrann et al., 2013). This study showed that FNDC5 is induced with exercise and cleaved and secreted as irisin in mice. Endurance exercise (using a free running wheel) also increased irisin levels in the hippocampus of mice. In primary cortical neurons, overexpression of FNDC5 increased BDNF expression. Most interestingly, peripheral delivery of FNDC5 to the liver via adenoviral vectors (10^{11} adenoviral particles per animal, i.v., sacrified 7 days later) resulted in elevated blood irisin levels and increased expression of BDNF and other neuroprotective genes in the hippocampus. While this study did not prove that irisin crosses the blood-brain barrier, peripheral FNDC5 was sufficient to produce neuroprotective effects in the brain.

The following high-profile publication on irisin's neuroprotective role was a 2019 Nature Medicine paper (Lourenco et al., 2019). In this study, they first showed that FNDC5 and irisin levels are reduced in the hippocampus and CSF of Alzheimer's patients (described above) and in experimental models of Alzheimer's disease. Knockdown of brain FNDC5/irisin impaired synaptic plasticity (measured by long-term potentiation) and novel object recognition memory in mice. In contrast, boosting brain levels of FNDC5/irisin (by hippocampal infusion of recombinant irisin, 75 pmol/site) rescued synaptic plasticity and memory in two mouse models of Alzheimer's disease (APPswe/PSEN1ΔE9 mice and mice infused with Aβ oligomers). An exercise protocol (daily swimming, 1 hour/day, 5 days/week) for 5 weeks protected mice from Aβ oligomer-induced memory impairment while also preventing the decrease in FNDC5 and irisin levels (mRNA and protein). Thus, irisin appears to be a novel mediator of the beneficial effects of exercise on synaptic function and memory in models of Alzheimer's disease.

Peripheral overexpression of FNDC5/irisin (via AdFNDC5 administration into the caudal vein of mice) also increased FNDC5 and irisin levels in the hippocampus and rescued memory impairment in mice infused with Aβ oligomers (Lourenco et al., 2019). In these mice, hippocampal levels of FNDC5/irisin were decreased but intravenous AdFNDC5 administration prevented this decrease.

In contrast, inhibition of either peripheral or brain FNDC5/irisin attenuated the neuroprotective actions of physical exercise on synaptic plasticity and memory in these mice.

A follow-up study demonstrated that irisin is sufficient to confer the benefits of exercise on cognitive function (Islam et al., 2021). This was achieved with the use of a global Fndc5-knockout mice. These mice exhibited impaired cognitive functions (e.g., pattern separation) but this deficit could be rescued by delivering irisin directly into the hippocampal dentate gyrus. Additionally, peripheral delivery of irisin via AAV overexpression in the liver (tail vein injection of AAV8-Irisin-FLAG, $1x10^{10}$ genome copies) resulted in increased irisin levels in the brain, which was sufficient to improve cognitive functions in two mouse models of Alzheimer's disease (APP/PS1, 5xFAD mice). Although this does not definitively prove that irisin penetrates the blood-brain barrier, these results demonstrate that peripheral irisin increases brain irisin protein levels and improves cognitive function.

In transgenic htau mice, irisin treatment (recombinant human irisin protein, 100 µg/kg weekly, i.p.) beginning at presymptomatic age (4 months old) significantly reduced p-tau and the proinflammatory cytokine, TNF-α, in the hippocampus and serum of females compared to vehicle-treated controls (Bretland et al., 2021). However, irisin treatment did not alter p-tau levels in male htau mice and appeared to increase both neural and systemic TNF-α levels. P-tau in prefrontal cortex, brainstem and hypothalamus did not statistically change with irisin treatment in female or male htau mice. In this study, exogenous treatment with recombinant irisin did not alter neural FNDC5/irisin levels in mice, while serum levels of irisin were doubled in all animals.

Irisin treatment showed cognitive improvements in several mouse models. In a mouse model of diabetes (induced by streptozotocin), irisin treatment (0.5 mg/kg/day, prepared in normal saline, i.p.) improved cognitive function (measured by Y-maze, novel object recognition) while also preventing the elevation of inflammation biomarkers (IL-1β, IL-6, GFAP) and the loss of a synaptic protein (synaptophysin)(Wang et al., 2019). Irisin also inhibited the activation of p38, STAT3, and NFκB proteins. In a mouse model of cerebral ischemia (middle cerebral artery occlusion), pretreatment with exogenous irisin (10 µg/kg, i.v.) prevented cognitive impairment while upregulating protein expressions of klotho, MnSOD, and FOXO3a, and reducing reactive oxygen species generation (Jin et al., 2021).

In aged rats (20 months old), exercise training (voluntary free wheel running exercise) for 90 days significantly improved spatial memory and increased protein expressions of BDNF, FNDC5, PGC-1α,

mTOR, ARC, c-fos, ERK, SIRT, and FOXO in the hippocampus compared to aged rats that did not exercise (Belviranli and Okudan, 2018).

Several studies in culture systems further validated irisin's mechanisms of neuroprotection. In rat hippocampal culture as well as in cultured human adult cortical slides, exposure to Aβ oligomers resulted in reductions of FNDC5 and irisin both at the mRNA and protein levels (Lourenco et al., 2019). In cultured hippocampal neurons exposed to Aβ oligomers, treatment with recombinant irisin prevented dendritic spine loss and reduced Aβ oligomer binding to neurons. In human cortical slices and in mouse hippocampal slices, treatment with recombinant irisin stimulated the cAMP/PKA/CREB pathway that is important for memory formation. In a cell culture study of astrocytes and hippocampal neurons exposed to Aβ, irisin pretreatment attenuated the release of IL-6 and IL-1β from astrocytes and decreased the expression of COX-2 and p-AKT (Wang et al., 2018). Neuroprotective benefits of irisin were mediated by inhibition of astrocytic release of IL-6 and IL-1β. In a 3D cell culture model of Alzheimer's disease, irisin significantly reduces Aβ pathology by binding to astrocytic integrin αV/β5 receptors and increasing astrocytic release of the Aβ-degrading enzyme neprilysin (NEP) (Kim et al., 2023). This is mediated by downregulation of ERK-STAT3 signaling.

APOE4 interactions: It is not known whether an intervention with irisin would affect APOE4 carriers differently from non-carriers, as no studies have tested irisin as an intervention in humans. In a study of 35 Alzheimer's patients, 49 mild cognitive impairment, and 23 cognitively normal people, plasma irisin levels were comparable between APOE4 carriers and non-carriers (Kim et al., 2022). APOE4 noncarriers (but not carriers) showed significant positive association of plasma irisin levels with language ($p = 0.032$), executive function ($p = 0.023$), and total CERAD-K scores ($p = 0.039$), while APOE4 carriers did not show any significant associations in neuropsychological tests. APOE4 carriers (but not non-carriers) showed significant inverse association of plasma irisin levels with volumes of right anterior cingulate gyrus ($p=0.037$) and bilateral superior temporal gyrus (right, $p = 0.007$; left, $p=0.019$).

Aging and related health concerns: In humans, both higher and lower circulating irisin levels have been associated with disease and mortality. No studies have tested irisin as an intervention in humans. Preclinical studies generally show protective benefits.

Types of evidence:

- 19 meta-analyses or systematic reviews of observational studies examining circulating irisin levels

- 0 clinical trials
- 10 observational studies examining circulating irisin levels
- 1 genetic SNP study of centenarians and non-centenarians
- 1 meta-analysis of preclinical studies on bone health
- Numerous laboratory studies

There have not been any studies in humans that have tested irisin as an intervention for preventing age-related diseases. However, numerous studies have probed whether circulating levels of irisin might be associated with disease versus health.

Irisin levels are elevated in some age-related conditions (obesity, gastrointestinal cancers, myocardial infarction, etc.), while lower in others (type 2 diabetes, breast cancer, osteoporosis, coronary artery disease, etc.) (Askari H et al., 2018).

Cancer: IRISIN LEVELS LOWER IN SOME AND HIGHER IN OTHER CANCERS
In an observational study of 101 women with ductal breast cancer and 51 healthy controls, serum irisin levels were lower in breast cancer patients compared to controls (2.47 ± 0.57 and 3.24 ± 0.66 µg/ml, respectively; $p<0.001$)(Provatopoulou et al., 2015). In this study, irisin could discriminate breast cancer patients at a cut-off point of 3.21 µg/ml, with 62.7% sensitivity and 91.1% specificity.

In an observational study of 75 bladder cancer patients and 75 healthy controls, serum irisin levels were significantly lower in bladder cancer patients compared to controls (1.07 µg/ml vs 1.80 µg/ml)(Esawy et al., 2020). In this study, irisin had 74.7% sensitivity and 90.7% specificity at a cutoff point of ≤1.2 µg/mL. Serum irisin levels also could predict bladder cancer stages, when adjusted for BMI and serum cholesterol level. Patients with low serum irisin levels also had a higher mortality rate when compared to those with high irisin levels (38.2% vs 5%).

In a meta-analysis of 29 different studies of various cancers, plasma irisin levels were significantly lower in people with cancer ($p<0.01$)(Vliora et al., 2022). Lower irisin levels in some cancers may be a reflection of cancer cachexia, a wasting syndrome that is accompanied by weight and muscle loss, which can lead to a decreased amount of irisin released. In studies where irisin concentrations were assessed on tissues, irisin levels were not significantly altered in cancer tissue compared to healthy tissue when all studies are analyzed together, though individual differences were observed (both increases and decreases) depending on the type of cancer tissue.

In an observational study of 138 patients with metastatic solid tumors who were followed up for a median duration of 13.8 months, overall survival was significantly correlated with CRP, activin, and myostatin, but irisin was not associated with overall survival (Kim et al., 2019).

Although irisin levels are lower in some cancers as described above (e.g., breast, bladder), studies report higher irisin levels in other cancers (e.g., gastric, colon, ovarian and hepatocellular)(Askari et al., 2018). Irisin could potentially suppress cancer by exerting apoptotic effects in malignant cells (activation of caspase 3 and 7), reducing migration, proliferation, and invasion of cancer cells by inhibiting the PI3K/AKT pathway, and retarding cell proliferation by promoting hyperthermia and reduction of ATP synthesis (Askari et al., 2018). However, other *in vitro* studies have reported that irisin did not regulate cell adhesion, proliferation, or malignancy in endometrial, colon, thyroid, and esophageal cancer cell lines (Moon et al., 2014).

When cancer cell lines were treated with irisin, cell viability was significantly decreased between 24 and 48 hours ($p<0.05$)(Vliora et al., 2022). Of 13 studies of cell lines treated with various concentrations of irisin, 10 studies reported an inhibiting role of irisin on tumor progression through decreased cell proliferation, migration, invasion, and viability. In some cancers (e.g., osteosarcoma), irisin inhibits the endothelial-to-mesenchymal transition through the modulation of STAT3/Snail pathway (Kong et al., 2017). In pancreatic cancer, irisin treatment inhibited cancer cell growth by downregulating the PI3K/Akt signaling pathway (Liu et al., 2018).

Coronary artery disease: IRISIN LEVELS ARE LOWER IN CAD
Coronary artery disease is responsible for about half of all cardiovascular deaths. Atherosclerosis is the primary cause of coronary artery disease, while other causes include hypertension, high blood cholesterol, endothelial dysfunction, vascular damage/injury, and inflammation (NHLBI.nih.gov).

In a meta-analysis of 7 case-control studies involving 867 patients with coronary artery disease and 700 controls, irisin levels were lower in coronary artery disease patients compared with controls (Guo et al., 2020). The pooled data showed that irisin levels were lower by 18.10 ng/mL in patients with cardiovascular disease or atherosclerosis.

In a longitudinal study of 517 people with coronary artery disease who were followed up for 12 months, serum irisin levels were lower in people with coronary artery disease (Pan et al., 2021). Serum irisin levels in people with acute coronary syndrome, stable coronary artery disease, nonobstructive coronary artery disease and normal coronary arteries were 196.62±72.05 ng/ml, 216.81±79.69 ng/ml,

245.26±77.92 ng/ml and 300.17±76.74 ng/ml, respectively. Additionally, serum irisin levels showed high areas under the curve (AUC) for coronary lesions (AUC=0.799), coronary artery disease (AUC=0.734), and acute coronary syndrome (AUC=0.681). Patients with higher irisin levels exhibited a higher event-free survival rate in both stable coronary artery disease and acute coronary syndrome groups after percutaneous coronary intervention.

In a comparative cross-sectional study of 62 patients with varying severity of coronary artery disease, irisin levels (measured by ELISA) were significantly higher in people with mild coronary artery disease (<50% stenosis; 15.3±4.6 µg/ml) compared to people with moderate-severe coronary artery disease (>50% stenosis; 9.3±2.4 µg/ml; p<0.001)(Tanveer et al., 2023). The degree of stenosis was confirmed by coronary angiography, which is thought to be the gold standard for the evaluation of coronary artery disease. Irisin levels were significantly inversely correlated with the % stenosis. The mean age of people with mild coronary artery disease was significantly younger than the mean of moderate-severe disease.

In preclinical studies, irisin exerts anti-atherosclerotic actions by reducing the recruitment of inflammatory cells like T lymphocytes and macrophages to atherosclerotic lesions (Zhang et al., 2016).

Ischemic stroke: LOWER IRISIN LEVELS ASSOCIATED WITH POOR OUTCOMES
In an observational study of 324 Chinese patients with first-ever acute ischemic stroke who were followed for 3 months, lower serum levels of irisin predicted the risk of poor functional outcomes and mortality (Wu et al., 2019). Irisin remained significantly associated with poor outcomes even after controlling for CRP or IL-6, suggesting that the effect of irisin on prognosis was independent of its association with inflammation. In a similar observational study of 1,530 Han Chinese patients with acute ischemic stroke who were followed for 6 months, poor outcome across the irisin quartiles ranged from 54.5% (lowest quartile) to 21.7% (highest quartile), and mortality rate ranged from 39.3% (lowest quartile) to 6.3% (highest quartile)(Tu et al., 2018).

In preclinical studies, irisin may improve cardiovascular problems by inhibiting inflammatory mediators, protecting cardiomyocytes from apoptosis in ischemic conditions, stabilizing mitochondrial membrane potential, and attenuating myocardial damage in ischemia-reperfusion injury by increasing antioxidative defenses (SOD, GPX, catalase) (Pan et al., 2021).

Heart failure: IRISIN LEVELS MAY VARY BY TYPE OF HEART FAILURE
In an observational study of 161 Chinese patients with acute heart failure who were followed for 1 year, serum irisin levels were higher in patients who were deceased at the one-year follow-up (Shen et al.,

2017). Kaplan-Meier survival analysis showed that acute heart failure patients with higher serum irisin had significantly higher mortality (OR=1.287; p<0.001). Because this study enrolled people from China, findings may not translate to other patient populations.

In a Mexican cross-sectional study of 32 chronic heart failure patients and 32 healthy controls, serum irisin levels were significantly lower in chronic heart failure patients (4.92 ng/ml; IQR 2.22–7.62 ng/ml) than in controls (6.45 ng/ml; IQR 4.66–8.24 ng/ml)(Huerta-Delgado et al., 2022). Serum irisin levels positively correlated with cardiac magnetic resonance parameters such as left ventricular ejection fraction (r=0.3; p<0.05), fraction shortening (r=0.4; p<0.05), and global radial strain (r=0.4; p<0.05)). Irisin levels inversely correlated with brain natriuretic peptide (r=-0.4; p<0.05), insulin levels (r=-0.1; p<0.05), and HOMA-IR (r=-0.2; p<0.05). No significant correlations were observed between irisin levels and inflammatory cytokines. Because this study is from Hispanic ethnicity, findings cannot be generalized to other patient populations. The authors hypothesize that with chronic heart failure, the hyperadrenergic compensatory state due to cardiac output abatement induces metabolic adjustments in cardiac tissue, including increased use of free fatty acids as an energy source, overproduction of acetyl-CoA, inhibition of glycolytic pathways, and uncoupling of mitochondrial electron gradients. These changes may lead to poor ATP production, excessive energy consumption, and reactive oxygen species production.

Inflammation: INCONCLUSIVE
In a meta-analysis of 14 observational studies including a total of 2,530 participants, there was no overall significant correlation between irisin and CRP levels (Eslampour et al., 2019). However, subgroup analyses showed significant positive, but weak, correlations between CRP and irisin levels in studies conducted among healthy participants, studies in which the male-to-female ratio was less than 1, in overweight or obese subjects, and in studies with a sample size of at least 100 participants.

Kidney disease: IRISIN LEVELS ARE LOWER IN CHRONIC KIDNEY DISEASE
Chronic kidney disease is commonly associated with diabetes, cardiovascular diseases, and obesity. In a meta-analysis of 9 studies including a total of 859 chronic kidney disease patients and 393 non-chronic kidney disease individuals found that circulating irisin levels were significantly lower in chronic kidney disease non-dialysis patients (WMD=-84.79; 95% CI, -170.23 to 0.50; p<0.05), peritoneal dialysis patients (WMD=-235.81; 95% CI, -421.99 to -49.62; p=0.01), and hemodialysis patients (WMD=-217.46; 95% CI, -381.35 to -53.57; p=0.009) compared to healthy controls (Gan et al., 2022). Circulating irisin levels were lower in dialysis patients than in non-dialysis patients (p<0.05). When stratified by region, circulating irisin levels in patients with chronic kidney disease were lower in Asians (WMD=-279.06, p=0.007) than

in non-Asians (WMD=-217.46, p<0.001). Differences in irisin levels may be explained in part by the lower amount of exercise dialysis patients get compared to non-dialysis patients. Poorer nutritional status and lower skeletal muscle mass may also affect circulating irisin levels in people with chronic kidney disease. The biological basis for the differences in irisin levels by ethnicity remains to be explored. Because of the observational nature of these studies, they were not designed to determine causality. ELISA kits for irisin measurements included Phoenix Pharmaceuticals (4 studies), Cusabio Co (1 study), Amersham Biosciences (1 study), EIAaB Science Co (1 study), Avisera Biosciences (1 study), and AG-45A-K101 (1 study).

Lifespan: HIGHER IRISIN LEVELS MAY BE ASSOCIATED WITH HIGHER OR LOWER MORTALITY DEPENDING ON DISEASE; HIGHER IRISIN LEVELS CORRELATE WITH TELOMERE LENGTH
In a longitudinal study of people with coronary artery disease who were followed up for 12 months, patients with higher irisin levels exhibited a higher event-free survival rate in both stable coronary artery disease and acute coronary syndrome groups after percutaneous coronary intervention (Pan et al., 2021). In contrast, in an observational study of 161 Chinese patients with acute heart failure who were followed for 1 year, patients with higher serum irisin levels were more likely to be deceased at the one-year follow-up (Shen et al., 2017). Kaplan-Meier survival analysis showed that acute heart failure patients with higher serum irisin had significantly higher mortality (OR=1.287; p<0.001).

There are 2 single-nucleotide polymorphisms (SNPs) in the FNDC5 gene, rs16835198 and rs726344, which are associated with insulin sensitivity. However, in a study of 175 centenarians and 347 healthy non-centenarians from Spain, Italy and Japan, there were no differences between genotype/allele frequencies of the two SNPs in centenarians versus controls in any of the cohorts (Sanchis-Gomar et al., 2014). In a gene reporter activity study, the rs726344 SNP had functional significance, with the A-allele having higher luciferase activity compared with the G-allele (p=0.04). For the rs16835198 SNP, the T-allele tended to show higher luciferase activity compared with the G-allele, but the difference was not statistically significant (p=0.07).

In 81 healthy non-obese people (average age, 43), plasma irisin levels were significantly correlated with log-transformed relative telomere length (Rana et al., 2014).

Metabolic dysfunction-associated steatotic liver disease (MASLD): INCONCLUSIVE
MASLD (formerly known as nonalcoholic fatty liver disease, or NAFLD) is one of the most common causes of chronic liver disease and ranges from mild hepatic steatosis (fat deposition) to aggressive forms like MASH (metabolic dysfunction-associated steatohepatitis, characterized by inflammation and

oxidative damage), cirrhosis, and hepatocellular carcinoma (Askari et al., 2018). MASLD is associated with increased risks of diabetes, cardiovascular disease, and all-cause mortality (reviewed in Chan et al., 2023). Studies that examined circulating levels of irisin in MASLD have found inconsistent results, with some showing lower levels with MASLD and others showing higher levels compared to controls.

In a meta-analysis of 5 case-control studies with a total of 1,087 participants, circulating irisin levels did not show significant differences between MASLD patients and healthy controls (Hu et al., 2020). However, subgroup analyses showed that irisin levels were higher in MASLD patients compared to healthy controls in Asians, and higher in mild MASLD patients compared to moderate-to-severe MASLD patients. It is not known whether or how irisin might affect the pathology of MASLD.

In a 2023 meta-analysis of 11 observational studies including a total of 1,277 MASLD cases and 944 non-MASLD controls, circulating irisin levels were comparable between MASLD patients and non-MASLD controls, including in BMI-matched and lean controls (Qui et al., 2023). When analysis was restricted to studies where MASLD was ascertained by magnetic resonance or liver biopsy rather than ultrasonography, serum irisin was reduced in MASLD compared to controls (based on 5 studies, SMD -0.63, 95% CI, -1.14 to -0.13). Meta-analysis also showed that circulating irisin did not differ between mild and moderate-to-severe MASLD (based on 7 studies; SMD 0.02, 95% CI, -0.25 to 0.30), and this association was not significantly moderated by study location (Europe versus Asia). Irisin ELISA kits included Phoenix Pharmaceuticals (4 studies), BioVendor, Brno (3 studies), R&D, Minneapolis (1 study), Cell Biolabs (1 study), Aviscera Biosciences (1 study), and not specified (1 study). Most studies (9 out of 11 studies) used fasting serum samples for irisin measurement.

In preclinical studies, irisin treatment has anti-inflammatory effects and reduces inflammatory mediators including TNF-α, IL-6, phosphorylated NF-κB, phosphorylated p-38, and COX-2 in hepatocytes, while also reducing oxidative stress (Askari et al., 2018).

Myocardial infarction: IRISIN LEVELS ARE HIGHER IN MYOCARDIAL INFARCTION
In a cohort study of 399 patients with acute myocardial infarction, elevated risks of cardiovascular mortality, stroke, heart failure, and revascularization were seen among those with the highest concentrations of irisin, with concentrations higher than the 75th percentile of the overall distribution having a 4-fold increase in risk (HR=3.96; 95% CI, 1.55 to 10.11; p<0.01)(Hsieh et al., 2018).

Based on Kaplan–Meier curves, higher serum irisin concentration (> 0.6 µg/mL) was associated with increased risk for early adverse cardiovascular events. However, no association between irisin concentrations and total cholesterol, HDL cholesterol, or LDL cholesterol was seen (Hsieh et al., 2018).

Obesity: IRISIN LEVELS ARE HIGHER IN OVERWEIGHT/OBESE PEOPLE
In a meta-analysis of 18 case-control studies including a total of 2,247 participants, circulating irisin levels in overweight/obese people were higher than those in healthy controls (p=0.003)(Jia et al., 2019). In a subgroup analysis by ethnicity, irisin levels were higher in overweight/obesity people in Africa but not in European, Asian, or American populations. Also a subgroup analysis by age showed that obese children exhibited a higher irisin level than age-matched controls but irisin levels in adult patients were not significantly different from controls.

Osteoporosis: IRISIN LEVELS ARE LOWER WITH OSTEOPOROSIS
In a meta-analysis of 7 studies including a total of 1,018 middle-aged and older participants, those with osteoporosis had decreased irisin levels (mean difference, -87.91)(Zhou et al., 2019). A subgroup analysis revealed an even lower level of irisin in postmenopausal women and in those with a history of fractures. Irisin levels were weakly and positively correlated with femoral neck or lumbar spine bone mineral density. Preclinical studies have shown that irisin treatment promoted osteoblast differentiation and proliferation, while inhibiting the differentiation of osteoclast precursor cells (Zhang et al., 2017; Ma et al., 2018).

In a meta-analysis of 6 preclinical studies evaluating the effects of irisin on bone health, irisin administration enhanced bone quality, but bone mineral density (BMD) increased only slightly in osteoporotic rodents (BMD: mean difference=0.03 mg/cm3; 95% CI, 0.01 to 0.05)(Pereira et al., 2022). In healthy/sham animals, irisin treatment showed a null effect on BMD compared to placebo, suggesting that there are no significant benefits on the bones of healthy animals.

Thyroid dysfunction: IRISIN LEVELS ARE LOWER IN HYPOTHYROIDISM
In a meta-analysis of 11 observational studies including 1,210 participants, irisin levels were significantly lower in patients with hypothyroidism (mean difference, -10.37)(Shan et al., 2020). A subgroup analysis showed an even lower level of irisin in patients with clinical-type hypothyroidism (mean difference, -17.03) and hypothyroidism caused by autoimmune disease (mean difference, -19.38). There were no differences in irisin levels between patients with hyperthyroidism and controls. A possible inverse correlation was found between irisin and TSH and positive correlations between irisin and both free T3

and free T4. Irisin was also correlated with TSH receptor antibodies. It is not known whether or how irisin might affect the pathology of hypothyroidism.

Type 2 diabetes mellitus (T2DM): IRISIN LEVELS ARE LOWER IN T2DM
In a meta-analysis of 26 case-control or cross-sectional studies involving a total of 3,667 participants, irisin levels were significantly lower in patients with T2DM compared to non-diabetic individuals (Song et al., 2021). This was true in both the plasma and serum. The ethnic subgroup analysis showed that irisin levels were significantly lower in patients with T2DM in Asia, Europe, and Turkey.

In a meta-analysis of 17 studies enrolling 1,912 participants who are non-diabetic (3 randomized trials, others are case-control or cross-sectional observational studies), circulating irisin levels were inversely associated with insulin sensitivity (r=-0.17); however, this association was small (Qiu et al., 2016). A larger correlation coefficient between circulating irisin and insulin resistance was observed in a subpopulation of people with abnormal fasting glycemia (fasting blood glucose ≥ 6.1 mmol/L and < 7.0 mmol/L) compared to those with normal fasting blood glucose. These findings are counterintuitive but may be explained by the fact that this increase in irisin with insulin resistance may be compensatory to restore glucose metabolism or metabolic disturbances in non-diabetic people. There could be a compensatory oversecretion of irisin prior to the development of diabetes, followed by a failure of irisin secretion once diabetes develops. Also, elevated irisin levels are associated with higher carbohydrate intake and increased levels of inflammatory markers such as IL-6, TNF-α, and CRP, which play roles in the development of insulin resistance. Because of the associations between diet, exercise, and irisin levels, further studies are needed to validate these relationships. A large-scale epidemiological study that analyzes the association between irisin and insulin resistance while properly controlling for many confounding factors, such as glycemic status, diet, exercise, race, sex, and others is needed.

In a mouse model of type 2 diabetes (high-fat diet), irisin treatment (0.5 mg/kg/day) for 2 weeks improved vascular function (Zhu et al., 2015). This improvement was through reduction of oxidative and nitrative stress (e.g., superoxide and peroxynitrite).

Safety: No studies have tested irisin as a therapy in humans. Levels are increased or decreased depending on different age-related conditions, so safety as a therapy is not yet clear. As a natural circulating hormone/myokine, it is likely safe at physiological levels.

Types of evidence:

- 8 meta-analyses of clinical trials using exercise as the intervention and irisin as the biomarker
- Numerous observational studies of circulating irisin levels in health and disease
- Several laboratory studies

No clinical trials have tested the efficacy of irisin in any disease indication. Numerous observational studies have measured the levels of circulating irisin in blood (serum, plasma) and the CSF in health and disease. While causation is unknown, irisin is increased in numerous conditions, including obesity, metabolic syndrome, gastrointestinal cancers, and others (Askari H et al., 2018), and we cannot rule out the possibility that these conditions may be worsened with irisin therapy.

The safest way to increase endogenous levels of irisin is through exercising. Numerous meta-analyses have been performed in an effort to determine which types of exercise, what duration, and what intensities are most effective in increasing irisin levels.

In a meta-analysis of 7 randomized controlled trials including a total of 282 adults, resistance training for at least 8 weeks increased circulating irisin levels, though the overall analysis did not achieve statistical significance (Cosio et al., 2021). Subgroup analyses showed significant increases in irisin for older adults ($p< 0.001$) and when training was demanding, and its intensity was progressive ($p=0.03$). Interventions that resulted in greater increases in irisin levels had shorter durations (8–12 weeks). Most studies used machine-based exercises for resistance training and one study used elastic bands.

In a 2022 network meta-analysis of 16 studies in a total of 608 healthy people, acute exercise training increased irisin levels more than chronic exercise, though the difference was not statistically significant (Kazeminasab et al., 2022). The meta-analysis also showed that acute aerobic exercise has a numerically greater effect on circulating irisin levels than acute anaerobic exercise. When comparing different types of chronic training, chronic aerobic training was associated with numerically lower irisin levels, while chronic anaerobic and chronic resistance trainings were associated with numerically higher irisin levels.

In a 2023 meta-analysis of 24 controlled studies, including a total of 921 adults, exercise training significantly increased circulating irisin (MD=0.01, 95% CI, 0.00 to 0.01, p=0.005), and decreased insulin

(p<0.00001), glucose (p<0.00001), and insulin resistance (p<0.00001) (Rahimi et al., 2022). Subgroup analyses revealed that resistance training (p=0.04) and combined training (resistance + aerobic; p=0.002) significantly increased irisin levels, but not aerobic training. Irisin was also increased with exercise in people with type 2 diabetes and prediabetes (p=0.002 for both), but not in people with metabolic syndrome (p=0.10). It is worth noting that exercise intensity, duration, and period of interventions varied across the included studies, which may have affected these findings.

In a 2024 meta-analysis of 36 studies of healthy adults, physical exercise induced a non-significant small increase in irisin levels (SMD=0.44; 95% CI, -0.04 to 0.91; p=0.07)(Bettariga et al., 2024). No statistically significant differences in irisin levels were seen between aerobic exercise and resistance exercise, and no differences were seen based on physical status (sedentary, physically active, and trained). Age was not significantly associated with changes in irisin. Irisin expression increased up to 60 minutes after a single bout of exercise, which was statistically significant, but decreased to baseline levels over the subsequent 24-hour period. While not statistically significant, larger effects were observed when subjects performed a single bout of aerobic exercise compared to resistance exercise.

In a 2024 meta-analysis of 7 controlled studies including a total of 217 overweight or obese adults, exercise training for a minimum of 8 weeks significantly increased serum irisin levels (SMD=0.957; p=0.005) compared to the passive control group (Torabi et al., 2024). High-intensity interval training (HIIT) had a more pronounced effect on increasing serum irisin levels (SMD=1.229, p<0.001) than other exercise protocols (e.g., aerobic, resistance). The effects of exercise on irisin levels varied based on body weight, with significant changes in overweight individuals (p<0.001) and non-significant changes for obese individuals (p=0.1). Effects also varied by age, with significant changes for those under 40 years old (p<0.001) and non-significant changes for those over 40 years old (p=0.322). This difference by age could be attributed to the decline in muscle mass with aging. Significant effects of exercise on irisin levels were observed in men (p<0.001) but the effects were not significant for women (p=0.285). In women, only the HIIT protocol resulted in significant increases in serum irisin levels.

In a 2023 meta-analysis of 16 studies including a total of 412 healthy adults, acute effects of endurance training on circulating irisin were determined (Cosio et al., 2023). After one session of continuous endurance training (10-50 minutes), a significant increase in circulating irisin was found (d=0.33, 95% CI, 0.20 to 0.46, p<0.001). Subgroup analysis of running, treadmill, and cycle-ergometer exercise modes suggested that cycle ergometer had the highest effect, then running, then treadmill; however, all exercise modes reported significant increases (p=0.013, p<0.001, and p<0.001, respectively). Increases in irisin were seen following a single session of continuous training independent of previous level of

physical activity, exercise mode, baseline circulating irisin, duration, or intensity. Interval endurance training did not significantly change circulating irisin levels in this meta-analysis (d=0.16, 95% CI, -0.12 to 0.44, p=0.202). Because there were fewer studies investigating interval training, with widely variable training protocols, further studies are needed to understand the true effects of interval training on irisin levels. For measurement of irisin, kits from Phoenix Pharmaceuticals Inc were used the most; other kits were from Shanghai Sunred Biological Technology Co Ltd and Elabscience Biotechnology Co. Ltd.

Drug interactions: Irisin has not been used as an intervention in humans, and therefore, drug interactions are unknown.

Sources and dosing:

No studies have tested irisin as a therapeutic intervention in humans. Irisin is available in research-grade form. Irisin has also been studied as a circulating biomarker in health and disease. In mouse studies, irisin intervention doses have ranged from 10-500 µg/kg via i.v. or i.p. (Wang et al., 2019; Jin et al., 2021; Bretland et al., 2021).

To measure circulating irisin levels, robust measurement methods such as mass spectrometry is recommended; in many studies, ELISA kits are often used but these have not been the most reliable (Cosio et al., 2021).

Based on a study of 122 healthy young individuals, circulating irisin levels are at their lowest at 6:00am and at their highest at 9:00pm (Anastasilakis et al., 2014).

Research underway:

There are currently no clinical trials testing the efficacy of an irisin intervention, based on ClinicalTrials.gov. However, there are several trials using irisin expression as biomarkers in various conditions, including cognitive function, bone health in people with spinal cord injury, type 2 diabetes with obesity, cancer, and acne vulgaris (Clinicaltrials.gov). Numerous NIH grants have been awarded to Christiane Wrann, DVM, PhD, at Massachusetts General Hospital for exploring irisin as a novel target for Alzheimer's disease and cognitive function in preclinical models (R21 AG062904; R56 AG064580; R01 NS117694; R56 AG072054). Wrann and Bruce Spiegelman, PhD, of Dana-Farber Cancer Institute and Harvard Medical School hold a patent on irisin and are co-founders of Aevum Therapeutics, a company

developing drugs to treat neurodegenerative and neuromuscular disorders (MGH press release, August 2021).

The most efficient protocol to increase irisin in humans has not been established. While acute exercise protocols in humans increase plasma irisin levels more than chronic protocols, there is no consensus on the ideal type, protocol, and duration of exercise that most robustly increases irisin levels (de Freitas et al., 2020).

Search terms:

Pubmed, Google: irisin

- + cognitive, + memory, + dementia, + meta-analysis, + Cochrane, + mortality, + safety

Websites visited for irisin:

- Clinicaltrials.gov
- NIH RePORTER
- Examine.com
- DrugAge (0)
- Geroprotectors (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)