The Association Between Regular Physical Exercise, Sleep Patterns, Fasting, and Autophagy for Healthy Longevity and Well-Being: A Narrative Review

Sicheng Min¹, Bojan Masanovic², Bo³, Te Bu¹*, Radenko M. Matic⁴,⁵, Ivan Vasiljevic⁶, Marina Vukotic⁷, Jiaomu Li¹, Jovan Vukovic⁸, Tao Fu⁶, Blazo Jabucanin⁹, Rajko Bujkovic⁷ and Stevo Popovic²,⁸

¹ College of Physical Education, Hunan Normal University, Changsha, China, ² Faculty for Sport and Physical Education, University of Montenegro, Niksic, Montenegro, ³ MontenegroSport, Podgorica, Montenegro, ⁴ Faculty of Sport and Physical Education, University of Novi Sad, Novi Sad, Serbia, ⁵ Western Balkan Sport Innovation Lab, Podgorica, Montenegro, ⁶ College of Exercise and Health Sciences, Tianjin University of Sport, Tianjin, China, ⁷ Faculty of Business Studies, Mediterranean University, Podgorica, Montenegro, ⁸ Montenegrin Sports Academy, Podgorica, Montenegro

This narrative review of the literature assessed whether regular physical exercise and sleep patterns, fasting and autophagy, altogether can be an adequate strategy for achieving healthy longevity and well-being within different stage of life. There are a large number of studies dealing with well-being and healthy longevity; however, few of them have given us a specific formula for how to live long and healthy. Despite all the advances that have been made to create adequate physical exercise programs, sleep patterns or nutritional protocols, the relation between different types of fasting, nutritional supplementation as well as regular physical exercise and sleep patterns have not yet been satisfactorily resolved to cause the best effects of autophagy and, therefore, well-being and healthy longevity. In this way, future studies should clarify more efficiently the relationship between these variables to understand the association between regular physical exercise, sleep patterns, fasting and autophagy for healthy longevity and well-being.

Keywords: exercise, sleep, fasting, autophagy, health, longevity, well-being

INTRODUCTION

The twentieth century is characterized as the century of world population growth and it is considered one of the most significant achievements of civilization, while the twenty-first century is characterized as the century of aging. The global average life expectancy was extended by 5.5 years in the period from 2000 to 2016 (Vukovic, 2021), which is the largest increase since the 60s of the twentieth century. According to United Nations projections, the number of people over the age of 60 will more than double by 2050, from the current 840 million to over 2 billion people (Vukovic, 2021).

There are a large number of studies dealing with healthy longevity and well-being; however, few of them have given us a specific formula for how to live long and healthy. Yet there is one man
who has brought us closer to our goal, and that is Yoshinori Ohsumi, a 2016 Nobel Prize-winning researcher in Physiology or Medicine for his initial interpretation of the mechanisms of autophagy (Antunes et al., 2018). Although the contributions of this great scientist are very well-known in the field of science, the global public, unfortunately, is not adequately acquainted with his conclusions and recommendations, as well as the outputs of a large number of studies that followed his work. For this reason, this narrative study aimed to point out that an adequate physical activity, sleep patterns, fasting, and autophagy may be highly correlated with to healthy longevity and well-being.

According to Antunes et al. (2018), autophagy is “an evolutionarily conserved lysosomal catabolic process by which cells degrade and recycle intracellular endogenous (damaged organelles, misfolded or mutant proteins and macromolecules) and exogenous (viruses and bacteria) components to maintain cellular homeostasis.” Therefore, autophagy has, lately, been used in solving various health problems, including one of the greatest enemies of longevity such as cancer (Galluzzi et al., 2015; Amaravadi et al., 2016), and one of the global epidemic and the most blatantly visible yet neglected global public health problem nowadays such as obesity (Lavallard et al., 2012), as well as infections and inflammatory diseases (Cadwell, 2016), neurodegeneration (Menzies et al., 2017), metabolic and cardiovascular diseases (Bravo-San Pedro et al., 2017), et cetera. Thus, it is not wrong to assume that autophagy represents a well-trodden path in lifespan extension and well-being, as well as it is the primary mechanism that can help removing damaged organelles, such as mitochondria, which may have a direct impact on aging (Yen and Klionsky, 2008).

On the other hand, it is very important to emphasize that regular physical activity, sleep patterns and proper nutrition are also important factors in achieving healthy longevity and well-being. So, the main goal of this study is to offer basic knowledge of association between regular physical exercise, sleep patterns, fasting and autophagy in the process of achieving healthy longevity and well-being through narrative review of scientific literature.

**PHYSICAL EXERCISE**

It is well-known that physical exercise, defined as “planned, structured and repetitive physical activity, has been an important force to alter physiological characteristics of human being during the process of evolution” (cited in Andreotti et al., 2020). On the other hand, physical exercise is well-connected to the aging process. This is reflected in by molecular and cellular changes over a longer period of time and it can lead to the deterioration of physiological parameters important to keeping a human body alive and healthy (cited in Andreotti et al., 2020). So, aging is “a physiological process characterized by a progressive decline of biological functions and an increase in destructive processes in cells and organs, while physical activity and exercise positively affects the expression of skeletal muscle markers involved in longevity pathways” (Mancini et al., 2019). Therefore, it is very important to understand the role of physical exercise in the process of achieving healthy longevity within different stage of life from childhood to old-age.

It is generally known that physical exercise is a natural activity during childhood, but it is very important to emphasize that habits are acquired then, but also improve certain physical abilities and characteristics. Special attention needs to be paid from adolescence onwards. Namely, physical exercise can have beneficial effects on the ability to pay attention and cognitive function in adolescents that are the findings of a study conducted by Vanhelst et al. (2016) and de Greeff et al. (2018). Also, during adolescence, certain cases of depression can occur, and physical exercise has been shown to be an effective factor in reducing the symptoms of depression, both in adolescents and young people, it was found in the studies that were conducted by Balchin et al. (2016), Sadeghi et al. (2016), Radovic et al. (2017), and Bailey et al. (2018). Physical exercise is also useful for the working population, but it is the most useful for the elderly population, who are constantly recommended regular physical exercise. However, few of older people follow the recommendations, especially moderate to vigorous physical exercise; even, some believe that physical exercise could be potentially harmful (Franco et al., 2015). According to Hupin et al. (2015), moderate physical activity can reduce mortality risk up to 22%, so it is not surprising that Cotman and Berchtold (2007) have concluded that “among the various interventions that affect aging, physical exercise seems to be the main ally in the prevention of aging-related diseases” and, therefore, the main ally of healthy longevity and well-being.

In summary, regular physical exercise increases skeletal muscle fat oxidation and anti-oxidative potential, stimulates musculoskeletal metabolic adaptations, and results in beneficial improvements in the cardiovascular system (Andreotti et al., 2020). Also, regular physical exercise improves quality of sleep and increases brain-derived neurotrophic factor production, and can decrease neuronal death and improve cognitive performance (Mancini et al., 2019). Regular physical exercise can also cause many other effects that can affect positive aging and health; however, the molecular effects of exercise training on regulation of autophagy and processes involved in longevity promotion are not completely explained by the scientific society, and there is no general agreement on this issue (Andreotti et al., 2020).

**SLEEP PATTERNS**

In regular conditions, people spend about one-third of their life either sleeping or attempting to do so. The key significance of sleeping time is enabling enough time for recovery functions of the organism which is crucial for effects in human health, well-being, longevity, and optimal daytime functioning (Sorathia and Ghori, 2016; Bertozzi et al., 2017). This fact confirmed that enough quality sleep is necessary to help each person maintain other activities in their daily routine. Therefore, it’s clear that human health and well-being are associated with regular sleep patterns as an essential factor for 24 h of human functioning and help to the maintenance of homeostatic needs (Tufik et al., 2009). On another side, some estimations highlighted that every third person globally has sleep-related problems (Roth,
2007). These problems with sleep disorders can be caused by different factors, such as physical or medical, psychiatric, aging, genetics, medications, lifestyle, and socio-demographic factors (smoking, exercise, education, age, gender, et cetera). Further, sleep disorders can increase the number of cardiovascular (Basnet et al., 2016) and metabolic diseases (Karthikeyan et al., 2019), which are frequently causes of human diseases and mortality.

Researchers put a lot of effort to reveal contextual factors which are associated with managing sleep-related problems, intending to impact on physical, mental, social, and emotional health and well-being of people. Some conclusions revealed the negative effect of physical load at the job and intensive physical exercise on insomnia (Dubinina et al., 2021). Further, the importance of quality of sleep in a psychological context showed that depression is associated with sleep problems (Basnet et al., 2016). Also, conscientiousness, as a personal trait, can be an essential moderator in the protection of individuals of poor sleep (Williams and Moroz, 2009). On the contrary, human dispositional optimism contributes to a lower risk of chronic insomnia (Weitzer et al., 2021), and regular sleep has significant importance to cognitive health and higher level dopaminergic activity (Yang et al., 2014). Further, Eisenberger and Cole (2012) revealed the importance of social relationships in the same context.

Contemporary managing sleep-related problems require a deep approach through an interdisciplinary and holistic approach. That is a reason why many researchers point out that improvement in managing sleep problems contributes to a higher quality of life, well-being, and longevity in a population (Basnet et al., 2016).

**FASTING**

Fasting is “characterized by the complete deprivation of food but not water, with intervening periods of normal food intake” (Mattson et al., 2017). It has been known since ancient times, and it has remained in modern religions as a significant activity in religious rites. Although ancient religious knowledge was not based on adequate scientific facts, it is still interesting to mention it, mostly because it turned out to be correct, and the main question is how ancient people came to such valid knowledge. However, the goal of this study is not to deal with knowledge of ancient people and their methods in reaching it, but to determine contemporary knowledge and methods that would improve the health status of contemporary people and prolong their lives. Therefore, in the description of current knowledge of fasting, it is important to highlight that, according to the suggestions of Mattson et al. (2017), it has been found that fasting can “improve cardiometabolic health, reduce cancer incidence, reduce the rate of tumor growth, regenerate organs by increasing stem cell production, and increase lifespan,” which significantly leads to the conclusion that it has a significant impact on improving human health status and longevity. In addition, there is scientific evidence, presented to the scientific community by Antoni et al. (2017) and Tinsley and Horne (2018), which has suggested that “fasting decreases body weight, insulin levels, blood pressure, inflammation, and appetite, and that it improves insulin sensitivity and lipid profiles,” which in many ways can also improve a human health status and longevity.

The previous paragraph described how fasting can improve a human health status and longevity in the general sense of the words. However, further analysis of this issue opens up new scientific questions that should be answered and offered to potential readers of this manuscript. Namely, it is important to emphasize that fasting is not in itself starvation but it represents a way of life that requires a certain sacrifice. For that reason, not all people are ready to approach it in the same way, so there are different types of fasting, each tailored to the individual in order to improve its health status and longevity. On the one hand, there are still religious priests, who fast in accordance with their centuries-old rules and maintain their health status at an adequate level, which leads to their longevity. On the other hand, there are a large number of people who are not able to organize their diet in accordance with the needs of their body. The modern lifestyle has led to the fact that their daily meals are not prepared in an adequate way, but “fast food” is taken. Meals are extensive and contain many non-nutritious ingredients, and are ingested both during the day and overnight, without any plan. Accordingly, the modern world has encountered a problem that is reflected in obesity. Namely, obesity is a serious problem, as it is associated with poorer mental health outcomes and reduced quality of life [NCD Risk Factor Collaboration (NCD-RisC), 2019]. Obesity is also linked to leading causes of death worldwide, including diabetes, heart disease, stroke and some cancers [NCD Risk Factor Collaboration (NCD-RisC), 2017]. For this reason, there are a large number of governmental and non-governmental organizations that show interest in the use of fasting for the treatment of obesity as it has been proven to be significantly correlated with the improvement of health status and longevity. However, there is no a general formula that can be suitable for each individual and different types of fasting have been defined over time. Next to the most recognized continuous energy restriction, it is interesting to present some alternative dietary weight loss strategies. Rynders et al. (2019) have created a strategy that “involves restricting energy intake to certain periods of the day or prolonging the fasting interval between meals (i.e., intermittent energy restriction)”. The strategy in question includes intermittent fasting and time-restricted feeding. Intermittent fasting is reflected to >60% energy restriction on 2–3 days per week, or on alternate days, and it covers “a broad class of interventions that alternate periods of eating and extended fasting, where it is associated with substantial weight loss in short periods of time, during around 8–12 weeks (Rynders et al., 2019).” According to the same authors, intermittent fasting interventions include “periodic 24-h fasts, intermittent energy restriction (e.g., the 5:2 diet), and time-restricted feeding that includes Ramadan fasting.” On the other hand, time-restricted feeding is “limiting the daily period of food intake to 8–10 h or less on most days of the week (Rynders et al., 2019).” Mattson et al. (2017) have created another strategy based on the duration. The strategy in question includes intermittent fasting and periodic fasting. According to mentioned authors, intermittent fasting suggests alternate day fasting (≥ 16 h) or 48 h
of fasting/week, while periodic fasting suggests a minimum of 3
days of fasting every 2 or more weeks. Further analysis of the
literature would lead to a number of other strategies, but the
authors of this manuscript believe that the presented strategies
are sufficient for each of the potential readers to choose one
for themselves.

In summary, all the mentioned types of fasting in the previous
paragraph have proven to be useful when it comes to improving
human health status in many ways and, therefore, longevity.
To make this claim more convincing, it is necessary, first of
all, to refer to the research of Ravussin et al. (2019) who
discovered that “time-restricted feeding has shown to facilitate
weight loss through the meal-timing interventions by decreasing
appetite rather than by increasing energy expenditure, where
time-restricted feeding showed lowered values of ghrelin and
leptin.” Also, the following three studies (Harvie et al., 2011;
Gnanou et al., 2015; Panizza et al., 2019) confirm the assumptions
that “intermittent energy restriction, combined by the specific
diet have shown to generate a loss of body weight and fat
mass,” while two more studies emphasized that “Ramadan fasting
produced a weight loss through an increased energy expenditure
(Lessan and Ali, 2019) and metabolic benefits (Fernando et al.,
2019).” However, it is not enough to conclude this chapter only
with recommendations related to limiting food intake, but it is
important to note the part of the day in which food is consumed.
Namely, it is a well-known fact that achieving an adequate
muscle mass is a key factor for attaining a good body image,
so Argiles et al. (2016) claim that “muscle is increasingly being
recognized as a key tissue for the maintenance of an adequate
health status.” The authors of this manuscript invite readers to
pay special attention to proper nutrition during the period of
food intake. They suggest there are a number of studies that
recommend taking protein immediately after exercise, especially
whey protein, which “acutely stimulates significant increases
in post-exercise muscle protein synthesis (Atherton and Smith,
2012).” As proteins are widely used for active and sedentary
people as a product for muscle growth, in addition to fasting, it is
very important to use a diet rich in protein to lose weight and low
in carbohydrates.

**AUTOPHAGY**

Although the introductory part of this manuscript significantly
deals with autophagy, it is still necessary to deal with another
part of this topic, in order for potential readers to get a complete
picture of this issue. Namely, it is very important to point out
the conclusions of Thevelein et al. (2000) who emphasize that
“aging cells gradually accumulate various deleterious changes,
resulting in a decline in cellular function and eventually leading
to cell death and disease.” Also, the same group of authors points
out that “the accumulation of damaged macromolecules and
organelles is one of the most persistent changes in aging cells,”
while, Cuervo and Dice (1998) add that autophagy is “associated
with the decline of different catabolic pathways.” Cuervo et al.
(2005) in one of their recent studies concluded that the absence of
autophagy in the elderly is one of the main causes that lead to the
accumulation of biological “waste” reflected in damaged proteins
and organelles. This group of authors based their assumptions
on the facts obtained by Melendez et al. (2003), Kuma et al.
(2004), as well as Juhasz et al. (2007) in their research on mice.
These authors found that the loss of autophagy gene function led
to the accumulation of damaged proteins and organelles within
the cells, and that this accelerated the aging of mice, and thus
shortened their lifespan. On the other hand, a study conducted
by Simonsen et al. (2008) proved that elevating autophagy activity
increases life span in the same species of mice, since the process
of autophagy saved aged cells, so that there was no accumulation
doing dysfunctional mitochondria.

Autophagy is an evolutionarily conserved lysosomal catabolic
process. In this process, the cells break down and recycle
damaged organelles, incorrectly assembled proteins, then
mutated proteins and macro molecules, as well as exogenous
components such as bacteria and viruses. Therefore, autophagy is
a process that aims to preserve cellular homeostasis in the human
body. However, it is worth emphasizing that even autophagy
cannot be viewed as a unique process characteristic of all types of
activities that are initiated in that process. Namely, there are three
main types of autophagy: (1) microautophagy, (2) chaperone-
mediated autophagy and (3) microautophagy. The specificity
of each types of autophagy is reflected in the load type and the
route of delivery to the lysosome. Mijaljica et al. (2011) defined
microautophagy as a process that “involves the direct engulfment
cargo in endosomal/lysosomal membrane invaginations.” On
the other hand, Kaushik and Cuervo (2012) described chaperone-
mediated autophagy as a process that “recycles soluble proteins
with an exposed amino acid motif that is recognized by the
heat shock protein HSC70,” while macroautophagy, which is
the best characterized type of autophagy, represents a process
in which cytoplasmic constituents, which are encompassed by
double-membrane vesicles called autophagosomes, fuse with
lysosomes to form autolysis, and there the burden is degraded or
recycled (Mizushima and Komatsu, 2011; Galluzzi et al., 2017).

In summary, autophagy is an essential process that takes place
in human body with the goal of removing dysfunctional and
unwanted parts of cells as well as regenerating existing cells
to make them newer and healthier, so autophagy represents
an evolutionary self-preservation mechanism through which
humans can clean and repair its body (Marx, 2015). This explains
the literal meaning of autophagy that is derived from the Ancient
Greek for “self-eating”—“auto” means “self” and “phagy” means
“eating.” From this reason, it should be easy to assume that
autophagy should positively affect healthy longevity and well-
being; however, there are some scientific studies to suggest that
autophagy can have positive, but also negative health effects,
so it is necessary to seek medical advice beforehand starting
it (Schiaffarella and Hill, 2016). Nevertheless, scientists still do
not have a clear picture of all health implications of autophagy,
so further researches are necessary, especially with the human
subjects (most of researches have been conducted on non-human
subjects). The part the scientists do know is connected to fact
that the main benefits of autophagy are based on anti-aging
principles and trying to turn the body clock back and create new
and young cells. The scientists do also know that autophagy is
increased when our cells are stressed, in order to protect human body and helps in the process of enhancing healthy longevity and well-being (Alirezaei et al., 2010). Although it is the fact that autophagy occurs naturally it is very important to set up a research question if the autophagy can be stimulated by some specific triggers. Some research strongly suggests that both fasting (intermittent fasting) and calorie restriction (ketogenic diets) can stimulate autophagy in the human body (Bagherniya et al., 2018), as well as, both regular physical activity (Brandt et al., 2018) and regular sleeping (Bedont et al., 2021).

PHYSICAL EXERCISE, SLEEP, FASTING AND AUTOPHAGY: PRACTICAL SUGGESTIONS FOR WELL-BEING AND HEALTHY LONGEVITY

Movement is one of the basic needs of human being, which has sustained him during evolutionary development; however, most of the time the human being moved more than he needed to. In order to reduce the volume of heavy physical work, which was synonymous with the survival of human being for a long period of time, human being devised modern technologies that have taken over the role of human being in performing the aforementioned jobs. However, contemporary human being did not cope with the new circumstances, it can be said that human being even abused the ability to bring its movement and overall physical activity below the acceptable minimum necessary for the survival of human being as a healthy individual. If it is added to this the issue of the appearance of inorganic food on a large scale, it is clear that the diseases faced by contemporary human being and premature mortality are not a surprise.

Whether it will indulge in an inactive lifestyle and allow to be overwhelmed by the epidemic of immobility, but also all other epidemics that threaten us every day directly in front of or just around the corner, it is a main contemporary question. But it is a question that human population must not long to answer. There are solutions, but for them the common man must first find out and then persevere to get results, since the path to health and good energy requires certain sacrifices. Although autophagy is not an unknown term in scientific circles, it is increasingly becoming available to non-scientific audiences, especially after the guidelines that arrived from world-famous athletes, in the first place Novak Djokovic, the number one tennis racket. While waiting for stronger scientific confirmation, it is necessary to stick to the theories and knowledge that are currently available. So, the authors of this narrative review made recommendation, from the available practical and theoretical experience, to walk at least one kilometer every day, to sleep between seven and 9 h per night (for healthy adults), between seven and 8 h per night (for people over 65 years old), while in childhood and teens this period should be prolonged, not to take food for 16 h, just to drink exclusively water, tea and coffee without any additives (Pietrocola et al., 2014), between dinner at 6 pm and breakfast at 10 am the next day. On the other hand, the timetable does not need to be strict, so any individual can schedule any suitable timetable, just to keep 16 h food restrictions. For those who do not prefer to fast every day, the authors recommend a periodic fasting. This means minimum 3 days of fasting (the same food restrictions as described in the previous example) every 2 or more weeks.

Available theoretical knowledge and experience of individuals promise to raise every individual who consistently adheres to the above recommendations, in addition to biological benefits, and raising psycho-physical abilities, as well as the emergence of “youthful” energy, which gives a person the impetus to feel faster, stronger and more capable, much easier, enters into daily activities.

The fact is that a healthy, asleep and mobile citizen is a socially useful citizen. He represents a good producer, but also an equally useful consumer who, in the best way, maintains the economic chain at an adequate level. In such circumstances, that citizen is satisfied at home, satisfied on the street and satisfied at work, and society, with the majority of such citizens, is a welfare society, to which we should all aspire.

CONCLUSION

This narrative review highlights the studies that explain regular physical exercise and sleep patterns, as well as fasting, and autophagy as a strategy for healthy longevity and well-being. Currently, any of these methods have been used for achieving healthy longevity and well-being within different stage of life from childhood to old-age; however, focusing on combination of all four methods instead of using just one should be the primary aim in the process of reaching healthy longevity and well-being in full capacity. Despite all the advances that have been made to create adequate physical exercise programs, sleep patterns or nutritional protocols, the relation between different types of fasting, nutritional supplementation and regular physical exercise and sleep patterns have not yet been satisfactorily resolved to cause the best effects of autophagy and, therefore, healthy longevity and well-being. Previous researches gave some guides how to create adequate protocols to reach the best effects of autophagy, but no studies answered the most important questions how to recognize the autophagy threshold and how to use various factors such as fasting and calorie restriction as well as regular physical activity and regular sleeping to stimulate autophagy and decrease the autophagy threshold. In this way, since there are no previous studies, the first future study should create a theory of autophagy threshold, while the rest of future studies should be clinical trials that would confirm independent and joint positive effects of regular physical exercises and sleep patterns, as well as fasting and autophagy on healthy longevity and well-being.

AUTHOR CONTRIBUTIONS

SM and BM formulated the research goals and aims, developed and designed the methodology, prepared the published work, and specifically wrote the initial draft. TB prepared the published work and specifically acquired the financial support for the project leading to this publication. RM, IV, MV, JL, JV, TF, BJ, RB, and SP prepared the published work, specifically with critical reviews, editing, and revisions. All authors commented on the draft and contributed to the final version, approved the

Min et al. Various Factors for Longevity and Well-Being
publication of the manuscript, and agreed to be accountable for all aspects of the work.

**FUNDING**

The study was supported by the Non-profit Central Research Institute Fund of Chinese Academy of Medical Science (Grant Number: 2020-JKCS-022).

**REFERENCES**

Alirezaei, M., Kenball, C. C., Flynn, C. T., Wood, M. R., Whitten, J. L., and Kiosses, W. B. (2010). Short-term fasting induces profound neuronal autophagy. *Autophagy* 6, 702–710. doi: 10.4161/auto.6.6.12376

Amaravadi, R., Kimmelman, A. C., and White, E. (2016). Recent insights into the function of autophagy in cancer. *Genes Dev.* 30, 1913–1930. doi: 10.1101/gad.287524.116

Andreotti, D. Z., Silva, J., Matumoto, A. M., Orellana, A. M., de Mello, P. S., and Kawamoto, E. M. (2020). Effects of physical exercise on autophagy and apoptosis in aged brain: human and animal studies. *Front. Nutr.* 7:94. doi: 10.3389/fnut.2020.00094

Antoni, R., Johnston, K. L., Collins, A. L., and Robertson, M. D. (2017). Effects of intermittent fasting on glucose and lipid metabolism. *Proc. Nutr. Soc.* 76, 361–368. doi: 10.1017/S0029651816002986

Antunes, F., Erustes, A. G., Costa, A. J., Nascimento, A. C., Bincolletto, C., Ureshino, R. P., et al. (2018). Autophagy and intermittent fasting: the connection for cancer therapy? *Clinics* 73:e814s. doi: 10.6061/clinics/2018/e814s

Argiles, J. M., Campos, N., Lopez-Pedrosa, J. M., Rueda, R., and Rodriguez-Mañas, L. (2016). Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. *J. Am. Med. Dir. Assoc.* 17, 789–796. doi: 10.1016/j.jamda.2016.04.019

Atherton, P. J., and Smith, K. (2012). Muscle protein synthesis in response to nutrition and exercise. *J. Physiol.* 590, 1049–1057. doi: 10.1113/jphysiol.2011.225003

Bagherniya, M., Butler, A. E., Barreto, G. E., and Sahebkar, A. (2018). The effect of fasting or calorie restriction on autophagy induction: a review of the literature. *Aging Res. Rep.* 47, 183–197. doi: 10.1016/j.arr.2018.08.004

Bailey, A. P., Hetrick, S. E., Rosenbaum, S., Purcell, R., and Parker, A. G. (2018). *Treating depression with physical activity in adolescents and young adults: a systematic review and meta-analysis of randomised controlled trials.*

Bedont, J. L., Toda, H., Shi, M., Park, C. H., Quake, C., Stein, C., et al. (2021). Short intermittent fasting: the connection for cancer therapy? *Front. Physiol.* 12:3363. doi: 10.3389/fphys.2021.705212

Eisenberger, N. I., and Cole, S. W. (2012). Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health. *Nat. Neurosci.* 15, 669–674. doi: 10.1038/nn.3086

Fernando, H. A., Zibellini, J., Harris, R. A., Seimov, R. V., and Sainsbury, A. (2019). Effect of Ramadan fasting on weight and body composition in healthy non–athlete adults: a systematic review and meta-analysis. *Nutrients* 11:478. doi: 10.3390/nu11020478

Franco, M. R., Tong, A., Howard, K., Sherrington, C., Ferreira, P. H., Pinto, R. Z., et al. (2015). Older people’s perspectives on participation in physical activity: a systematic review and thematic synthesis of qualitative literature. *Br. J. Sports Med.* 49, 1268–1276. doi: 10.1136/bjsports-2014-094015

Galluzzi, L., Baehrecke, E. H., Ballabio, A., Boya, P., Bravo-San Pedro, J. M., Ceconi, F., et al. (2017). Molecular definitions of autophagy and related processes. *EMBO J.* 36, 1811–1836. doi: 10.15252/embj.20179697

Galluzzi, L., Pietrocolla, F., Bravo-San Pedro, J. M., Amaravadi, R. K., Baehrecke, E. H., Ceconi, F., et al. (2015). Autophagy in malignant transformation and cancer progression. *EMBO J.* 34, 856–880. doi: 10.15252/embj.201490784

Gnanou, J. V., Caszo, B. A., Khalil, K. M., Abdullah, S. L., Knight, V. F., and Bidin, M. (2015). Effects of Ramadan fasting on glucose homeostasis and adiponectin levels in healthy adult males. *J. Diabetes Metab. Disord.* 14:55. doi: 10.1186/s40260-015-0183-9

Harvie, M. N., Pegington, M., Mattson, M. P., Frystyk, J., Dillon, B., Evans, G., et al. (2011). The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int. J. Obes.* 35, 714–727. doi: 10.1038/ijo.2010.171

Hupin, D., Roche, F., Gremeaux, V., Chatard, J. C., Oriol, M., Gaspoz, J. M., et al. (2015). Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥60 years: a systematic review and meta-analysis. *Br. J. Sports Med.* 49, 1262–1267. doi: 10.1136/bjsports-2014-094306

Huhasz, G., Erdi, B., Sass, M., and Neufeld, T. P. (2007). Agt7-dependent autophagy promotes neuronal health, stress tolerance, and longevity but is dispensable for metamorphosis in *Drosophila*. *Genes Dev.* 21, 3061–3066. doi: 10.1101/gad.160707

Karlikhayk, R., Spence, D. W., and Pandi-Perumal, S. R. (2019). The contribution of modern 24-hour society to the development of type 2 diabetes mellitus: the role of insufficient sleep. *Sleep Sci.* 12, 227–231. doi: 10.5935/1984-0063.20190061

Kaushik, S., and Cuervo, A. M. (2012). Chaperone-mediated autophagy: a unique way to enter the lysosome world. *Trends Cell Biol.* 22, 407–417. doi: 10.1016/j.tcb.2012.05.006

**ACKNOWLEDGMENTS**

This research has been done within a national project under the title effects of autophagy and physical activity on body composition, body mass index, stress, health behavior, cognitive abilities and social inclusion of the elderly (EAPA-BCH) that was approved by the Ministry of Science in Montenegro (No. 03/1-062/20-346/3 from 29 April 2020).
Kuma, A., Hatano, M., Matsu, M., Yamamoto, A., Nakaya, H., Yoshimori, T., et al. (2004). The role of autophagy during the early neonatal starvation period. *Nature* 432, 1032–1036. doi: 10.1038/nature03029

Lavallard, V. J., Meijer, A. J., Codogno, P., and Gual, P. (2012). Autophagy: signaling and obesity. *Pharmacol. Rev.* 66, 513–525. doi: 10.1124/j.phrs.2012.09.003

Lessan, N., and Ali, T. (2019). Energy metabolism and intermittent fasting: the ramadan perspective. *Nutrients* 11, 1192. doi: 10.3390/nu11051192

Mancini, A., Vitucci, D., Randers, M. B., Schmidt, J. F., Hagman, M., Andersen, T. R., et al. (2019). Lifelong football training: effects on autophagy and healthy longevity promotion. *Front. Physiol.* 10.132. doi: 10.3389/fphys.2019.00113

Marx, V. (2015). Autophagy: eat thyself, sustain thyself. *Nat. Methods* 12, 1121–1125. doi: 10.1038/nmeth.3661

Matsen, M. P., Longo, V. D., and Harvie, M. (2017). Impact of intermittent fasting on health and disease processes. *Ageing Res. Rev.* 39, 46–58. doi: 10.1016/j.arr.2016.10.005

Melendez, A., Tallóczy, Z., Seaman, M., Escalener, E. L., Hall, D. H., and Levine, B. (2003). Autophagy genes are essential for dauer development and life-span extension in *C. elegans*. *Science* 301, 1387–1391. doi: 10.1126/science.1087782

Menzies, F. M., Fleming, A., Caricasole, A., Bento, C. F., Andrews, S. P., Ashkenazi, A., et al. (2017). Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities. *Neuron* 93, 1015–1034. doi: 10.1016/j.neuron.2017.01.022

Mijažiča, D., Prescott, M., and Devenish, R. J. (2011). Microautophagy in mammalian cells: revisiting a 40-year-old conundrum. *Autophagy* 7, 673–682. doi: 10.4161/aut.7.7.14733

Mizushima, N., and Komatsu, M. (2011). Autophagy: renovation of cells and tissues. *Cell* 147, 728–741. doi: 10.1016/j.cell.2011.10.026

NCD Risk Factor Collaboration (NCD-RisC) (2017). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 390, 2627–2642. doi: 10.1016/S0140-6736(17)32129-3

NCD Risk Factor Collaboration (NCD-RisC) (2019). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. *Nature* 569, 260–264. doi: 10.1038/s41586-019-1171-x

Panizza, C. E., Lim, U., Yonemori, K. M., Cassel, K. D., Wilkens, L. R., and Harvie, M. N., et al. (2019). Effects of intermittent energy restriction combined with a Mediterranean diet on reducing visceral adiposity: a randomized active comparator pilot study. *Nutrients* 11, 1386. doi: 10.3390/nu11061386

Pietrocola, F., Malik, S. A., Marino, G., Vaccelli, E., Senovilla, L., Chab, K., et al. (2014). Coffee induces autophagy in vivo. *Cell Cycle* 13, 1987–1994. doi: 10.4161/cc.28929

Radovic, S., Gordon, M. S., and Melvin, G. A. (2017). Should we recommend exercise to adolescents with depressive symptoms? A meta-analysis. *J. Paediatr. Child Health* 53, 214–220. doi: 10.1111/jpc.13426

Ravussin, E., Beyl, R. A., Poggiofagello, E., Hsia, D. S., and Peterson, C. M. (2016). Physical activity is associated with attention capacity in adolescents. *J. Pediatrics* 168, 126–131.e2. doi: 10.1016/j.jpeds.2015.09.029

Vukovic, J. (2021). Effects of Low Intensity Strength Training on Physical Form, Health Biomarkers and Quality of Life of Institutionalized Third Age Women (in Serbian). Unpublished Doctoral dissertation, Novi Sad: University of Novi Sad, Faculty of Sport and Physical Education.

Weitzer, J., Papantoniou, K., Lazarow-Sebastia, C., Seidel, S., Klosch, G., and Schernhammer, E. (2021). The contribution of dispositional optimism to understanding insomnia symptomatology: findings from a cross-sectional population study in Austria. *J. Sleep Res.* 30:13132. doi: 10.1111/jsr.13132

Williams, P. G., and Moroz, T. L. (2009). Personality vulnerability to stress-related sleep disruption: pathways to adverse mental and physical health outcomes. *Pers. Individ. Dif.* 46, 598–603. doi: 10.1016/j.paid.2008.12.017

Yang, G., Lai, C. S., Cichon, J., Ma, L., Li, W., and Gan, W. B. (2014). Sleep promotes branch-specific formation of dendritic spines after learning. *Science* 344, 1173–1178. doi: 10.1126/science.1249098

Yen, W. L., and Klionsky, D. J. (2008). How to live long and prosper: autophagy, mitochondria, and aging. *Physiology* 23, 248–262. doi: 10.1152/physiol.00013.2008

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Min, Masanovic, Bu, Matic, Vasiljevic, Vukotic, Li, Vukovic, Fu, Jabucanin, Bujkovic and Popovic. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.