



**HAL**  
open science

## Exercise sustains the hallmarks of health

Yan Qiu, Benjamin Fernández-García, H. Immo Lehmann, Guoping Li, Guido Kroemer, Carlos López-Otín, Junjie Xiao

► **To cite this version:**

Yan Qiu, Benjamin Fernández-García, H. Immo Lehmann, Guoping Li, Guido Kroemer, et al.. Exercise sustains the hallmarks of health. *Journal of Sport and Health Science*, 2022, 12 (1), pp.8 - 35. 10.1016/j.jshs.2022.10.003 . hal-04596365

**HAL Id: hal-04596365**

**<https://hal.science/hal-04596365>**

Submitted on 8 Jun 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

1 **Review**

2

3 **Exercise sustains the hallmarks of health**

4

5 Yan Qiu<sup>a,b,†</sup>, Benjamin Fernández-García<sup>c,d,†</sup>, H. Immo Lehmann<sup>e</sup>, Guoping Li<sup>e</sup>, Guido  
6 Kroemer<sup>f,g,h,\*</sup>, Carlos López-Otín<sup>i,j,\*</sup>, Junjie Xiao<sup>a,b,\*</sup>

7 <sup>a</sup>Institute of Geriatrics (Shanghai University), Affiliated Nantong Hospital of Shanghai  
8 University (The Sixth People's Hospital of Nantong), School of Medicine, Shanghai  
9 University, Nantong 226011, China

10 <sup>b</sup>Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, Shanghai  
11 Engineering Research Center of Organ Repair, School of Life Science, Shanghai  
12 University, Shanghai 200444, China

13 <sup>c</sup>Health Research Institute of the Principality of Asturias (ISPA), Oviedo 33011, Spain

14 <sup>d</sup>Department of Morphology and Cell Biology, Anatomy, University of Oviedo, Oviedo  
15 33006, Spain

16 <sup>e</sup>Cardiovascular Division of the Massachusetts General Hospital and Harvard Medical  
17 School, Boston, MA 02114, USA

18 <sup>f</sup>Centre de Recherche des Cordeliers, Equipe labellisée par la Ligue contre le cancer,  
19 Université de Paris Cité, Sorbonne Université, Inserm U1138, Institut Universitaire de  
20 France, Paris 75231, France

21 <sup>g</sup>Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, Villejuif 94805,  
22 France.

23 <sup>h</sup>Institut du Cancer Paris CARPEM, Department of Biology, Hôpital Européen Georges  
24 Pompidou, AP-HP, Paris 75015, France

25 <sup>i</sup>Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Instituto

26 Universitario de Oncología, Universidad de Oviedo, Oviedo 33006, Spain  
27 <sup>‡</sup>Centro de Investigación Biomédica en Red Enfermedades Cáncer (CIBERONC),  
28 Oviedo 33006, Spain  
29 <sup>†</sup>These two authors contributed equally to this work.  
30 \*Correspondence authors  
31 Email addresses: [Junjiexiao@shu.edu.cn](mailto:Junjiexiao@shu.edu.cn) (J. Xiao); [kroemer@orange.fr](mailto:kroemer@orange.fr) (G. Kroemer);  
32 [clo@uniovi.es](mailto:clo@uniovi.es) (C. López-Otín)

33

34 Received 17 May 2022; revised 10 August 2022; accepted 2 September 2022

35

### 36 **Highlights**

- 37 1. Regular exercise confers multiple health benefits and better survival
- 38 2. Regular moderate-intensity of exercise sustains the major hallmarks of health
- 39 3. The health benefits of exercise lies in the remarkable integrative adaptation of  
40 multiple tissues and organs
- 41 4. Exercise appears as a protective strategy to maintain health in response to stress
- 42 5. Regular exercise is considered a non-pharmacological polypill for patients with  
43 certain comorbidities.

44

45

46 Running title

47 Exercise sustains health

48

49

50 **Abstract**

51 Exercise has long been known for its active role in improving physical fitness and  
52 sustaining health. Regular moderate-intensity exercise improves all aspects of human  
53 health and is widely accepted as a preventative and therapeutic strategy for various  
54 diseases. It is well documented that exercise maintains and restores homeostasis at the  
55 organismal, tissue, cellular, and molecular levels to stimulate positive physiological  
56 adaptations that consequently protect against various pathological conditions. Here we  
57 mainly summarize how moderate-intensity exercise affects the major hallmarks of  
58 health, including the integrity of barriers, containment of local perturbations, recycling  
59 and turnover, integration of circuitries, rhythmic oscillations, homeostatic resilience,  
60 hormetic regulation, as well as repair and regeneration. Furthermore, we summarize the  
61 current understanding of the mechanisms responsible for beneficial adaptations in  
62 response to exercise. This review aimed at providing a comprehensive summary of the  
63 vital biological mechanisms through which moderate-intensity exercise maintains  
64 health and opens a window for its application in other health interventions. We hope  
65 that continuing investigation in this field will further increase our understanding of the  
66 processes involved in the positive roles of moderate-intensity exercise and thus get us  
67 closer to the identification of new therapeutics that improve quality of life.

68

69 **Keywords:** Beneficial effects of exercise; Exercise-related physiological adaptations;  
70 Hallmarks of health; Moderate-intensity exercise; Therapeutic exercise

71

72

73

74

75 **1. Introduction**

76 While modernization has contributed to increased population longevity, it has also  
77 witnessed a continuous rise in non-communicable diseases such as obesity,  
78 hypertension, type 2 diabetes, cancer, etc. Non-communicable diseases are now  
79 considered “the number one killer” globally, as they lead to more than 80% of deaths  
80 in certain countries.<sup>1, 2</sup> The prevalence of non-communicable diseases can be at least  
81 partly attributed to insufficient physical activity or exercise.<sup>3</sup> According to data from  
82 the World Health Organization, in 2016, more than one-quarter of adults worldwide  
83 were physically inactive.<sup>4</sup> The worldwide pandemic of physical inactivity should be a  
84 public health priority. It is well known that a healthy lifestyle is associated with a  
85 significantly lower risk of total mortality and a longer life expectancy.<sup>5</sup> Together with  
86 a healthy and adequate dietary pattern, exercise represents a promising strategy for  
87 reducing the risk of chronic metabolic and inflammatory diseases, such as those related  
88 to obesity. In general, physical activity is defined as any movement requiring energy,  
89 such as walking, manual labor, or housework. By contrast, exercise refers to a routine  
90 of physical activity that is planned and structured with the aim of improving physical  
91 fitness.<sup>6</sup> In this review, we use the term “regular exercise” to refer to regular moderate-  
92 intensity exercise at a <70% maximal oxygen uptake (VO<sub>2</sub>max).

93 It has been strongly recommended that children and adults should limit the amount  
94 of sedentary time, which is associated with adverse health outcomes, including all-  
95 cause mortality and the incidence of cardiovascular disease, cancer, and type 2 diabetes.  
96 Replacing sedentary behavior with physical activity of any intensity (including light  
97 intensity) is beneficial for health. For substantial health benefits, World Health  
98 Organization recommends adults should undertake at least 150-300 min of moderate-  
99 intensity or 75-150 min of vigorous-intensity aerobic physical activity throughout the

100 week, or an equivalent combination of moderate-intensity and vigorous-intensity  
101 aerobic physical activity.<sup>7</sup> Adults are recommended to increase moderate-intensity  
102 aerobic physical activity to more than 300 min, or perform more than 150 min of  
103 vigorous-intensity aerobic physical activity throughout the week or an equivalent  
104 combination of moderate-intensity and vigorous-intensity aerobic physical activity for  
105 additional health benefits. Adults are also recommended to do muscle-strengthening  
106 activities that involve all major muscle groups for 2 or more days a week at a moderate  
107 or greater intensity.<sup>7</sup> Next to aerobic activities, adults aged 65 years and older are  
108 recommended to do multicomponent physical activity that includes functional balance  
109 and strength training at a moderate or higher intensity for at least 3 days a week.<sup>7</sup>

110 There is evidence showing that 30 metabolic equivalent task-h of pre-pregnancy is  
111 associated with a 12% reduction in the relative risk of gestational diabetes mellitus, and  
112 7 h of physical activity per week before and during pregnancy is associated with a 30%  
113 reduction and 37% reduction of risk, respectively.<sup>8</sup> Additionally, 500 metabolic  
114 equivalent task-min/week of aerobic physical activity, which is equivalent to 150 min  
115 of moderate-intensity or 75 min of vigorous-intensity physical activity weekly, led to a  
116 14% risk reduction in all-cause mortality in patients with cardiovascular disease and  
117 a 7% risk reduction in healthy adults.<sup>9</sup> And children and adolescents aged 5-17 years  
118 performed an average of 60 min of moderate-to-vigorous intensity physical activity per  
119 day, which was associated with multiple beneficial health outcomes including  
120 cardiorespiratory fitness, muscular fitness, bone health, and cardiometabolic health.<sup>10</sup>

121 A large body of studies supports the notion that regular exercise plays an important  
122 role in reducing the risk of cardiovascular disease<sup>11, 12</sup> and improving the health  
123 outcomes of patients with multiple other pathologies, including obesity, type 2 diabetes,  
124 multiple sclerosis, stroke, age-related sarcopenia, and some types of cancer.<sup>13-18</sup> The

125 epidemiological studies report that a higher level of physical activity is associated with  
126 lower mortality risk in individuals with or without cardiovascular disease, yet the  
127 benefits of physical activity with respect to mortality appear to be greater in people with  
128 cardiovascular disease as compared to those without cardiovascular disease.<sup>9</sup> Moreover,  
129 regular physical activity or exercise is associated with a reduced risk of adverse health  
130 outcomes generally (e.g., disability levels, mortality) and with better survival.<sup>19-21</sup>  
131 Exercise could partially reverse chronic conditions and multimorbidity related to low  
132 physical activity and can be employed as a preventive approach to improve quality of  
133 life.<sup>22, 23</sup> Furthermore, greater amounts and higher intensities of physical activity, as  
134 well as distinct types of physical activity (e.g., aerobic, muscle and bone-strengthening  
135 activities), are associated with multiple beneficial health outcomes (e.g.,  
136 cardiorespiratory fitness, muscular fitness, bone health, and cardiometabolic health) for  
137 children and adolescents aged 5-17 years.<sup>10</sup>

138 Regular moderate-intensity types of exercise, such as strength, endurance, balance,  
139 flexibility and coordination, benefit all aspects of human health and are widely accepted  
140 as a therapeutic and preventative strategy for various diseases, including cardiovascular  
141 diseases (e.g., cardiomyopathy, cardiac ischemia/reperfusion injury, heart failure),  
142 metabolic diseases (e.g., hyperlipidemia, metabolic syndrome, type 2 diabetes),  
143 neurological diseases (e.g., Parkinson's disease, multiple sclerosis), and pulmonary  
144 diseases, etc.<sup>24, 25</sup> However, if physical exercise undercuts a minimum intensity level,  
145 no significant changes in body homeostasis are to be expected. In untrained individuals,  
146 sudden bouts of vigorous-intensity exercise can lead to adverse cardiovascular events  
147 and prolonged intense exercise may increase the incidence of infarction.<sup>26</sup> Therefore,  
148 the intensity and mode of exercise are of critical importance for producing positive  
149 effects on health.

150 The biology of exercise is complex and involves adaptive responses in multiple organ  
151 systems. Movement and physical activity is an evolutionary survival advantage that  
152 turns skeletal muscle into a systemic modulator to meet energy demand.<sup>27</sup> Exercise is a  
153 dynamic energy-demanding activity that not only involves the cardiovascular,  
154 respiratory, and musculoskeletal systems but also affects the immunological and  
155 endocrine systems. Despite broad investigation on the efficacy of exercise, the  
156 underlying mechanisms of its benefits remain elusive. Although quite a few papers have  
157 summarized the psychosocial and biological responses to exercise, most of them are  
158 focused on specific diseases or organ systems. To our knowledge, few studies report  
159 exercise-induced changes from the perspective of the overall “organization” of  
160 organisms as well as the underlying mechanisms.

161 In a recent paper, two of the co-authors of this study proposed 8 hallmarks of health:  
162 integrity of barriers, containment of local perturbations, recycling and turnover,  
163 integration of circuitries, rhythmic oscillations, homeostatic resilience, hormetic  
164 regulation, as well as repair and regeneration.<sup>28</sup> Although more investigations are  
165 needed, a wealth of evidence indicates that exercise can affect most of these hallmarks  
166 (**Fig. 1**). This review aims to provide a comprehensive summary of the vital biological  
167 changes through which exercise produces beneficial effects on health. In addition, this  
168 review summarizes the mechanisms through which exercise interventions are effective  
169 in preventing diseases, specifically age-related diseases (Alzheimer’s disease,  
170 Parkinson’s disease), type 2 diabetes, cardiovascular diseases (cardiomyopathy, cardiac  
171 ischemia/reperfusion injury, and heart failure), and certain cancers (breast and  
172 colorectal cancer). For better reading comprehension, we have included  
173 **Supplementary Table 1**, which details exercise protocols in animal studies, **Table 1**,  
174 which details exercise protocols in human studies, and **Table 2**, which summarizes the



175 evidence based on randomized control trials cited in this review.

176

## 177 **2. Exercise protects the integrity of barriers**

178 Human health is linked to the integrity of barriers at the level of organelles  
179 (mitochondria and nuclei), cell membranes, internal barriers (blood-brain), and barriers  
180 against the external (intestinal, respiratory, and cutaneous) environment. Exercise  
181 confers health benefits partly by regulating the integrity of these barriers, as explained  
182 below (**Fig. 2**).

### 183 *2.1. Exercise maintains mitochondrial integrity*

184 Mitochondrial health is of vital importance for cellular function in various tissues, and,  
185 as a result, contributes to overall vitality in health and disease. Mitochondria generate  
186 cellular ATP and, thus, are key actors in whole-body energy regulation. During exercise,  
187 there is a greater demand for ATP, which is mediated by increasing mitochondrial  
188 biogenesis and enhancing mitochondrial function.<sup>29</sup> The effects of exercise on  
189 mitochondria have been intensively studied, with muscle mitochondria being the most  
190 well studied. Exercise training upregulates skeletal muscle sirtuins (SIRTs), which  
191 contribute to mitochondrial biogenesis and maintenance of the antioxidant system.  
192 Specifically, acute exercise (a single bout of exercise) activates SIRT1 in skeletal  
193 muscle, while several sessions of high-intensity interval training (HIIT) and aerobic or  
194 resistance exercise training activate SIRT1 and SIRT3.<sup>30</sup>

195 Importantly, aerobic exercise causes significant changes in mitochondrial content  
196 and quality that are good for metabolic health.<sup>31</sup> For example, the number of myonuclei  
197 is increased in rats in response to resistance training, and this increase can be retained  
198 for a long-term detraining period. When re-subjected to resistance training, the newly  
199 acquired myonuclei contribute to a greater degree of muscle hypertrophy and

200 mitochondrial biogenesis.<sup>32</sup> Taken together, these results provide further support for the  
201 assertion that exposing young muscles to resistance exercise training may help to  
202 restore age-related muscle loss associated with mitochondrial dysfunction in later life.<sup>32</sup>

203 Mitochondria are also involved in calcium metabolism, contribute to the formation  
204 of intracellular reactive oxygen species (ROS), and play a leading role in the initiation  
205 of apoptosis; therefore, they are essential to maintaining cellular homeostasis and act  
206 as important signaling organelles in different tissues. Exercise may decisively influence  
207 all these mitochondrial functions.

208 The mitochondrial membranes compose the battleground on which opposing signals  
209 fight to determine the cell's fate. The unique lipid composition and structure of  
210 mitochondrial membranes are critical for the proper functioning of mitochondria.  
211 Quality control of mitochondrial protein synthesis plays an important role in  
212 maintaining mitochondrial integrity.<sup>33</sup> In particular, mitochondrial membrane  
213 permeabilization, a tightly regulated process, has been described as an essential feature  
214 of cell death.<sup>34</sup> Acute exercise, as an allostatic stimulus, causes a temporary alteration  
215 of the interaction between mitochondria and other organelles such as the endoplasmic  
216 reticulum (ER), due to the upregulation of regulated in development and DNA damage  
217 1).<sup>35</sup>

218 The beneficial effects of exercise on health are at least partly due to the improvement  
219 of mitochondrial membrane structure and, thus, mitochondrial function. It is reported  
220 that endurance-trained athletes (e.g., cross-country and soccer players) show a higher  
221 density of mitochondrial cristae, which is related to oxygen consumption and oxidative  
222 capacity.<sup>36</sup> Both 17-week voluntary wheel running exercise and 8-week endurance  
223 training (treadmill running) confer protection against non-alcoholic steatohepatitis-  
224 induced alterations in rat mitochondrial membrane composition, as revealed by the

225 increased ratio of phosphatidylcholine to phosphatidylethanolamine,<sup>37</sup> because the ratio  
226 is a key regulator of membrane integrity.<sup>38</sup> More recent studies indicate that 8-week  
227 endurance training could inhibit non-alcoholic steatohepatitis-induced mitochondrial  
228 permeability transition pore opening, indicating decreased mitochondrial membrane  
229 permeability.<sup>39</sup> Seven days of treadmill exercise can prevent mitochondrial outer  
230 membrane permeabilization in the rat model of cerebral ischemic injury by increasing  
231 caveolin-1 expression, thus inhibiting of excessive cytochrome C release from  
232 mitochondria,<sup>40</sup> reducing mitochondrial damage and protecting mitochondrial integrity.  
233 In addition, 12 weeks of moderate-intensity treadmill exercise exerts cardioprotection  
234 in diabetic mice by down-regulating mammalian sterile 20-like kinase 1, which  
235 enhances mitochondrial membrane potential.<sup>41</sup>

### 236 *2.2. Exercise and the sarcoplasmic reticulum (SR)*

237 The SR is a structure involved in Ca<sup>2+</sup> mobilization for muscle contraction. Disruption  
238 of the SR is implicated in muscular dystrophy, cardiomyopathy, sarcopenia due to aging,  
239 and neurodegenerative diseases.<sup>42</sup> Exercise decreases lipid peroxidation and calpain  
240 activity in the SR, thereby preventing heat stress.<sup>43</sup>

### 241 *2.3. Exercise and nuclear envelope (NE) integrity*

242 The double membrane structure of the NE serves as a barrier that separates the genome  
243 from the cytoplasm in eukaryotic cells. Disruption of the NE and exposure of chromatin  
244 endanger cell viability and induce genome instability. Thus, the integrity of NE is  
245 critical for cell survival. The NE homeostasis is maintained through a balance between  
246 the various forces imposed upon the nuclei, which can be disrupted under certain  
247 conditions (e.g., alterations in the expression of lamins, migration and invasion,  
248 micronuclei, telomere fusion, heterochromatin modulation, virus infection, the loss of  
249 ATR, retinoblastoma protein or P53) resulting in transient NE collapse.<sup>44</sup>

250 Few studies have focused on the role of exercise on NE integrity. The NE provides a  
251 semi-permeable barrier, with its structural integrity being maintained partly by the  
252 intermediate filament proteins called lamins (A, B, and C), which are encoded by the  
253 *LMNA* gene. Six weeks of moderate exercise attenuates dilated cardiomyopathy  
254 development in heterozygous *LMNA* knockout (*LMNA*<sup>+/-</sup>) mice whose cardiomyocytes  
255 show altered nuclear shape.<sup>45</sup> The selectivity of the transit channel is controlled by the  
256 proteins of the nuclear pore complex.<sup>46</sup> It has been reported that 4 months of running  
257 wheel exercise is capable of preventing the decline of Lamin B1 and nuclear pore  
258 complex protein in older sedentary mice<sup>46</sup>, indicating that exercise can sustain the  
259 integrity of the NE.

#### 260 *2.4. Exercise and plasma membrane (PM) integrity*

261 PM integrity is essential for cellular function and survival. Besides serving as a physical  
262 barrier between the extra- and intra-cellular environment, the PM bridges intracellular  
263 signaling and extracellular signals (e.g., ions, hormones, cytokines, enzymes), thus  
264 allowing for cellular communication with the surrounding environment. Rupture of the  
265 PM can have deleterious consequences on a cell's fate. Cells are equipped with repair  
266 mechanisms to ensure membrane integrity, including membrane fusion and  
267 replacement strategies, means for removal of the damaged membrane, and protein-  
268 driven membrane remodeling and wound closure methods.<sup>47</sup> Exercise can induce  
269 changes in the lipid composition of membranes that affect fluidity and cellular  
270 function.<sup>48</sup> For example, a 2-week course of treadmill exercise (13.5 m/min, 10% grade,  
271 50 min/day) administered to high-fat diet (HFD)-fed mice prevents cholesterol  
272 accumulation in the PM of skeletal muscle cells.<sup>49</sup> The excess of PM cholesterol may  
273 contribute to insulin resistance in the skeletal muscle of mice who are fed an HFD.<sup>50</sup>  
274 Moreover, acute endurance exercise (120 min) is capable of increasing the expression

275 of fatty acid translocase/CD36 and PM fatty acid-binding protein in human and rat  
276 muscle, indicating increased fatty acid transport in exercised muscle.<sup>51</sup>

### 277 *2.5. Exercise supports the integrity of the blood-brain barrier (BBB)*

278 The BBB is an active interface that separates the systemic circulation from the central  
279 nervous system with a dual function: the barrier limits the entry of blood-derived  
280 potentially toxic or harmful substances into the brain, and the carrier function is  
281 responsible for the transport of molecules and cells into and out of the central nervous  
282 system as well as for the removal of metabolites. Every cell type (e.g., endothelial cells,  
283 astrocytes, pericytes) and extracellular matrix makes an indispensable contribution to  
284 the BBB's integrity.<sup>52</sup> Specifically, pathways like Wnt/ $\beta$ -catenin, sonic hedgehog,  
285 retinoic acid, angiopoietins, and others are involved in the regulation of barrier  
286 maintenance.<sup>53</sup>

287 Exercise has been shown to maintain BBB selective permeability in health and  
288 disease.<sup>54</sup> For example, a previous study showed that both strength training and  
289 endurance training exercises could prevent BBB disruption in a mouse model of  
290 multiple sclerosis by increasing the expression of tight-junction proteins (occludins and  
291 claudin-4) and decreasing the expression of platelet and endothelial cell adhesion  
292 molecule 1.<sup>55</sup> Moreover, exercise can protect against BBB disruption occurring in the  
293 context of substance use disorders.<sup>56</sup> Of note, in a clinical trial, a 14-week-long  
294 combined resistance and aerobic exercise training intervention is capable of  
295 maintaining BBB integrity and decreasing chronic inflammation in older women.<sup>57</sup>  
296 Mechanistically, regular exercise may diminish BBB permeability by enhancing  
297 antioxidative capacity, reducing oxidative stress, diminishing inflammation, enhancing  
298 neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and improving  
299 tight junction.<sup>54, 55, 58</sup> On the other hand, the BBB has a selective permeability in order

300 to receive systemic signals. Acute exercise increases phosphoinositide 3-kinase (PI3K)-  
301 p110 $\alpha$  protein in the hypothalamus enhancing the regulation of food intake.<sup>59</sup>

## 302 *2.6. Exercise effects on intestinal barrier integrity*

303 The intestine acts as a barrier to the external environment that defends against the  
304 invasion of pathogens and harmful food ingredients. The intestinal epithelial tight  
305 junction proteins (e.g., occluding, claudins, and zonula occludens) and gut microbiome  
306 play a pivotal role in the maintenance of barrier integrity.<sup>60</sup> Accumulating evidence  
307 suggests that exercise affects the integrity of the intestinal barrier. For instance, small  
308 intestinal permeability is increased in healthy individuals after 1 h of treadmill running  
309 at 80% VO<sub>2</sub>max.<sup>61</sup> Moreover, a significant increase in intestinal permeability has been  
310 observed in participants immediately after completing a standard marathon (42.16  
311 km).<sup>62</sup> Gut barrier permeability was elevated in runners who completed two 1-h-long  
312 bouts of submaximal treadmill exercise (65% VO<sub>2</sub>max, determined by a graded  
313 treadmill test<sup>63</sup>) under normoxic and hypoxic conditions.<sup>64</sup> Similarly, endurance  
314 exercise (1100 miles in 10 days) is associated with increased intestinal permeability in  
315 racing dogs.<sup>65</sup> Another study reports that mice subjected to acute treadmill running at  
316 80% VO<sub>2</sub>max (determined by a progressive exercise test on a small rodent treadmill)  
317 until exhaustion (running for at least 30 min) exhibit increased permeability in the small  
318 intestinal.<sup>66</sup>

319 Intestinal barrier permeability is impaired under heat stress<sup>67</sup> and with strenuous  
320 exercise<sup>68</sup> due, in part, to visceral hypoperfusion during exercise. Of note, glutamine  
321 supplementation appears to attenuate intestinal permeability and maintain intestinal  
322 integrity in response to a 60-min treadmill run at 70% of VO<sub>2</sub>max in an environmental  
323 chamber set at 30 °C with 40-45% humidity.<sup>69</sup> It has also been shown that 5 weeks of  
324 combined aerobic and resistance training counteracts HFD-induced rat microbial

325 dysbiosis, thus protecting intestinal barrier integrity.<sup>70</sup> Furthermore, 6 weeks of aerobic  
326 exercise (10 m/min for 30 min/day, 6 days/week) can protect against obstructive  
327 jaundice-induced intestinal mucosal barrier damage in mice.<sup>71</sup> Mechanistically,  
328 exercise increases the level of endogenous H<sub>2</sub>S and inhibits the high mobility group  
329 box 1-toll-like receptors 4-nuclear factor-kappa B pathway, thereby protecting the  
330 intestinal mucosal barrier.<sup>71</sup> Also, 7 weeks of swimming exercise (1 or 1.5 h/day for 5  
331 days/week) attenuates the effect of dextran sulfate sodium-induced rat intestinal  
332 aggression by improving crypt status through regulating inflammation, oxidative stress,  
333 and apoptosis.<sup>72</sup> Moreover, training improves zonula occludens 1, occludin, claudin-2,  
334 and the intestinal peptide transporter-1 messenger RNA expression.<sup>68</sup> Thus, physical  
335 exercise has an ambiguous, context-dependent effect on intestinal barrier integrity.

### 336 *2.7. The effects of exercise on the barrier integrity in the respiratory tract*

337 The respiratory system, roughly divided into the upper (nasal passages, pharynx, larynx)  
338 and the lower (trachea, bronchial tree, lungs) respiratory tract, provides a physical,  
339 secretory, and immunologic barrier to exclude harmful substances such as ozone,  
340 particulate matter, and pathogens, etc.<sup>73</sup> As a mucosal organ system directly contacts  
341 with the external environment, protection of the respiratory barrier is vital to human  
342 health. The mechanisms contributing to increased epithelial permeability involve  
343 internal (type 2 cytokines such as interleukin-4 (IL-4) and IL-13), external  
344 (environmental molecules such as allergens, pathogens, pollutants), genetic (e.g.,  
345 protocadherin-1, cadherin-related family member 3, orosomucoid-like 3) and  
346 epigenetic (e.g., DNA methylation, histone deacetylases) factors.<sup>74</sup>

347 Although exercise can trigger bronchial hyperresponsiveness in cold and dry  
348 environments,<sup>75</sup> it also has numerous health benefits, including its positive effects on  
349 individuals with chronic respiratory disease.<sup>76</sup> For example, 12 weeks of aerobic

350 exercise (30 min of treadmill running) combined with respiratory muscle stretching  
351 improves the functional exercise capacity and reduced dyspnea in patients with chronic  
352 obstructive pulmonary disease.<sup>77</sup> Even low levels of physical activity in older patients  
353 with cardiovascular disease are associated with decreased mortality and hospitalization  
354 from pneumonia.<sup>78</sup> Thus, exercise training has been recommended to support  
355 pulmonary rehabilitation in chronic disease management.<sup>79</sup>

356 Exercise exerts beneficial effects on cardiovascular and respiratory diseases partly  
357 via endothelial protection,<sup>80, 81</sup> and also by decreasing the Th2 inflammatory response  
358 of the airways.<sup>82</sup> During exercise, fitness level could modulate the concentration and  
359 secretion of salivary antimicrobial proteins, which function as the first line of defense  
360 against invading microorganisms.<sup>83</sup> However, the effects of exercise on the integrity of  
361 the respiratory tract, including epithelial and endothelial barriers, has not been  
362 investigated in detail. In fact, it is well known that athletes have an increased risk of  
363 developing upper respiratory tract infections.<sup>84</sup> It seems that prolonged intensive  
364 exercise compromises the barrier function of respiratory epithelium,<sup>85</sup> and increases the  
365 incidence of upper respiratory tract infections.<sup>86, 87</sup> However, this topic remains the  
366 subject of debate.<sup>88</sup> Otherwise, compared to continuous exercise, the matched-intensity  
367 and volume intermittent exercise leads to lesser respiratory epithelial cell damage,<sup>89</sup>  
368 indicating that intermittent exercise may benefit respiratory tract health.

#### 369 *2.8. Exercise and the skin integrity*

370 Skin is the body's primary defense structure and is composed of the epidermis and the  
371 dermis. In general, the epidermis consists of epithelial cells that are responsible for the  
372 skin barrier and thus protect from the harmful effects of the external environment.  
373 While the dermis contains the extracellular matrix that includes collagen, elastin, and  
374 glycosaminoglycans.<sup>90</sup> Skin integrity is restored by a complex multi-step process that



375 includes blood clot formation, inflammation, re-epithelialization, granulation tissue  
376 formation, neovascularization and remodeling. Skin repair requires the activation of a  
377 variety of modulators, such as growth factors, cytokines, matrix metalloproteinases,  
378 cellular receptors, and extracellular matrix components.<sup>91</sup> Research evidence reveals  
379 that regular exercise confers advantageous effects on skin integrity. For example, a  
380 epidemiology study reports a clear correlation between skin integrity and exercise in  
381 older adults. Individuals that do not practice regular exercise have a higher risk of  
382 damage to skin integrity (27.02%) compared to those who exercise regularly (8.77%).<sup>92</sup>  
383 Moreover, endurance running exercise (15 m/min for 45 min, 3 times/week for 5  
384 months) prevents the age-associated thinning of the dermis in mitochondrial DNA  
385 mutator mice (PolG; *PolgA*<sup>D257A/D257A</sup>), a model of progeroid aging.<sup>93</sup> In obese mice, 8  
386 weeks of voluntary exercise improves the dermal collagen density and decreases the  
387 amount of subcutaneous tissue and adipocyte size.<sup>94</sup> A later study demonstrates that  
388 endurance exercise protects against age-associated structural deterioration of skin that  
389 compromises its barrier function in both humans and mice, and it identifies exercise-  
390 induced IL-15 as a novel mediator of skin health.<sup>95</sup> Functional studies indicate that daily  
391 IL-15 administration mimics part of the anti-aging effects of exercise on the skin in  
392 mice.<sup>95</sup>

### 393 **3. Exercise benefits the maintenance of local homeostasis**

394 While a single bout of exercise may cause local perturbation, long-term moderate-  
395 intensity exercise generally contributes to the maintenance of systemic homeostasis and  
396 the improvement of health (**Fig. 3**).

#### 397 *3.1. Exercise promotes barrier healing*

398 Skin wound healing is a major health concern. Exercise is a relatively cheap and  
399 effective strategy that could be adopted clinically to prevent or treat damage to the

400 skin.<sup>96,97</sup> Moderate-intensity aerobic exercises have been shown to promote skin wound  
401 healing in both humans and mice.<sup>98,99</sup> In addition, 4 weeks of voluntary wheel exercise  
402 decreases skin graft rejection and increases graft survival through CD4<sup>+</sup> T cell  
403 proliferation and interferon- $\gamma$  production.<sup>100</sup> A recent study reports that exercise-  
404 associated microRNA-122-5p (miR-122-5p) is capable of promoting wound healing  
405 via increasing capillary density in perilesional skin tissues of mice.<sup>101</sup> However, the  
406 molecular and cellular mechanisms through which exercise stimulates healing require  
407 further investigation.

408 Of note, the intensity of exercise could influence the healing process. For example,  
409 in a mouse study, compared to high (80% VO<sub>2</sub>max) and strenuous intensity (90%  
410 VO<sub>2</sub>max), moderate-intensity physical training (70% VO<sub>2</sub>max) is particularly efficient  
411 in improving wound healing.<sup>102</sup> Moreover, in diabetic mice, low-intensity treadmill  
412 exercise (12 m/min for 30 min, 5% incline, 5 days/week for 3 weeks) benefits the  
413 wound healing process, while high-intensity treadmill exercise (18 m/min for 30 min,  
414 5% incline, 5 days/week for 3 weeks) does not.<sup>103</sup>

### 415 *3.2. Exercise prevents the invasion of foreign bodies*

416 The invasion of foreign bodies (e.g., pathogens) represents a threat to health. Lifestyle  
417 intervention, including exercise, have been identified as an effective approach to  
418 controlling certain conditions associated with viral infection. The antiviral role of  
419 exercise has received great amount of attention. Several scientific findings indicate that  
420 exercise training contributes to the improvement of physiologic and functional  
421 parameters in patients with human immunodeficiency virus (HIV) or acquired  
422 immunodeficiency syndrome (AIDS).<sup>104</sup> Exercise could help to prevent viral infection  
423 and/or promote viral clearance. For example, regular physical activity is associated with  
424 decreased risk of infection.<sup>105, 106</sup> In mice, chronic exercises at moderate intensity may

425 have an attenuating effect on influenza infection by decreasing viral load and illness  
426 severity.<sup>107</sup> Indeed, exercise is considered to be supportive of the medical care and  
427 treatment of HIV-infected patients.<sup>108</sup>

428 A large body of investigations has highlighted the indispensable role of the immune  
429 system in combating viral infection. Exercise is well-known to have a major effect on  
430 the functioning of the immune system. In particular, regular moderate exercise is  
431 considered to be a safe and cost-effective strategy to enhance the immune system and  
432 provide protection against pathogenic viral infection.<sup>108, 109</sup> Recent studies reveal that a  
433 regular program of aerobic exercise with an intensity of 55-80% VO<sub>2</sub>max is associated  
434 with increased immunological biomarkers such as circulating leukocytes, lymphocytes,  
435 monocytes, and neutrophils, and thus helps reduce the risk of coronavirus disease  
436 2019.<sup>110, 111</sup> Aerobic exercise affects several molecules in various tissues that are  
437 involved in severe acute respiratory syndrome coronavirus 2 virus entry angiotensin-  
438 converting enzyme 2, FURIN, and transmembrane protease serine 2. However, the  
439 overall effect on the disease is not yet known.<sup>112</sup>

### 440 *3.3. Exercise improves systemic inflammation*

441 Exercise training exerts anti-inflammatory effects on the periphery and the brain.<sup>113</sup> For  
442 example, in mice, moderate voluntary wheel running (30 days of access to wheels)  
443 attenuates colitis symptoms and reduces inflammation in response to oral  
444 administration of dextran sodium sulfate.<sup>114</sup> In addition, regular training in mice  
445 attenuates sepsis-induced lung damage; the effect is mediated by a reduced  
446 inflammatory response, modulated by decreased IL-1 $\beta$  and increased IL-10.<sup>115</sup>

447 Moreover, the percentage of inflammatory CD14<sup>+</sup>CD16<sup>+</sup> monocytes is reduced in  
448 older adults (65-80 years old) after completing a 12-week-long (3 days/week) combined  
449 endurance (20 min at 70-80% heart-rate reserve) and resistance exercise (8 sets of

450 exercises, 2 sets at 70-80% of one-repetition maximum),<sup>116</sup> suggesting reduced  
451 systemic inflammation in exercised older individuals. Similarly, studies focusing on  
452 healthy adults who are aged 40 years or older show that more frequent physical activity  
453 is associated with lower systemic cellular and molecular inflammation, as evidenced  
454 by a lower level of white blood cell counts and neutrophil counts, as well as lower levels  
455 of C-reactive protein, IL-6, IL-10, IL-1 receptor antagonist, and soluble tumor necrosis  
456 factor receptor-I.<sup>117, 118</sup>

457 Furthermore, mice subjected to regular voluntary running show decreased  
458 hematopoietic activity and reduced circulating leukocyte numbers compared to  
459 sedentary mice, indicating that regular physical activity confers health benefits partially  
460 via decreased systemic inflammation.<sup>119</sup> Mechanistic studies indicate that voluntary  
461 running exercise regulates hematopoietic activity via lowering leptin production in  
462 adipose tissue, augmenting hematopoietic stem and progenitor cell quiescence via  
463 modulation of their niche, and reducing the hematopoietic output of inflammatory  
464 leukocytes.<sup>119</sup>

#### 465 *3.4. Exercise and the innate and acquired immune responses*

466 Proper immune function is fundamental for maintaining health in most chronic  
467 conditions. In recent years, the role of exercise training in regulating the immune  
468 system has received considerable attention.<sup>120, 121</sup> Most of the current published  
469 literature suggests that regular moderate exercise exerts a positive effect on the immune  
470 system, thus reducing the incidence of disease.<sup>122</sup> Exercise modulates both innate and  
471 adaptive immune responses, particularly upregulating the activity of natural killer (NK)  
472 cells at rest,<sup>123</sup> but also neutrophils, and macrophages following moderate exercise  
473 (about 60% of VO<sub>2</sub>max).<sup>120, 121, 124</sup> In addition, in healthy individuals, regular exercise  
474 is associated with decreased tumor necrosis factor- $\alpha$  expression levels, reduced pro-

475 inflammatory adipokine levels, downregulated Toll-like receptor levels on monocytes  
476 and macrophages, and increased circulating levels of anti-inflammatory cytokines.<sup>125</sup>  
477 Moreover, in healthy young men, 1-h of cycling at 70% of VO<sub>2</sub>max is sufficient to  
478 induce the number of circulating peripheral blood mononuclear cells,<sup>126</sup> which are  
479 composed of monocytes and lymphocytes and have a critical role in immune  
480 function.<sup>127-129</sup>

481 Of note, moderate-to-vigorous intensity endurance exercise bouts may also exert  
482 positive immunological effects.<sup>88</sup> For example, master athletes with lifelong regular  
483 exercise exhibit signs of anti-inflammatory regulation, as revealed by higher plasma  
484 IL-10 levels compared to the age-matched untrained control group.<sup>130</sup> Further  
485 investigation demonstrates that the circulating IL-10 levels in lifelong trained athletes  
486 are similar to those in young adults.<sup>131</sup> Moreover, clinical trials show that regular  
487 moderate exercise (60-70% of VO<sub>2</sub>max) significantly improves the immune response  
488 to vaccination in adults over age 65,<sup>132, 133</sup> indicating an improved adaptive immune  
489 function in older adults.

### 490 *3.5. Exercise benefits the anti-cancer immunosurveillance*

491 It is well-accepted that the immune system has the ability to suppress certain types of  
492 cancer, and immunotherapy is recognized as a promising strategy in the treatment of  
493 cancer. A sedentary lifestyle has recently emerged as a potential independent risk factor  
494 for cancer. Conversely, exercise is associated with a reduced risk of certain cancers,  
495 including colon cancer, endometrial cancer, breast cancer, etc.<sup>134</sup> Moreover, the  
496 Mendelian randomization analysis also found that genetically elevated physical activity  
497 levels were associated with lower risks of breast and colorectal cancer,<sup>135, 136</sup>  
498 highlighting the promotion of physical activity as a critical intervention to reduce the  
499 incidence and prevalence of these cancers. Mechanistically, exercise reduces tumor size

500 partly via enhancing immune function. For example, tumor-bearing mice subjected to  
501 voluntary exercise (wheel running) shows a more than 60% decrease in tumor volume  
502 across different tumor models, an effect that has been attributed to the exercise-  
503 associated mobilization of NK cells, which is necessary and sufficient for this anti-  
504 tumor effect.<sup>137</sup> Moreover, evidence indicates acute exercise could induce a preferential  
505 redeployment of NK cell subsets with a highly-differentiated phenotype and confer  
506 protection against tumor cells.<sup>138</sup> Thus, exercise could play a role in the prevention and  
507 treatment of cancer.

### 508 *3.6. The protective role of exercise on cellular senescence and its clearance*

509 Cellular senescence has been linked to multiple aging-related illnesses and risk factors.  
510 Many stimuli, such as telomere erosion, oxidants, ultraviolet B light, and DNA  
511 damaging chemotherapies that engage the DNA damage response, can induce cellular  
512 senescence.<sup>139</sup> Long-term endurance training upregulates telomerase activity and  
513 telomere-stabilizing proteins and decreases the levels of apoptosis modulators  
514 (including cell cycle checkpoint kinase 2, p16<sup>INK4a</sup>, and p53), pointing to the protective  
515 role of exercise has on cellular senescence.<sup>140, 141</sup>

516 One biomarker and effector of senescence is p16<sup>INK4a</sup>. The expression of p16<sup>INK4a</sup> in  
517 peripheral blood T lymphocytes increases with age.<sup>142</sup> The level of p16<sup>INK4a</sup> is positively  
518 associated with circulating IL-6 concentrations, which is a marker of cellular  
519 senescence. One recent study reports the 4-week treadmill exercise has a significant  
520 effect on attenuating senescence in white adipose tissue, as indicated by decreased p16  
521 level. In old mice, exercise induces changes in the immune-cell distribution (e.g., NK  
522 cells, CD8<sup>+</sup> T cells, eosinophils, neutrophils), which may contribute to the anti-  
523 senescence effect of exercise.<sup>143</sup> Since p16<sup>INK4a</sup> expression is strongly correlated with  
524 reduced exercise,<sup>142</sup> this is further evidence that exercise may prevent cellular

525 senescence by downregulating p16<sup>INK4a</sup> expression. In the aging rat model, 12 weeks of  
526 swimming training significantly reduces the senescence markers (p53 and p21) and  
527 inflammatory cytokine (IL-6) in the liver.<sup>144</sup>

528 However, in some settings, exercise elicits positive impacts on health via promoting  
529 senescence. As an example, the pro-senescent effect of exercise on fibro-adipogenic  
530 progenitors contributes to muscle regeneration and the improvement of muscle  
531 function.<sup>145</sup>

#### 532 **4. Benefits of exercise in recycling and turnover**

533 The proper recycling and turnover of different components of the organism (e.g., cell,  
534 organelle, protein) enables healthy cell and organismal development. Each of the  
535 subcellular, cellular, and supracellular units composing the organism is replaced  
536 continually by newly synthesized ones to maintain cellular homeostasis. The health  
537 benefits of exercise may be partly due to its remarkable ability to induce cellular  
538 remodeling, including cell self-renewal and the turnover of dysfunctional organelles  
539 **(Fig. 4).**

##### 540 *4.1. The effects of exercise on cell death, removal, and replacement*

541 It is reported that regular moderate exercise promotes cell survival and reduces cell  
542 death. Regular exercise is well-known to promote cardiomyocyte proliferation and  
543 growth while preventing cardiomyocyte apoptosis. Mechanistically, the  
544 CCAAT/enhancer-binding protein  $\beta$ -CBP/p300-interacting transactivators with E  
545 (glutamic acid)/D (aspartic acid)-rich-carboxyl terminal domain (C/EBP $\beta$ -CITED4)  
546 signaling and the insulin-like growth factor 1 (IGF1) signaling are well-established as  
547 essential regulating pathways that mediate exercise-related cardiomyocyte proliferation.  
548 Additionally, the C/EBP $\beta$  and IGF1-PI3k/Akt pathways play vital roles in exercise-  
549 induced cardiomyocyte growth. Exercise also prevents cardiomyocyte death through

550 pathways for SIRT1 and peroxisome-proliferator-activated receptor coactivator  
551 (PGC1 $\alpha$ ) as well as for apoptosis signal-regulating kinase 1/p38 signaling, etc.<sup>146</sup>  
552 Moreover, 21 days of voluntary wheel running exercise is capable of enhancing cardiac  
553 myocyte survival and preventing cell death in the heart through the regulation of  
554 telomerase reverse transcriptase, endothelial nitric oxide synthase and IGF1.<sup>141</sup>  
555 Accordingly, treadmill exercise-induced myokine (Myonectin) inhibits hypoxia-  
556 induced cardiomyocyte apoptosis via activation of the cyclic adenosine  
557 monophosphate/Akt signaling pathway.<sup>147</sup> It has been reported that long-term exercise-  
558 derived plasma exosomes are capable of attenuating hypoxia/reoxygen-induced  
559 cardiomyocyte apoptosis via exosomal miR-342-5p.<sup>148</sup> Mechanistically, miR-342-5p  
560 prevents cell apoptosis by targeting the mRNAs coding for caspase 9 and mitogen-  
561 activated protein kinase 9 (MAPK9, also known as JNK2), and it promotes  
562 cardiomyocyte survival by elevating Akt phosphorylation.<sup>148</sup> Furthermore, swimming  
563 exercise-induced long non-coding RNA (lncRNA), cardiac physiological hypertrophy-  
564 associated regulator (CPhar), reduces oxygen-glucose deprivation/reperfusion-induced  
565 apoptosis in cultured neonatal mouse cardiomyocytes.<sup>149</sup> Finally, in rats subjected to  
566 injury of the optic nerve, 4 weeks of treadmill running (5 days per week for 30 min  
567 each day at a moderate intensity of 9 m/min) significantly increases the survival rate of  
568 retinal ganglion cells, likely due to an increase in the local expression of BDNF.<sup>150</sup>

#### 569 *4.2. Exercise and autophagy*

570 Virtually all eukaryotic cells depend on autophagy to maintain cellular homeostasis.  
571 Autophagy is a highly conservative recycling mechanism that is responsible for the  
572 turnover of cellular proteins and organelles. The mechanism that regulates autophagy  
573 is complex, and its upstream signaling pathway mainly includes mammalian target of  
574 rapamycin (mTOR)-dependent and mTOR-independent signaling.<sup>151, 152</sup> Mitophagy, a



575 form of vital autophagic response for the turnover of dysfunctional or aged  
576 mitochondria, serves to maintain mitochondrial quality control. The regulatory  
577 mechanisms of mitophagy mainly involve putative kinase 1-Parkin pathway and  
578 receptor-mediated mitophagy.<sup>153</sup> In mammals, 2 major types of receptors have been  
579 implicated in mitophagy. One group includes BCL2 interacting protein 3 (BNIP3) and  
580 NIP3-like protein X (NIX), and the other group contains FYN14 domain-containing  
581 protein 1 (FUNDC1).<sup>154</sup>

582 The regulation of autophagy during exercise training is a dynamic and complex  
583 process.<sup>155</sup> On the one hand, exercise promotes the level of basal autophagy and  
584 enhances cell viability. For instance, endurance exercise training (long-term voluntary  
585 running) stimulates autophagy in the skeletal muscle of mice.<sup>156</sup> This exercise-induced  
586 increase of basal autophagy is required for muscle adaptation and improvement of  
587 physical performance in endurance and resistance.<sup>157, 158</sup> The common regulatory  
588 pathways underlying exercise-induced autophagy involve the activation of adenosine-  
589 monophosphate-activated protein kinase (AMPK)-unc-51-like kinase 1 signaling  
590 pathway, forkhead box O (FoxO), and PGC1 $\alpha$ , etc.<sup>159, 160</sup> On the other hand, exercise  
591 could play a role in adjusting the level of autophagy in disease states. For example, 8  
592 weeks of treadmill exercise improves cardiac autophagic flux in a rat model of post-  
593 myocardial infarction (MI)-induced heart failure.<sup>161</sup>

594 Importantly, exercise-induced autophagy seems to mediate many of its beneficial  
595 effects.<sup>162</sup> Thus, exercise-stimulated autophagy plays an important role in muscle  
596 glucose homeostasis. Mice with a BCL2 mutation (Thr69Ala, Ser70Ala and Ser84Ala)  
597 that prevents this exercise-induced increase in autophagy exhibit deficient exercise  
598 endurance and deficient glucose metabolism in muscle during acute exercise. Moreover,  
599 in such B-cell lymphoma-2 (BCL2)-mutated mice, long-term exercise loses its capacity

600 to prevent type 2 diabetes induced by an HFD.<sup>163</sup> It has also been found that exercise  
601 stimulates autophagy in the brain.<sup>164</sup> As compared to wild-type mice, systemic  
602 autophagy-deficient (*Atg4b*<sup>-/-</sup>) mice exhibit reduced levels of resistance capacity after  
603 exercise training, and exercise-induced hippocampal adult neurogenesis is undetectable  
604 within them.<sup>158</sup> Altogether, these data highlight the essential role of autophagy in  
605 exercise-induced neurogenesis.

606 Nonetheless, it is worth noting that excessive exercise induces excessive  
607 autophagy.<sup>165</sup> Thus, the inhibition of autophagy reportedly alleviates heart injury  
608 induced by strenuous exercise.<sup>165</sup> Ultimately, exercise without overtraining helps to  
609 prevent the development and progression of Alzheimer's disease via improving  
610 mitochondrial fitness, which may be accomplished by mitigating mitochondrial  
611 dysfunction with SIRT1-FOXO1/3-putative kinase 1-Parkin-mediated mitophagy.<sup>166,</sup>

612 <sup>167</sup>

## 613 **5. The effects of exercise on the different circuitries**

614 The maintenance of whole-body health involves the successful crosstalk among  
615 multiple tissues and organs as well as the body-microbiota at the cellular and systemic  
616 levels. Exercise evokes the coordinated and integrated adaptation of different circuitries,  
617 including the intracellular circuitries, inside-outside communication, interorgan  
618 communication, and the dialog between microbiota and the organism (**Fig. 5**).

### 619 *5.1. Intracellular circuitries*

620 The health-promoting effects of exercise involve a wide range of metabolic changes,  
621 which are mediated by numerous molecules, such as metabolites, proteins, non-coding  
622 RNAs, extracellular vesicles, etc. Firstly, exercise modifies the energy sensor  
623 AMPK.<sup>168</sup> Moreover, ketone bodies are markedly elevated in response to exercise. In  
624 addition to serving as a bioenergetic fuel, ketone bodies function as signaling

625 metabolites and confer a variety of benefits for performance and recovery.<sup>169</sup> The  
626 transcription of genes is also influenced by exercise. For example, exercise can  
627 downregulate cardiac homeodomain interacting protein kinase 2, the suppression of  
628 which prevents the apoptosis of cardiomyocytes and protects against MI by reducing  
629 the activation of tumor protein P53.<sup>170</sup> Mice subjected to 3 weeks of swimming exercise  
630 exhibit elevated adenosine deaminases acting on RNA2, which is an enzyme that  
631 deaminates adenosine to inosine nucleotide in double-stranded RNA and functions as a  
632 protective factor in MI and doxorubicin-induced cardiac injury.<sup>171</sup> Swimming exercise  
633 also upregulates the levels of cardiac miR-486 and lncRNA-CPhar, both of which  
634 confer protection against cardiac ischemia/reperfusion injury in mice.<sup>149, 172</sup>  
635 Furthermore, exercise can induce cytokines that prevent myocardial fibrosis.<sup>173</sup>  
636 Interestingly, circulating miRNAs could be considered biomarkers of the response to  
637 exercise.<sup>174, 175</sup>

638 Exercise-associated health benefits may involve epigenetic changes. For example,  
639 exercise directly modulates the epigenetics of cardiac and other tissues, thereby  
640 mitigating the risk of developing cardiac disease and conferring cardioprotective effects  
641 via exerkinases.<sup>176</sup> Exercise also improves brain health by reducing DNA methylation in  
642 the mouse hippocampus.<sup>177</sup>

### 643 *5.2. Inside-outside communication*

644 The endocrine system is strongly affected by exercise. For instance, the expression of  
645 fibroblast growth factor-21 (FGF21) increases in response to experimental acute  
646 exercise.<sup>178-182</sup> FGF21 is an endocrine member of the FGF superfamily responsible for  
647 the modulation of energy homeostasis, glucose and lipid metabolism, and insulin  
648 sensitivity. In adipose tissue, exercise training downregulates lipid content and  
649 inflammation, promotes browning and thermogenesis, and modulates the production of

650 adipokines.<sup>183-185</sup> Treadmill exercise reportedly protects mice from HFD-induced  
651 metabolic dysfunction, including hyperglycemia, hyperinsulinemia and hyperlipidemia,  
652 by enhancing FGF21 sensitivity in adipose tissue.<sup>186, 187</sup>

653 In addition, the plasma levels of growth differentiation factor-15 increase  
654 immediately in runners following a marathon race.<sup>188</sup> It has also been induced in  
655 response to an experimental single bout of exercise<sup>189</sup> and a cycling race.<sup>190</sup> The  
656 exercise-induced levels of circulating growth differentiation factor-15 correlate with  
657 the duration of endurance exercise.<sup>191</sup>

### 658 *5.3. Functional units in organs*

659 Exercise is a complex process that involves the coordinated and integrated adaptation  
660 of numerous cells, tissues, and organs. In response to chronic exercise training, organs  
661 such as the heart and skeletal muscle undergo physiological remodeling and may grow  
662 in size, which is called hypertrophy. The plasticity of the organ allows for adaptation  
663 to multiple cell types or functional units. For example, cardiac hypertrophy requires  
664 increased cardiomyocyte growth, cardiomyocyte fate reprogramming, enhanced  
665 angiogenesis and lymphangiogenesis, mitochondrial remodeling, enhanced endothelial  
666 function, and quiescent cardiac fibroblasts.<sup>146</sup>

667 Exercise protects against pathogenic changes in organs or tissues. For example, a 9-  
668 week treadmill exercise program has been shown to reverse the diabetes-induced  
669 ultrastructure changes in the heart. Specifically, in diabetic rats, exercise inhibits the  
670 reduction of mitochondrial mass, decreases the percentage of dysfunctional  
671 mitochondrial, and prevents the increase of collagen fiber cross-sectional surface area  
672 in the heart.<sup>192</sup> In aging rats, a 3-week treadmill exercise program increases  
673 angiogenesis, leading to improved brain function.<sup>193</sup> High-intensity interval exercise (5  
674 days a week for 7 weeks)-induced increase of vascularization is mediated via the lactate

675 receptor (hydroxycarboxylic acid receptor 1), which upregulates cerebral vascular  
676 endothelial growth factor A (VEGFA).<sup>194</sup>

#### 677 *5.4. Organs, tracts, and systemic circuitries*

678 Exercise induces adaptive responses throughout the entire body. For example, exercise  
679 stimulates the upregulation of heat shock proteins (HSPs),<sup>195</sup> which are a widespread  
680 family of molecular chaperones that play a variety of vital roles in maintaining cellular  
681 functions via regulation of chaperone activity, protein folding, and remodeling  
682 processes.<sup>196</sup> Specifically, HSP72 is upregulated in the circulation system and multiple  
683 organs (including the liver, skeletal muscle, heart, brain, etc.) in response to various  
684 forms and types of exercise.<sup>197</sup> Overexpression of HSP72 (induced by heat shock  
685 therapy, transgenesis or specific drugs) protects against HFD-induced glucose  
686 intolerance and skeletal muscle insulin resistance.<sup>198, 199</sup> Moreover, induction of HSP72  
687 in mice increases mitochondrial mass and endurance running capacity.<sup>200</sup> Therefore, the  
688 upregulation of HSP72 might account for at least some of the beneficial effects of  
689 exercise on diabetes, obesity and ischemic brain injury.<sup>201, 202</sup> However, the precise role  
690 of exercise-induced HSP72 expression in treating metabolic diseases warrants further  
691 investigation.

692 Exercise induces numerous adaptive responses in tissues and organ systems as well  
693 as with respect to interorgan communication. Many of these adaptations are observed  
694 primarily in skeletal muscle, which plays a major role in modulating whole-body  
695 functional capacity and health outcomes. In response to exercise, skeletal muscle  
696 secretes myokines, extracellular vehicles, and metabolites that facilitate crosstalk with  
697 other tissues. This crosstalk is thought to benefit the function of multiple systems and  
698 organs, such as the brain, heart, adipose tissue, gut, immune system, etc. It is  
699 noteworthy that the adaptive responses are not limited to skeletal muscle. Exercise also

700 results in the secretion of adipokines (e.g., transforming growth factor  $\beta$ , leptin) and  
701 hepatokines as well as by-products of gut microbiota (e.g., short-chain fatty acids  
702 (SCFA)) that play key roles in interorgan communication and, thus, mediate many of  
703 the beneficial effects of exercise.<sup>203</sup> Furthermore, exercise has been shown to modulate  
704 the composition of the gut microbiome, which may mediate improvements in both the  
705 gut and the brain. Exercise could also increase level of serotonin, which is a vital  
706 neurotransmitter and hormone and is involved in the regulation of intestinal secretion  
707 and motility.<sup>204</sup> In addition, a recent study reported that the extracellular vehicles  
708 secreted by brown adipose tissue contribute to exercise-mediated cardioprotection by  
709 delivering the cardioprotective miRNAs into the heart.<sup>205</sup>

#### 710 *5.5. The meta-organism*

711 It is well known that the gut microbiota plays an essential role in many aspects of human  
712 biology, affecting metabolism, endocrine, and immune functions. Dysbiosis of the gut  
713 microbiome is associated with multiple pathological states, including systemic  
714 inflammation, obesity, cancer, mental disorders, and others.<sup>206</sup> Beyond its local effects  
715 on the barrier function of the intestinal mucosa, the gut microbiota provides several  
716 compounds and micronutrients that mediates long-range effects on the immune and  
717 neuroendocrine systems.<sup>207, 208</sup>

718 Endurance and resistance exercise have been shown to have a differential effect on  
719 the gut microbiota of mice.<sup>209</sup> Moreover, a number of studies have determined that  
720 exercise influences the gut by enhancing the number of beneficial microbial species,  
721 thereby enriching microbiota diversity and functional metabolism in both humans and  
722 mice.<sup>206, 210-212</sup> Thus male elite professional rugby players have lower inflammatory and  
723 improved metabolic markers relative to healthy controls with a similar body mass index.  
724 As compared to controls, athletes carry a more diverse gut microbiota, and several taxa

725 are significantly higher.<sup>213</sup> In mice, antibiotic-mediated depletion of gut microbiota  
726 compromises exercise performance.<sup>214</sup> In addition, monocolonization of germ-free  
727 mice with *Bacteroides fragilis*, which is a health-associated gram-negative bacterium,  
728 increases endurance exercise time.<sup>214</sup>

729 In sum, exercise-induced shifts in the microbial composition of the gut may  
730 contribute to the beneficial effects of physical activity on obesity, metabolic diseases,  
731 and neurological disorders.<sup>215</sup> Indeed, exercise-induced alteration of the gut  
732 microbiome may regulate brain function.<sup>204</sup> For example, SCFA, as microbiota-derived  
733 products, favor microglia maturation and function in the brain. Supplementation of  
734 SCFA is capable of reversing microglial defects observed in mice with lacking a healthy  
735 gut microbiota.<sup>216</sup>

## 736 **6. The effects of exercise on rhythmic oscillations**

737 The circadian rhythms represent a number of daily oscillations in physiology and  
738 behavior that take place over a 24-h period and enable the body and brain to adapt to  
739 daily changes in the environment. Virtually all cells of the body express a molecular  
740 clock that requires extremely precise regulation. Exercise is a nonphotic cue capable of  
741 restoring the transiently disturbed clock.<sup>217</sup> Here we present examples of how exercise  
742 modulates the circadian rhythms.

### 743 *6.1. Mechanics of the circadian clock*

744 The circadian rhythms are a common trait of practically all living organisms.  
745 Accumulating evidence reveals that disruption of mammalian circadian rhythms is  
746 deleterious to health. For instance, mice with muscle-specific deletion of *Bmall*, which  
747 is the core clock gene, exhibit impaired insulin-stimulated glucose uptake and  
748 metabolism, indicating that disruption of the intrinsic muscle clock system leads to  
749 muscle insulin resistance.<sup>218</sup> In addition, night shift work-related disturbance of the

750 circadian clock is associated with a higher risk of type 2 diabetes in humans.<sup>219, 220</sup>

751 Several reviews have highlighted the positive effects of exercise on circadian  
752 disturbances.<sup>221-223</sup> In particular, exercise acts as a strong zeitgeber (time cue) for the  
753 skeletal muscle clock.<sup>224</sup> We know that exercise is capable of readjusting the molecular  
754 circadian clock and, thus, reducing the harmful effects of disrupted sleep patterns,<sup>221,</sup>  
755 <sup>225</sup> however, exercising at different times of the day can lead to markedly different  
756 stimulation of signaling pathways and exercise performance.<sup>226, 227</sup> In a recent study,  
757 mice exhibit better performance in the maximal running test during the early daytime,  
758 and clear differences are observed in the muscle transcriptome, proteome, and  
759 phosphoproteome patterns of mice subjected to day-time exercise as compared to those  
760 subjected to night-time exercise.<sup>228</sup> However, few studies have focused on how to apply  
761 physical exercise to achieve the restoration of circadian rhythms or on the metabolic  
762 consequences and associated health outcomes of exercising at different times of the day.

### 763 *6.2. Exercise contributes to the maintenance of immune rhythmicity*

764 The immune system exhibits rhythmicity, and the rhythmic expression of clock genes  
765 has been implicated in both innate and adaptive immune cells.<sup>229, 230</sup> Moreover, the  
766 impairment of clock gene signaling causes chronic inflammation or aggravates the  
767 symptoms in older adults.<sup>231</sup> Evidence indicates that lifelong regular exercise (no less  
768 than 20 years) decelerates the aging-related decline of immune system function and  
769 contributes to the maintenance of the circadian rhythm throughout life.<sup>131, 232, 233</sup> In  
770 addition, clock gene expression patterns following acute exhaustive exercise are  
771 different in lifelong athletes compared to those in the sedentary group. Specifically, the  
772 acute bout of exercise modulates the clock machinery mainly in effector-memory CD4<sup>+</sup>  
773 T cells.<sup>234</sup>

## 774 **7. Benefits of exercise in homeostatic resilience**



775 Physiological homeostasis is a major requisite for the survival of any organisms.  
776 However, exposure to stressful life events is common. Hence, the maintenance of  
777 positive adaptation by individuals in the face of stress is important. Resistance to  
778 environmental risk experience or adaptation to stress/adversity is known as  
779 “resilience”,<sup>235</sup> and resilience can be regulated via neural, genetic, metabolic,  
780 immunological, and microbiome-based mechanisms. Exercise appears to be a  
781 protective strategy for improving homeostatic resilience and preserving human health  
782 and a good quality of life. Engaging in exercise that leads to improved cardiorespiratory  
783 fitness can reduce the risk of various diseases and these beneficial effects involve the  
784 widespread adaptations of multiple tissues (**Fig. 6**). Here we present examples of how  
785 exercise modulates homeostatic resilience.

#### 786 *7.1. Neural mechanisms*

787 The brain is the key organ of stress response. Stress and stress hormones causes both  
788 adaptive and maladaptive effects on the brain throughout life.<sup>236</sup> Moderate-intensity  
789 exercise improves brain function and helps to maintain brain health.<sup>237, 238</sup> Exercise  
790 elicits a wide range of biological changes in the nervous system. In addition to  
791 alleviating clinical symptoms, the advantageous effects of exercise include improved  
792 afferent signals, autonomic balance, mitochondrial function, increased neurogenesis,  
793 and synaptic plasticity, as well as improved metabolism and angiogenesis.<sup>238-242</sup>

794 Adult hippocampal neurogenesis is a complex and highly dynamic process that can  
795 be regulated by exercise.<sup>243</sup> Mice subjected to endurance training (voluntary wheel  
796 running and treadmill running) and resistance training (climb the ladder) are associated  
797 with a significantly increased rate of proliferation of neural progenitor cells, indicating  
798 enhanced neurogenesis.<sup>158, 244</sup> Several receptor signaling cascades have been implicated  
799 in the exercise-modulated enhancement of adult hippocampal neurogenesis, including

800 neurotrophic factors, such as BDNF, and neurotransmitters.<sup>245, 246</sup> In addition,  
801 dexamethasone-induced Ras-related protein 1 (Dexas1), a small GTPase, modulates  
802 exercise-induced neurogenesis in the adult hippocampus. Dexas1 deletion leads to a  
803 reduced proliferation of neural progenitors, suppressed pro-mitogenic pathways, and  
804 an increased number of mature newborn granule neurons in exercised mice. At the  
805 molecular level, the deletion of dexamethasone-induced Ras-related protein 1 abolishes  
806 exercise-triggered activation of extracellular signal-regulated kinase and cyclic  
807 adenosine monophosphate response element binding protein, and it prevents the  
808 increase of N-methyl-D-aspartate receptor subunit NR2A, *bdnf*, *vegf-a*, and  
809 tropomyosin receptor kinase B in the dentate gyrus.<sup>247</sup>

## 810 7.2. Genetic factors

811 Genetic factors have been found to influence an individual's level of resilience. Results  
812 from adult twin studies show that between 31% to 52% of observed individual  
813 differences in resilience to stressful life events can be explained by genetic factors.<sup>248-</sup>  
814 <sup>250</sup> Research suggests that the BDNF and neurotrophic tyrosine kinase receptor type 2  
815 gene polymorphisms are associated with stress tolerance.<sup>251, 252</sup> In addition, the BDNF  
816 polymorphism appears to modulate exercise-induced cognitive benefits. For example,  
817 exercise-induced cognitive improvement has been observed to be more profound in  
818 terms of the mental status and word recall of individuals carrying the *BDNF* Val66Met  
819 variant than of individuals with the *BDNF* Val66Val genotype (wild type).<sup>253</sup>

820 Interestingly, genetic factors appear to influence exercise participation. For example,  
821 a study based on the exercise participation of 37,051 pairs of twins from 7 countries  
822 (Australia, Denmark, Finland, the Netherlands, Norway, Sweden, and the United  
823 Kingdom) shows that the resemblance in exercise participation during leisure time of  
824 monozygotic (genetically identical) twins is higher than that for dizygotic twins, who

825 share about half of their segregating genes on average.<sup>254</sup> Moreover, genetic factors may  
826 confound the observed association between low levels of physical activity and higher  
827 disease and mortality risk.<sup>255-257</sup>

828 In addition, several genetic polymorphisms related to elite athletes seem to be  
829 associated with exercise performance.<sup>258</sup> For example, elite-level athletes show higher  
830 frequency of the IGF1 promoter T allele polymorphism.<sup>259</sup> Notably, the effect of these  
831 gene variations seems to be influenced by the types of exercise. The prevalence of  
832 carrying both IL-6 G174C and insulin-like growth factor-binding protein 3 (IGFBP3)  
833 A202C mutations is obviously higher among long-distance swimmers (major event:  
834 400-1500 m) compared to long-distance runners (major event: 5000 m marathon), and  
835 among short-distance swimmers (major event: 50-100 m) compared to power athletes  
836 (major event 100-200 m sprinters and jumpers). The IGFBP3 A202C polymorphism  
837 may compensate for the potential genetically non-beneficial effect of the higher IL-6  
838 G174C.<sup>260</sup> In addition, the IGF1 C1245T (rs35767) single-nucleotide polymorphism  
839 with the minor T allele is significantly associated with higher circulating IGF1  
840 concentrations.<sup>261</sup> In summary, exercise-related genetic polymorphisms at least partly  
841 contribute to the maintenance of body health.

842 Of note, current Mendelian randomization studies have reported findings that  
843 conflict with those of traditional observational studies. For example, observational  
844 studies show that the level of physical activity is inversely correlated with the risk of  
845 several diseases, including type 2 diabetes and cardiovascular disease. However, the  
846 two-sample Mendelian randomization study reveals that physical (in)activity is  
847 unrelated to the risk of type-2 diabetes<sup>262</sup> and cardiovascular disease, including  
848 coronary artery disease, MI, and ischemic stroke.<sup>263</sup> Thus, future work should pay more  
849 attention to the biological processes influenced by exercise as well as to the underlying

850 mechanisms, which may explain the confusing results.

### 851 *7.3. Hormones and metabolism*

852 Exercise is a powerful regulator of metabolism. Generally, aerobic and resistance  
853 exercise training is associated with improved metabolic health. Organs such as skeletal  
854 muscle, the liver, the brain, and adipose tissue are important metabolic communicators,  
855 and interorgan communication during exercise contributes to whole-body  
856 homeostasis.<sup>264</sup> Exercise-induced increase of energy demand is associated with  
857 increased mobilization of substrates, including carbohydrate, fat, and glucose, during  
858 and after exercise.<sup>265</sup> The utilization of extracellular substrates is partly mediated by  
859 rapid and coordinated changes in the endocrine system. The hormones associated with  
860 the endocrine system exhibit autocrine, paracrine, or endocrine actions on the tissues  
861 of the body that regulate a variety of processes such as growth and development,  
862 metabolism or immune responses.<sup>266, 267</sup> Exercise causes strong effects on the release  
863 of these hormone-like substances and thus the processes these substances modulate.<sup>6</sup>  
864 Two major hormones whose functions are influenced by exercise are insulin and thyroid  
865 hormone. Exercise increases insulin sensitivity through several molecular pathways,  
866 including upregulation of glucose transporter protein 4 in the cell membrane of insulin-  
867 dependent cells, improvement of  $\beta$  cell function, modulation of insulin receptor  
868 substrate 1 phosphorylation, induction of angiogenesis, reduction in adipokines,  
869 improvement of the redox state, and downregulation of ceramide plasma levels.<sup>268</sup>  
870 Therefore, exercise has been recommended as the management strategy for patients  
871 diagnosed with type 2 diabetes.<sup>269</sup> Changes in thyroid hormone levels (e.g., T3, T4) are  
872 observed following exercise. However, it is hard to draw any conclusions concerning  
873 the effects of exercise on thyroid hormone.<sup>270</sup> These controversial results could be due  
874 to the physical status of the subjects, the type, intensity, and duration of exercise, or the

875 differences in age and gender among subjects. In general, the effects of exercise on the  
876 endocrine system are of a positive nature and help to improve functional aspects of  
877 tissue and organs, resulting in improved health. For instance, exercise prevents the loss  
878 of activity of the endocrine system with aging.<sup>271</sup>

879 Metabolic adaptation is related to the specific type and mode of exercise. For  
880 example, regular endurance exercise enhances muscle capillarity, increases  
881 mitochondrial biogenesis, and promotes the fiber-type shift towards the type 1  
882 phenotype, but it has no significant effect on the fiber cross-sectional area. On the  
883 contrary, strength training induces muscle hypertrophy, mainly due to the greater  
884 muscle fiber cross-sectional area.<sup>265</sup>

#### 885 *7.4. Immune system*

886 The immune system responds to any type of insult that challenges cellular homeostasis.  
887 While a single bout of exercise may represent a perturbation to homeostasis, long-term  
888 moderate-intensity exercise can benefit the immune system by enhancing  
889 immunosurveillance and immunocompetence.<sup>272</sup> Regular exercise leads to an elevated  
890 anti-inflammatory capacity, which is a critical factor in maintaining health, particularly  
891 in the context of chronic diseases.<sup>273</sup> For example, the number of inflammatory  
892 CD14<sup>+</sup>CD16<sup>+</sup> monocytes decreases after 12 weeks of combined moderate-strength and  
893 endurance training, indicating a reduction of more proinflammatory monocyte  
894 subtypes.<sup>116</sup> In addition, acute bouts of exercise also elicit beneficial effects on  
895 immunological health partly through transiently mobilizing immune cells to peripheral  
896 tissues to conduct immune surveillance.<sup>274</sup>

897 Long-term exercise can prevent the age-associated degradation of immune system  
898 function (known as immunosenescence), which is characterized by considerable shifts  
899 in the balance of leukocyte subsets and a decline in various immune cell functions.<sup>275</sup>

900 As an example, long-term exercise from adulthood to old age (training time =  $49 \pm 8$   
901 years (mean  $\pm$  SD)) induces a healthy profile of inflammatory-related cytokines, as  
902 indicated by a decline in inflammatory biomarkers, including decreased levels of white  
903 blood cell counts, neutrophil counts, IL-6, IL-10, IL-1 receptor antagonist, and soluble  
904 tumor necrosis factor receptor-1.<sup>118</sup> Additionally, participation in long-term (training  
905 time =  $45.1 \pm 11.0$  years) easy- to moderate-intensity exercise is associated with a more  
906 differentiated adaptive immune response.<sup>123</sup> Furthermore, athletes with lifelong aerobic  
907 training have a lower percentage of senescent T cells when compared to healthy  
908 controls,<sup>232</sup> suggesting that exercise has a beneficial effect on immune function.

### 909 *7.5. Gut microbiota*

910 The human gut microbiota contains numerous microorganisms essential to maintaining  
911 homeostasis and normal gut physiology. Gut microbiota composition is highly variable.  
912 Each individual is linked to a unique gut microbiota profile that plays an important role  
913 in their metabolism and in the maintenance of a healthy host microorganism.  
914 Sometimes, the gut microbiota composition may vary within a single individual<sup>276</sup>  
915 because the gut's ecosystem development and stability can be affected by intrinsic and  
916 extrinsic factors, including exercise and diet, which in turn can influence health.<sup>277</sup>

917 Exercise-induced alterations in the diversity, composition, and functional profiles of  
918 the intestinal microbiome have been widely documented.<sup>278, 279</sup> Moderate endurance  
919 exercise has been shown to expand the number of beneficial microbial species, enrich  
920 microflora diversity, and promote the development of commensal bacteria.<sup>215, 278</sup> All  
921 these effects are beneficial for the host and contribute to the improvement of their health  
922 status. Indeed, elite athletes elicit uniquely beneficial and diverse gut microbiome  
923 characteristics, including a higher gut microbial diversity and a shift toward bacterial  
924 species associated with increased production of the SCFA implicated in the

925 maintenance of intestinal barrier integrity and regulation of host immune function.<sup>280</sup>  
926 Furthermore, exercise-induced gut microbial changes confer protection against certain  
927 diseases. For example, treadmill running exercise ameliorates cardiac dysfunction in  
928 MI mice by altering the diversity and community structure of the gut microbiome.  
929 Mechanistically, exercise increases the metabolites, 3-hydroxyphenylacetic acid (3-HA)  
930 and 4-HA, which are thought to protect against cardiac dysfunction by activating  
931 nuclear factor E2-related factor 2 (Nrf2).<sup>281</sup>

932 Interestingly, the composition of the gut microbiota can be differently modulated by  
933 distinct types and modes of exercise. For instance, 4 weeks of resistance and endurance  
934 exercise training leads to significant differences in the gut microbiota composition in  
935 mice.<sup>209</sup> Accordingly, mice subjected to endurance training exhibit higher diversity and  
936 evenness of gut microbiota. Specifically, endurance training is associated with a greater  
937 relative abundance of *Desulfovibrio* and *Desulfovibrio* sp., whilst *Clostridium* and  
938 *C.cocleatum* are enriched in mice that undergo resistance training.<sup>209</sup>

## 939 **8. Benefits of exercise in hormetic regulation**

940 There is some evidence that mild stressors inducing hormesis can contribute to the  
941 extension of lifespan and healthspan.<sup>282</sup> A single bout of exercise represents a challenge  
942 to cellular homeostasis. However, regular exercise confers multiple health benefits and  
943 better survival (**Fig. 7**). Therefore, it is possible that the beneficial outcomes of exercise  
944 may be achieved partly by hormetic regulation (**Fig. 6**).

### 945 *8.1. Exercise and mitohormesis*

946 Mitohormesis is characterized as hormesis in mitochondria and is associated with the  
947 adaptive response processes that maintain cellular homeostasis. In response to a  
948 disturbance, mitochondria can generate and transmit a signal to the nucleus that triggers  
949 a transcriptional response leading to mitochondrial and non-mitochondrial adaptations.

950 Although direct evidence linking mitohormesis to the exercise response is limited,  
951 mounting studies suggest that mitohormesis plays a role in mediating exercise-induced  
952 adaptations. Various signals are released from the mitochondria in response to exercise,  
953 with ROS being the primary candidate for inducing mitohormetic response.<sup>283</sup>  
954 Mitochondrial ROS are vital signaling molecules necessary for health-promoting and  
955 lifespan-extending effects.<sup>284</sup> The benefits of exercise are at least partly regulated by  
956 ROS signaling,<sup>285</sup> and Nrf2 is one of the important regulators that mediates redox  
957 homeostasis during exercise. Exercise induces the activation of Nrf2, which modulates  
958 the gene level of endogenous antioxidant synthesis and ROS-eliminating enzymes.<sup>286</sup>  
959 However, low-level and high-level mitochondrial stress could lead to opposing  
960 metabolic effects. In a recent study, severe mitochondrial stress due to mitoribosomal  
961 protein CR6-interacting factor 1 (*Crif1*) homo deficiency in hypothalamic  
962 proopiomelanocortin neurons of mice appeared to causes adult-onset obesity while  
963 mild mitochondrial stress caused by *Crif1* heterodeficiency in proopiomelanocortin  
964 neurons was associated with higher metabolic turnover and resistance to diet-induced  
965 obesity in mice. The beneficial metabolic effects induced by mild stress are mediated  
966 by enhanced thermogenesis and mitochondrial unfolded protein responses (UPR<sup>mt</sup>) in  
967 distal adipose tissue. Interestingly, regular exercise with moderate intensity resembles  
968 the metabolic phenotype of *Crif1* heterodeficiency, indicating the important regulatory  
969 role of mitohormetic in moderate-intensity regular exercise.<sup>287</sup>

## 970 8.2. *The benefits of exercise on healthspan*

971 Healthspan is characterized as healthy life expectancy or the period of life spent free of  
972 illness and disability.<sup>288</sup> In addition to a healthy diet and mental well-being, the positive  
973 effects of regular moderate exercise on the prevention, treatment, and management of  
974 chronic disease affecting healthspan are well-established. For example, in a landmark



975 21-year longitudinal study, it is reported that participation in long-term running and  
976 other vigorous exercises among older adults is associated with less disability and lower  
977 mortality in later life.<sup>19</sup> Regular exercise induces systemic adaptations in virtually all  
978 organ systems, producing multifaceted benefits for health. In Particular, exercise can  
979 attenuate multi-system age-related declines and help maintain physical fitness generally,  
980 including cardiorespiratory fitness and muscle function as well as flexibility and  
981 balance. The mechanisms through which exercise improves cardiorespiratory fitness  
982 include nitric oxide-induced vasodilatation, VEGFA-mediated angiogenesis, and  
983 VEGFR3-mediated lymphangiogenesis, etc.<sup>146, 289</sup> The main signaling pathways  
984 involved in the effects of exercise on muscle include calcium/calmodulin-dependent  
985 protein kinase signaling, MAPK signaling, AMPK signaling, SIRT6, PGC1 $\alpha$ , etc. <sup>290,</sup>  
986 <sup>291</sup>

987 Moreover, exercise benefits brain health via antioxidant defense (e.g., glutathione  
988 peroxidase, superoxide dismutase), neurotrophic factors (e.g., BDNF, VEGF, nerve  
989 growth factor), neurogenesis (e.g., BDNF, VEGF, IGF1), and protein homeostasis (e.g.,  
990 proteasomes, neprilysin, tau ubiquitination), etc.<sup>291</sup> Exercise also reduces adipocyte size  
991 and lipid content, increases mitochondrial activity, and alters adipokines secretion in  
992 white adipose tissue.<sup>292</sup> In mice, the exercise-induced adaptations in white adipose  
993 tissue improve glucose tolerance and insulin sensitivity, indicating improved whole-  
994 body metabolic health.<sup>293, 294</sup> These positive effects of exercise are supposed to be  
995 mediated by exercise training-induced adipokines.<sup>294</sup> Furthermore, exercise may  
996 enhance immune function and prevent immunosenescence, as explained in section 7.2.  
997 Altogether, adaptations in multiple tissues and organ systems contribute to the  
998 maintenance of whole-body health. Thus, exercise has been proposed as medicine to  
999 delay dependence and prolong healthspan.<sup>295</sup>

1000 *8.3. The effects of exercise on lifespan*

1001 A large body of study suggests that exercise is a promising intervention for extending  
1002 a healthy lifespan.<sup>296, 297</sup> The positive effects of exercise on lifespan are mainly achieved  
1003 through the attenuation of aging phenotypes or by delaying the process of aging. One  
1004 of the essential regulator of the antiaging effects of exercise is AMPK.<sup>298</sup> Activating  
1005 AMPK is sufficient to promote longevity in multiple organisms.<sup>299, 300</sup> In muscle  
1006 specifically, AMPK is an important regulator of exercise effects that are activated by  
1007 increased AMP/ATP and (nicotinamide adenine dinucleotide/ nicotinamide adenine  
1008 dinucleotide hydride) ratio.<sup>301</sup>

1009 Generally, regular exercise is considered to be fundamental to overall health and  
1010 longevity. However, some of the commonly ascribed beneficial effects of exercise seem  
1011 to be unsupported by current randomized control trial studies. For example, current  
1012 randomized control trial evidence shows that exercise does not prevent premature  
1013 mortality or cardiovascular disease in older adults or in people with chronic  
1014 conditions.<sup>302</sup> Thus, additional large-scale investigations would be of value, especially  
1015 high-quality studies with insights on molecular mechanisms.

1016 **9. The effects of exercise on repair and regeneration**

1017 The prompt repair and regeneration response to damage is a hallmark of health.<sup>28</sup> Here  
1018 we present examples of how exercise modulates the process of repair and regeneration  
1019 in response to damage (**Fig. 6**).

1020 *9.1. DNA damage and repair*

1021 Oxidative DNA damage is associated with increased risk of chronic diseases, such as  
1022 cancer, neurodegenerative disease, atherosclerosis, and diabetes.<sup>303, 304</sup> Therefore,  
1023 interventions aimed at repairing DNA strand breaks or lesions could be useful for  
1024 inhibiting or delaying the progression of diseases. Regular moderate exercise confers

1025 substantial health benefits, including a lower risk of the above-mentioned diseases.<sup>24</sup>

1026 Exercise has been directly implicated in the enhancement of DNA damage repair. As  
1027 an example, 8 weeks of treadmill running leads to a decreased accumulation of  
1028 oxidative damage to DNA and proteins in rat skeletal muscle.<sup>305</sup> Moreover, exercise  
1029 may promote the inherent DNA repair abilities of neurons through upregulation of  
1030 BDNF.<sup>306</sup> Several mechanisms have been implicated in the decrease of exercise-  
1031 associated oxidative damage in the brain, including upregulation of antioxidant  
1032 capacity, reduced production of oxidants, and consequently reduced nuclear DNA  
1033 damage.<sup>307</sup> However, acute and strenuous exercise could induce oxidative stress via  
1034 increased accumulation of reactive oxygen and nitrogen species, which may have  
1035 negative effects on DNA stability.<sup>308</sup> Additionally, high-intensity normoxic exercise  
1036 induces DNA double-strand breaks, as revealed by increased detection of gamma-H2A  
1037 histone family member X and p53-binding protein 1. Furthermore, levels of these  
1038 oxidative stress biomarkers are significantly increased following exercise in hypoxia.<sup>309</sup>

1039 Therefore, a better understanding of the effects of different types of exercise on DNA  
1040 damage and repair is necessary. Future studies focusing on exercise-induced  
1041 mechanisms are critical for developing better approaches to improving health.

#### 1042 *9.2. Protein damage and proteostasis*

1043 Proteostasis refers to the dynamic processes contributing to the maintenance of protein  
1044 homeostasis, which depends on adjustment in protein synthesis and degradation.  
1045 Disturbance of proteostasis contributes to the pathogenesis of many degenerative  
1046 diseases through the aggregation of damaged proteins.<sup>310, 311</sup> Regular exercise induces  
1047 substantial positive effects on health, with muscle being its predominant effector.<sup>312</sup> For  
1048 example, aerobic exercise increases the capacity for maintaining mitochondrial  
1049 proteostasis in skeletal and heart muscle.<sup>313</sup> Regular voluntary wheel running reduces

1050 the accumulation of cytotoxic misfolded proteins in the heart of  $\alpha$ B-crystallin mutated  
1051 (CryAB<sup>R120G</sup>) mice, a model of desmin-related cardiomyopathy, by increasing  
1052 autophagy.<sup>314</sup> One week of exercise training could reverse angiotensin II-induced  
1053 muscle atrophy by activating peroxisome proliferator-activated receptor gamma and  
1054 inhibiting miR-29b.<sup>315</sup> Exercise also causes protein degradation followed by a similar  
1055 scale rebuilding process, thus maintaining protein homeostasis.<sup>316</sup>

1056 Moreover, exercise activates autophagy and re-establishes proteostasis in cardiac  
1057 diseases. For example, 4 weeks of treadmill running improves skeletal muscle  
1058 autophagic flux and proteostasis in the rat model of neurogenic myopathy.<sup>317</sup>

### 1059 *9.3. The ER stress response*

1060 The ER is a versatile organelle that involves the synthesis and folding of proteins as  
1061 well as calcium homeostasis and signaling. Perturbation of ER function causes ER  
1062 stress and subsequently activates the unfolded protein response (UPR), which is  
1063 conducive to cellular homeostasis. However, if the ER stress remains unmitigated or is  
1064 too strong and the UPR fails to restore ER function, the cells may degrade part of the  
1065 ER via autophagy in order to maintain homeostasis in the ER. Defects in ER  
1066 homeostasis have been implicated in the pathogenesis of metabolic diseases.<sup>318, 319</sup>  
1067 Exercise training represents a promising strategy for reestablishing ER homeostasis in  
1068 cardiovascular diseases and obesity. For instance, 8 weeks of treadmill exercise can  
1069 reestablish cardiac protein quality control and reduces ER stress, which is associated  
1070 with improved cardiac function in the failed hearts of rats.<sup>320</sup> Moreover, 8 weeks of  
1071 swimming exercise is capable of suppressing aging-induced ER stress and ameliorating  
1072 cardiac dysfunction in aged mice by enhancing cyclic guanosine monophosphate  
1073 (cGMP)-protein kinase G signaling. Likewise, the inhibition of cGMP-specific  
1074 phosphodiesterase type 5 leads to reduced ER stress and improved cardiac function in

1075 aged mice while activation of ER stress eliminates the protective effect of exercise in  
1076 the same population.<sup>321</sup> Furthermore, in humans, 3 months of moderate exercise  
1077 alleviates obesity-related ER stress by downregulating glucose-regulated protein 78  
1078 signaling.<sup>322</sup> In a mouse model of Alzheimer's disease, exercise improves vascular  
1079 function and attenuates ER stress.<sup>323</sup>

1080 Additionally, in a recent study, acute exercise is reported to activate ER-phagy, which  
1081 is a selective ER autophagy regulated by ER-localized receptors, in order to ensure  
1082 proper cellular homeostasis. Mechanistically, ER-phagy receptor named family with  
1083 sequence similarity 134, member B anchors and fragments ER and then binds with  
1084 microtubule-associated protein light-chain-3 to promote ER membrane degradation.<sup>324</sup>  
1085 This study suggests that acute exercise-induced ER-phagy may serve as an important  
1086 adaptive stress response to maintain ER homeostasis.

#### 1087 *9.4. Mitochondrial stress responses*

1088 Mitochondria are essential semi-autonomous cellular organelles that are maintained  
1089 through complex remodeling processes, including biogenesis, dynamic fission and  
1090 fusion, and mitophagy. These remodeling processes collectively contribute to  
1091 mitochondria quality control. Mitochondrial stress induced by aggravated misfolded  
1092 mitochondria proteins in the mitochondrial matrix, an impaired protein quality control  
1093 system, mitonuclear imbalance, or inhibition of the electron transport chain can trigger  
1094 the UPR<sup>mt</sup>.<sup>325</sup>

1095 Regular endurance exercise is a powerful stimulus that promotes mitochondrial  
1096 remodeling. Activation of the UPR<sup>mt</sup> may mediate some of the exercise-induced  
1097 mitochondrial adaptations.<sup>326</sup> For example, the activation of UPR<sup>mt</sup> is observed in  
1098 skeletal muscle during the acute phase of the contractile period and chronic contractile  
1099 activity.<sup>327</sup>

1100 Exercise also increases levels of the mitochondrial encoded peptide mitochondrial  
1101 open-reading-frame of the 12S rRNA-c, which can directly mediate mitonuclear  
1102 communication by translocating to the nucleus and regulating adaptive nuclear gene  
1103 expression to promote cellular homeostasis. Treatment of mice with mitochondrial  
1104 open-reading-frame of the 12S rRNA-c is associated with metabolic benefits, such as  
1105 weight loss, enhanced antioxidant capacity, and increased insulin sensitivity.<sup>328, 329</sup>

#### 1106 *9.5. Lysosomal damage response*

1107 Lysosomes are the main organelles that accounts for proteolytic degradation and  
1108 recycling.<sup>330</sup> Exercise influences the release of lysosomal enzymes in several cell  
1109 types,<sup>331, 332</sup> suggesting that physical activity could modulate the lysosomal membrane  
1110 permeability. Thus, 4 weeks of aerobic exercise could mitigate the HFD-associated  
1111 lysosomal membrane permeabilization via the reduction of ROS.<sup>333</sup> However, studies  
1112 focused on exercise-induced changes in lysosomal are still limited.

1113 Finally, lysosomal biogenesis is also elevated in response to exercise. The increased  
1114 lysosomal biogenesis coordinates with mitophagy to enhance the breakdown of  
1115 dysfunctional mitochondria, thereby contributing to the maintenance of mitochondrial  
1116 quality.<sup>334</sup>

#### 1117 *9.6. Tissue-level regeneration*

1118 The positive effects of exercise on cardiac regeneration are well-established. Regular  
1119 endurance exercise is capable of promoting heart growth and inducing cardiac  
1120 remodeling.<sup>335, 336</sup> An enlarged heart due to regular exercise training is associated with  
1121 normal or enhanced heart function. Moreover, it is well-known that exercise confers  
1122 protection against heart failure.<sup>337</sup> Mechanistically, exercise-induced cardiac adaptation  
1123 mainly includes cardiomyocyte growth, cardiomyocyte fate reprogramming,  
1124 angiogenesis and lymphangiogenesis, mitochondrial remodeling, epigenetic alteration,

1125 enhanced endothelial function, quiescent cardiac fibroblast, and improved cardiac  
1126 metabolism.<sup>146, 338</sup> For instance, 3 weeks of swimming exercise causes a remarkable  
1127 increase in cardiac lymphangiogenesis via VEGFR3 activation. By contrast, VEGFR3  
1128 inhibition is capable of mitigating exercise-induced cardiac growth, indicating the  
1129 essential role of cardiac lymphangiogenesis in exercise-associated cardiac growth.<sup>339</sup>  
1130 In particular, IGF1-PI3K signaling is one of the essential pathways responsible for  
1131 exercise-related heart enlargement and protection.<sup>340</sup>

1132 Skeletal muscle exhibits high plasticity and adaptation in response to various  
1133 demands. Adult skeletal muscle has the remarkable ability to regenerate after injury due  
1134 to the ability of muscle stem cells, also called satellite cells, to generate both new  
1135 myofibers and new muscle stem cells.<sup>341</sup> Exercise training is a strong stimulator of  
1136 muscle plasticity, as it activates several intracellular signaling pathways that mediate  
1137 muscle growth and adaptations.<sup>342</sup> For example, 4 weeks of treadmill training improves  
1138 muscle regeneration and induces muscle hypertrophy via the IGFBP7-Akt-mTOR axis  
1139 in mice.<sup>343</sup> Moderate exercise improves tendon injury healing in aging rats by  
1140 increasing the number of tendon stem/progenitor cells.<sup>344</sup>

#### 1141 *9.7. Cell identity reprogramming*

1142 Research studies demonstrate that exercise training can trigger metabolic  
1143 reprogramming in multiple cell types and, thus, alter their functional phenotypes. For  
1144 example, 16 weeks of treadmill exercise induces macrophage phenotypic switching  
1145 from M1 to M2 in the adipose tissue of obese mice, indicating improved inflammatory  
1146 outcomes in exercised obese mice.<sup>345</sup> Additionally, 10 weeks of treadmill running could  
1147 promote the differentiation of mesenchymal stem cells into osteoblasts to increase  
1148 hematopoiesis.<sup>346</sup> Moreover, 4 weeks of exercise training before surgery offers  
1149 protection against hepatic injury via the metabolic reprogramming of immune cells.

1150 Specifically, exercise encourages Kupffer cells toward an anti-inflammatory phenotype  
1151 with trained immunity.<sup>347</sup>

## 1152 **10. Integrative effects of exercise on health**

1153 Exercise maintains and restores homeostasis at the organismal, tissue, cellular, and  
1154 molecular levels to stimulate positive physiological adaptations and subsequently, to  
1155 protect against various disease conditions.<sup>27</sup> The health benefit of regular exercise  
1156 training involve the acclimatization to repeated metabolic, thermoregulatory, hypoxic,  
1157 oxidative, and mechanical stress. An individual exercise bout elicits a rapid, but  
1158 transient response while the repetition of the stimulus causes compensatory  
1159 physiological changes that confer protection against greater subsequent stress.<sup>348, 349</sup>

1160 Exercise elicits systemic impacts. The preventive and therapeutic potential of  
1161 exercise to combat the development and progression of various diseases lies in the  
1162 remarkable integrative adaptation that takes place at the whole-organism level.  
1163 Exercise-related physiological adaptations are characterized by complex interplay  
1164 among multiple organ systems, including the skeletal muscle, lung, heart, brain,  
1165 vascular system, liver, adipose tissue, etc.<sup>350, 351</sup> Exercise therapy has been proposed as  
1166 an effective pre-operative therapy providing a series of positive effects on a patient's  
1167 physical fitness prior to surgery, on their recovery period, and on the length of hospital  
1168 stay.<sup>352-354</sup> It has been suggested the protective effects of pre-operative exercise are  
1169 largely due to an enhanced tolerance to systemic perturbation as well as an improved  
1170 metabolism. For example, 4 weeks of aerobic pre-operative exercise is capable of  
1171 significantly ameliorating liver injury and inflammation in mice with hepatic  
1172 ischemia/reperfusion injury. Mechanistically, exercise promotes the production of high  
1173 mobility group box 1 and upregulates the itaconate metabolism in Kupffer cells, thereby  
1174 inducing anti-inflammatory trained immunity.<sup>347</sup>



## 1175 **11. Conclusions and prospect**

1176 The beneficial effects of exercise have been well-documented for a range of improved  
1177 metabolic and cardiorespiratory fitness-related outcomes.<sup>355</sup> Regular exercise is  
1178 essentially considered a non-pharmacological polypill for patients with certain  
1179 comorbidities. Therapeutic exercise can be adopted to prevent, manage, and treat  
1180 diseases such as obesity, type 2 diabetes, cardiovascular disease, aging-related muscle  
1181 atrophy, and certain cancers. However, caution should be taken when interpreting these  
1182 discoveries, as exercise protocols may vary across studies.

1183 Exercise is a complex, multidimensional process that is challenging to accurately  
1184 assess in free-living individuals. The lack of consistency in the methods applied to  
1185 quantify exercise is a limitation to data analysis and may hinder the translation from  
1186 experimental findings to clinical practice. Thus, future work involving exercise should  
1187 be performed based on strictly designed and well-reported trials with good  
1188 reproducibility.<sup>356</sup>

1189 In this review, we have attempted to summarize the health benefit of exercise from  
1190 the view of biological causes. Due to limited space, it is hard to provide a  
1191 comprehensive review for each individual topic. However, the topics and  
1192 characteristics that have been discussed may provide a mechanistic view for exercise-  
1193 related studies. As the biology of exercise is complex, we have listed examples to  
1194 explain the effects of exercise on each topic and characteristic, which may be helpful  
1195 for gaining a comprehensive understanding the exercise-induced adaptations.

1196 Regarding the conflicting findings between current Mendelian randomization studies  
1197 and traditional observational studies in section 7.2, future researchers should perform  
1198 more mechanistic studies in order to unravel the biological pathways of exercise. In  
1199 addition, exercise-stimulated interorgan communication is less well-investigated.

1200 Further detailed study of exercise-related interorgan communications and its underlying  
1201 mechanisms may shed light on the identification of exercise-responsive molecules.  
1202 Regular exercise is undoubtedly beneficial for overall health. Yet, the mechanisms that  
1203 underlie the multiple health benefits of exercise are complex, and efforts devoted to  
1204 exploring the adaptation of organelles (e.g., mitochondria, nuclei, ER) may be helpful  
1205 for understanding the positive effects of exercise.

1206 Further investigation of the mechanisms underlying the beneficial effects of exercise  
1207 will help to improve the design and maximize the curative effects of exercise  
1208 interventions. Therefore, there is a need for prior in-depth knowledge of the scientific  
1209 basis of exercise in order to better understand the effects of potential subsequent  
1210 interventions oriented toward the modification of exercise methods for health  
1211 promotion and to research specific molecules that may improve the health of those who  
1212 are unable to exercise. We hope that continuing investigation in this field will increase  
1213 our understanding of the processes involved in the beneficial role of exercise and  
1214 facilitate the identification of new therapeutics to improve quality of life.

1215

## 1216 **Acknowledgments**

1217 This work was supported by grants from the National Key Research and Development  
1218 Project (2018YFE0113500 to JX), the National Natural Science Foundation of China  
1219 (82020108002 and 82225005 to JX), the Science and Technology Commission of  
1220 Shanghai Municipality (21XD1421300 and 20DZ2255400 to JX), the “Dawn” Program  
1221 of Shanghai Education Commission (19SG34 to JX) and the Sailing Program from  
1222 Science and Technology Commission of Shanghai (21YF1413700 to YQ). GK is  
1223 supported by the Ligue contre le Cancer (équipe labellisée); Agence National de la  
1224 Recherche (ANR) – Projets blancs; AMMICa US23/CNRS UMS3655; Association

1225 pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Fondation pour la  
1226 Recherche Médicale (FRM); a donation by Elior; Equipex Onco-Pheno-Screen;  
1227 European Joint Programme on Rare Diseases (EJPRD); Gustave Roussy Odyssea, the  
1228 European Union Horizon 2020 Projects Oncobiome and Crimson; Fondation Carrefour;  
1229 Institut National du Cancer (INCa); Institut Universitaire de France; LabEx Immuno-  
1230 Oncology (ANR-18-IDEX-0001); a Cancer Research ASPIRE Award from the Mark  
1231 Foundation; the RHU Immunolife; Seerave Foundation; SIRIC Stratified Oncology  
1232 Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer  
1233 Research and Personalized Medicine (CARPEM). This study contributes to the IdEx  
1234 Université de Paris ANR-18-IDEX-0001. C.L-O. is supported by European Union  
1235 (DeAge ERC Advanced Grant), Instituto de Salud Carlos III, Ministerio de Sanidad  
1236 (Spain) and SAF program from Ministerio de Ciencia e Innovación (Spain). B.F-G. is  
1237 supported by Red de Investigación en Ciencias del Deporte “in motu salus”. Consejo  
1238 Superior de Deportes, Spain.

1239

#### 1240 **Competing interests**

1241 GK has held research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma,  
1242 PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sotio, Tollys,  
1243 Vascage and Vasculox/Tioma. GK has consulted for Reithera. GK is on the Board of  
1244 Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder  
1245 of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK  
1246 is the inventor of multiple patents covering therapeutic targeting of aging, cancer, cystic  
1247 fibrosis and metabolic disorders. Among these, patents were licensed to Bayer  
1248 (WO2014020041-A1, WO2014020043-A1), Bristol-Myers Squibb (WO2008057863-  
1249 A1), Osasuna Therapeutics (WO2019057742A1), Pharmamar (WO2022049270A1 and

1250 WO2022048775-A1), Raptor Pharmaceuticals (EP2664326-A1), Samsara  
1251 Therapeutics (GB202017553D0) and Therafast Bio (EP3684471A1). The other authors  
1252 declare that they have no competing interests.

1253

#### 1254 **Authors contributions**

1255 YQ and BFG drafted the manuscript. GK, CLO and JX camp up with the idea and  
1256 edited the manuscript. HIL and GL reviewed and edited the manuscript. All authors  
1257 have read and approved the final version of this manuscript, and agree with the order  
1258 of presentation of the authors.

1259

#### 1260 **References**

- 1261 1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and  
1262 national life expectancy, all-cause mortality, and cause-specific mortality for  
1263 249 causes of death, 1980-2015: A systematic analysis for the global burden of  
1264 disease study 2015. *Lancet* 2016;**388**:1459-544.
- 1265 2. World Health Organization. *Noncommunicable diseases*; 2021. Available from:  
1266 <https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases>.  
1267 [accessed 09. 09. 2022]
- 1268 3. Yin X, Chen M, He R, et al. Association of leisure sedentary time with common  
1269 chronic disease risk factors: A longitudinal study of china health and nutrition  
1270 surveys. *Int J Health Plann Manage* 2021;**36**:100-12.
- 1271 4. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient  
1272 physical activity from 2001 to 2016: A pooled analysis of 358 population-based  
1273 surveys with 1.9 million participants. *Lancet Glob Health* 2018;**6**:e1077-e86.
- 1274 5. Li Y, Pan A, Wang DD, et al. Impact of healthy lifestyle factors on life

- 1275           expectancies in the us population. *Circulation* 2018;**138**:345-55.
- 1276   6.    Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. Physical  
1277           activity and depression: Towards understanding the antidepressant mechanisms  
1278           of physical activity. *Neurosci Biobehav Rev* 2019;**107**:525-39.
- 1279   7.    *Who guidelines on physical activity and sedentary behaviour*. Geneva; 2020.
- 1280   8.    Aune D, Sen A, Henriksen T, Saugstad OD, Tonstad S. Physical activity and the  
1281           risk of gestational diabetes mellitus: A systematic review and dose-response  
1282           meta-analysis of epidemiological studies. *Eur J Epidemiol* 2016;**31**:967-97.
- 1283   9.    Jeong SW, Kim SH, Kang SH, et al. Mortality reduction with physical activity  
1284           in patients with and without cardiovascular disease. *Eur Heart J* 2019;**40**:3547-  
1285           55.
- 1286   10.   Chaput JP, Willumsen J, Bull F, et al. 2020 who guidelines on physical activity  
1287           and sedentary behaviour for children and adolescents aged 5-17 years:  
1288           Summary of the evidence. *Int J Behav Nutr Phys Act* 2020;**17**:141.
- 1289   11.   Channon KM. Exercise and cardiovascular health: New routes to reap more  
1290           rewards. *Cardiovasc Res* 2020;**116**:e56-e8.
- 1291   12.   Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in  
1292           cardiovascular disease: Beyond attenuation of traditional risk factors. *Nat Rev*  
1293           *Cardiol* 2018;**15**:731-43.
- 1294   13.   Mendes R, Sousa N, Almeida A, et al. Exercise prescription for patients with  
1295           type 2 diabetes-a synthesis of international recommendations: Narrative review.  
1296           *Br J Sports Med* 2016;**50**:1379-81.
- 1297   14.   Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. Exercise prescription for  
1298           patients with multiple sclerosis; potential benefits and practical  
1299           recommendations. *BMC Neurol* 2017;**17**:185.

- 1300 15. Han P, Zhang W, Kang L, et al. Clinical evidence of exercise benefits for stroke.  
1301 *Adv Exp Med Biol* 2017;**1000**:131-51.
- 1302 16. Landi F, Marzetti E, Martone AM, Bernabei R, Onder G. Exercise as a remedy  
1303 for sarcopenia. *Curr Opin Clin Nutr Metab Care* 2014;**17**:25-31.
- 1304 17. Wannamethee SG, Shaper AG, Walker M. Physical activity and risk of cancer  
1305 in middle-aged men. *Br J Cancer* 2001;**85**:1311-6.
- 1306 18. Matos B, Patricio D, Henriques MC, et al. Chronic exercise training attenuates  
1307 prostate cancer-induced molecular remodelling in the testis. *Cell Oncol (Dordr)*  
1308 2021;**44**:311-27.
- 1309 19. Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and  
1310 mortality among aging runners: A 21-year longitudinal study. *Arch Intern Med*  
1311 2008;**168**:1638-46.
- 1312 20. Stessman J, Hammerman-Rozenberg R, Cohen A, Ein-Mor E, Jacobs JM.  
1313 Physical activity, function, and longevity among the very old. *Arch Intern Med*  
1314 2009;**169**:1476-83.
- 1315 21. Buchner DM. Physical activity and prevention of cardiovascular disease in  
1316 older adults. *Clin Geriatr Med* 2009;**25**:661-75, viii.
- 1317 22. Dhalwani NN, O'Donovan G, Zaccardi F, et al. Long terms trends of  
1318 multimorbidity and association with physical activity in older english  
1319 population. *Int J Behav Nutr Phys Act* 2016;**13**:8.
- 1320 23. Vancampfort D, Koyanagi A, Ward PB, et al. Chronic physical conditions,  
1321 multimorbidity and physical activity across 46 low- and middle-income  
1322 countries. *Int J Behav Nutr Phys Act* 2017;**14**:6.
- 1323 24. Ruegsegger GN, Booth FW. Health benefits of exercise. *Cold Spring Harb*  
1324 *Perspect Med* 2018;**8**.

- 1325 25. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise  
1326 as therapy in 26 different chronic diseases. *Scand J Med Sci Sports* 2015;**25**  
1327 **Suppl 3**:1-72.
- 1328 26. Franklin BA, Thompson PD, Al-Zaiti SS, et al. Exercise-related acute  
1329 cardiovascular events and potential deleterious adaptations following long-term  
1330 exercise training: Placing the risks into perspective-an update: A scientific  
1331 statement from the american heart association. *Circulation* 2020;**141**:e705-e36.
- 1332 27. Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of  
1333 exercise. *Cell* 2014;**159**:738-49.
- 1334 28. Lopez-Otin C, Kroemer G. Hallmarks of health. *Cell* 2021;**184**:33-63.
- 1335 29. Hoppeler H, Fluck M. Plasticity of skeletal muscle mitochondria: Structure and  
1336 function. *Med Sci Sports Exerc* 2003;**35**:95-104.
- 1337 30. Vargas-Ortiz K, Perez-Vazquez V, Macias-Cervantes MH. Exercise and sirtuins:  
1338 A way to mitochondrial health in skeletal muscle. *Int J Mol Sci* 2019;**20**.
- 1339 31. Memme JM, Erlich AT, Phukan G, Hood DA. Exercise and mitochondrial health.  
1340 *J Physiol* 2021;**599**:803-17.
- 1341 32. Lee H, Kim K, Kim B, et al. A cellular mechanism of muscle memory facilitates  
1342 mitochondrial remodelling following resistance training. *J Physiol*  
1343 2018;**596**:4413-26.
- 1344 33. Richter U, Lahtinen T, Martinen P, Suomi F, Battersby BJ. Quality control of  
1345 mitochondrial protein synthesis is required for membrane integrity and cell  
1346 fitness. *J Cell Biol* 2015;**211**:373-89.
- 1347 34. Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization  
1348 in cell death. *Physiol Rev* 2007;**87**:99-163.
- 1349 35. Merle A, Jollet M, Britto FA, et al. Endurance exercise decreases protein

- 1350 synthesis and er-mitochondria contacts in mouse skeletal muscle. *J Appl Physiol*  
1351 (1985) 2019;**127**:1297-306.
- 1352 36. Nielsen J, Gejl KD, Hey-Mogensen M, et al. Plasticity in mitochondrial cristae  
1353 density allows metabolic capacity modulation in human skeletal muscle. *J*  
1354 *Physiol* 2017;**595**:2839-47.
- 1355 37. Goncalves IO, Maciel E, Passos E, et al. Exercise alters liver mitochondria  
1356 phospholipidomic profile and mitochondrial activity in non-alcoholic  
1357 steatohepatitis. *Int J Biochem Cell Biol* 2014;**54**:163-73.
- 1358 38. Li Z, Agellon LB, Allen TM, et al. The ratio of phosphatidylcholine to  
1359 phosphatidylethanolamine influences membrane integrity and steatohepatitis.  
1360 *Cell Metab* 2006;**3**:321-31.
- 1361 39. Goncalves IO, Passos E, Diogo CV, et al. Exercise mitigates mitochondrial  
1362 permeability transition pore and quality control mechanisms alterations in  
1363 nonalcoholic steatohepatitis. *Appl Physiol Nutr Metab* 2016;**41**:298-306.
- 1364 40. Pan G, Zhang H, Zhu A, et al. Treadmill exercise attenuates cerebral ischaemic  
1365 injury in rats by protecting mitochondrial function via enhancement of caveolin-  
1366 1. *Life Sci* 2021;**264**:118634.
- 1367 41. Zhao HX, Zhang Z, Zhou HL, Hu F, Yu Y. Exercise training suppresses mst1  
1368 activation and attenuates myocardial dysfunction in mice with type 1 diabetes.  
1369 *Can J Physiol Pharmacol* 2020;**98**:777-84.
- 1370 42. Zhang SS, Zhou S, Crowley-McHattan ZJ, Wang RY, Li JP. A review of the role  
1371 of endo/sarcoplasmic reticulum-mitochondria  $Ca^{2+}$  transport in diseases and  
1372 skeletal muscle function. *Int J Environ Res Public Health* 2021;**18**.
- 1373 43. Guarnier FA, Michelucci A, Serano M, et al. Aerobic training prevents  
1374 heatstrokes in calsequestrin-1 knockout mice by reducing oxidative stress. *Oxid*



1375 *Med Cell Longev* 2018;**2018**:4652480.

1376 44. Gauthier BR, Comaills V. Nuclear envelope integrity in health and disease:  
 1377 Consequences on genome instability and inflammation. *Int J Mol Sci* 2021;**22**.

1378 45. Chandar S, Yeo LS, Leimena C, et al. Effects of mechanical stress and carvedilol  
 1379 in lamin a/c-deficient dilated cardiomyopathy. *Circ Res* 2010;**106**:573-82.

1380 46. Gillon A, Nielsen K, Steel C, Cornwall J, Sheard P. Exercise attenuates age-  
 1381 associated changes in motoneuron number, nucleocytoplasmic transport  
 1382 proteins and neuromuscular health. *Geroscience* 2018;**40**:177-92.

1383 47. Dias C, Nylandsted J. Plasma membrane integrity in health and disease:  
 1384 Significance and therapeutic potential. *Cell Discov* 2021;**7**:4.

1385 48. Noland RC. Exercise and regulation of lipid metabolism. *Prog Mol Biol Transl  
 1386 Sci* 2015;**135**:39-74.

1387 49. Ambery AG, Tackett L, Penque BA, Brozinick JT, Elmendorf JS. Exercise  
 1388 training prevents skeletal muscle plasma membrane cholesterol accumulation,  
 1389 cortical actin filament loss, and insulin resistance in c57bl/6j mice fed a  
 1390 western-style high-fat diet. *Physiol Rep* 2017;**5**.

1391 50. Grice BA, Barton KJ, Covert JD, et al. Excess membrane cholesterol is an early  
 1392 contributing reversible aspect of skeletal muscle insulin resistance in c57bl/6nj  
 1393 mice fed a western-style high-fat diet. *Am J Physiol Endocrinol Metab*  
 1394 2019;**317**:E362-E73.

1395 51. Bradley NS, Snook LA, Jain SS, Heigenhauser GJ, Bonen A, Spriet LL. Acute  
 1396 endurance exercise increases plasma membrane fatty acid transport proteins in  
 1397 rat and human skeletal muscle. *Am J Physiol Endocrinol Metab* 2012;**302**:E183-  
 1398 9.

1399 52. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and

- 1400 disruption of the blood-brain barrier. *Nat Med* 2013;**19**:1584-96.
- 1401 53. Liebner S, Dijkhuizen RM, Reiss Y, Plate KH, Agalliu D, Constantin G.  
1402 Functional morphology of the blood-brain barrier in health and disease. *Acta*  
1403 *Neuropathol* 2018;**135**:311-36.
- 1404 54. Malkiewicz MA, Szarmach A, Sabisz A, Cubala WJ, Szurowska E, Winklewski  
1405 PJ. Blood-brain barrier permeability and physical exercise. *J*  
1406 *Neuroinflammation* 2019;**16**:15.
- 1407 55. Souza PS, Goncalves ED, Pedroso GS, et al. Physical exercise attenuates  
1408 experimental autoimmune encephalomyelitis by inhibiting peripheral immune  
1409 response and blood-brain barrier disruption. *Mol Neurobiol* 2017;**54**:4723-37.
- 1410 56. Malkiewicz MA, Malecki A, Toborek M, Szarmach A, Winklewski PJ.  
1411 Substances of abuse and the blood brain barrier: Interactions with physical  
1412 exercise. *Neurosci Biobehav Rev* 2020;**119**:204-16.
- 1413 57. Chupel MU, Minuzzi LG, Furtado G, et al. Exercise and taurine in inflammation,  
1414 cognition, and peripheral markers of blood-brain barrier integrity in older  
1415 women. *Appl Physiol Nutr Metab* 2018;**43**:733-41.
- 1416 58. Roh HT, So WY. The effects of aerobic exercise training on oxidant-antioxidant  
1417 balance, neurotrophic factor levels, and blood-brain barrier function in obese  
1418 and non-obese men. *J Sport Health Sci* 2017;**6**:447-53.
- 1419 59. Gaspar RC, Nakandakari S, Munoz VR, et al. Acute physical exercise increases  
1420 pi3k-p110alpha protein content in the hypothalamus of obese mice. *J Anat*  
1421 2021;**238**:743-50.
- 1422 60. Chelakkot C, Ghim J, Ryu SH. Mechanisms regulating intestinal barrier  
1423 integrity and its pathological implications. *Exp Mol Med* 2018;**50**:1-9.
- 1424 61. Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on

- 1425 intestinal permeability. *J Appl Physiol (1985)* 1997;**82**:571-6.
- 1426 62. Walter E, Gibson OR, Stacey M, Hill N, Parsons IT, Woods D. Changes in  
1427 gastrointestinal cell integrity after marathon running and exercise-associated  
1428 collapse. *Eur J Appl Physiol* 2021;**121**:1179-87.
- 1429 63. Falgiano PA, Gillum TL, Schall ZJ, Strag HR, Kuennen MR. Dietary curcumin  
1430 supplementation does not alter peripheral blood mononuclear cell responses to  
1431 exertional heat stress. *Eur J Appl Physiol* 2018;**118**:2707-17.
- 1432 64. Hill GW, Gillum TL, Lee BJ, et al. Prolonged treadmill running in normobaric  
1433 hypoxia causes gastrointestinal barrier permeability and elevates circulating  
1434 levels of pro- and anti-inflammatory cytokines. *Appl Physiol Nutr Metab*  
1435 2020;**45**:376-86.
- 1436 65. Davis MS, Willard MD, Williamson KK, Steiner JM, Williams DA. Sustained  
1437 strenuous exercise increases intestinal permeability in racing alaskan sled dogs.  
1438 *J Vet Intern Med* 2005;**19**:34-9.
- 1439 66. Gutekunst K, Kruger K, August C, Diener M, Mooren FC. Acute exercises  
1440 induce disorders of the gastrointestinal integrity in a murine model. *Eur J Appl*  
1441 *Physiol* 2014;**114**:609-17.
- 1442 67. Pires W, Veneroso CE, Wanner SP, et al. Association between exercise-induced  
1443 hyperthermia and intestinal permeability: A systematic review. *Sports Med*  
1444 2017;**47**:1389-403.
- 1445 68. Freitas AKL, Silva MTB, Silva CMS, et al. Alanyl-glutamine protects the  
1446 intestinal barrier function in trained rats against the impact of acute exhaustive  
1447 exercise. *Braz J Med Biol Res* 2020;**53**:e9211.
- 1448 69. Pugh JN, Sage S, Hutson M, et al. Glutamine supplementation reduces markers  
1449 of intestinal permeability during running in the heat in a dose-dependent manner.

- 1450 *Eur J Appl Physiol* 2017;**117**:2569-77.
- 1451 70. Carbajo-Pescador S, Porrás D, García-Mediavilla MV, et al. Beneficial effects  
1452 of exercise on gut microbiota functionality and barrier integrity, and gut-liver  
1453 crosstalk in an in vivo model of early obesity and non-alcoholic fatty liver  
1454 disease. *Dis Model Mech* 2019;**12**.
- 1455 71. Shao C, Li Y, Chen J, et al. Physical exercise repairs obstructive jaundice-  
1456 induced damage to intestinal mucosal barrier function via h2s-mediated  
1457 regulation of the hmgb1/toll like receptors 4/nuclear factor kappa b pathway.  
1458 *Front Physiol* 2021;**12**:732780.
- 1459 72. Qin L, Yao ZQ, Chang Q, et al. Swimming attenuates inflammation, oxidative  
1460 stress, and apoptosis in a rat model of dextran sulfate sodium-induced chronic  
1461 colitis. *Oncotarget* 2017;**8**:7391-404.
- 1462 73. LeMessurier KS, Tiwary M, Morin NP, Samarasinghe AE. Respiratory barrier  
1463 as a safeguard and regulator of defense against influenza a virus and  
1464 streptococcus pneumoniae. *Front Immunol* 2020;**11**:3.
- 1465 74. Hellings PW, Steelant B. Epithelial barriers in allergy and asthma. *J Allergy Clin*  
1466 *Immunol* 2020;**145**:1499-509.
- 1467 75. Enhorning G, Hohlfeld J, Krug N, Lema G, Welliver RC. Surfactant function  
1468 affected by airway inflammation and cooling: Possible impact on exercise-  
1469 induced asthma. *Eur Respir J* 2000;**15**:532-8.
- 1470 76. Spruit MA, Rochester CL, Pitta F, et al. Pulmonary rehabilitation, physical  
1471 activity, respiratory failure and palliative respiratory care. *Thorax* 2019;**74**:693-  
1472 9.
- 1473 77. Wada JT, Borges-Santos E, Porrás DC, et al. Effects of aerobic training  
1474 combined with respiratory muscle stretching on the functional exercise capacity

- 1475 and thoracoabdominal kinematics in patients with copd: A randomized and  
1476 controlled trial. *Int J Chron Obstruct Pulmon Dis* 2016;**11**:2691-700.
- 1477 78. Jung MH, Yi SW, An SJ, et al. Association of physical activity and lower  
1478 respiratory tract infection outcomes in patients with cardiovascular disease. *J*  
1479 *Am Heart Assoc* 2022;**11**:e023775.
- 1480 79. Spruit MA, Singh SJ, Garvey C, et al. An official american thoracic  
1481 society/european respiratory society statement: Key concepts and advances in  
1482 pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;**188**:e13-64.
- 1483 80. Gao J, Pan X, Li G, Chatterjee E, Xiao J. Physical exercise protects against  
1484 endothelial dysfunction in cardiovascular and metabolic diseases. *J Cardiovasc*  
1485 *Transl Res* 2021.
- 1486 81. Good RB, Gilbane AJ, Trinder SL, et al. Endothelial to mesenchymal transition  
1487 contributes to endothelial dysfunction in pulmonary arterial hypertension. *Am J*  
1488 *Pathol* 2015;**185**:1850-8.
- 1489 82. Vieira RP, Silva RA, Oliveira-Junior MC, et al. Exercise deactivates leukocytes  
1490 in asthma. *Int J Sports Med* 2014;**35**:629-35.
- 1491 83. Kunz H, Bishop NC, Spielmann G, et al. Fitness level impacts salivary  
1492 antimicrobial protein responses to a single bout of cycling exercise. *Eur J Appl*  
1493 *Physiol* 2015;**115**:1015-27.
- 1494 84. Sivamaruthi BS, Kesika P, Chaiyasut C. Effect of probiotics supplementations  
1495 on health status of athletes. *Int J Environ Res Public Health* 2019;**16**.
- 1496 85. Chimenti L, Morici G, Paterno A, et al. Bronchial epithelial damage after a half-  
1497 marathon in nonasthmatic amateur runners. *Am J Physiol Lung Cell Mol Physiol*  
1498 2010;**298**:L857-62.
- 1499 86. Peters EM. Exercise, immunology and upper respiratory tract infections. *Int J*

- 1500 *Sports Med* 1997;**18 Suppl 1**:S69-77.
- 1501 87. Peters EM, Bateman ED. Ultramarathon running and upper respiratory tract  
1502 infections. An epidemiological survey. *S Afr Med J* 1983;**64**:582-4.
- 1503 88. Campbell JP, Turner JE. There is limited existing evidence to support the  
1504 common assumption that strenuous endurance exercise bouts impair immune  
1505 competency. *Expert Rev Clin Immunol* 2019;**15**:105-9.
- 1506 89. Combes A, Dekerle J, Dumont X, et al. Continuous exercise induces airway  
1507 epithelium damage while a matched-intensity and volume intermittent exercise  
1508 does not. *Respir Res* 2019;**20**:12.
- 1509 90. Bonifant H, Holloway S. A review of the effects of ageing on skin integrity and  
1510 wound healing. *Br J Community Nurs* 2019;**24**:S28-S33.
- 1511 91. Rousselle P, Montmasson M, Garnier C. Extracellular matrix contribution to  
1512 skin wound re-epithelialization. *Matrix Biol* 2019;**75-76**:12-26.
- 1513 92. Chen CT, Tung HH, Tung TH, Denq JC. Nutrition, exercise, and skin integrity  
1514 among frail older adults in taiwan. *Adv Skin Wound Care* 2017;**30**:364-71.
- 1515 93. Safdar A, Bourgeois JM, Ogborn DI, et al. Endurance exercise rescues  
1516 progeroid aging and induces systemic mitochondrial rejuvenation in mtdna  
1517 mutator mice. *Proc Natl Acad Sci U S A* 2011;**108**:4135-40.
- 1518 94. Lorincz K, Haluszka D, Kiss N, et al. Voluntary exercise improves murine  
1519 dermal connective tissue status in high-fat diet-induced obesity. *Arch Dermatol*  
1520 *Res* 2017;**309**:209-15.
- 1521 95. Crane JD, MacNeil LG, Lally JS, et al. Exercise-stimulated interleukin-15 is  
1522 controlled by ampk and regulates skin metabolism and aging. *Aging Cell*  
1523 2015;**14**:625-34.
- 1524 96. Pence BD, Woods JA. Exercise, obesity, and cutaneous wound healing:

- 1525 Evidence from rodent and human studies. *Adv Wound Care (New Rochelle)*  
1526 2014;**3**:71-9.
- 1527 97. O'Brien J, Finlayson K, Kerr G, Edwards H. Evaluating the effectiveness of a  
1528 self-management exercise intervention on wound healing, functional ability and  
1529 health-related quality of life outcomes in adults with venous leg ulcers: A  
1530 randomised controlled trial. *Int Wound J* 2017;**14**:130-7.
- 1531 98. Emery CF, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Frid DJ. Exercise  
1532 accelerates wound healing among healthy older adults: A preliminary  
1533 investigation. *J Gerontol A Biol Sci Med Sci* 2005;**60**:1432-6.
- 1534 99. Keylock KT, Vieira VJ, Wallig MA, DiPietro LA, Schrementi M, Woods JA.  
1535 Exercise accelerates cutaneous wound healing and decreases wound  
1536 inflammation in aged mice. *Am J Physiol Regul Integr Comp Physiol*  
1537 2008;**294**:R179-84.
- 1538 100. Rael VE, Chen L, McIntosh CM, Alegre ML. Exercise increases skin graft  
1539 resistance to rejection. *Am J Transplant* 2019;**19**:1560-7.
- 1540 101. Lou J, Wu J, Feng M, et al. Exercise promotes angiogenesis by enhancing  
1541 endothelial cell fatty acid utilization via liver-derived extracellular vesicle mir-  
1542 122-5p. *J Sport Health Sci* 2021.
- 1543 102. Zogaib FG, Monte-Alto-Costa A. Moderate intensity physical training  
1544 accelerates healing of full-thickness wounds in mice. *Braz J Med Biol Res*  
1545 2011;**44**:1025-35.
- 1546 103. Keylock T, Meserve L, Wolfe A. Low-intensity exercise accelerates wound  
1547 healing in diabetic mice. *Wounds* 2018;**30**:68-71.
- 1548 104. Gomes-Neto M, Conceicao CS, Oliveira Carvalho V, Brites C. A systematic  
1549 review of the effects of different types of therapeutic exercise on physiologic

- 1550 and functional measurements in patients with hiv/aids. *Clinics (Sao Paulo)*  
1551 2013;**68**:1157-67.
- 1552 105. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A  
1553 prospective study of age and lifestyle factors in relation to community-acquired  
1554 pneumonia in us men and women. *Arch Intern Med* 2000;**160**:3082-8.
- 1555 106. Pape K, Ryttergaard L, Rotevatn TA, et al. Leisure-time physical activity and  
1556 the risk of suspected bacterial infections. *Med Sci Sports Exerc* 2016;**48**:1737-  
1557 44.
- 1558 107. Sim YJ, Yu S, Yoon KJ, Loiacono CM, Kohut ML. Chronic exercise reduces  
1559 illness severity, decreases viral load, and results in greater anti-inflammatory  
1560 effects than acute exercise during influenza infection. *J Infect Dis*  
1561 2009;**200**:1434-42.
- 1562 108. Dianatinasab M, Ghahri S, Dianatinasab A, Amanat S, Fararouei M. Effects of  
1563 exercise on the immune function, quality of life, and mental health in hiv/aids  
1564 individuals. *Adv Exp Med Biol* 2020;**1228**:411-21.
- 1565 109. da Silveira MP, da Silva Fagundes KK, Bizuti MR, Starck E, Rossi RC, de  
1566 Resende ESDT. Physical exercise as a tool to help the immune system against  
1567 covid-19: An integrative review of the current literature. *Clin Exp Med*  
1568 2021;**21**:15-28.
- 1569 110. Alawna M, Amro M, Mohamed AA. Aerobic exercises recommendations and  
1570 specifications for patients with covid-19: A systematic review. *Eur Rev Med*  
1571 *Pharmacol Sci* 2020;**24**:13049-55.
- 1572 111. Abdelbasset WK. Stay home: Role of physical exercise training in elderly  
1573 individuals' ability to face the covid-19 infection. *J Immunol Res*  
1574 2020;**2020**:8375096.



- 1575 112. Tamura Y, Jee E, Kouzaki K, Kotani T, Nakazato K. Effects of endurance  
1576 training on the expression of host proteins involved in sars-cov-2 cell entry in  
1577 c57bl/6j mouse. *Physiol Rep* 2021;**9**:e15014.
- 1578 113. Valenzuela PL, Castillo-Garcia A, Morales JS, et al. Exercise benefits on  
1579 alzheimer's disease: State-of-the-science. *Ageing Res Rev* 2020;**62**:101108.
- 1580 114. Cook MD, Martin SA, Williams C, et al. Forced treadmill exercise training  
1581 exacerbates inflammation and causes mortality while voluntary wheel training  
1582 is protective in a mouse model of colitis. *Brain Behav Immun* 2013;**33**:46-56.
- 1583 115. de Araujo CC, Silva JD, Samary CS, et al. Regular and moderate exercise before  
1584 experimental sepsis reduces the risk of lung and distal organ injury. *J Appl*  
1585 *Physiol (1985)* 2012;**112**:1206-14.
- 1586 116. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD. Exercise  
1587 training-induced lowering of inflammatory (cd14+cd16+) monocytes: A role in  
1588 the anti-inflammatory influence of exercise? *J Leukoc Biol* 2008;**84**:1271-8.
- 1589 117. Abramson JL, Vaccarino V. Relationship between physical activity and  
1590 inflammation among apparently healthy middle-aged and older us adults. *Arch*  
1591 *Intern Med* 2002;**162**:1286-92.
- 1592 118. de Gonzalo-Calvo D, Fernandez-Garcia B, de Luxan-Delgado B, et al. Long-  
1593 term training induces a healthy inflammatory and endocrine emergent  
1594 biomarker profile in elderly men. *Age (Dordr)* 2012;**34**:761-71.
- 1595 119. Frodermann V, Rohde D, Courties G, et al. Exercise reduces inflammatory cell  
1596 production and cardiovascular inflammation via instruction of hematopoietic  
1597 progenitor cells. *Nat Med* 2019;**25**:1761-71.
- 1598 120. Nieman DC. Exercise immunology: Practical applications. *Int J Sports Med*  
1599 **1997**;**18 Suppl 1**:S91-100.

- 1600 121. Oh S, Chun S, Hwang S, et al. Vitamin d and exercise are major determinants  
1601 of natural killer cell activity, which is age- and gender-specific. *Front Immunol*  
1602 2021;**12**:594356.
- 1603 122. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune  
1604 functions. *Prog Mol Biol Transl Sci* 2015;**135**:355-80.
- 1605 123. Moro-Garcia MA, Fernandez-Garcia B, Echeverria A, et al. Frequent  
1606 participation in high volume exercise throughout life is associated with a more  
1607 differentiated adaptive immune response. *Brain Behav Immun* 2014;**39**:61-74.
- 1608 124. Bartlett DB, Fox O, McNulty CL, et al. Habitual physical activity is associated  
1609 with the maintenance of neutrophil migratory dynamics in healthy older adults.  
1610 *Brain Behav Immun* 2016;**56**:12-20.
- 1611 125. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA.  
1612 The anti-inflammatory effects of exercise: Mechanisms and implications for the  
1613 prevention and treatment of disease. *Nat Rev Immunol* 2011;**11**:607-15.
- 1614 126. Ulven SM, Foss SS, Skjolsvik AM, et al. An acute bout of exercise modulate  
1615 the inflammatory response in peripheral blood mononuclear cells in healthy  
1616 young men. *Arch Physiol Biochem* 2015;**121**:41-9.
- 1617 127. Visvikis-Siest S, Marteau JB, Samara A, Berrahmoune H, Marie B, Pfister M.  
1618 Peripheral blood mononuclear cells (pbmcs): A possible model for studying  
1619 cardiovascular biology systems. *Clin Chem Lab Med* 2007;**45**:1154-68.
- 1620 128. Liuzzo G, Angiolillo DJ, Buffon A, et al. Enhanced response of blood  
1621 monocytes to in vitro lipopolysaccharide-challenge in patients with recurrent  
1622 unstable angina. *Circulation* 2001;**103**:2236-41.
- 1623 129. Hou W, Gibbs JS, Lu X, et al. Viral infection triggers rapid differentiation of  
1624 human blood monocytes into dendritic cells. *Blood* 2012;**119**:3128-31.

- 1625 130. Minuzzi LG, Rama L, Bishop NC, et al. Lifelong training improves anti-  
1626 inflammatory environment and maintains the number of regulatory t cells in  
1627 masters athletes. *Eur J Appl Physiol* 2017;**117**:1131-40.
- 1628 131. Minuzzi LG, Chupel MU, Rama L, et al. Lifelong exercise practice and  
1629 immunosenescence: Master athletes cytokine response to acute exercise.  
1630 *Cytokine* 2019;**115**:1-7.
- 1631 132. Woods JA, Keylock KT, Lowder T, et al. Cardiovascular exercise training  
1632 extends influenza vaccine seroprotection in sedentary older adults: The immune  
1633 function intervention trial. *J Am Geriatr Soc* 2009;**57**:2183-91.
- 1634 133. Kohut ML, Arntson BA, Lee W, et al. Moderate exercise improves antibody  
1635 response to influenza immunization in older adults. *Vaccine* 2004;**22**:2298-306.
- 1636 134. Leitzmann M, Powers H, Anderson AS, et al. European code against cancer 4th  
1637 edition: Physical activity and cancer. *Cancer Epidemiol* 2015;**39 Suppl 1**:S46-  
1638 55.
- 1639 135. Papadimitriou N, Dimou N, Tsilidis KK, et al. Physical activity and risks of  
1640 breast and colorectal cancer: A mendelian randomisation analysis. *Nat Commun*  
1641 2020;**11**:597.
- 1642 136. Zhang X, Theodoratou E, Li X, et al. Genetically predicted physical activity  
1643 levels are associated with lower colorectal cancer risk: A mendelian  
1644 randomisation study. *Br J Cancer* 2021;**124**:1330-8.
- 1645 137. Pedersen L, Idorn M, Olofsson GH, et al. Voluntary running suppresses tumor  
1646 growth through epinephrine- and il-6-dependent nk cell mobilization and  
1647 redistribution. *Cell Metab* 2016;**23**:554-62.
- 1648 138. Bigley AB, Rezvani K, Chew C, et al. Acute exercise preferentially redeploys  
1649 nk-cells with a highly-differentiated phenotype and augments cytotoxicity

- 1650 against lymphoma and multiple myeloma target cells. *Brain Behav Immun*  
1651 2014;**39**:160-71.
- 1652 139. Childs BG, Baker DJ, Kirkland JL, Campisi J, van Deursen JM. Senescence and  
1653 apoptosis: Dueling or complementary cell fates? *EMBO Rep* 2014;**15**:1139-53.
- 1654 140. Werner C, Furster T, Widmann T, et al. Physical exercise prevents cellular  
1655 senescence in circulating leukocytes and in the vessel wall. *Circulation*  
1656 2009;**120**:2438-47.
- 1657 141. Werner C, Hanhoun M, Widmann T, et al. Effects of physical exercise on  
1658 myocardial telomere-regulating proteins, survival pathways, and apoptosis. *J*  
1659 *Am Coll Cardiol* 2008;**52**:470-82.
- 1660 142. Liu Y, Sanoff HK, Cho H, et al. Expression of p16(ink4a) in peripheral blood t-  
1661 cells is a biomarker of human aging. *Aging Cell* 2009;**8**:439-48.
- 1662 143. Yoon KJ, Ahn A, Park SH, et al. Exercise reduces metabolic burden while  
1663 altering the immune system in aged mice. *Aging (Albany NY)* 2021;**13**:1294-  
1664 313.
- 1665 144. Huang CC, Chiang WD, Huang WC, Huang CY, Hsu MC, Lin WT.  
1666 Hepatoprotective effects of swimming exercise against d-galactose-induced  
1667 senescence rat model. *Evid Based Complement Alternat Med*  
1668 2013;**2013**:275431.
- 1669 145. Saito Y, Chikenji TS, Matsumura T, Nakano M, Fujimiya M. Exercise enhances  
1670 skeletal muscle regeneration by promoting senescence in fibro-adipogenic  
1671 progenitors. *Nat Commun* 2020;**11**:889.
- 1672 146. Qiu Y, Pan X, Chen Y, Xiao J. Hallmarks of exercised heart. *J Mol Cell Cardiol*  
1673 2022;**164**:126-35.
- 1674 147. Otaka N, Shibata R, Ohashi K, et al. Myonectin is an exercise-induced myokine

- 1675 that protects the heart from ischemia-reperfusion injury. *Circ Res*  
1676 2018;**123**:1326-38.
- 1677 148. Hou Z, Qin X, Hu Y, et al. Longterm exercise-derived exosomal mir-342-5p: A  
1678 novel exerkine for cardioprotection. *Circ Res* 2019;**124**:1386-400.
- 1679 149. Gao R, Wang L, Bei Y, et al. Lncrna cphar induces cardiac physiological  
1680 hypertrophy and promotes functional recovery after myocardial ischemia-  
1681 reperfusion injury. *Circulation* 2021.
- 1682 150. He YY, Wang L, Zhang T, Weng SJ, Lu J, Zhong YM. Aerobic exercise delays  
1683 retinal ganglion cell death after optic nerve injury. *Exp Eye Res*  
1684 2020;**200**:108240.
- 1685 151. Dikic I, Elazar Z. Mechanism and medical implications of mammalian  
1686 autophagy. *Nat Rev Mol Cell Biol* 2018;**19**:349-64.
- 1687 152. Cao W, Li J, Yang K, Cao D. An overview of autophagy: Mechanism, regulation  
1688 and research progress. *Bull Cancer* 2021;**108**:304-22.
- 1689 153. Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular  
1690 homeostasis, physiology and pathology. *Nat Cell Biol* 2018;**20**:1013-22.
- 1691 154. Onishi M, Yamano K, Sato M, Matsuda N, Okamoto K. Molecular mechanisms  
1692 and physiological functions of mitophagy. *EMBO J* 2021;**40**:e104705.
- 1693 155. Wang L, Wang J, Cretoiu D, Li G, Xiao J. Exercise-mediated regulation of  
1694 autophagy in the cardiovascular system. *J Sport Health Sci* 2020;**9**:203-10.
- 1695 156. Grumati P, Coletto L, Schiavinato A, et al. Physical exercise stimulates  
1696 autophagy in normal skeletal muscles but is detrimental for collagen vi-  
1697 deficient muscles. *Autophagy* 2011;**7**:1415-23.
- 1698 157. Lira VA, Okutsu M, Zhang M, et al. Autophagy is required for exercise training-  
1699 induced skeletal muscle adaptation and improvement of physical performance.

1700 *FASEB J* 2013;**27**:4184-93.

1701 158. Codina-Martinez H, Fernandez-Garcia B, Diez-Planelles C, et al. Autophagy is  
 1702 required for performance adaptive response to resistance training and exercise-  
 1703 induced adult neurogenesis. *Scand J Med Sci Sports* 2020;**30**:238-53.

1704 159. Park SS, Seo YK, Kwon KS. Sarcopenia targeting with autophagy mechanism  
 1705 by exercise. *BMB Rep* 2019;**52**:64-9.

1706 160. Escobar KA, Cole NH, Mermier CM, VanDusseldorp TA. Autophagy and aging:  
 1707 Maintaining the proteome through exercise and caloric restriction. *Aging Cell*  
 1708 2019;**18**:e12876.

1709 161. Campos JC, Queliconi BB, Bozi LHM, et al. Exercise reestablishes autophagic  
 1710 flux and mitochondrial quality control in heart failure. *Autophagy*  
 1711 2017;**13**:1304-17.

1712 162. Halling JF, Pilegaard H. Autophagy-dependent beneficial effects of exercise.  
 1713 *Cold Spring Harb Perspect Med* 2017;**7**.

1714 163. He C, Bassik MC, Moresi V, et al. Exercise-induced bcl2-regulated autophagy  
 1715 is required for muscle glucose homeostasis. *Nature* 2012;**481**:511-5.

1716 164. He C, Sumpter R, Jr., Levine B. Exercise induces autophagy in peripheral  
 1717 tissues and in the brain. *Autophagy* 2012;**8**:1548-51.

1718 165. Liu H, Lei H, Shi Y, et al. Autophagy inhibitor 3-methyladenine alleviates  
 1719 overload-exercise-induced cardiac injury in rats. *Acta Pharmacol Sin*  
 1720 2017;**38**:990-7.

1721 166. Zhao N, Xia J, Xu B. Physical exercise may exert its therapeutic influence on  
 1722 alzheimer's disease through the reversal of mitochondrial dysfunction via sirt1-  
 1723 foxo1/3-pink1-parkin-mediated mitophagy. *J Sport Health Sci* 2021;**10**:1-3.

1724 167. Zhang Y, Liao B, Hu S, et al. High intensity interval training induces

- 1725 dysregulation of mitochondrial respiratory complex and mitophagy in the  
1726 hippocampus of middle-aged mice. *Behav Brain Res* 2021;**412**:113384.
- 1727 168. Ovens AJ, Scott JW, Langendorf CG, Kemp BE, Oakhill JS, Smiles WJ. Post-  
1728 translational modifications of the energy guardian amp-activated protein kinase.  
1729 *Int J Mol Sci* 2021;**22**.
- 1730 169. Evans M, Cogan KE, Egan B. Metabolism of ketone bodies during exercise and  
1731 training: Physiological basis for exogenous supplementation. *J Physiol*  
1732 2017;**595**:2857-71.
- 1733 170. Zhou Q, Deng J, Yao J, et al. Exercise downregulates hipk2 and hipk2 inhibition  
1734 protects against myocardial infarction. *EBioMedicine* 2021;**74**:103713.
- 1735 171. Wu X, Wang L, Wang K, et al. Adar2 increases in exercised heart and protects  
1736 against myocardial infarction and doxorubicin-induced cardiotoxicity. *Mol Ther*  
1737 2021.
- 1738 172. Bei Y, Lu D, Bar C, et al. Mir-486 attenuates cardiac ischemia/reperfusion injury  
1739 and mediates the beneficial effect of exercise for myocardial protection. *Mol*  
1740 *Ther* 2022.
- 1741 173. Xu M, Jiang H, Xiao J. Exercise protects sympathetic stress-induced myocardial  
1742 fibrosis by regulating cytokines. *J Cardiovasc Transl Res* 2020;**13**:570-1.
- 1743 174. Fernandez-Sanjurjo M, de Gonzalo-Calvo D, Fernandez-Garcia B, et al.  
1744 Circulating microrna as emerging biomarkers of exercise. *Exerc Sport Sci Rev*  
1745 2018;**46**:160-71.
- 1746 175. Fernandez-Sanjurjo M, Diaz-Martinez AE, Diez-Robles S, et al. Circulating  
1747 microrna profiling reveals specific subsignatures in response to a maximal  
1748 incremental exercise test. *J Strength Cond Res* 2021;**35**:287-91.
- 1749 176. Wu G, Zhang X, Gao F. The epigenetic landscape of exercise in cardiac health

- 1750 and disease. *J Sport Health Sci* 2021;**10**:648-59.
- 1751 177. Urdinguio RG, Tejedor JR, Fernandez-Sanjurjo M, et al. Physical exercise  
1752 shapes the mouse brain epigenome. *Mol Metab* 2021;**54**:101398.
- 1753 178. Cuevas-Ramos D, Almeda-Valdes P, Meza-Arana CE, et al. Exercise increases  
1754 serum fibroblast growth factor 21 (fgf21) levels. *PLoS One* 2012;**7**:e38022.
- 1755 179. Kim KH, Kim SH, Min YK, Yang HM, Lee JB, Lee MS. Acute exercise induces  
1756 fgf21 expression in mice and in healthy humans. *PLoS One* 2013;**8**:e63517.
- 1757 180. Hansen JS, Clemmesen JO, Secher NH, et al. Glucagon-to-insulin ratio is  
1758 pivotal for splanchnic regulation of fgf-21 in humans. *Mol Metab* 2015;**4**:551-  
1759 60.
- 1760 181. Hansen JS, Pedersen BK, Xu G, Lehmann R, Weigert C, Plomgaard P. Exercise-  
1761 induced secretion of fgf21 and follistatin are blocked by pancreatic clamp and  
1762 impaired in type 2 diabetes. *J Clin Endocrinol Metab* 2016;**101**:2816-25.
- 1763 182. Slusher AL, Whitehurst M, Zoeller RF, Mock JT, Maharaj M, Huang CJ.  
1764 Attenuated fibroblast growth factor 21 response to acute aerobic exercise in  
1765 obese individuals. *Nutr Metab Cardiovasc Dis* 2015;**25**:839-45.
- 1766 183. Gorgens SW, Eckardt K, Jensen J, Drevon CA, Eckel J. Exercise and regulation  
1767 of adipokine and myokine production. *Prog Mol Biol Transl Sci* 2015;**135**:313-  
1768 36.
- 1769 184. Stanford KI, Middelbeek RJ, Goodyear LJ. Erratum. Exercise effects on white  
1770 adipose tissue: Beiging and metabolic adaptations. *Diabetes* 2015;**64**:2361-  
1771 2368. *Diabetes* 2015;**64**:3334.
- 1772 185. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in  
1773 the regulation of human adipose tissue physiology. *Physiol Rev* 2012;**92**:157-  
1774 91.



- 1775 186. Geng L, Liao B, Jin L, et al. Exercise alleviates obesity-induced metabolic  
1776 dysfunction via enhancing fgf21 sensitivity in adipose tissues. *Cell Rep*  
1777 2019;**26**:2738-52 e4.
- 1778 187. Zhang H, Fealy CE, Kirwan JP. Exercise training promotes a gdf15-associated  
1779 reduction in fat mass in older adults with obesity. *Am J Physiol Endocrinol*  
1780 *Metab* 2019;**316**:E829-E36.
- 1781 188. Campderros L, Sanchez-Infantes D, Villarroya J, et al. Altered gdf15 and fgf21  
1782 levels in response to strenuous exercise: A study in marathon runners. *Front*  
1783 *Physiol* 2020;**11**:550102.
- 1784 189. Kleinert M, Clemmensen C, Sjoberg KA, et al. Exercise increases circulating  
1785 gdf15 in humans. *Mol Metab* 2018;**9**:187-91.
- 1786 190. Conte M, Martucci M, Mosconi G, et al. Gdf15 plasma level is inversely  
1787 associated with level of physical activity and correlates with markers of  
1788 inflammation and muscle weakness. *Front Immunol* 2020;**11**:915.
- 1789 191. Klein AB, Nicolaisen TS, Ortenblad N, et al. Pharmacological but not  
1790 physiological gdf15 suppresses feeding and the motivation to exercise. *Nat*  
1791 *Commun* 2021;**12**:1041.
- 1792 192. Searls YM, Smirnova IV, Fegley BR, Stehno-Bittel L. Exercise attenuates  
1793 diabetes-induced ultrastructural changes in rat cardiac tissue. *Med Sci Sports*  
1794 *Exerc* 2004;**36**:1863-70.
- 1795 193. Ding YH, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y. Cerebral angiogenesis and  
1796 expression of angiogenic factors in aging rats after exercise. *Curr Neurovasc*  
1797 *Res* 2006;**3**:15-23.
- 1798 194. Morland C, Andersson KA, Haugen OP, et al. Exercise induces cerebral vegf  
1799 and angiogenesis via the lactate receptor hear1. *Nat Commun* 2017;**8**:15557.

- 1800 195. Archer AE, Von Schulze AT, Geiger PC. Exercise, heat shock proteins and  
1801 insulin resistance. *Philos Trans R Soc Lond B Biol Sci* 2018;**373**.
- 1802 196. Rosenzweig R, Nillegoda NB, Mayer MP, Bukau B. The hsp70 chaperone  
1803 network. *Nat Rev Mol Cell Biol* 2019;**20**:665-80.
- 1804 197. Henstridge DC, Febbraio MA, Hargreaves M. Heat shock proteins and exercise  
1805 adaptations. Our knowledge thus far and the road still ahead. *J Appl Physiol*  
1806 (1985) 2016;**120**:683-91.
- 1807 198. Chung J, Nguyen AK, Henstridge DC, et al. Hsp72 protects against obesity-  
1808 induced insulin resistance. *Proc Natl Acad Sci U S A* 2008;**105**:1739-44.
- 1809 199. Gupte AA, Bomhoff GL, Morris JK, Gorres BK, Geiger PC. Lipoic acid  
1810 increases heat shock protein expression and inhibits stress kinase activation to  
1811 improve insulin signaling in skeletal muscle from high-fat-fed rats. *J Appl*  
1812 *Physiol (1985)* 2009;**106**:1425-34.
- 1813 200. Henstridge DC, Bruce CR, Drew BG, et al. Activating hsp72 in rodent skeletal  
1814 muscle increases mitochondrial number and oxidative capacity and decreases  
1815 insulin resistance. *Diabetes* 2014;**63**:1881-94.
- 1816 201. Celik O, Yildiz BO. Obesity and physical exercise. *Minerva Endocrinol (Torino)*  
1817 2021;**46**:131-44.
- 1818 202. Wang YL, Lin CH, Chen CC, et al. Exercise preconditioning attenuates  
1819 neurological injury by preserving old and newly formed hsp72-containing  
1820 neurons in focal brain ischemia rats. *Int J Med Sci* 2019;**16**:675-85.
- 1821 203. McGee SL, Hargreaves M. Exercise adaptations: Molecular mechanisms and  
1822 potential targets for therapeutic benefit. *Nat Rev Endocrinol* 2020;**16**:495-505.
- 1823 204. Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome-gut-brain  
1824 axis. *Gut Microbes* 2019;**10**:555-68.

- 1825 205. Zhao H, Chen X, Hu G, et al. Small extracellular vesicles from brown adipose  
1826 tissue mediate exercise cardioprotection. *Circ Res* 2022;**130**:1490-506.
- 1827 206. Allen JM, Mailing LJ, Niemi GM, et al. Exercise alters gut microbiota  
1828 composition and function in lean and obese humans. *Med Sci Sports Exerc*  
1829 2018;**50**:747-57.
- 1830 207. Gomaa EZ. Human gut microbiota/microbiome in health and diseases: A review.  
1831 *Antonie Van Leeuwenhoek* 2020;**113**:2019-40.
- 1832 208. Wosinska L, Walsh CJ, O'Connor PM, et al. In vitro and in silico based  
1833 approaches to identify potential novel bacteriocins from the athlete gut  
1834 microbiome of an elite athlete cohort. *Microorganisms* 2022;**10**.
- 1835 209. Fernandez J, Fernandez-Sanjurjo M, Iglesias-Gutierrez E, et al. Resistance and  
1836 endurance exercise training induce differential changes in gut microbiota  
1837 composition in murine models. *Front Physiol* 2021;**12**:748854.
- 1838 210. Allen JM, Berg Miller ME, Pence BD, et al. Voluntary and forced exercise  
1839 differentially alters the gut microbiome in c57bl/6j mice. *J Appl Physiol (1985)*  
1840 2015;**118**:1059-66.
- 1841 211. Choi JJ, Eum SY, Rampersaud E, Daunert S, Abreu MT, Toborek M. Exercise  
1842 attenuates pcb-induced changes in the mouse gut microbiome. *Environ Health*  
1843 *Perspect* 2013;**121**:725-30.
- 1844 212. Kang SS, Jeraldo PR, Kurti A, et al. Diet and exercise orthogonally alter the gut  
1845 microbiome and reveal independent associations with anxiety and cognition.  
1846 *Mol Neurodegener* 2014;**9**:36.
- 1847 213. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary  
1848 extremes impact on gut microbial diversity. *Gut* 2014;**63**:1913-20.
- 1849 214. Hsu YJ, Chiu CC, Li YP, et al. Effect of intestinal microbiota on exercise

- 1850 performance in mice. *J Strength Cond Res* 2015;**29**:552-8.
- 1851 215. Monda V, Villano I, Messina A, et al. Exercise modifies the gut microbiota with  
1852 positive health effects. *Oxid Med Cell Longev* 2017;**2017**:3831972.
- 1853 216. Erny D, Hrabe de Angelis AL, Jaitin D, et al. Host microbiota constantly control  
1854 maturation and function of microglia in the cns. *Nat Neurosci* 2015;**18**:965-77.
- 1855 217. Mancilla R, Krook A, Schrauwen P, Hesselink MKC. Diurnal regulation of  
1856 peripheral glucose metabolism: Potential effects of exercise timing. *Obesity*  
1857 *(Silver Spring)* 2020;**28 Suppl 1**:S38-S45.
- 1858 218. Dyar KA, Ciciliot S, Wright LE, et al. Muscle insulin sensitivity and glucose  
1859 metabolism are controlled by the intrinsic muscle clock. *Mol Metab* 2014;**3**:29-  
1860 41.
- 1861 219. Vetter C, Dashti HS, Lane JM, et al. Night shift work, genetic risk, and type 2  
1862 diabetes in the uk biobank. *Diabetes Care* 2018;**41**:762-9.
- 1863 220. Bescos R, Boden MJ, Jackson ML, et al. Four days of simulated shift work  
1864 reduces insulin sensitivity in humans. *Acta Physiol (Oxf)* 2018;**223**:e13039.
- 1865 221. Gabriel BM, Zierath JR. Circadian rhythms and exercise - re-setting the clock  
1866 in metabolic disease. *Nat Rev Endocrinol* 2019;**15**:197-206.
- 1867 222. Tahara Y, Aoyama S, Shibata S. The mammalian circadian clock and its  
1868 entrainment by stress and exercise. *J Physiol Sci* 2017;**67**:1-10.
- 1869 223. Youngstedt SD, Elliott JA, Kripke DF. Human circadian phase-response curves  
1870 for exercise. *J Physiol* 2019;**597**:2253-68.
- 1871 224. Wolff G, Esser KA. Scheduled exercise phase shifts the circadian clock in  
1872 skeletal muscle. *Med Sci Sports Exerc* 2012;**44**:1663-70.
- 1873 225. Choi Y, Cho J, No MH, et al. Re-setting the circadian clock using exercise  
1874 against sarcopenia. *Int J Mol Sci* 2020;**21**.

- 1875 226. Facer-Childs E, Brandstaetter R. The impact of circadian phenotype and time  
1876 since awakening on diurnal performance in athletes. *Curr Biol* 2015;**25**:518-22.
- 1877 227. Facer-Childs E, Brandstaetter R. Circadian phenotype composition is a major  
1878 predictor of diurnal physical performance in teams. *Front Neurol* 2015;**6**:208.
- 1879 228. Maier G, Delezie J, Westermark PO, Santos G, Ritz D, Handschin C.  
1880 Transcriptomic, proteomic and phosphoproteomic underpinnings of daily  
1881 exercise performance and zeitgeber activity of training in mouse muscle. *J*  
1882 *Physiol* 2022;**600**:769-96.
- 1883 229. Scheiermann C, Gibbs J, Ince L, Loudon A. Clocking in to immunity. *Nat Rev*  
1884 *Immunol* 2018;**18**:423-37.
- 1885 230. Nobis CC, Dubeau Laramee G, Kervezee L, Maurice De Sousa D, Labrecque  
1886 N, Cermakian N. The circadian clock of cd8 t cells modulates their early  
1887 response to vaccination and the rhythmicity of related signaling pathways. *Proc*  
1888 *Natl Acad Sci U S A* 2019;**116**:20077-86.
- 1889 231. de Souza Teixeira AA, Lira FS, Rosa-Neto JC. Aging with rhythmicity. Is it  
1890 possible? Physical exercise as a pacemaker. *Life Sci* 2020;**261**:118453.
- 1891 232. Minuzzi LG, Rama L, Chupel MU, et al. Effects of lifelong training on  
1892 senescence and mobilization of t lymphocytes in response to acute exercise.  
1893 *Exerc Immunol Rev* 2018;**24**:72-84.
- 1894 233. Lavin KM, Perkins RK, Jemiolo B, Raue U, Trappe SW, Trappe TA. Effects of  
1895 aging and lifelong aerobic exercise on basal and exercise-induced inflammation.  
1896 *J Appl Physiol (1985)* 2020;**128**:87-99.
- 1897 234. de Souza Teixeira AA, Minuzzi LG, Lira FS, et al. Improvement in the anti-  
1898 inflammatory profile with lifelong physical exercise is related to clock genes  
1899 expression in effector-memory cd4+ t cells in master athletes. *Exerc Immunol*

- 1900            *Rev* 2021;**27**:67-83.
- 1901    235.    Rutter M. Implications of resilience concepts for scientific understanding. *Ann*  
1902            *N Y Acad Sci* 2006;**1094**:1-12.
- 1903    236.    McEwen BS. Physiology and neurobiology of stress and adaptation: Central  
1904            role of the brain. *Physiol Rev* 2007;**87**:873-904.
- 1905    237.    Deslandes A, Moraes H, Ferreira C, et al. Exercise and mental health: Many  
1906            reasons to move. *Neuropsychobiology* 2009;**59**:191-8.
- 1907    238.    Lee CB, Baek SS. Impact of exercise on hippocampal neurogenesis in  
1908            hyperglycemic diabetes. *J Exerc Rehabil* 2020;**16**:115-7.
- 1909    239.    Voss MW, Soto C, Yoo S, Sodoma M, Vivar C, van Praag H. Exercise and  
1910            hippocampal memory systems. *Trends Cogn Sci* 2019;**23**:318-33.
- 1911    240.    Teixeira AL, Fernandes IA, Vianna LC. Cardiovascular control during exercise:  
1912            The connectivity of skeletal muscle afferents to the brain. *Exerc Sport Sci Rev*  
1913            2020;**48**:83-91.
- 1914    241.    Mahalakshmi B, Maurya N, Lee SD, Bharath Kumar V. Possible  
1915            neuroprotective mechanisms of physical exercise in neurodegeneration. *Int J*  
1916            *Mol Sci* 2020;**21**.
- 1917    242.    Oosterwijk JV, Marusic U, De Wandele I, et al. The role of autonomic function  
1918            in exercise-induced endogenous analgesia: A case-control study in myalgic  
1919            encephalomyelitis/chronic fatigue syndrome and healthy people. *Pain*  
1920            *Physician* 2017;**20**:E389-E99.
- 1921    243.    Xu X, Fu Z, Le W. Exercise and parkinson's disease. *Int Rev Neurobiol*  
1922            2019;**147**:45-74.
- 1923    244.    van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances  
1924            neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci*

- 1925            *USA* 1999;**96**:13427-31.
- 1926    245.    Berg DA, Belnoue L, Song H, Simon A. Neurotransmitter-mediated control of  
1927            neurogenesis in the adult vertebrate brain. *Development* 2013;**140**:2548-61.
- 1928    246.    Vilar M, Mira H. Regulation of neurogenesis by neurotrophins during adulthood:  
1929            Expected and unexpected roles. *Front Neurosci* 2016;**10**:26.
- 1930    247.    Bouchard-Cannon P, Lowden C, Trinh D, Cheng HM. Dexas1 is a homeostatic  
1931            regulator of exercise-dependent proliferation and cell survival in the  
1932            hippocampal neurogenic niche. *Sci Rep* 2018;**8**:5294.
- 1933    248.    Amstadter AB, Myers JM, Kendler KS. Psychiatric resilience: Longitudinal  
1934            twin study. *Br J Psychiatry* 2014;**205**:275-80.
- 1935    249.    Boardman JD, Blalock CL, Button TM. Sex differences in the heritability of  
1936            resilience. *Twin Res Hum Genet* 2008;**11**:12-27.
- 1937    250.    Waaktaar T, Torgersen S. Genetic and environmental causes of variation in trait  
1938            resilience in young people. *Behav Genet* 2012;**42**:366-77.
- 1939    251.    Aizawa S, Ishitobi Y, Masuda K, et al. Genetic association of the transcription  
1940            of neuroplasticity-related genes and variation in stress-coping style. *Brain  
1941            Behav* 2015;**5**:e00360.
- 1942    252.    Notaras M, van den Buuse M. Neurobiology of bdnf in fear memory, sensitivity  
1943            to stress, and stress-related disorders. *Mol Psychiatry* 2020;**25**:2251-74.
- 1944    253.    Liu T, Canon MD, Shen L, et al. The influence of the bdnf val66met  
1945            polymorphism on the association of regular physical activity with cognition  
1946            among individuals with diabetes. *Biol Res Nurs* 2021;**23**:318-30.
- 1947    254.    Stubbe JH, Boomsma DI, Vink JM, et al. Genetic influences on exercise  
1948            participation in 37,051 twin pairs from seven countries. *PLoS One* 2006;**1**:e22.
- 1949    255.    Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of

- 1950 all-cause mortality: The roles of genetics and childhood environment. *Am J*  
1951 *Epidemiol* 2002;**156**:985-93.
- 1952 256. Waller K, Kujala UM, Rantanen T, et al. Physical activity, morbidity and  
1953 mortality in twins: A 24-year prospective follow-up. *Eur J Epidemiol*  
1954 2010;**25**:731-9.
- 1955 257. Ballin M, Nordstrom A, Nordstrom P. Cardiovascular disease and all-cause  
1956 mortality in male twins with discordant cardiorespiratory fitness: A nationwide  
1957 cohort study. *Am J Epidemiol* 2020;**189**:1114-23.
- 1958 258. Silva HH, Silva MG, Cerqueira F, Tavares V, Medeiros R. Genomic profile in  
1959 association with sport-type, sex, ethnicity, psychological traits and sport injuries  
1960 of elite athletes. *J Sports Med Phys Fitness* 2022;**62**:418-34.
- 1961 259. Eliakim A. Endocrine response to exercise and training-closing the gaps.  
1962 *Pediatr Exerc Sci* 2016;**28**:226-32.
- 1963 260. Ben-Zaken S, Meckel Y, Nemet D, Kassem E, Eliakim A. The combined  
1964 frequencies of the il-6 g-174c and igfbp3 a-202c polymorphisms among  
1965 swimmers and runners. *Growth Horm IGF Res* 2020;**51**:17-21.
- 1966 261. Palles C, Johnson N, Coupland B, et al. Identification of genetic variants that  
1967 influence circulating igf1 levels: A targeted search strategy. *Hum Mol Genet*  
1968 2008;**17**:1457-64.
- 1969 262. Meisinger C, Linseisen J, Leitzmann M, Baurecht H, Baumeister SE.  
1970 Association of physical activity and sedentary behavior with type 2 diabetes and  
1971 glycemic traits: A two-sample mendelian randomization study. *BMJ Open*  
1972 *Diabetes Res Care* 2020;**8**.
- 1973 263. Bahls M, Leitzmann MF, Karch A, et al. Physical activity, sedentary behavior  
1974 and risk of coronary artery disease, myocardial infarction and ischemic stroke:



- 1975 A two-sample mendelian randomization study. *Clin Res Cardiol*  
 1976 2021;**110**:1564-73.
- 1977 264. Murphy RM, Watt MJ, Febbraio MA. Metabolic communication during  
 1978 exercise. *Nat Metab* 2020;**2**:805-16.
- 1979 265. Moghetti P, Bacchi E, Brangani C, Dona S, Negri C. Metabolic effects of  
 1980 exercise. *Front Horm Res* 2016;**47**:44-57.
- 1981 266. Hackney AC, Lane AR. Exercise and the regulation of endocrine hormones.  
 1982 *Prog Mol Biol Transl Sci* 2015;**135**:293-311.
- 1983 267. Kraemer WJ, Ratamess NA, Hymer WC, Nindl BC, Fragala MS. Growth  
 1984 hormone(s), testosterone, insulin-like growth factors, and cortisol: Roles and  
 1985 integration for cellular development and growth with exercise. *Front*  
 1986 *Endocrinol (Lausanne)* 2020;**11**:33.
- 1987 268. Yaribeygi H, Atkin SL, Simental-Mendia LE, Sahebkar A. Molecular  
 1988 mechanisms by which aerobic exercise induces insulin sensitivity. *J Cell*  
 1989 *Physiol* 2019;**234**:12385-92.
- 1990 269. Hamasaki H. Interval exercise therapy for type 2 diabetes. *Curr Diabetes Rev*  
 1991 2018;**14**:129-37.
- 1992 270. Hackney AC, Davis HC, Lane AR. Growth hormone-insulin-like growth factor  
 1993 axis, thyroid axis, prolactin, and exercise. *Front Horm Res* 2016;**47**:1-11.
- 1994 271. Janssen JA. Impact of physical exercise on endocrine aging. *Front Horm Res*  
 1995 2016;**47**:68-81.
- 1996 272. Nieman DC, Pence BD. Exercise immunology: Future directions. *J Sport*  
 1997 *Health Sci* 2020;**9**:432-45.
- 1998 273. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl*  
 1999 *Physiol (1985)* 2005;**98**:1154-62.

- 2000 274. Campbell JP, Turner JE. Debunking the myth of exercise-induced immune  
2001 suppression: Redefining the impact of exercise on immunological health across  
2002 the lifespan. *Front Immunol* 2018;**9**:648.
- 2003 275. Weyh C, Kruger K, Strasser B. Physical activity and diet shape the immune  
2004 system during aging. *Nutrients* 2020;**12**.
- 2005 276. Rinninella E, Raoul P, Cintoni M, et al. What is the healthy gut microbiota  
2006 composition? A changing ecosystem across age, environment, diet, and diseases.  
2007 *Microorganisms* 2019;**7**.
- 2008 277. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the  
2009 neonatal gastrointestinal tract. *Am J Clin Nutr* 1999;**69**:1035S-45S.
- 2010 278. Clauss M, Gerard P, Mosca A, Leclerc M. Interplay between exercise and gut  
2011 microbiome in the context of human health and performance. *Front Nutr*  
2012 2021;**8**:637010.
- 2013 279. Bai J, Hu Y, Bruner DW. Composition of gut microbiota and its association with  
2014 body mass index and lifestyle factors in a cohort of 7-18 years old children from  
2015 the american gut project. *Pediatr Obes* 2019;**14**:e12480.
- 2016 280. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic  
2017 interactions. *Science* 2012;**336**:1262-7.
- 2018 281. Zhou Q, Deng J, Pan X, et al. Gut microbiome mediates the protective effects  
2019 of exercise after myocardial infarction. *Microbiome* 2022;**10**:82.
- 2020 282. Pardon MC. Hormesis is applicable as a pro-healthy aging intervention in  
2021 mammals and human beings. *Dose Response* 2009;**8**:22-7.
- 2022 283. Merry TL, Ristow M. Mitohormesis in exercise training. *Free Radic Biol Med*  
2023 2016;**98**:123-30.
- 2024 284. Ristow M, Zarse K. How increased oxidative stress promotes longevity and

- 2025 metabolic health: The concept of mitochondrial hormesis (mitohormesis). *Exp*  
2026 *Gerontol* 2010;**45**:410-8.
- 2027 285. Gomez-Cabrera MC, Salvador-Pascual A, Cabo H, Ferrando B, Vina J. Redox  
2028 modulation of mitochondriogenesis in exercise. Does antioxidant  
2029 supplementation blunt the benefits of exercise training? *Free Radic Biol Med*  
2030 2015;**86**:37-46.
- 2031 286. Kasai S, Shimizu S, Tatara Y, Mimura J, Itoh K. Regulation of nrf2 by  
2032 mitochondrial reactive oxygen species in physiology and pathology.  
2033 *Biomolecules* 2020;**10**.
- 2034 287. Kang GM, Min SH, Lee CH, et al. Mitohormesis in hypothalamic pomc neurons  
2035 mediates regular exercise-induced high-turnover metabolism. *Cell Metab*  
2036 2021;**33**:334-49 e6.
- 2037 288. Kennedy BK, Berger SL, Brunet A, et al. Geroscience: Linking aging to chronic  
2038 disease. *Cell* 2014;**159**:709-13.
- 2039 289. Sarzynski MA, Ghosh S, Bouchard C. Genomic and transcriptomic predictors  
2040 of response levels to endurance exercise training. *J Physiol* 2017;**595**:2931-9.
- 2041 290. Gremeaux V, Gayda M, Lepers R, Sosner P, Juneau M, Nigam A. Exercise and  
2042 longevity. *Maturitas* 2012;**73**:312-7.
- 2043 291. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, et al. Exercise attenuates  
2044 the major hallmarks of aging. *Rejuvenation Res* 2015;**18**:57-89.
- 2045 292. Lehnig AC, Stanford KI. Exercise-induced adaptations to white and brown  
2046 adipose tissue. *J Exp Biol* 2018;**221**.
- 2047 293. Stanford KI, Middelbeek RJ, Townsend KL, et al. A novel role for subcutaneous  
2048 adipose tissue in exercise-induced improvements in glucose homeostasis.  
2049 *Diabetes* 2015;**64**:2002-14.

- 2050 294. Stanford KI, Middelbeek RJ, Goodyear LJ. Exercise effects on white adipose  
2051 tissue: Beiging and metabolic adaptations. *Diabetes* 2015;**64**:2361-8.
- 2052 295. Guan Y, Yan Z. Molecular mechanisms of exercise and healthspan. *Cells*  
2053 2022;**11**.
- 2054 296. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of  
2055 moderate to vigorous intensity and mortality: A large pooled cohort analysis.  
2056 *PLoS Med* 2012;**9**:e1001335.
- 2057 297. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality:  
2058 A detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*  
2059 2015;**175**:959-67.
- 2060 298. Carapeto PV, Aguayo-Mazzucato C. Effects of exercise on cellular and tissue  
2061 aging. *Aging (Albany NY)* 2021;**13**:14522-43.
- 2062 299. Su Y, Wang T, Wu N, et al. Alpha-ketoglutarate extends drosophila lifespan by  
2063 inhibiting mtor and activating ampk. *Aging (Albany NY)* 2019;**11**:4183-97.
- 2064 300. Liu H, Ding J, Kohnlein K, et al. The gid ubiquitin ligase complex is a regulator  
2065 of ampk activity and organismal lifespan. *Autophagy* 2020;**16**:1618-34.
- 2066 301. Viollet B, Lantier L, Devin-Leclerc J, et al. Targeting the ampk pathway for the  
2067 treatment of type 2 diabetes. *Front Biosci (Landmark Ed)* 2009;**14**:3380-400.
- 2068 302. Ballin M, Nordstrom P. Does exercise prevent major non-communicable  
2069 diseases and premature mortality? A critical review based on results from  
2070 randomized controlled trials. *J Intern Med* 2021;**290**:1112-29.
- 2071 303. Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-ohdg: A marker of oxidative  
2072 stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. *Clin*  
2073 *Chim Acta* 2004;**339**:1-9.
- 2074 304. Ayala-Pena S. Role of oxidative DNA damage in mitochondrial dysfunction and

- 2075           huntington's disease pathogenesis. *Free Radic Biol Med* 2013;**62**:102-10.
- 2076   305.   Radak Z, Naito H, Kaneko T, et al. Exercise training decreases DNA damage  
2077           and increases DNA repair and resistance against oxidative stress of proteins in  
2078           aged rat skeletal muscle. *Pflugers Arch* 2002;**445**:273-8.
- 2079   306.   Schmidt RH, Nickerson JM, Boatright JH. Exercise as gene therapy: Bdnf and  
2080           DNA damage repair. *Asia Pac J Ophthalmol (Phila)* 2016;**5**:309-11.
- 2081   307.   Vilela TC, de Andrade VM, Radak Z, de Pinho RA. The role of exercise in brain  
2082           DNA damage. *Neural Regen Res* 2020;**15**:1981-5.
- 2083   308.   Wagner KH, Reichhold S, Neubauer O. Impact of endurance and ultraendurance  
2084           exercise on DNA damage. *Ann N Y Acad Sci* 2011;**1229**:115-23.
- 2085   309.   Williamson J, Hughes CM, Burke G, Davison GW. A combined gamma-h2ax  
2086           and 53bp1 approach to determine the DNA damage-repair response to exercise  
2087           in hypoxia. *Free Radic Biol Med* 2020;**154**:9-17.
- 2088   310.   Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease.  
2089           *Science* 2002;**296**:1991-5.
- 2090   311.   Davis AA, Leysn CEG, Holtzman DM. Intercellular spread of protein  
2091           aggregates in neurodegenerative disease. *Annu Rev Cell Dev Biol* 2018;**34**:545-  
2092           68.
- 2093   312.   Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill.  
2094           *Physiology (Bethesda)* 2013;**28**:330-58.
- 2095   313.   Musci RV, Hamilton KL, Miller BF. Targeting mitochondrial function and  
2096           proteostasis to mitigate dynapenia. *Eur J Appl Physiol* 2018;**118**:1-9.
- 2097   314.   Bhuiyan MS, Pattison JS, Osinska H, et al. Enhanced autophagy ameliorates  
2098           cardiac proteinopathy. *J Clin Invest* 2013;**123**:5284-97.
- 2099   315.   Liu Q, Chen L, Liang X, et al. Exercise attenuates angiotensin-induced muscle

- 2100 atrophy by targeting pparggamma/mir-29b. *J Sport Health Sci* 2021.
- 2101 316. Dokladny K, Myers OB, Moseley PL. Heat shock response and autophagy--  
2102 cooperation and control. *Autophagy* 2015;**11**:200-13.
- 2103 317. Campos JC, Baehr LM, Gomes KMS, et al. Exercise prevents impaired  
2104 autophagy and proteostasis in a model of neurogenic myopathy. *Sci Rep*  
2105 2018;**8**:11818.
- 2106 318. Toth A, Nickson P, Mandl A, Bannister ML, Toth K, Erhardt P. Endoplasmic  
2107 reticulum stress as a novel therapeutic target in heart diseases. *Cardiovasc*  
2108 *Hematol Disord Drug Targets* 2007;**7**:205-18.
- 2109 319. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of  
2110 metabolic disease. *Cell* 2010;**140**:900-17.
- 2111 320. Bozi LH, Jannig PR, Rolim N, et al. Aerobic exercise training rescues cardiac  
2112 protein quality control and blunts endoplasmic reticulum stress in heart failure  
2113 rats. *J Cell Mol Med* 2016;**20**:2208-12.
- 2114 321. Chang P, Zhang X, Zhang M, et al. Swimming exercise inhibits myocardial er  
2115 stress in the hearts of aged mice by enhancing cgmpk signaling. *Mol Med Rep*  
2116 2020;**21**:549-56.
- 2117 322. Khadir A, Kavalakatt S, Abubaker J, et al. Physical exercise alleviates er stress  
2118 in obese humans through reduction in the expression and release of grp78  
2119 chaperone. *Metabolism* 2016;**65**:1409-20.
- 2120 323. Hong J, Hong SG, Lee J, et al. Exercise training ameliorates cerebrovascular  
2121 dysfunction in a murine model of alzheimer's disease: Role of the p2y2 receptor  
2122 and endoplasmic reticulum stress. *Am J Physiol Heart Circ Physiol*  
2123 2020;**318**:H1559-H69.
- 2124 324. Jin S, Li L, Ren Z, Li J, Wang R, Ding H. Fam134b-mediated er-phagy

- 2125 alleviates endoplasmic reticulum stress of rat soleus muscle in response to acute  
2126 exercise. *Gen Physiol Biophys* 2022;**41**:71-8.
- 2127 325. Wang SF, Chen S, Tseng LM, Lee HC. Role of the mitochondrial stress response  
2128 in human cancer progression. *Exp Biol Med (Maywood)* 2020;**245**:861-78.
- 2129 326. Zhang Y, Oliveira AN, Hood DA. The intersection of exercise and aging on  
2130 mitochondrial protein quality control. *Exp Gerontol* 2020;**131**:110824.
- 2131 327. Memme JM, Oliveira AN, Hood DA. Chronology of upr activation in skeletal  
2132 muscle adaptations to chronic contractile activity. *Am J Physiol Cell Physiol*  
2133 2016;**310**:C1024-36.
- 2134 328. Kim KH, Son JM, Benayoun BA, Lee C. The mitochondrial-encoded peptide  
2135 mots-c translocates to the nucleus to regulate nuclear gene expression in  
2136 response to metabolic stress. *Cell Metab* 2018;**28**:516-24 e7.
- 2137 329. Woodhead JST, Merry TL. Mitochondrial-derived peptides and exercise.  
2138 *Biochim Biophys Acta Gen Subj* 2021;**1865**:130011.
- 2139 330. Rajawat YS, Hilioti Z, Bossis I. Aging: Central role for autophagy and the  
2140 lysosomal degradative system. *Ageing Res Rev* 2009;**8**:199-213.
- 2141 331. Tassi C, Mancuso F, Gambelunghe C, et al. Beta-n-acetylhexosaminidase  
2142 activity and isoenzyme profile in the kidney and urine of trained rats.  
2143 *Immunopharmacol Immunotoxicol* 2001;**23**:573-83.
- 2144 332. Salminen A, Hongisto K, Vihko V. Lysosomal changes related to exercise  
2145 injuries and training-induced protection in mouse skeletal muscle. *Acta Physiol*  
2146 *Scand* 1984;**120**:15-9.
- 2147 333. Guo R, Yu Q, Liang EC, Fung ML, Tipoe GL. Cathepsin-b dependent  
2148 autophagy ameliorates steatohepatitis in chronic exercise rats. *Histol*  
2149 *Histopathol* 2020;**35**:833-47.

- 2150 334. Triolo M, Hood DA. Mitochondrial breakdown in skeletal muscle and the  
2151 emerging role of the lysosomes. *Arch Biochem Biophys* 2019;**661**:66-73.
- 2152 335. Bernardo BC, Ooi JYY, Weeks KL, Patterson NL, McMullen JR. Understanding  
2153 key mechanisms of exercise-induced cardiac protection to mitigate disease:  
2154 Current knowledge and emerging concepts. *Physiol Rev* 2018;**98**:419-75.
- 2155 336. Nakamura M, Sadoshima J. Mechanisms of physiological and pathological  
2156 cardiac hypertrophy. *Nat Rev Cardiol* 2018;**15**:387-407.
- 2157 337. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anza C. Exercise and heart  
2158 failure: An update. *ESC Heart Fail* 2018;**5**:222-32.
- 2159 338. Wang H, Xie Y, Guan L, Elkin K, Xiao J. Targets identified from exercised heart:  
2160 Killing multiple birds with one stone. *NPJ Regen Med* 2021;**6**:23.
- 2161 339. Bei Y, Huang Z, Feng X, et al. Lymphangiogenesis contributes to exercise-  
2162 induced physiological cardiac growth. *J Sport Health Sci* 2022.
- 2163 340. Bass-Stringer S, Tai CMK, McMullen JR. Igf1-pi3k-induced physiological  
2164 cardiac hypertrophy: Implications for new heart failure therapies, biomarkers,  
2165 and predicting cardiotoxicity. *J Sport Health Sci* 2020.
- 2166 341. Le Moal E, Pialoux V, Juban G, et al. Redox control of skeletal muscle  
2167 regeneration. *Antioxid Redox Signal* 2017;**27**:276-310.
- 2168 342. Nader GA, Esser KA. Intracellular signaling specificity in skeletal muscle in  
2169 response to different modes of exercise. *J Appl Physiol (1985)* 2001;**90**:1936-  
2170 42.
- 2171 343. Chen Z, Li L, Wu W, et al. Exercise protects proliferative muscle satellite cells  
2172 against exhaustion via the igfbp7-akt-mtor axis. *Theranostics* 2020;**10**:6448-66.
- 2173 344. Zhang J, Yuan T, Wang JH. Moderate treadmill running exercise prior to tendon  
2174 injury enhances wound healing in aging rats. *Oncotarget* 2016;**7**:8498-512.



- 2175 345. Kawanishi N, Yano H, Yokogawa Y, Suzuki K. Exercise training inhibits  
2176 inflammation in adipose tissue via both suppression of macrophage infiltration  
2177 and acceleration of phenotypic switching from m1 to m2 macrophages in high-  
2178 fat-diet-induced obese mice. *Exerc Immunol Rev* 2010;**16**:105-18.
- 2179 346. Baker JM, De Lisio M, Parise G. Endurance exercise training promotes  
2180 medullary hematopoiesis. *FASEB J* 2011;**25**:4348-57.
- 2181 347. Zhang H, Chen T, Ren J, et al. Pre-operative exercise therapy triggers anti-  
2182 inflammatory trained immunity of kupffer cells through metabolic  
2183 reprogramming. *Nat Metab* 2021;**3**:843-58.
- 2184 348. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of  
2185 skeletal muscle adaptation. *Cell Metab* 2013;**17**:162-84.
- 2186 349. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: The  
2187 evidence. *CMAJ* 2006;**174**:801-9.
- 2188 350. Koelwyn GJ, Zhuang X, Tammela T, Schietinger A, Jones LW. Exercise and  
2189 immunometabolic regulation in cancer. *Nat Metab* 2020;**2**:849-57.
- 2190 351. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent  
2191 regulation of the tumour microenvironment. *Nat Rev Cancer* 2017;**17**:620-32.
- 2192 352. Vermillion SA, James A, Dorrell RD, et al. Preoperative exercise therapy for  
2193 gastrointestinal cancer patients: A systematic review. *Syst Rev* 2018;**7**:103.
- 2194 353. Nakajima H, Yokoyama Y, Inoue T, et al. Clinical benefit of preoperative  
2195 exercise and nutritional therapy for patients undergoing hepato-pancreato-  
2196 biliary surgeries for malignancy. *Ann Surg Oncol* 2019;**26**:264-72.
- 2197 354. Pouwels S, Stokmans RA, Willigendael EM, et al. Preoperative exercise therapy  
2198 for elective major abdominal surgery: A systematic review. *Int J Surg*  
2199 2014;**12**:134-40.

2200 355. Xiao J, Rosenzweig A. Exercise and cardiovascular protection: Update and  
2201 future. *J Sport Health Sci* 2021;**10**:607-8.

2202 356. Bei Y, Wang L, Ding R, et al. Animal exercise studies in cardiovascular research:  
2203 Current knowledge and optimal design-a position paper of the committee on  
2204 cardiac rehabilitation, chinese medical doctors' association. *J Sport Health Sci*  
2205 2021.

2206

2207

2208

2209

2210

2211

2212

2213

2214

2215

2216

2217

2218

2219

2220

2221

2222

2223

2224

2225 **Figure legends**

2226

2227 Fig. 1. Summary of the main regulatory mechanisms by which exercise sustains health.

2228 Exercise impacts the major hallmarks of health, including the integrity of barriers,

2229 containment of local perturbations, recycling and turnover, integration of circuitries,

2230 rhythmic oscillations, homeostatic resilience, hormetic regulation, as well as repair and

2231 regeneration.

2232

2233 Fig. 2. Effects of exercise on the integrity of barriers and the underlying mechanisms.

2234 The biological changes of barriers through which exercise sustains health. FABPpm =

2235 plasma membrane fatty acid-binding protein; FAT = fatty acid translocase; HMGB1 =

2236 high mobility group box 1; IL-15 = interleukin-15; Mst1 = mammalian sterile 20-like

2237 kinase 1; NF- $\kappa$ B = nuclear factor-kappa B; NPC = nuclear pore complex; PECAM-1 =

2238 platelet and endothelial cell adhesion molecule 1; REDD1 = regulated in development

2239 and DNA damage 1; TLR4 = toll-like receptors 4.

2240

2241 Fig. 3. Benefits of exercise on the maintenance of local homeostasis and the involved

2242 mechanisms. Regular exercise at moderate intensity generally contributes to the

2243 maintenance of systemic homeostasis. ACE2 = angiotensin-converting enzyme 2; IFN $\gamma$

2244 = interferon- $\gamma$ ; IL = interleukin; miR = microRNA; NK cells = natural killer cells;

2245 TMPRSS2 = transmembrane protease serine 2; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ ; WBC

2246 = white blood cell counts.

2247

2248 Fig. 4. Benefits of exercise for recycling and turnover. (A) The critical regulators and

2249 signaling pathways involved in the positive effects of exercise on cellular remodeling,

2250 including cell proliferation, cell growth, cell survival, and cell death. (B) The regulation  
2251 of autophagy during exercise training. The common regulatory pathways underlying  
2252 exercise-induced autophagy involve the activation of AMPK-ULK1 signaling pathway,  
2253 FoxO and PGC1 $\alpha$ , etc. AMPK = adenosine monophosphate-activated protein kinase;  
2254 ASK1 = apoptosis signal-regulating kinase 1; BDNF = brain-derived neurotrophic  
2255 factor; cAMP = cyclic adenosine monophosphate; C/EBP $\beta$  = CCAAT/enhancer-  
2256 binding protein  $\beta$ ; CITED4 = CBP/p300-interacting transactivators with E (glutamic  
2257 acid)/D (aspartic acid)-rich-carboxyl terminal domain; CPhar = cardiac physiological  
2258 hypertrophy-associated regulator; eNOS = endothelial nitric oxide synthase; FoxO =  
2259 forkhead box O; IGF1 = insulin-like growth factor 1; miR = microRNA; PGC1 $\alpha$ ,  
2260 peroxisome-proliferator-activated receptor coactivator 1 $\alpha$ ; PI3K = phosphoinositide 3-  
2261 kinase; SIRT1 = sirtuin 1; TERT = telomerase reverse transcriptase; ULK1 = unc-51-  
2262 like kinase 1.

2263

2264 Fig. 5. Exercise has systemic effects. Exercise leads to systemic effects by evoking the  
2265 coordinated and integrated adaptation of multiple organ systems. Exercise results in the  
2266 secretion of myokines, adipokines (e.g., TGF $\beta$ , leptin) and hepatokines as well as by-  
2267 products of gut microbiota (e.g., SCFA) that have key roles in interorgan  
2268 communication and, thus, mediate many of the beneficial effects of exercise. 5-HT =  
2269 serotonin; FGF21 = fibroblast growth factor-21; GDF15 = growth differentiation  
2270 factor-15; HSP72 = heat shock protein 72; SCFA = short-chain fatty acids; SIRT1 =  
2271 sirtuin 1; TGF $\beta$  = transforming growth factor- $\beta$ .

2272

2273 Fig. 6. Exercise-associated beneficial adaptations in response to stress. Exercise confers  
2274 multiple health benefits via different strategies, including improving resilience,

2275 hormetic regulation, and modulating the process of repair and regeneration in response  
2276 to damage. ER = endoplasmic erticulum; UPR<sup>mt</sup> = mitochondrial unfolded protein  
2277 responses.

2278

2279 Fig. 7. Regular exercise confers multiple health benefits and better survival. The  
2280 adaptations in multiple tissues and organ systems contribute to the maintenance of  
2281 whole-body health. AMPK = adenosine monophosphate-activated protein kinase;  
2282 BDNF = brain-derived neurotrophic factor; CaMK = calcium/calmodulin-dependent  
2283 protein kinase; GPx = glutathione peroxidase; IGF1 = insulin-like growth factor 1;  
2284 MAPK = mitogen-activated protein kinase; NGF = nerve growth factor; NK cells =  
2285 natural killer cells; NO = nitric oxide; PGC1 $\alpha$  = peroxisome-proliferator-activated  
2286 receptor coactivator 1 $\alpha$ ; SIRT6 = sirtuins; SOD = superoxide dismutase; VEGF =  
2287 vascular endothelial growth factor; VEGFA = vascular endothelial growth factor A;  
2288 VEGFR3 = vascular endothelial growth factor receptor 3.

2289

2290

2291

2292

2293

2294

2295

2296

2297

2298

2299

2300 Table 1. The detailed exercise protocols in human studies cited in this review.

2301

2302 Table 2. Effects of exercise on health outcomes in humans with different conditions.

2303

2304

2305

2306

2307

2308

2309

2310

2311

2312

2313

2314

2315

2316

2317

2318

2319

2320

2321

2322

2323

2324

2325 **Supplementary material**

2326

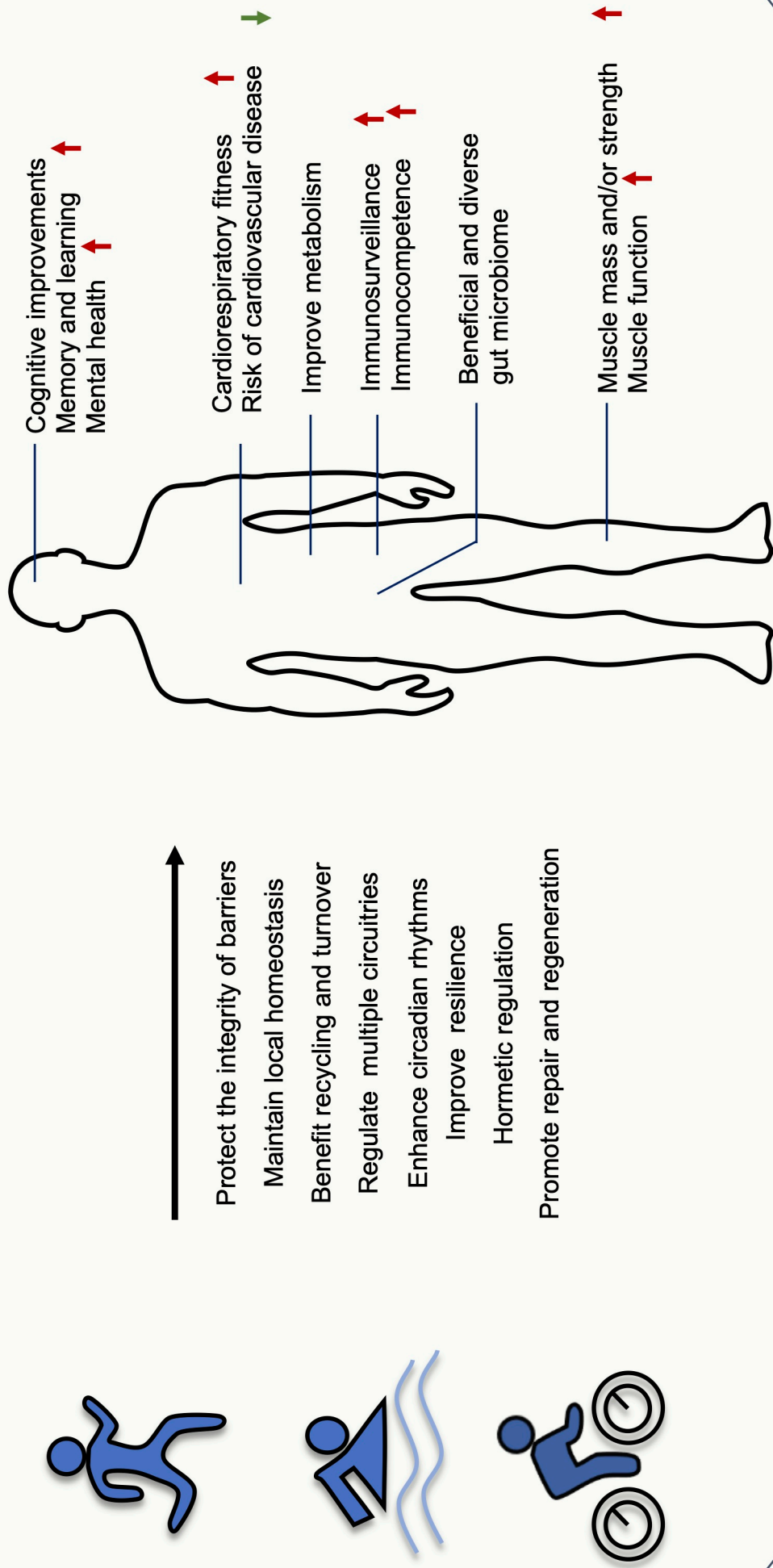
2327 Supplementary Table 1. The detailed exercise protocols in animal studies cited in this

2328 review.

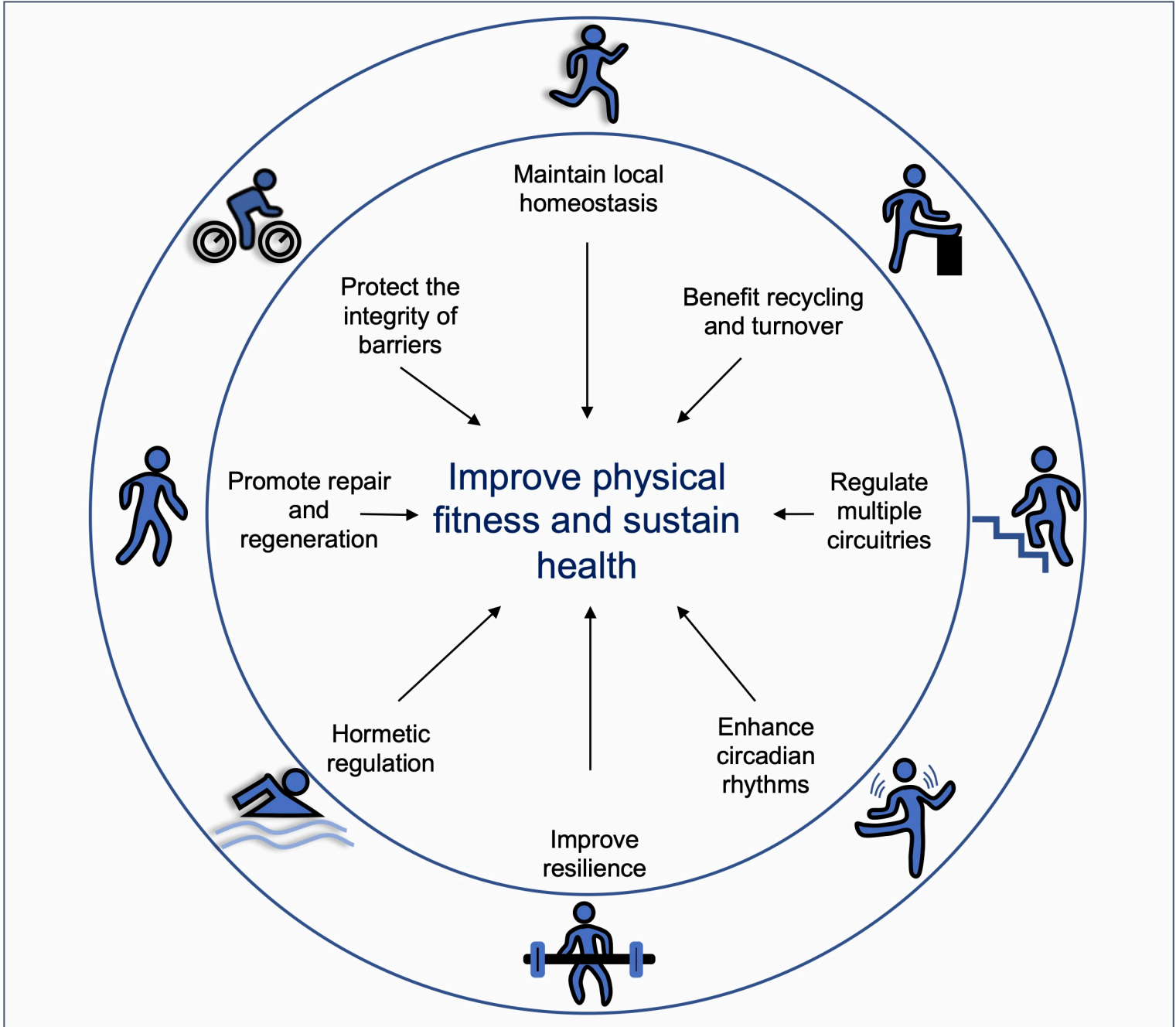
2329

2330

# Exercise sustains the hallmarks of health





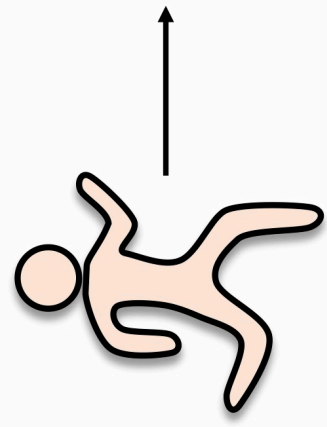
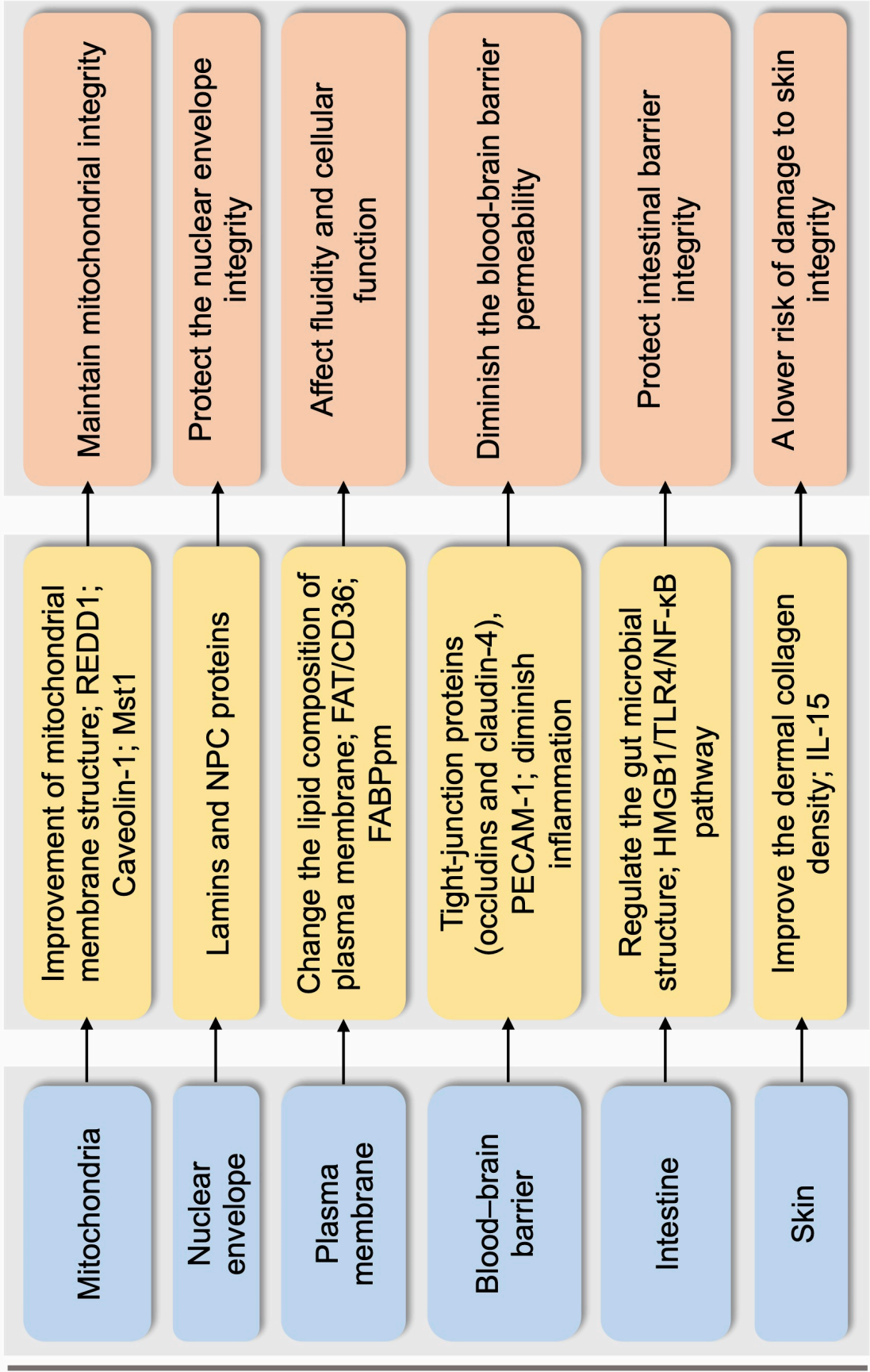


**Fig.1**

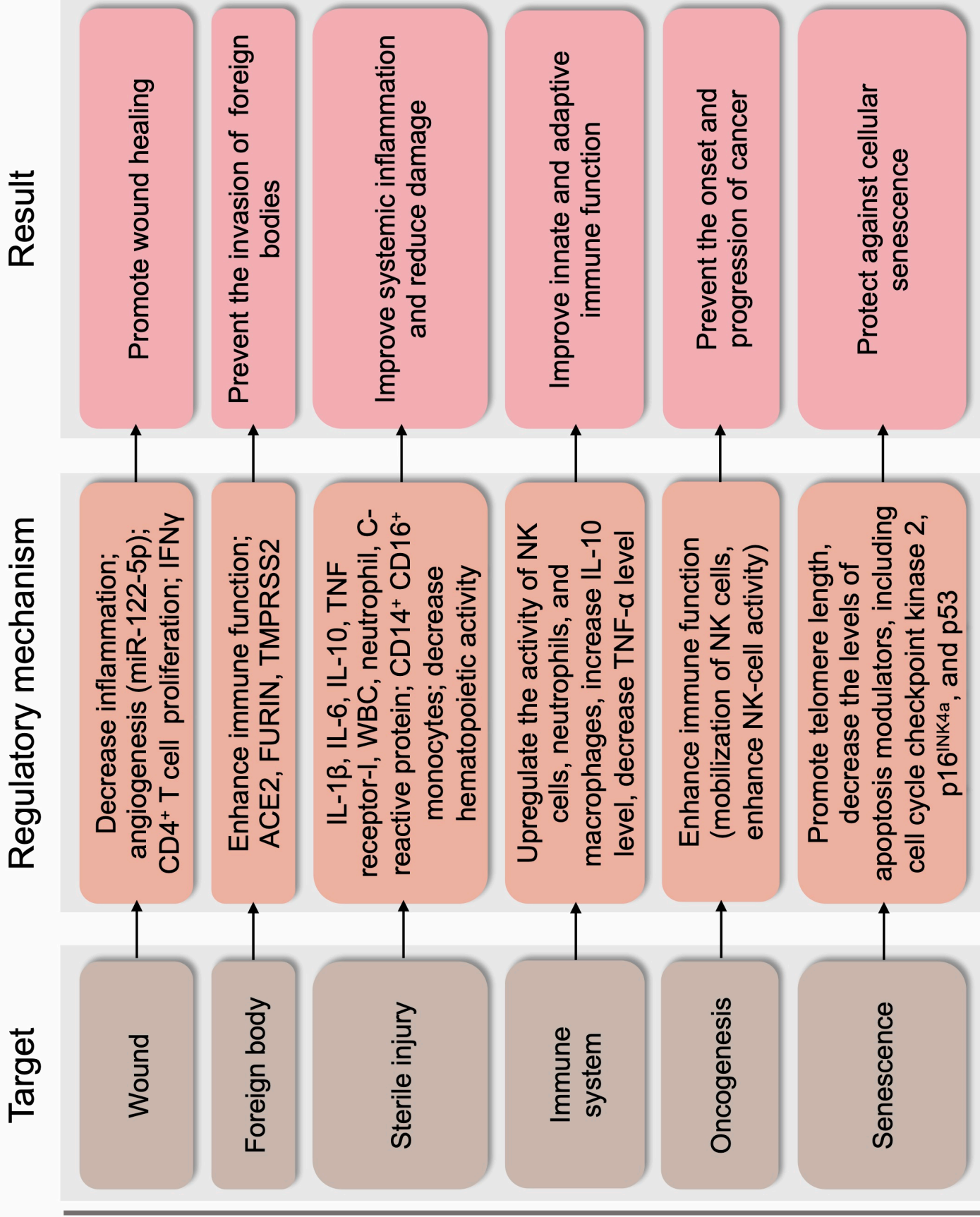
**Outcome**

**Regulatory mechanism**

**Barrier**

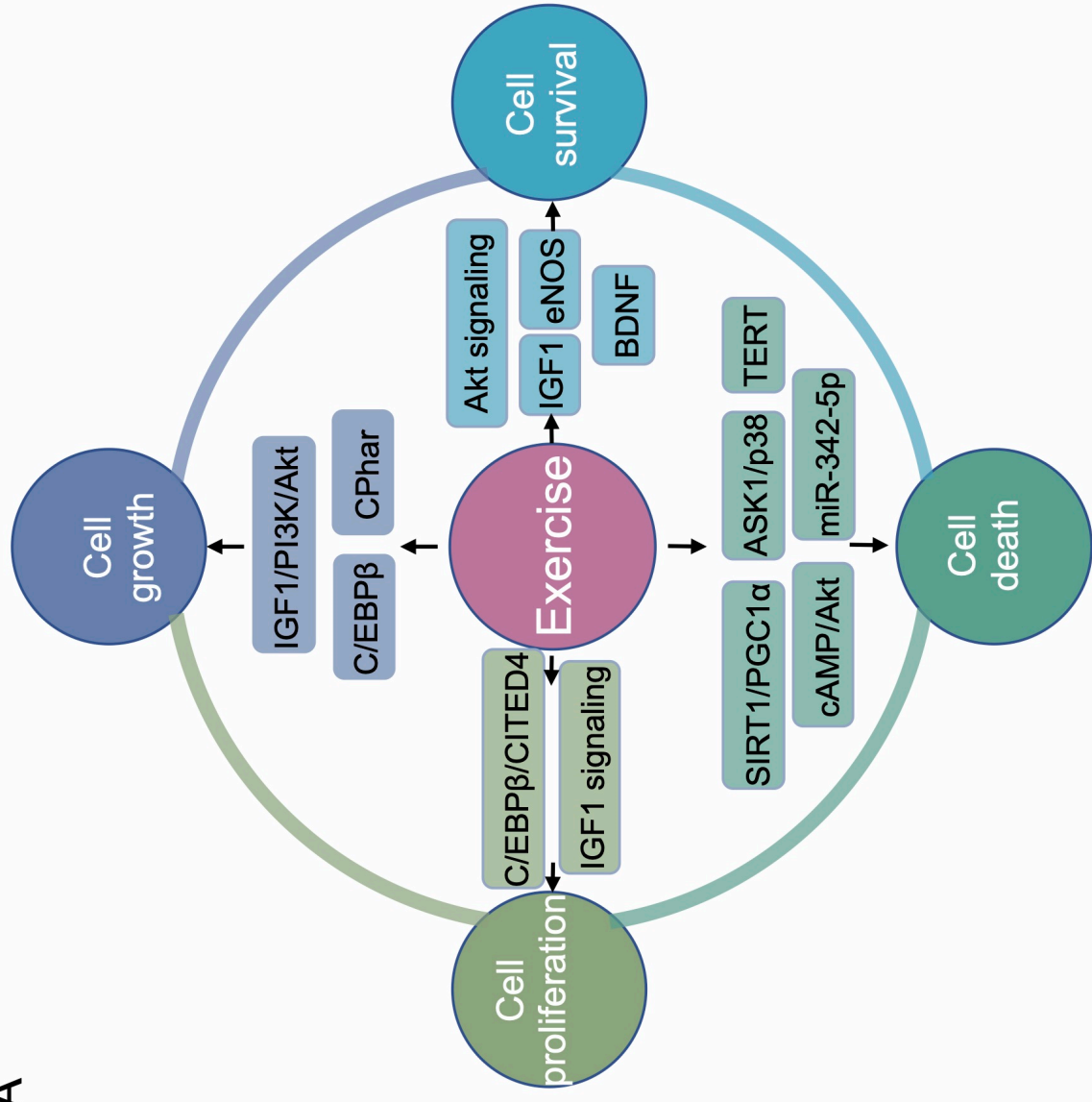


**Fig.2**



**Fig.3**

A



B

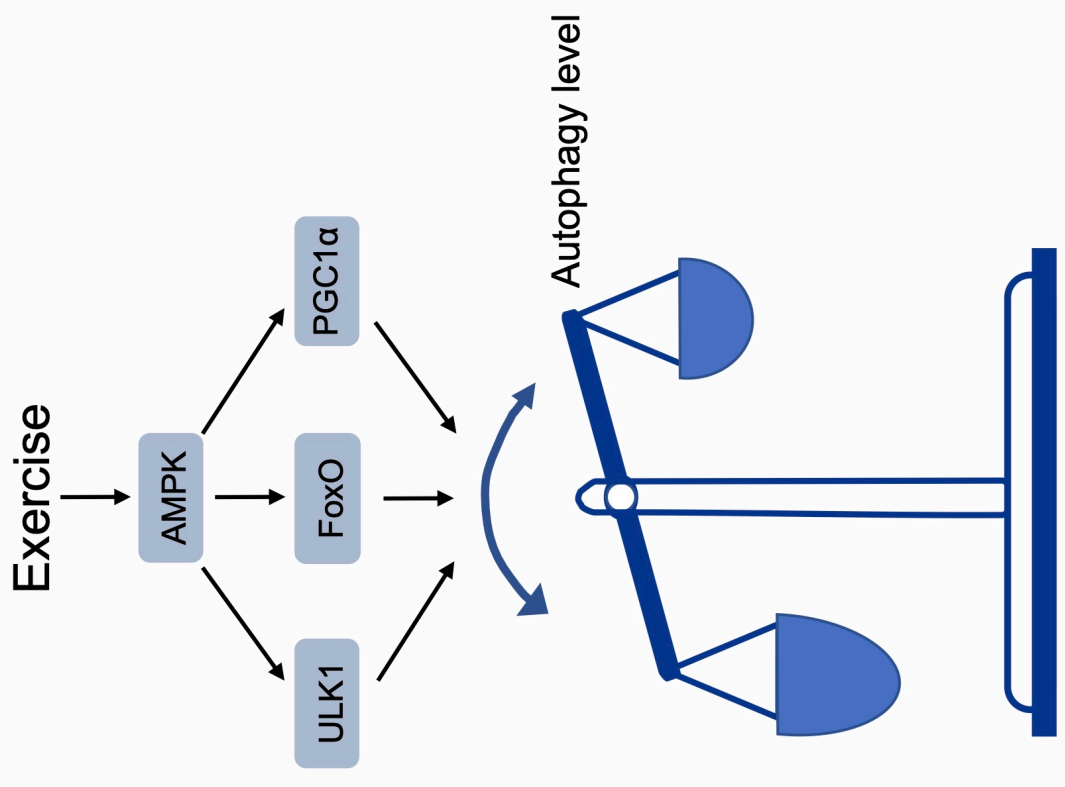
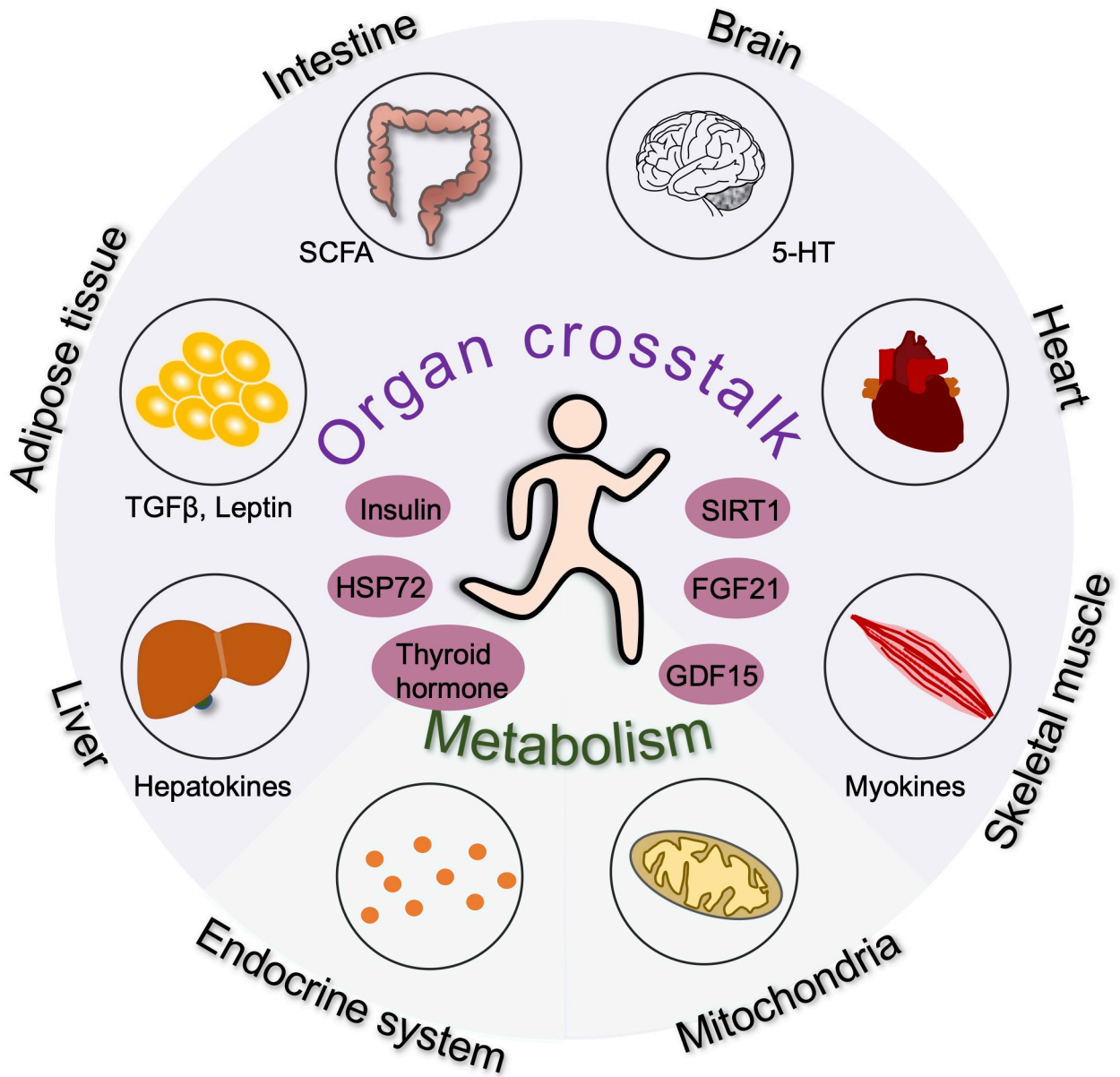
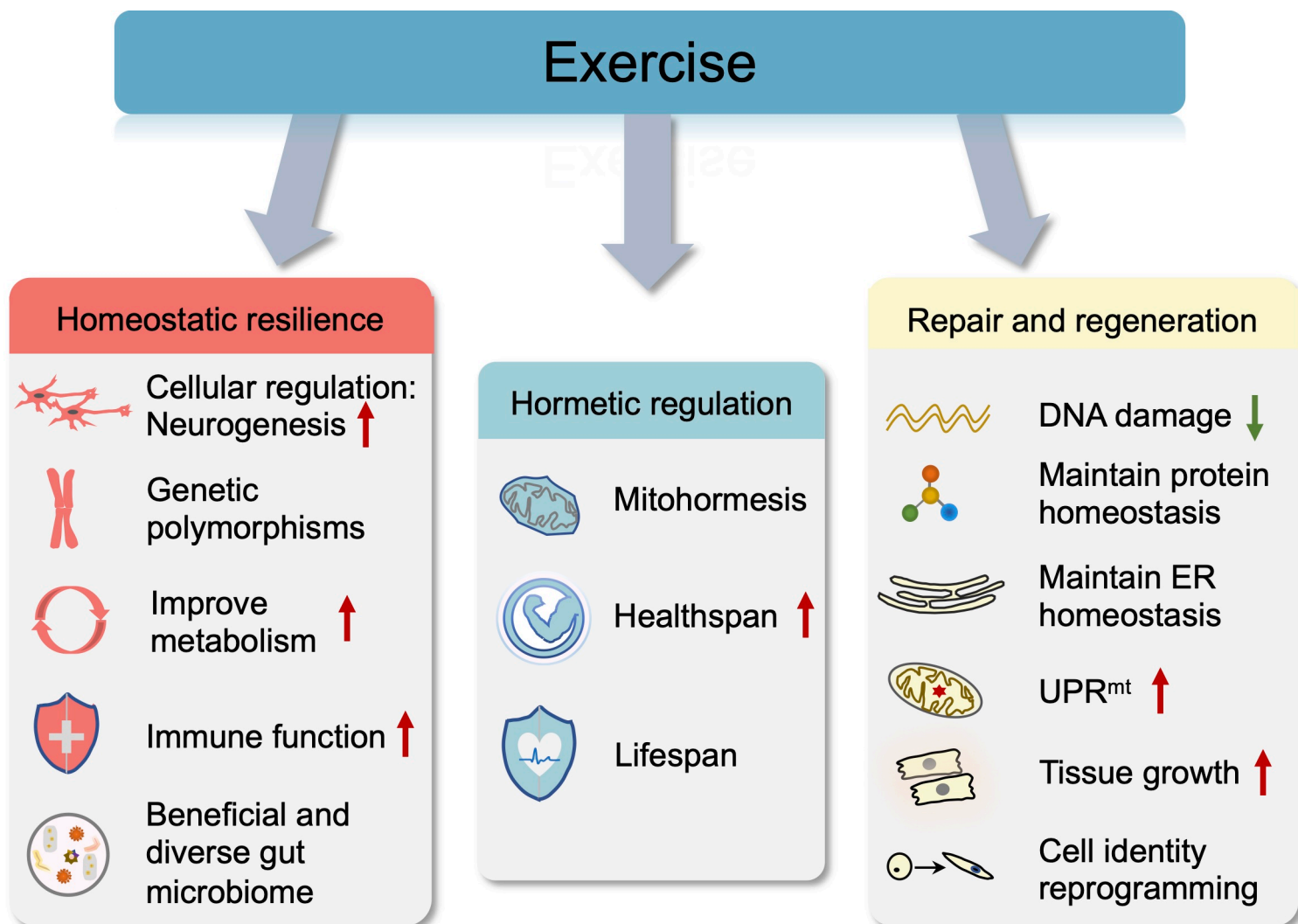


Fig.4

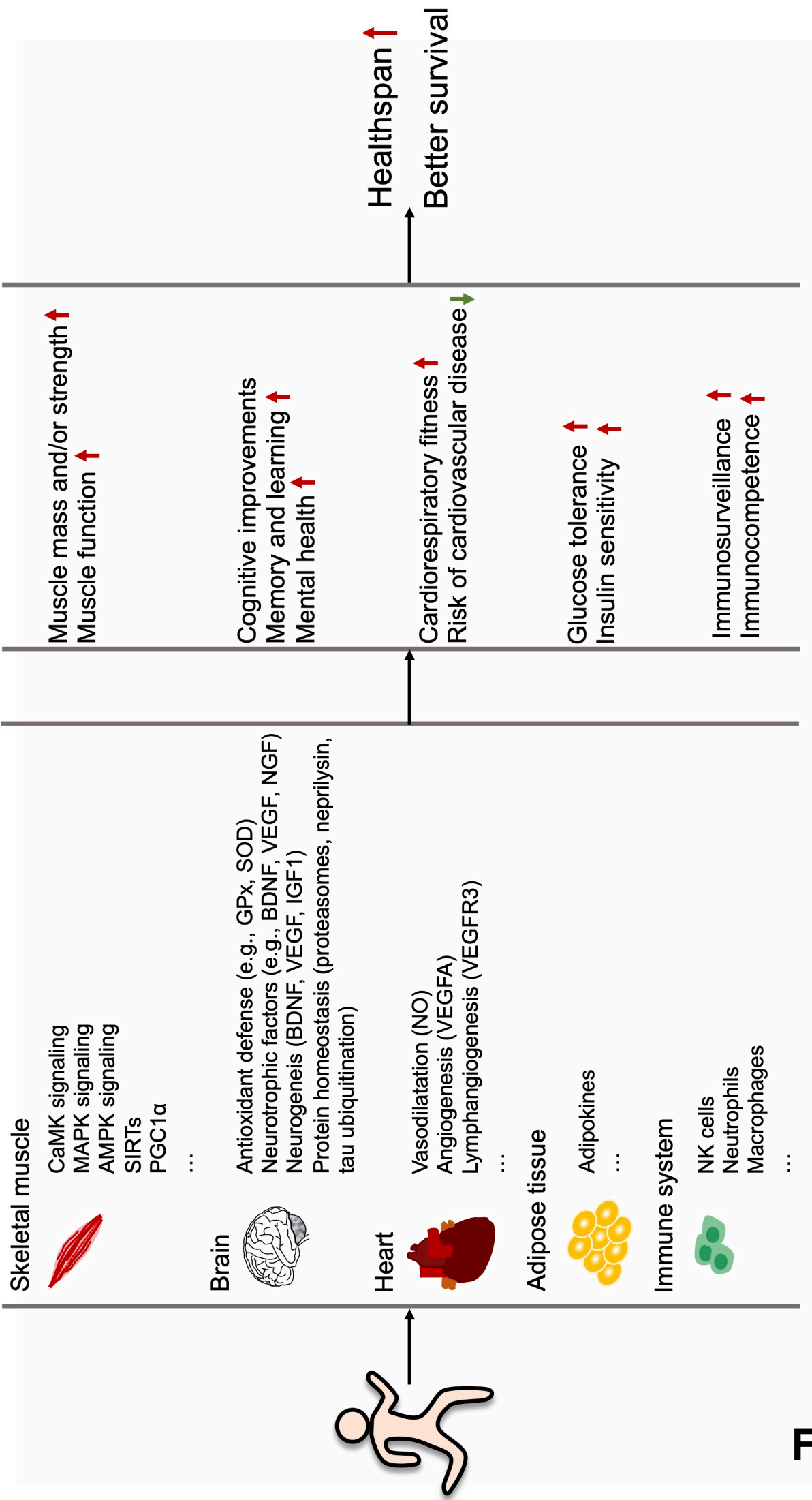


**Fig.5**





**Fig.6**



**Fig.7**

Table 1. The detailed exercise protocols in human studies cited in this review.

Reference	Exercise protocols	Subject	Effect	Mechanism
51	120 min cycling at 60% VO <sub>2</sub> max, which is determined by an incremental ride to exhaustion on a cycle ergometer	Human	Increase fatty acid transport	Increase FAT/CD36 and FABPpm
61	1 h of treadmill running at 80% VO <sub>2</sub> max, 0% grade	Human	Increase small intestinal permeability	/
62	A standard marathon (42.16 km)	Human	Increase intestinal permeability	/
64	Two 1-h-long bouts of submaximal treadmill exercise at 65% VO <sub>2</sub> max	Human	Increase gut barrier permeability	/
95	45 min cycling (start with 30 min cycling at 65% of HR <sub>max</sub> and progressed by 5% every other week until intensity reached 75% of HR <sub>max</sub> ), twice per week for 12 weeks	Human (65-86 years old)	Attenuate skin aging and enhance mitochondrial biogenesis	Increase IL-15 level
116	12 weeks combined endurance (20 min treadmill walking at 70-80% heart-rate reserve) and resistance exercise (8 sets of exercises, 2 sets at 70-80% of one-repetition maximum, 30 min), 3 days/week	Human (65-80 years old)	Reduced systemic inflammation	Reductions in CD14 <sup>+</sup> CD16 <sup>+</sup> monocytes
126	1-h cycling at 70% of VO <sub>2</sub> max	Human	Increased levels of inflammatory gene	/



138	Three 30-min bouts of cycling exercise at -5%, +5%, or +15% of lactate threshold	Human	Augment cytotoxicity against tumor cells	Enhanced NK cell activity
188	Marathon (a 42.2-km running race)	Athlete	Increased plasma level of GDF15	Changes in circulating immune cells levels
190	1 h cycling exercise at 67% of VO <sub>2</sub> max	Human	Increased plasma level of GDF15	/
234	Maximal exercise test, start cycling with a 75 W load for 3 min (warm-up stage) followed by increments of 25 W every 3 min until volitional exhaustion	Human	Significant modulation of clock genes in effector-memory CD4 <sup>+</sup> T cells	/
322	3 months of moderate exercise involves a combination of treadmill or cycling, each exercise session included 10 min warm-up and cool-down steps at 50%-60% of HR <sub>max</sub> , along with 40 min of the prescribed exercise program at 65%-80% of HR <sub>max</sub> , 3 times/week	Obese human subject (30 kg/m <sup>2</sup> ≤ BMI < 40 kg/m <sup>2</sup> )	Alleviate obesity-related ER stress	Downregulate GPR78 signaling

Note: “/” stands for “unknown”.

Abbreviations: BMI = body mass index; ER = endoplasmic reticulum; FABPpm = plasma membrane fatty acid-binding protein; FAT = fatty acid translocase; GDF15 = growth differentiation factor-15; GRP78 = glucose-regulated protein 78; HRmax = maximal heart rate; IL-15 = interleukin-15; NK cell = natural killer cell; VO<sub>2</sub>max = maximal O<sub>2</sub> uptake; W = watt.

Table 2. Effects of exercise on health outcomes in humans with different conditions.

Reference	Design	Participant condition	No. of participants	Age (years; mean $\pm$ SD)	Intervention	Outcome
57	RCT	Woman living in a nursing home support center; capacity to practice exercise without causing harm to themselves with approval of the medical department	25 (C = 12; I = 13)	C = 82.0 $\pm$ 7.5, I = 83.5 $\pm$ 7.3	14 weeks of combined resistance (e.g., front squat, bench over row, standing reverse fly, etc) and aerobic exercise training (e.g., stimulated walking, hip marching, standing rear leg extension, etc.) twice a week	Maintained concentrations of peripheral markers for BBB integrity and improved cytokine balance
77	RCT	Patients with moderate-to-severe COPD	30 (C = 15; I = 15)	>40 <sup>a</sup>	30 min of respiratory muscle-stretching exercise (intervention group) or upper and lower limb muscle-stretching (control group), followed by 30 min of aerobic training (treadmill running), twice a week for 12 weeks	Aerobic training combined with respiratory muscle-stretching increases the functional exercise capacity with decreased dyspnea in patients with COPD
89	RCT	Healthy young adults	16	24 $\pm$ 5	A 30-min CE and a 60-min IE (1-min work and 1-min rest) at 70% of their maximum work rate on separate occasions in a random order	The 30-min CE caused mild airway damage, while a time- or work-matched IE did not
97	RCT	Patients with venous leg ulcers	59 (C = 30; I = 29)	71.5 $\pm$ 14.6	12 weeks home-based progressive resistance exercise	A trend toward healing at a faster rate and better functional outcomes
98	RCT	Healthy adults	28 (C = 15; I = 13)	61.0 $\pm$ 5.5	1 h exercise per day (start with 10 min of warm-up floor exercises and stretching, followed by 30 min cycling, 15 min of brisk walking and or jogging and arm-strengthening exercise, 5 min	Enhance rates of wound healing

---

132	RCT	Healthy adults	144 (Cardio = 74; Flex = 70)	69.9 ± 0.4	of cool-down exercise), 3 days per week for 3 months  10-month cardio intervention (began at 45%-55% of VO <sub>2</sub> max and progressed to 60%-70% of VO <sub>2</sub> max within 3 months, 3 days/week, the duration of each session increased from 10-15 min to approximately 45-60 min by the 4 <sup>th</sup> month) was compared to Flex intervention (2 days/week for approximately 75 min/session)	Cardio intervention resulted in a longer-lasting seroprotective response to influenza vaccination
-----	-----	----------------	---------------------------------	------------	--	---

---

<sup>a</sup>The data is not mean ± SD.

Abbreviations: BBB = blood-brain barrier; C = control; Cardio = cardiovascular exercise group; CE = continuous exercise; COPD = chronic obstructive pulmonary disease; Flex = flexibility and balance group; I = intervention; IE = intermittent exercise; RCT = randomized controlled trial; VO<sub>2</sub>max = maximal oxygen uptake.

## Supplementary Table 1

The detailed exercise protocols in animal studies cited in this review.

Reference	Exercise protocols	Subject	Effects	Mechanisms
<b>Integrity of barriers</b>				
35	45 min running at 12 m/min, or the first 25 min running at 12 m/min followed by increments of 2 m/min every 5 min, with the last 5 min running at 20 m/min	Mouse	Alteration of the interaction between mitochondria and other organelles such as the ER	Upregulate REDD1
37	17-week voluntary wheel running exercise or 8-week treadmill running at a speed of 25 m/min, 0% grade, 1 h/day, 5 days/week	Rat model of NASH	Protect against NASH-induced alterations in mitochondrial membrane composition	Increase the PC/PE ratio
39	1 h of running at 25 m/min/day, 0% grade, 5 days/week, 8 weeks	Rat model of NASH	Decrease mitochondrial membrane permeability	Inhibit mPTP opening
40	30 min of running at 10 m/min/day for 7 days, 0° slope	Rat model of cerebral ischemic	Protect mitochondrial integrity	Increase caveolin-1 level
41	30 min at 4 m/min/day for the first week, 30 min at 6 m/min/day for the second week, 45 min at 8 m/min/day for the third week, 45 min at 10 m/min/day for the fourth week, 60 min at 10 m/min for the following 8 weeks, 10% slope	Diabetic mouse	Enhance mitochondrial membrane potential	Decrease Mst1

45	40 min running at 17 m/min, 5° incline, 5 sessions/week for 6 weeks	<i>Lmna</i> (+/-) mouse	Attenuate DCM development	/
46	4 months of running wheel exercise	Older mouse	Sustain the NE integrity	Increase Lamin B1 and NPC protein
49	50 min at 13.5 m/min/day for 2 weeks, 10% grade	HFD-fed mouse	Prevent cholesterol accumulation in the PM of skeletal muscle cells	/
51	120 min of treadmill running at 20 m/min	Rat	Increase fatty acid transport	Increase FAT/CD36 and FABPpm
55	Strength training (consists of climbing and ladder carrying a load corresponding to 25% of the animal's body weight, trained 5 days/week for 4 weeks), endurance training (incremental treadmill running at 13-17 m/min, 5 days/week for 4 week	Mouse model of multiple sclerosis	Prevent BBB disruption	Increase tight-junction proteins (occludins and claudin-4) and decrease PECAM-1
59	Treadmill running at 60% of exhaustion velocity for a total of 165 min, distributed among three 45 min exercise sessions with a 15-min interval between them	Obese mouse	Enhance the regulation of food intake	Increase PI3K-p110 $\alpha$ protein
65	1100 miles in 10 days	Dog	Increase intestinal permeability	/
70	5 weeks of combined aerobic (30 min continuous running at 20-25 cm/s, 10-25° incline) and resistance training (eight 2-min running bouts at 20-25 cm/s separated by 1 min of rest, 10-25° incline)	HFD-fed rat	Preserve intestinal barrier integrity	Counteract HFD-induced microbial imbalance

71	6 weeks of running at 10 m/min for 30 min per day, 6 days/week, 0% slope	Mouse model of obstructive jaundice	Protect intestinal mucosal barrier	Inhibit the HMGB1/TLR4/NF- $\kappa$ B pathway
72	7 weeks of swimming exercise, 1 or 1.5 h/day for 5 days per week	Rat model of DSS-induced chronic colitis	Ameliorate colon barrier disruption	Regulate inflammation, oxidative stress, and apoptosis
93	45 min running at 15 m/min, 3 times/week for 5 months	PolG mouse	Prevent age-associated thinning of the dermis	/
94	40 min of running wheel exercise per day for 8 weeks	HFD-fed mouse	Reduce amount of subcutaneous tissue and adipocyte size	Improve dermal collagen density
95	Running at 16 m/min for the first week, then increased to 18 m/min for 26 consecutive days, 1 h/day, 10° uphill grade	Mouse (5 months old)	Attenuate skin aging and enhance mitochondrial biogenesis	Increase IL-15 level
	Running at 10 m/min for the first week, 12 m/min for the second week, and 14 m/min for the next 19 consecutive days, 1 h/day, 10° uphill grade	Mouse (23 months old)		
<b>Maintenance of local homeostasis</b>				
99	30 min of running at ~70% VO <sub>2max</sub> daily for 8 days	Mouse	Reduce wound size	Decrease inflammation
100	4 weeks of voluntary wheel running exercise	Mouse	Decrease skin graft rejection and increases graft survival	Proliferate CD4 <sup>+</sup> T cell and increase production of interferon- $\gamma$

101	1 h of treadmill running at 18 m/min for 9 continuous days, 0° inclination	Mouse	Promote wound healing	Increase capillary density via miR-122-5p
107	5 days/week for 14 weeks (running from 8 m/min (week 1) to 18 m/min (week 8), exercise duration gradually increases during weeks 1-4, from weeks 5-8, running 40-45 min /day, then 45 min/day at 18 m/min for 6 weeks)	Mouse	Attenuate influenza infection	Decrease viral load and illness severity
112	8 weeks of treadmill running at 17-25 m/min, 60-90 min, 5 sessions/week	Mouse	Alter the levels of host proteins involved in SARS-CoV-2 cell entry	Regulate ACE2, FURIN, and TMPRSS2, <i>etc.</i>
114	30 days of voluntary wheel running exercise	Mouse model of DSS-induced colitis	Reduce colitis symptoms and colon inflammation	/
115	30 min of treadmill running at 8-12 m/min and 5% grade (~65%-70% VO <sub>2max</sub> ), 3 times/week for 8 weeks	Mouse model of sepsis	Attenuate sepsis-induced lung damage	Decrease and increase IL-10
119	6 weeks of voluntary wheel running	Mouse	Reduce inflammatory cell production and cardiovascular inflammation	Decrease hematopoietic activity
137	4 weeks of voluntary wheel running prior to tumor cell inoculation	Mouse	Reduce tumor growth by over 60% percent	Mobilization of NK cells
140	4 weeks of voluntary wheel running	Mouse	Prevent cellular senescence	Upregulate telomerase activity and telomere-stabilizing proteins

141	21 days of voluntary wheel running	Mouse	Prevent cellular senescence	Upregulate telomerase activity and telomere-stabilizing proteins
143	4 weeks of treadmill exercise, running at 6° incline, 2 min at 0 m/min, speed of 5 m/min, 8 m/min, 10 m/min for 1 min each, then 30 min running at 12 m/min (week 1), increase 2 m/min each week, and cool down at 5 m/min for 2 min for 1 session (37 min), 2 sessions/day	Mouse (84 weeks old)	Reduce senescence in adipose tissue	Change the immune-cell distribution
144	60 min of swimming exercise for 12 weeks, 5 times/week	D-Galactose-induced aging rat model	Suppress the senescence process of the liver	Downregulate p53 and p21
Recycling and turnover				
141	21 days of voluntary wheel running	Mouse	Enhance cardiac myocyte survival and prevent cardiac cell death	Upregulate TERT, eNOS, IGF1
147	5 days of treadmill running per week, start with 30 min running with gradual speed increase (8, 11, 15, 18 and 22 cm/s, 4° slope, 6 min each step) for 1 week, then run at 22 cm/s and 4° slope for 1 h per day for 3 weeks	Mouse	Reduce cardiomyocyte apoptosis and myocardial infarct size after ischemia-reperfusion	Increase circulating myonectin levels via cAMP/Akt signaling
148	4-week swim training, twice daily (from 5:00 PM to 6:30 PM and 11:00 PM to 0:30 AM) for 7 days a week, the first day of swim training contains two 10-min sessions separated by at least 4 h. Sessions were gradually increased to 90 min/day for 1 week	Mouse	Reduce cardiomyocyte apoptosis and promote cardiomyocyte survival	Upregulate exosomal miR-342-5p level



149	3-week swim training, start from 10-min twice daily with a 10-min increase each day until reaching 90 min	Mouse	Promote cardiomyocyte growth and decrease cardiomyocyte apoptosis	Upregulate lncRNA, CPhar
150	4 weeks of treadmill running, 5 days per week for 30 min each day at 9 m/min	Rat model of optic nerve transection	Increase the survival rate of retinal ganglion cells	Upregulate BDNF
161	8 weeks of treadmill running, the speed and duration were progressively increased to elicit 60% of maximal speed (corresponding to the maximal lactate steady-state workload) at the second week of exercise, 5 days/week, 1 h/day	Rat model of MI-induced heart failure	Improve cardiac autophagic flux	/
<b>Different circuitries</b>				
170	4-week swim training (started with 10 min and increased by 10 min daily until 90 min, twice per day, the interval between two times is more than 4 h) or 8 weeks of running (started with 10 min at 5 m/min and increased 10 min and 2 m/min daily until 60 min at 15 m/min)	Mouse	Prevent cardiomyocyte apoptosis	Downregulate HIPK2 and p-P53
171	3-week swimming exercise, started with 10 min and increased by 10 min daily until 90 min, twice per day	Mouse	Protect against MI and doxorubicin-induced cardiac injury	Upregulate ADAR2
172	4-week swim exercise, started with 10 min and increased by 10 min daily until 90 min, twice a day	Mouse	Reduce cardiac ischemia-reperfusion injury	Upregulate miR-486

192	9 weeks of treadmill exercise, 5 days/week (week 1 started at 5 min/day and ended at 25 min/day, 15 m/min; week 2 started at 30 min/day and progressed to 50 min/day, 20 m/min)	Diabetic rat	Attenuate the diabetes-induced changes in collagen fibrils, cytoplasmic area, and level of mitochondrial impairment	/
193	30 min of treadmill running at 15 m/min a day, 6 days/week for 3 weeks	Aged rat (22 months old)	Increase angiogenesis	/
194	7 weeks of treadmill running, began with 10 min warm-up at 5 m/min, followed by 10 high-intensity (~90% of VO <sub>2</sub> max) intervals of 4 min each, separated by 2 min of active rest), 5 days/week, 25° incline	Mouse	Increase angiogenesis	Mediated via the lactate receptor HCAR1
<b>Rhythmic oscillations</b>				
224	2 h of voluntary wheel running or treadmill running per day for 4 weeks	Mouse	Shift the circadian clock in skeletal muscle	/
Homeostatic resilience				
158	2-week endurance training (5 min treadmill running at 10 cm/s and 0° slope, 5 min at 10 cm/s and 10° slope, 15 min at 15 cm/s and 10° slope, 20 min at 18.5 cm/s and 10° slope a day) or resistance training (climb 10 repetitions of 15 steps for one series, 6 series/day, week 1 (3 days without weight load, 2 days with 15 g weight load), week 2 (2 days without weight load, 3 days with 20 g weight load)), 5 days/week	Mouse	Increase hippocampal neurogenesis	/

244	2 to 4 months of voluntary wheel running	Mouse	Increase hippocampal neurogenesis	/
281	8 weeks of treadmill running, began with 10 min at 5 m/min, then gradually increased distance 2 m/min daily until 60 min at 15 m/min	Mouse model of MI	Change the gut microbial community structure	Increase 3-HPA and 4-HPA
209	4 weeks of treadmill running exercise at 12-24 m/min and 15-50 min/day, 5 days/week, 10° slope	Mouse	A greater relative abundance of <i>Desulfovibrio</i> and <i>Desulfovibrio</i> sp.	/
209	Climbing exercise with 400-2000 steps and a 20-50 g weight load per session, an accumulations work of 260 mJ (g m <sup>2</sup> /s <sup>2</sup> ) was achieved daily, 5 days/week for 4 weeks	Mouse	A greater relative abundance of <i>Clostridium</i> and <i>C.cocleatum</i>	/
<b>Homeostatic regulation</b>				
287	2 weeks of treadmill running between 1800 and 2000 hours, each exercise section contained 15 min warm-up (treadmill speed gradually increased from 5 to 18 m/min over 15 min) and 50 min running at 18 m/min as well as a 5 min cooling-down period	Mouse	Increase UPR <sup>mt</sup> in POMC neurons and inguinal white adipose tissue	Increase IL-6 levels
<b>Repair and regeneration</b>				
305	8 weeks of treadmill running (resulted in a nearly 40% increase in VO <sub>2</sub> max)	Aged rat (30 months old)	Decrease the accumulation of oxidative damage of DNA and proteins in skeletal muscle	/
314	7 months of voluntary wheel running	CryAB <sup>R120G</sup> mouse	Reduce the accumulation of cytotoxic misfolded proteins in the heart	Increase autophagy

315	60 min of treadmill training at 15 m/min and 15° inclination per day for 1 week	Mouse model of AngII-induced muscle atrophy	Attenuate muscle atrophy	Activate PPAR $\gamma$ and inhibit miR-29b
317	1 h of treadmill running at 60% of maximal aerobic capacity, 5 days/week for 4 weeks	Rat model of neurogenic myopathy	Improve skeletal muscle autophagic flux and proteostasis	/
320	1 h of treadmill exercise at 60% of the maximal speed that corresponds to the maximal lactate steady state workload per day, 5 days/week for 8 weeks	Rat model of MI	Re-establish cardiac protein quality control and reduce ER stress	/
321	1 h of swimming exercise, 5 days/week for 8 weeks	Aged mice (20 months)	Suppress aging-induced ER stress	Enhance cGMP-PKG signaling
323	1 h of treadmill exercise at 16 m/min and 5° incline, 5 days/week for 10-12 weeks	Mouse model of AD	Attenuate ER stress in AD mice brain	/
324	90 min downhill run with a slope of -16° and a speed of 16 m/min	Rat	Activate ER-phagy	FAM134B anchors and fragments ER, and then binds with LC3 to promote ER membrane degradation
327	3 h/day of chronic contractile activity, tibialis anterior and extensor digitorum longus muscles were subjected to stimulation (6 V, 10 Hz continuous, 0.1-ms pulse duration, 999 ms of rest per second), 2 days	Rat	Activate UPR <sup>mt</sup>	/
333	30 min/day of running exercise on a rotarod for	HFD-fed rat	Mitigate the HFD-associated lysosomal	Reduce ROS

	4 weeks			membrane permeabilization	
339	3 weeks of swimming exercise, began with 10 min twice a day and increased by 10 min/day until reaching 90 min twice a day	Mouse		Physiological cardiac growth	Increase lymph-angiogenesis via VEGFR3 activation
343	30 min/day of treadmill running at 12 m/min and 5°, 4 days/week for 4 weeks	Mouse		Improve muscle regeneration and induce muscle hypertrophy	Igfbp7-Akt-mTOR signaling
344	Running 30 min/day at 13 m/min, 5 days for 4 weeks	Aging rat (20 months old)		Improve tendon injury healing	Proliferation of tendon stem/progenitor cells
345	60 min/day of treadmill running at 12-20 m/min, 5 times/week for 16 weeks	HFD-fed mice		Induce the macrophage phenotypic switching from M1 to M2 in adipose tissue	/
346	3 days/week of treadmill running for 10 weeks, the speed of running began at 14 m/min for 45 min (week 1) and increased to 24 m/min for 45 min (week 10), the training protocol was always preceded by a 10 min warm-up at 10 m/min and followed by a 5 min cool-down at 10 m/min	Mouse		Promote the differentiation of mesenchymal stem cells into osteoblasts	/
347	1 h of treadmill running at 12.5 m/min per day, 5 days/week for 4 weeks	Mouse		Anti-inflammatory trained immunity of Kupffer cells	Metabolic reprogramming

Note: / stands for unknown.

Abbreviations: ACE2 = angiotensin-converting enzyme 2; AD = Alzheimer's disease; ADAR2 = adenosine deaminases acting on RNA2; AngII = angiotensin II; BBB = blood-brain barrier; BDNF = brain-derived neurotrophic factor; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; CPhar = cardiac physiological hypertrophy-associated regulator; CryAB<sup>R120G</sup> =  $\alpha$ B-crystallin mutated; DCM = dilated cardiomyopathy; DSS = dextran sodium sulfate; ER = endoplasmic reticulum; eNOS = endothelial nitric oxide synthase; FABPpm =

plasma membrane fatty acid-binding protein; FAM134B = family with sequence similarity 134, member B; FAT = fatty acid translocase; HCAR1 = hydroxycarboxylic acid receptor 1; HFD = high-fat diet; HIPK2 = homeodomain interacting protein kinase 2; HMGB1 = high mobility group box 1; HPA = hydroxyphenylacetic acid; IGF1 = insulin-like growth factor 1; Igfbp7 = insulin-like growth factor-binding protein 7; IL = interleukin; LC3 = microtubule-associated protein light-chain-3; MI = myocardial infarction; miR = microRNA; mPTP = mitochondrial permeability transition pore; Mst1 = mammalian sterile 20-like kinase 1; mTOR = mammalian target of rapamycin; NASH = non-alcoholic steatohepatitis; NE = nuclear envelope; NF- $\kappa$ B = nuclear factor-kappa B; NK cells = natural killer cells; NPC = nuclear pore complex; PC = phosphatidylcholine; PE = phosphatidylethanolamine; PECAM-1 = platelet and endothelial cell adhesion molecule 1; PI3K = phosphoinositide 3-kinase; PKG = protein kinase G; PM = plasma membrane; POMC = proopiomelanocortin; PPAR $\gamma$  = peroxisome proliferator-activated receptor gamma; REDD1 = regulated in development and DNA damage 1; ROS = reactive oxygen species; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TERT = telomerase reverse transcriptase; TMPRSS2 = transmembrane protease serine 2; TLR4 = toll-like receptor 4; UPR<sup>mt</sup> = mitochondrial unfolded protein responses; VEGFR3 = vascular endothelial growth factor receptor 3; VO<sub>2max</sub> = maximal oxygen uptake.