

Review

# Targeting mitochondrial phenotypes for non-communicable diseases

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## Abstract

The concept that “Exercise is Medicine” has been challenged by the rising prevalence of non-communicable chronic diseases (NCDs). This is partly due to the fact that the underlying mechanisms of how exercise influences energy homeostasis and counteracts high-fat diets and physical inactivity is complex and remains relatively poorly understood on a molecular level. In addition to genetic polymorphisms in humans that lead to gross variations in responsiveness to exercise, adaptation in mitochondrial networks is central to physical activity, inactivity, and diet. To harness the benefits of exercise for NCDs, much work still needs to be done to improve health effectively on a societal level such as developing personalized exercise interventions aided by advances in high-throughput genomics, proteomics, and metabolomics. We propose that understanding the mitochondrial phenotype according to the molecular information of genotypes, lifestyles, and exercise responsiveness in individuals will optimize exercise effects for prevention of NCDs.

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## 1. Introduction

The slogan of “Exercise is Medicine” promotes a global movement to reduce sedentary lifestyles. “Exercise is Medicine” attempts to raise physical activity (PA) levels to a standard medicine for clinical practice, because the benefits of exercise are purported to reduce the risk of non-communicable chronic diseases (NCDs), such as cardiovascular disease, type 2 diabetes and certain cancers. However, in the past decades, the global morbidity and mortality of NCDs is increasing regardless of the efforts of World Health Organization and national governments to promote physically more active lifestyle.<sup>1</sup>

The number of U.S. adults doing sufficient PA increased from 22% in 1996 to 51.6% in 2014.<sup>2</sup> In China, the number of adults attending PA also increased from 15.5% in 1996, to 28.2% in 2008, and to 33.9% in 2014.<sup>3</sup> There are remarkable achievements in promoting PA over the past decade in different countries. Nonetheless, it is discouraging that the mortality between ages 30 and 70 years due to NCDs increased in the US in 2000–2012 with NCDs accounting for 88% of total deaths in 2014. In China,

NCDs also increased in males after 2004 and in females during 2000–2012; NCDs account for 87% of total deaths in 2014.<sup>4</sup> The metabolic risk factors for development of NCDs such as body mass index (BMI) and fasting blood glucose showed a less optimistic trend during 1980–2008.<sup>5</sup> These statistics might indicate that there is no an apparent relationship between PA and NCDs risks. Nonetheless, if increases in BMI are reciprocal to increases in PA, it is possible that any benefits of moderate exercise are offset by increased food consumption. In this review, we look into those confounding factors and the possible underlying mechanisms, which may have shaded the outcomes of health benefit of exercise from “Exercise is Medicine”. The precision medicine initiative launched by the US claims that detailed genetic and other molecular information about a patient’s disease will be routinely used to deploy effective, patient-specific remedies in future.<sup>6</sup> It is urgent to promote personalized exercise intervention linking curative exercise effects to specific health outcomes in different populations. Nonetheless, the weighting of genetic and environmental factors contributing to exercise for health is poorly understood.

## 2. Energy balance challenged by unhealthy lifestyles

NCDs are often attributed to unhealthy diet and physical inactivity. Meanwhile, life expectancy is increasing with the

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ability of modern societies to provide high-quality medical and social facilities, regardless of these unhealthy lifestyles. To better evaluate the extent to which PA prevents NCDs, the mechanisms involving unhealthy lifestyles need to be explored at an evolutionary and physiological level. Energy balance is critical for the survival of all mammals. Current findings suggest that NCDs are mostly associated with metabolic disorder and its complications. Metabolic syndrome is often characterized by higher BMI, hyperglycemia, hyperlipidemia, insulin resistance, ectopic lipid accumulation, and mitochondrial dysfunction, for example, in type 2 diabetes and cardiovascular diseases.<sup>7,8</sup> With these considerations, it is necessary to focus our attention on those lifestyles that probably impair energy balance. High-fat diets are a major contributor to metabolic syndrome. Physiologically, high-fat diet leads to the impairment of fuel metabolism, increases in ectopic lipid accumulation in non-fat tissues (i.e., muscle and liver) and consequent adiposity. Evolutionarily, humans have undergone a dramatic shift in the composition of diet and motivation to eat.<sup>9</sup> Currently people have more reasons to eat something compared to our ancestors, because diet is an expression of culture and lifestyle, other than simply hunger. Unnecessary food intake overshoots the demand for energy and thereby impacts energy homeostasis. If excessive food consumption is the main reason for obesity, weight loss should be achieved by reducing food intake and increasing energy expenditure with PA. However, a cohort study that took place from 2004 to 2014 showed that PA and diet control might be not as effective as expected in obesity treatment. The authors reveal that the annual probability of attaining normal weight was 1/210 for men and 1/124 for women after obesity treatments.<sup>10</sup> Such a low probability is not encouraging for counteracting obesity through these means. It is noteworthy that the individual propensity to be physically active is determined by both genetic and environmental factors.<sup>11</sup> The individual propensity to be obesity-prone or obesity-resistant in response to high-fat diet is, for example, associated with the acyl chain length of phosphocholine species,<sup>12</sup> hypothalamic-pituitary-thyroid axis function,<sup>13</sup> proteomic profile of adipose tissues and liver.<sup>14,15</sup> This indicates that the individual propensity for PA and diet needs to be taken into consideration in obesity treatment frameworks.

In direct contrast to PA, physical inactivity leads to the development of insulin resistance.<sup>16</sup> Bed rest reduced expression of *PGC-1 $\alpha$*  and other genes involved in mitochondrial biogenesis, contributing to the development of insulin resistance.<sup>17</sup> Evolutionarily, humans were selected to avoid extraneous PA because energy from food was limited and exercise increases unnecessary energy expenditure. Consequently, physical inactivity (except for necessary physical work) was the best strategy for survival when availability of food was limited.<sup>18</sup> Nonetheless, physical work in hunting for food coupled to lower energy intakes might have provided sufficient amount of PA to retain such a level of metabolic activity that our ancestors were resistant to NCDs. The advent of modern technology has now relegated PA from a necessity of human existence to lifestyle choice. Since physical inactivity poses a challenge to public health, exercise remains a most efficacious treatment for metabolic diseases, such as diabetes and cardio-

vascular diseases. Exercise provokes widespread perturbations in cells, tissues, and organs and challenges whole-body homeostasis by increasing metabolic activity of contracting skeletal muscles.<sup>19</sup> In doing so, exercise promotes “metabolic flexibility”—the ability to maintain metabolic health even in the face of excessive energy consumption.

Together, the metabolic syndrome appears to be at the intersection of endocrinology, oncology, and cardiology, such that maintaining energy balance has emerged as a major target for treating NCDs. Evolutionarily, the changes in food consumption and physical inactivity pose a great challenge to energy system in humans who have been evolutionally selected for food shortage and necessary physical work. Pathologically, long-term exposure to high-energy diet and physical inactivity induces obesity, insulin resistance and decreased energy expenditure. Although the synergistic interaction between unhealthy lifestyles and exercise remains elusive, PA is known as the best way to tame metabolic disorders and restore energy balance.

### 3. Mitochondria and metabolic health

Many NCDs involve mitochondrial dysfunction.<sup>20</sup> While high-fat diets paradoxically result in an increase in mitochondrial biomass, they have also been associated with impaired mitochondrial respiratory capacity, mitochondrial biogenesis, insulin resistance, and metabolic inflexibility.<sup>21</sup> These same effects are related to physical inactivity.<sup>22</sup> By contrast, calorie restriction strengthens mitochondrial network and extends lifespan.<sup>23</sup> Exercise-induced mitochondrial biogenesis has been well documented, for example, in brain and skeletal muscle.<sup>24,25</sup> In these tissues mitochondrial plasticity follows the principle of “use it or lose it”; increased mitochondrial networks and mitochondrial function resulting from exercise are considered essential for health, while physical inactivity and sedentary behaviors are associated with mitochondrial dispersion (Fig. 1). It is now evident that mitochondria function as important signaling organelles; for example, via releasing metabolites, reactive oxygen species, and peptides and ions.<sup>26</sup> The quantity of mitochondria in cells is controlled by the master regulator of mitochondrial biogenesis, *PGC-1 $\alpha$*  signaling, and mitophagy pathways (mitochondrial breakdown). We speculate that physical inactivity undermines the endo-symbiotic relationship between mitochondria and host eukaryotic cells. Here, we provide a framework by which mitochondria are provoked to drive the formation of the whole-cell phenotype (Fig. 1). Mechanistically, exercise has been proved to improve energy metabolism and mitochondrial adaptability. Thus, PA is a hopeful means to hold back the prevalence of NCDs. However, there is a great gulf between the bench and the bedside. A leading review indicates that a person’s predisposition to engage in exercise is highly variable and simultaneously influenced by the environment, complex genomics, and their interactions.<sup>27</sup> In short, exercise is not always effective for everyone at any time. The development of individualized exercise prescription for the control of NCDs is an appealing concept. Unhealthy lifestyles impair energy balance, mitochondrial adaptability, and mitochondrial-coupled cell signaling implicated in the pathogenesis of NCDs. Why is target-

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