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**PHYSICAL INACTIVITY AS A GLOBAL HEALTH CRISIS: FROM EVOLUTIONARY ADAPTATIONS TO MODERN DISEASE**

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Physical inactivity has emerged as a global health crisis, affecting approximately 86% of the U.S. population and 31% of adults worldwide, marking a significant increase from 23.4% in 2000.

This "stealth pandemic" is a contributing cause to at least 35 chronic diseases and conditions, imposing substantial economic burden with annual healthcare costs estimated between \$131-333 billion in the United States alone. The direct and indirect global costs of physical inactivity were estimated at \$67.5 billion across 142 countries, underscoring its significant public health impact.

This research investigates the mechanisms through which physical inactivity contributes to chronic disease development by examining evolutionary adaptations and pathophysiological pathways. The study employs a comprehensive methodological approach incorporating multiple research models, including human epidemiological studies, twin studies for genetic predisposition analysis, animal selective breeding experiments examining voluntary running behavior, physical inactivity models (bed rest studies, spinal cord injury cases, limb immobilization), reduced daily step count interventions, and spaceflight studies. Additionally, molecular and cellular analyses, including transcriptomic and proteomic assessments, were conducted alongside meta-analyses and systematic reviews of existing literature.

The research revealed rapid and significant physiological declines associated with physical inactivity. Cardiorespiratory fitness decreases substantially, with a 26-29% reduction in cardiac output and stroke volume after 20 days of bed rest. Skeletal muscle experiences 23-27% atrophy within one week of immobilization, while metabolic dysfunction manifests rapidly, with significant insulin resistance developing within 2-3 days of inactivity. Vascular function deteriorates, characterized by reduced nitric oxide bioavailability and increased arterial stiffness, and chronic low-grade inflammation develops, contributing to various pathological conditions. Evolutionary insights suggest the existence of genes regulating physical inactivity behavior, potentially providing survival advantages in ancestral environments. However, these adaptations have become maladaptive in the modern sedentary environment, contributing to unprecedented levels of physical inactivity and associated health consequences.

Physical inactivity represents an underappreciated yet significant cause of chronic diseases, producing rapid physiological dysfunction across multiple systems. The distinct molecular signatures and pathways associated with physical inactivity, separate from those of physical activity, emphasize the need for targeted interventions. The research highlights the critical importance of addressing both biological predispositions and environmental factors in preventing inactivity-related diseases. The findings underscore the urgent need for population-level strategies to combat physical inactivity, particularly early-life interventions to establish healthy activity patterns. Without addressing the growing prevalence of physical inactivity, healthcare costs will continue to rise, emphasizing the importance of both preventive measures and therapeutic interventions.