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Review article

Impact of Environmental and Lifestyle Factors on Human Blood Physiology: Exercise, Altitude, Climate Change, and Sugar Substitutes

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Abstract

The human blood physiology is an active system that is closely connected with environmental and lifestyle changes, which affect such processes as erythropoiesis, coagulation, platelet activity, nitric oxide (NO) signaling system, and oxygen transport. It is a synthesis of evidence based on recent research (2020-2026) on four modulators that relate to each other physically: exercise, high-altitude hypoxia, climate change-induced high and low temperatures, and consumption of non-nutritive sugar substitutes such as erythritol. Adaptive changes that are generally observed in response to exercise and altitude are increased erythropoiesis and improved vascular functions, whereas maladaptive changes, including oxidative stress, inflammatory, and prothrombotic states, may be caused by the climate extremes and erythritol. Especially sensitive parameters of hematology, such as hemoglobin (Hb), hematocrit (Hct), platelets (PLT), red blood cell (RBC) count, and white blood cell (WBC) count, pose risks, and interconnections are possible, which increase risks in a changing climate. To give an example, workouts in the altitude or heat can increase the effects of dehydration and thrombosis, particularly with the current diets rich in erythritol. This review identifies the implications of public health to vulnerable groups (such as patients with cardiovascular risk factors), and it recommends combined exposure research. A consideration of these factors as a collective entity will enable us to inform dietary and training practices that better improve health in the face of environmental adversity.

Keywords: Hemoglobin, climate change, physiology, Exercise

1. Introduction

Blood is the main medium of oxygen, nutrients, and immune factors in the body, where its physiology is controlled by complex hematopoiesis, coagulation, and vascular homeostasis balances. RBCs are used to transport oxygen, platelets are used to clot, and plasma is used to maintain fluid balance (1). Environmental stressors can change these, causing conditions such as anemia, polycythemia, or thrombosis. Over the recent years, research has shown more and more interest in the mechanisms of alteration of these systems by lifestyle and environmental changes, due to current habits and climate changes (2).

One of the pillars of health, physical exercise causes acute hemoconcentration and chronic changes (such as RBC mass increase). Exposure to high altitudes,

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which mimics conditions of hypoxia, causes responses that are mediated by erythropoietin (EPO) to increase oxygen carrying capacity (3). Climate change intensifies extremes, and heat waves are associated with an increase in Hb and PLT, which puts cardiovascular systems under strain (4). Low-calorie sweeteners such as erythritol cause prothrombotic risks in the diet. The significance of learning these interactions is that global warming and sedentary lifestyles intersect with dietary trends (5).

This review is based on more than 80 studies, with a focus on 44 significant studies that examine the individual and synergistic impact on blood physiology. It uses graphics to be clear, such as the diagrams of RBC adaptations to exercise and blood viscosity variations with altitude, and tables with a summary of the changes in parameters. The results highlight the significance of individual intervention, especially in athletes and at-risk groups.

2. Exercise and Its Influence on Blood Physiology

Exercise has a significant effect on the physiology of blood, as it undergoes acute and long-term changes that result in the improvement of oxygen supply and metabolism. Acute bouts cause hemoconcentration, that is, a reduction in plasma volume because of the transfer of fluid into the tissues, leading to an increase in Hb, Hct, and RBC count by 5-15% (6). It is also noticeable in the literature on young trained athletes with short-term increases in leukocytes and enzymes, such as creatine kinase (CK) and lactate dehydrogenase (LDH), indicators of muscle stress and metabolic changes with endurance exercise (7). Such modifications are beneficial to the short-term energy requirements, but they may deplete untrained individuals. Chronic exercise produces a rise in the mass of RBCs through EPO upregulation, which leads to an increase in VO2max by 10-20%. Meta-analyses indicate that combined interval training with blood flow restriction (BFR) increases aerobic capacity (g=0.63) and muscle strength (g=0.88), and moderators such as intensity and cuff width affect the results (8). The increase in acute maximal exercise in Libyan cohorts was that Hb ranged 14.0 to 14.8 g/dL and PLT ranged 238 to 263 $x10^3$/uL, which were modified by gender and training condition. Low resistance aerobic activity in sedentary adults raised RBC (7-11%), Hb (8-8.3%), and Hct (5-14%) and did not change cardiometabolic enzymes, indicating hematological improvements in overall health (9). In addition to hematology, exercise changes metabolites, and of the over 9,815 molecules that change in bloodstreams during brief exercises, it is interrelated with anti-aging through plasma exchange and through NO signaling(10). The cardiovascular improvements are decreased resting blood pressure (BP) of 4-8 mmHg, with isometric exercise showing the most significant reductions. Exercise enhances cerebral blood flow, which may be through increasing hippocampal. Nevertheless, during hot environments, exercise increases oxidative stress, highlighting its interactions with climate. The deformability and metabolic changes of RBC as observed during exercise can be visualized, which helps in the unloading of oxygen (11) (Figure 1).

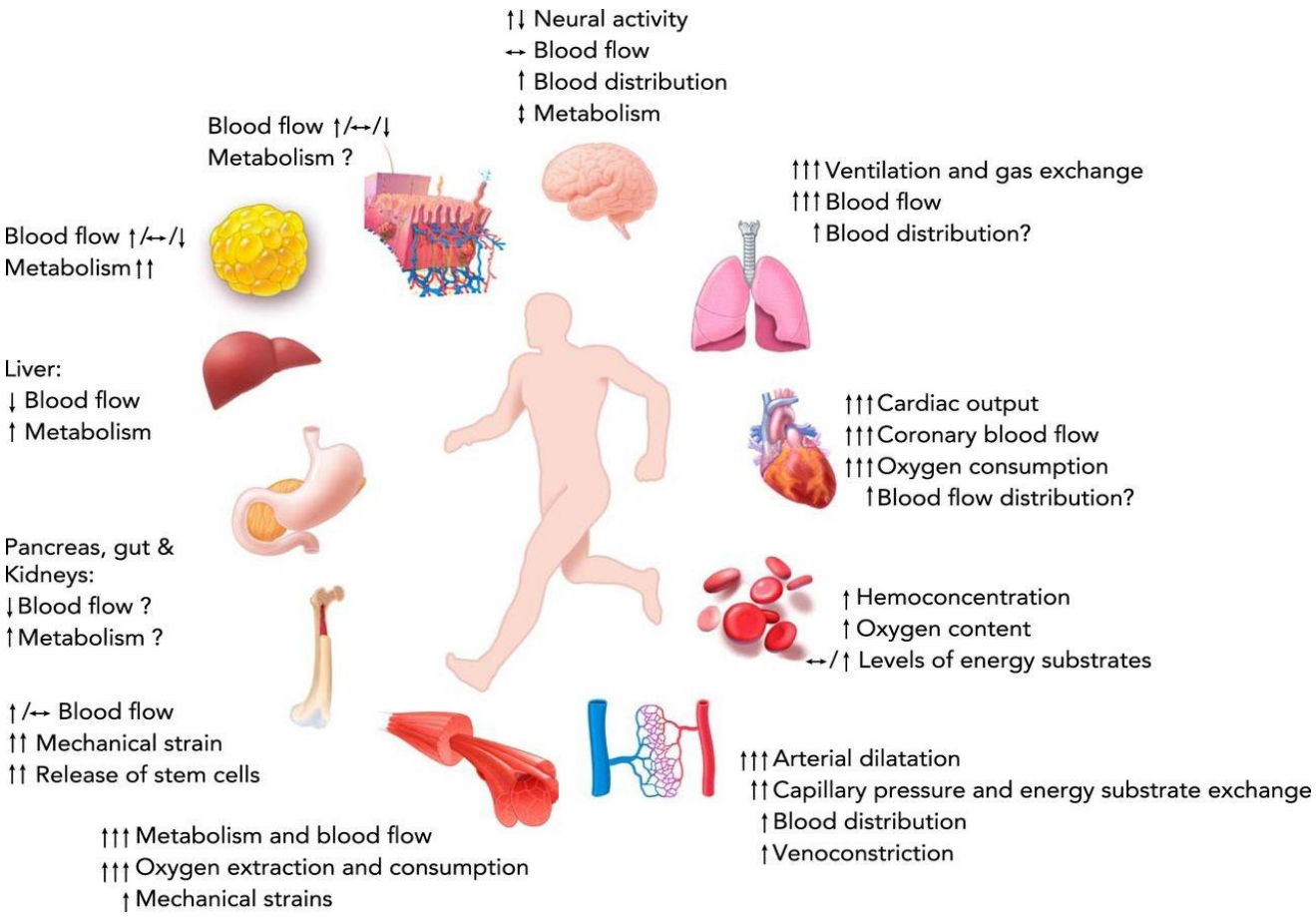

Figure 1: Physiological responses to exercise (12)

2.1 Hypoxia and Hematological Adaptations to High Altitude.

The exposure to high altitude (>1500 m) provokes hypoxia that triggers the process of blood physiology adaptation to sustain oxygen supply. In acute stages, there is a reduction in plasma volume (10-20 percent), leading to hemoconcentration and an increase in [Hb] to replenish arterial oxygen content. Weekly surges in EPO trigger erythropoiesis, resulting in the buildup of mass in the RBC and polycythemia. Physiological reactions comprise hyperventilation, augmented capillary thickness, and hypoxic pulmonary vasoconstriction (13).

Hb increases gradually in sojourners, and it becomes unsafe when viscosity and thrombosis increase excessively. The increments in Hb (0.30 g/dL per 1000 m) attributed to altitude in Saudi Arabia necessitate decreasing the anemia thresholds (14). Prolonged intermittent exposure, such as in mine workers, is associated with a slow increment in Hb (0.046 g/dL/year), which is not dependent on BMI. Adaptations to Tibetan populations include the low Hb of lowlanders (15).

There are cardiovascular changes, such as accelerated heart rate and decreased stroke volume, and right ventricular hypertrophy in the chronic process. The adaptations in blood flow (such as contraction of the spleen in divers) (16). Nevertheless, during hypoxia over extended periods, the acute hematological reaction is a 10-20% decreased plasma volume (PV) during the initial 24-48 hours, which is caused by diuretic and fluid

effects, and heightened sympathetic activity (17) (Figure 2). This hemoconcentration increases the hemoglobin concentration (Hb) as well as the hematocrit (Hct) and red blood cell (RBC) count, with the effect of partly replenishing the arterial oxygen content (CaO_2), although arteries remain under hypoxia (SaO2 usually decreasing to 80-90% at moderate altitudes). Research establishes that this PV contraction is one of the key mechanisms of increasing early [Hb], whereby values increase by 5-10 per cent in the initial week, regardless of actual erythropoiesis (18). Increased capillary density in tissues with time, hyperventilation (to increase alveolar PO2), and hypoxic pulmonary vasoconstriction (to optimize ventilation-perfusion matching) are also accompanied in this phase. Though it increases blood viscosity, which may hamper microcirculatory blood flow and add to the symptoms of acute mountain sickness (AMS) in people who are prone to erythropoiesis (19)

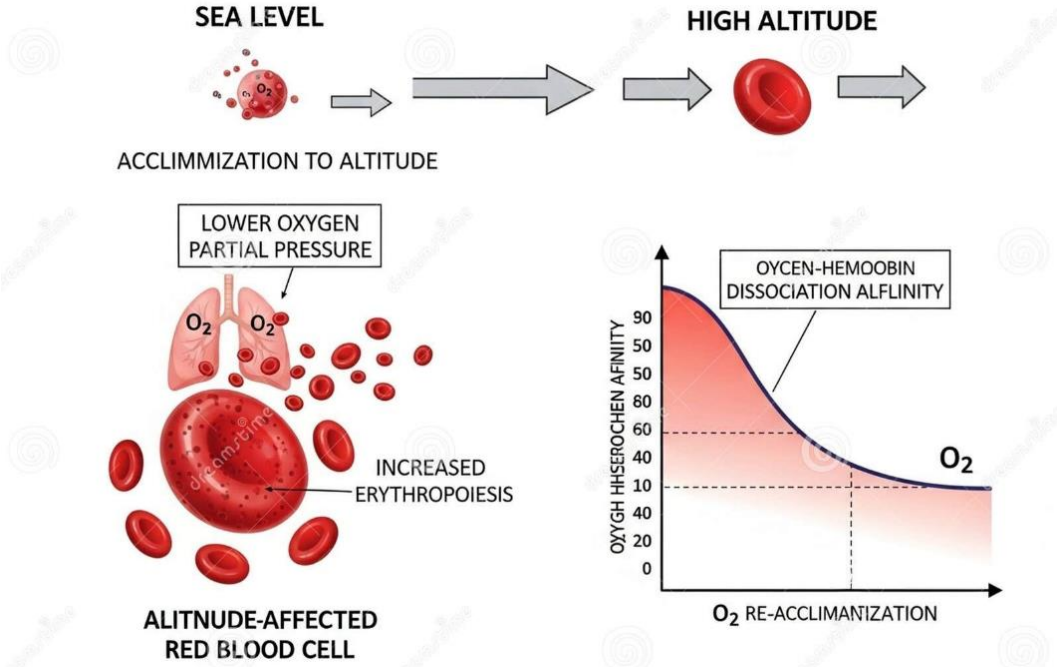

Figure 2: A diagram demonstrates the acclimatization to the high altitude, where the effects of the sea level and high altitude are compared to the red blood cells.

3. Climate Change and Disruptions to Blood Parameters

Climate change brings on temperature extremes that disturb blood physiology, whereby heat waves and cold spells change the hematological indices (4). The exposure to heat leads to the hemoconcentration of Hb (lag1 |2.6 g/L) and PLT (lag7 |9.7 x10^9/L) through dehydration and inflammation. Heat waves raised Hb and PLT, and cold waves raised Hb and reduced PLT in Tianjin cohorts, with more significant effects in susceptible groups. Hemolytic disorders of RBCs, such as sickle cell disease, become exacerbated by heat, and this leads to vaso-occlusive crisis (20). There is a positive correlation between increasing temperature and ALL incidence in Europe, and this could be through oxidative stress

and DNA damage. There are changes in the distribution of vector-borne diseases, which affect the transfusion safety (21). Seasonal fluctuations are higher Hb in winter as a result of changes in temperature and pressure. Ambient temperature is negatively associated with 13 blood indices, such as FBG and Hb, with age 40-60 being the most sensitive (22). The burden of heat on anemia poses compound risks to pregnant women and children with RBC disorders. These alterations, combined with diet and exercise, increase susceptibility to warming climates (23).

3.1 Temperature Extremes: Heat Waves and Cold Spells

Climate change is increasing the frequency, length, and intensity of heat waves and cold spells, resulting in direct perturbation in hematologic parameters due to physiological stress reactions. The heat waves (a long-term high temperature, more than 5 °C over the average temperature, over 3 days) are what cause the hemoconcentration, leading to excessive heat, causing people to sweat and lose fluid.(4) which thickens the blood and increases the Hb, Hct, and PLT counts. Peak Hb increases (2.6 g/L, 95% CI: 1.76-3.45) and PLT (9.71 x10^9/L, 95% CI: 6.26-13.17) at lag 1 day and lag 7 days, respectively, were also linked to heat waves in a cohort of blood donors in Tianjin, China (2014-2023) (both dehydration and activation of inflammation). Coagulation cascades are especially hyperirritable: because of heat, prothrombin time (PT) and activated partial thromboplastin time (APTT) decrease, leading to hypercoagulability, and thrombin time (TT) reduces due to cold fibrin formation (24). Heat waves increased systolic blood pressure (SBP: b=8.693, P=0.019) and DBP (b=3.665, P=0.040), and decreased TT and APTT, which are thrombotic risk factors in ischemic stroke patients (25). Cold waves also increased SBP (b=5.277, P=0.028) and fibrinogen (b=0.315, P=0.011), which promoted a prothrombotic condition. It has been estimated across the world that by the year 2050, 3.2 million more people will die due to heat waves alone, through indirect causes such as drought-induced anemia (26).

3.2 Mechanisms of Disruption

Climate extremes are physiologically associated with blood parameters by means of thermoregulation, inflammation, and hemostasis. Exposure to heat causes an increase in core body temperature that causes vasodilation and sweating, resulting in dehydration and hemoconcentration (27). This increases blood viscosity by thickening blood, which leads to platelet activation, which is manifested by more intense aggregation and reduced coagulation time. Heat-induced oxidative stress denatures proteins and induces systemic inflammation by increasing C-reactive protein (CRP) and cytokines, which further impair RBC integrity and cause anemia in chronic exposures (28). Under cold ischemic conditions, sympathetic activity stimulates vasoconstriction of peripheral vessels, decreases blood flow to the periphery, and concentrates central blood, which increases Hb at the expense of fibrinolysis, resulting in hypercoagulability. Air pollution, aggravated by climate change (PM 2.5 wildfires) (29), reduces the number of RBCs and mean corpuscular hemoglobin (MCHC) and elevates the platelet-to-lymphocyte (PLT) and platelet-to-c-reactive protein (PCT) ratio. The seasonality in the expression of genes in immune cells also differs, with peaks in the expression of inflammatory activities such as CRP, which are independent of demographics during winter (30).

3.3 Impacts on Vulnerable Populations

Disruptions caused by climate disproportionately impact vulnerable groups, such as pregnant women, children, the elderly, people with pre-existing conditions, etc. Every 1 °C rise in temperature increases childhood anemia risks in sub-Saharan Africa by 1.138 (95% CI: 1.134-1.142), and a 25 percent rise in heat-related hospitalization is predicted (31) During pregnancy, heat waves are

associated with increased risks because pregnant women with RBC disorders are more likely to experience vaso-occlusive crises in sickle cell disease and worsening thalassemia because of dehydration. The younger ones, 40-60 years old most susceptible and demonstrate more variations in Hb and PLT when the temperature changes, and cold waves promote mortality due to ischemic heart disease (32). Gender inequalities are born: climate change lowers the life expectancy of women more than that of men (0.50 years per 10-point index rise of climate), which is associated with anemia and nutritional insufficiency. The poorer world, such as Africa and South Asia are the most affected by poor infrastructure, adding to the failures of transfusion due to severe weather conditions (33).

4. Sugar Substitutes: Focus on Erythritol's Prothrombotic Effects

Sweeteners that are not nutritious, such as erythritol, commonly used in low-carb and keto diets, change the physiology of the blood, increasing thrombosis. Erythritol is a glucose-fermented sugar alcohol that is used as a replacement for sugar in consumed products like sugar-free gum, beverages, and baked goods. It is also 60-70% sweeter than sugar, yet contains insignificant calories, which is why it is used as a weight loss diet and type-2 diabetes management (34). Nevertheless, new studies (2023-2026) also point to its possible interference with hematological balance, especially by favoring platelet hyperreactivity and platelet clot formation. This part discusses the pharmacokinetics, clinical evidence, mechanisms of erythritol, its comparison with other sweeteners, and the overall health consequences with reference to its prothrombotic risks (35).

4.1 Pharmacokinetics and Acute Effects

Erythritol is quickly absorbed within the small intestine, with 90% of it being excreted directly into the urine and 10 percent being metabolized. When a normal dose (30 g, or equal to a sweetened beverage) is taken, plasma levels rise more than 1000-fold, from a baseline in the range of 3-5 umol/L to up to 4000-6000 umol/L, which lasts hours to days (36). This dramatic increase is in opposition to glucose, which produces little alteration in the functioning of the plates. Erythritol consumption can increase platelet aggregation in healthy volunteers in response to agonists, such as adenosine diphosphate (ADP) and thrombin receptor-activating peptide-6 (TRAP-6), makers of platelet aggregation, such as P-selectin and glycoprotein IIb/IIIa (GP IIb/IIIa) activation (5). Research indicates that all participants have increased platelet responsiveness, which is not mimicked by equicaloric glucose, and that a direct prothrombotic effect occurs. Such acute effects are dose-dependent, and even normal portions of them (in keto products) cause quantifiable clot formation, increasing in both ex vivo and in vivo of murine models. Endogenous erythritol, synthesized in the pentose phosphate pathway in hyperglycemia or oxidative stress, also has an association with cardiovascular risks, although dietary intake increases plasma levels way above physiologic thresholds (37).

4.2 Clinical Evidence from Recent Studies

Pivotal research from the Cleveland Clinic (2023–2024) links erythritol to a doubled risk of major adverse cardiovascular events (MACE), including heart attack, stroke, and death (Figure 3). In a 2024 intervention study published in Arteriosclerosis, Thrombosis and Vascular Biology, 20 healthy volunteers consuming erythritol-sweetened drinks showed significant platelet activation and thrombosis potential, absent in glucose controls. Cardiac patients with high baseline erythritol were twice as likely to experience MACE over three years (38). Mendelian randomization analyses (2025) provide genetic evidence: higher genetically predicted erythritol levels are associated with increased odds of coronary heart disease (OR=1.077, 95% CI: 1.060–1.090) and ischemic stroke (OR=1.157, 95% CI: 1.135–1.179), with suggestive

links to deep vein thrombosis (DVT; OR=1.117) (39). Pilot trials in critically ill patients and observational data suggest temporary platelet aggregation changes, but large intravenous doses do not confirm long-term risks. However, a 2025 study warns of brain vascular impairment: erythritol reduces nitric oxide (NO) by 20% in cerebral microvascular endothelial cells, increases endothelin-1 (ET-1) by 30%, and impairs tissue plasminogen activator (t-PA) release, potentially elevating stroke risk. These findings challenge erythritol's "generally recognized as safe" (GRAS) status by the FDA, prompting calls for reevaluation (40).

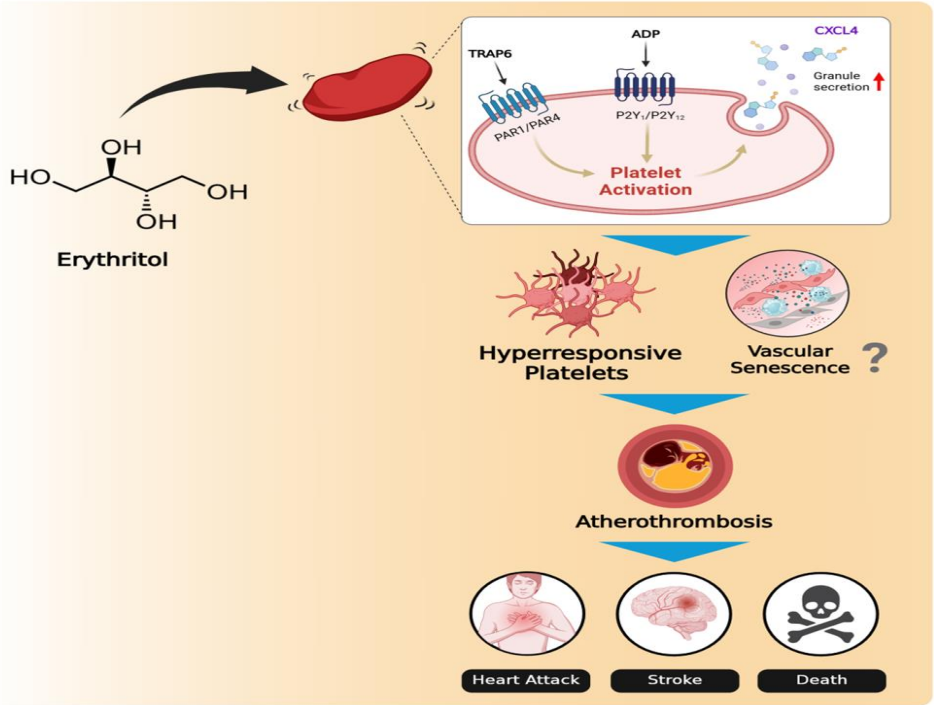

Figure 3. Erythritol and its potential effect on thrombotic risk (41)

Interconnections Among Factors

The four factors mentioned above, which are physical exercise, high-altitude hypoxia, temperature extremes that are caused by climate change, and intake of non-nutritive sugar substitutes (specifically erythritol), do not individually impact human blood physiology. Instead, they interact through shared pathways such as oxidative stress, inflammation, dehydration/hemoconcentration, erythropoiesis regulation (via EPO and HIF pathways), platelet reactivity, coagulation balance, and vascular function (NO signaling and endothelial integrity) (42). These synergies can amplify adaptive benefits in controlled scenarios (athletic training) or exacerbate maladaptive risks (thrombosis, impaired oxygen delivery) in everyday or vulnerable populations (43). In a warming world with rising use of low-carb diets, these interconnections highlight emerging public health concerns, especially for athletes, individuals with cardiovascular risks, or those in extreme environments (44).

Conclusions and Future Directions

Environmental and lifestyle factors profoundly shape blood physiology, with exercise and altitude offering adaptive benefits, while climate change and erythritol pose risks. Interconnections, like heat-amplified thrombosis with sweeteners, demand

holistic approaches. Hydration, balanced food, and surveillance should become the priority of the public health measures regarding vulnerable populations. Future studies should involve longitudinal research on synergies, where omics will be added to give personalized interventions. With their treatment, we shall be able to protect blood in the changing world.

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