Oxidative Stress Underpins Clinical, Social, and Genetic Risk Factors for Atherosclerotic Cardiovascular Disease

Clinical Medicine Insights: Cardiology
Volume 17: 1–10

DOI: 10.1177/11795468231170779

Emily Mewborn[1] and Ansley Stanfill[1,2,3]

[1]University of Tennessee Health Science Center, Memphis, TN, USA. [2]Department of Acute and Tertiary Care, College of Nursing, University of Tennessee Health Science Center, Memphis, TN, USA. [3]Department of Genetics, Genomics, and Informatics, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA.

ABSTRACT

BACKGROUND: Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide and is poorly predicted with current risk estimation tools. The biological mechanisms relating ASCVD risk factors to oxidative stress (OS) and how this accumulates ASCVD risk are misunderstood.

PURPOSE: To develop a comprehensive conceptual model explaining how expanded clinical, social, and genetic ASCVD risk factors accumulate ASCVD risk through OS.

CONCLUSIONS: OS (primarily from excess reactive oxygen species) and inflammation are present along the entire ASCVD pathophysiologic continuum. An expanded list of clinical and social ASCVD risk factors (including hypertension, obesity, diabetes, kidney disease, inflammatory diseases, substance use, poor nutrition, psychosocial stress, air pollution, race, and genetic ancestry) influence ASCVD largely through increased OS. Many risk factors exert a positive feedback mechanism to increase OS. One genetic risk factor, haptoglobin (Hp) genotype, is associated with higher ASCVD risk in diabetes and hypothesized to do the same in those with insulin resistance due to the Hp 2-2 genotype increasing OS.

IMPLICATIONS: Understanding the biological mechanisms of OS informs how these ASCVD risk factors relate to each other and compound ASCVD risk. Individualized ASCVD risk estimation should include a comprehensive, holistic perspective of risk factors to better address the clinical, social, and genetic influences of OS. Preventing and reducing OS is key to preventing ASCVD development or progression.

KEYWORDS: Oxidative stress, reactive oxygen species, endothelium, atherosclerosis, inflammation, risk

RECEIVED: January 16, 2023. **ACCEPTED:** March 31, 2023.

TYPE: Perspective

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Emily Mewborn, University of Tennessee Health Science Center, 874 Union Avenue, Suite G022B, Memphis, TN 38163, USA. Email: ecox9@uthsc.edu

Cardiovascular disease remains the number one cause of death in the United States and worldwide, causing 1 in 4 deaths,[1] many of which are attributable to the accumulation of endothelial lipid-rich plaque in cerebral, coronary, or peripheral arteries, thereby creating atherosclerotic cardiovascular disease (ASCVD). Despite attempts to understand the complex interplay between various clinical, social, and genetic risk factors, current ASCVD risk estimator calculators used in clinical practice fail to accurately and comprehensively assess an individual's ASCVD risk. The most recently recommended pooled cohort equation (PCE) often underestimates ASCVD risk in individuals with inflammatory disease or those of lower socioeconomic status.[2] Conversely, the PCE overestimates ASCVD risk in individuals with cumulative exposure to protective factors, including higher socioeconomic status, healthy nutrition, and exercise.[2] This article proposes a new, more comprehensive conceptual model depicting an individual's accumulation of ASCVD risk, mediated mainly through oxidative stress (OS). By accurately appropriating the underlying mechanisms of ASCVD risk factors to OS, individuals and their healthcare providers can better understand, prevent, and treat ASCVD.

Oxidative Stress and Atherosclerosis

Reactive oxygen species (ROS) are mainly produced by the normal cellular mitochondrial metabolism of oxygen but can also be generated by endothelial and inflammatory cells.[3] Main examples of ROS include hydroxyl radical (HO·), alkoxyradicals (RO·), hydrogen peroxide (H_2O_2), hydroperoxides (ROOH), hypochlorous acid (HOCl), peroxy radicals (ROO·), and superoxide ($O2^-$).[4,5] ROS are highly reactive and unstable.[6] In low quantities, ROS defend against pathogenic organisms.[7] However, OS occurs when the action of prooxidants overcomes that of antioxidants; therefore, excess ROS are unable to be cleared by the cells.[3,8] Exogenous and endogenous factors affect the balance of prooxidants and antioxidants. For example, deficient intake of dietary antioxidants or tobacco use, environmental pollutants, ultraviolet exposure, heavy metals, or specific medications increases exogenous prooxidants.[3,8] Disease processes that cause chronic inflammation (eg, autoimmune diseases) or iron overload are examples of endogenous contributors to OS.[3]

Inflammation and OS make contributions along the entire pathophysiologic continuum of ASCVD, where atherosclerosis can be considered a chronic inflammatory disease (Figure 1A).[9]

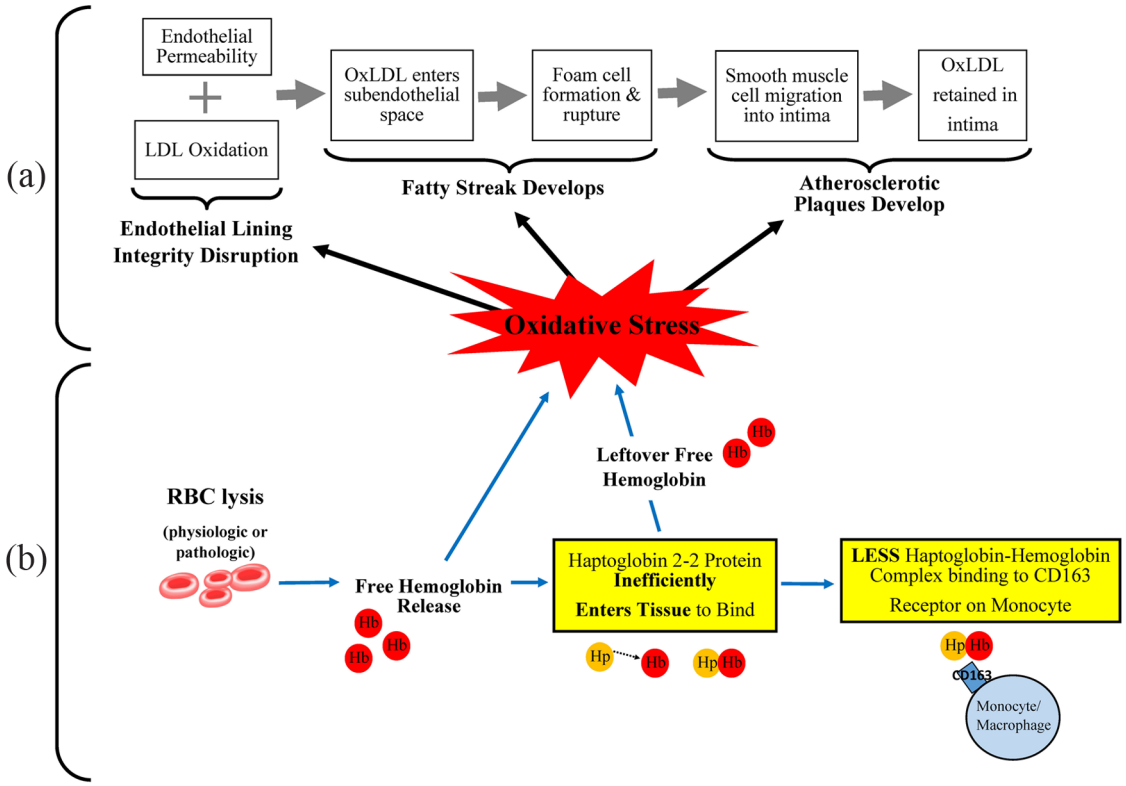

Figure 1 Oxidative stress influence on atherosclerosis continuum in Hp 2-2 genotype: (a) Oxidative stress influences every stage of atherosclerosis and (b) Process of haptoglobin 2-2 protein creating oxidative stress.
Abbreviations: LDL, low-density lipoprotein; oxLDL, oxidized low-density lipoproteins.

Without OS, most lipoproteins transcytose through endothelial cells without getting trapped or oxidized.[10] However, endothelial inflammation results from a host of insults on the arterial endothelial lining via OS. The imbalance of prooxidant and antioxidant forces, resulting in OS, causes endothelial permeability, and oxidizes low-density lipoproteins (oxLDL).[3,11] Disruption in the endothelial lining also decreases nitric oxide (NO) production and increases endothelin-1 production, increasing vascular resistance.[12] ROS also disrupt the production of endothelial nitric oxide synthase (eNOS), the enzyme that generates NO, rendering it dysfunctional where it becomes prooxidant versus antioxidant.[9] The OxLDL readily enters the subendothelial space (due to increased endothelial permeability), gets trapped, and aggregates, which are critical steps in atheroslcerosis.[10]

The oxLDL trapping occurs through a unique process with OS at the helm. OS stimulates platelets to produce platelet-derived growth factor (PDGF). PDGF promotes the transformation of contractile smooth muscle cells (SMCs) to migratory secretory SMCs, which migrate to the deep layer of the endothelial intima.[10] ROS can also promote this transformation.[9] Migratory secretory SMCs produce "sticky" proteoglycans, which trap the oxLDL in the arterial intima.[10,12] SMCs also produce cytokines, further worsening inflammation.[13]

The trapped oxLDL triggers a cascade of inflammatory and immune responses, including cytokines (ie, interleukin 1 beta, interleukin 6, interleukin 18, and tumor necrosis factor alpha), monocyte recruitment into the intima, and increased mitochondrial and inflammasome activity.[10] All of these processes perpetuate inflammation, therefore sustaining the OS.[3,10] The immune-mediated monocytes differentiate into macrophages, which phagocytize the oxLDL and become engorged.[10,14] This process creates pathognomonic foam cells, the hallmark of the early atherosclerotic fatty streak.[10,14] Secretory migratory SMCs can also ingest oxLDL to form foam cells. The foam cells produce ROS, pro-inflammatory chemokines, cytokines, and growth factor, worsening inflammation, and OS.[12,15] Atherosclerosis progresses as foam cells aggregate and form fibroatheromas.

These fibroatheromas contain a necrotic core filled with cellular debris and foam cells and are covered by a thin fibrous cap prone to rupture.[16] Eventually, OS, through excess ROS, can promote the production of matrix metalloproteinases, leading to fibrous cap erosion, plaque rupture, thrombus formation, and microvascular or macrovascular ischemia.[9,12] Fibroatheromas may remain dormant for many years until a precipitating imbalance of OS triggers plaque rupture. Appreciating the role of OS is critical to understanding how various risk factors contribute to ASCVD.

Clinical risk factors mediated by oxidative stress

Many traditional clinical risk factors increase ASCVD risk through OS, including hypertension (HTN), obesity, increased

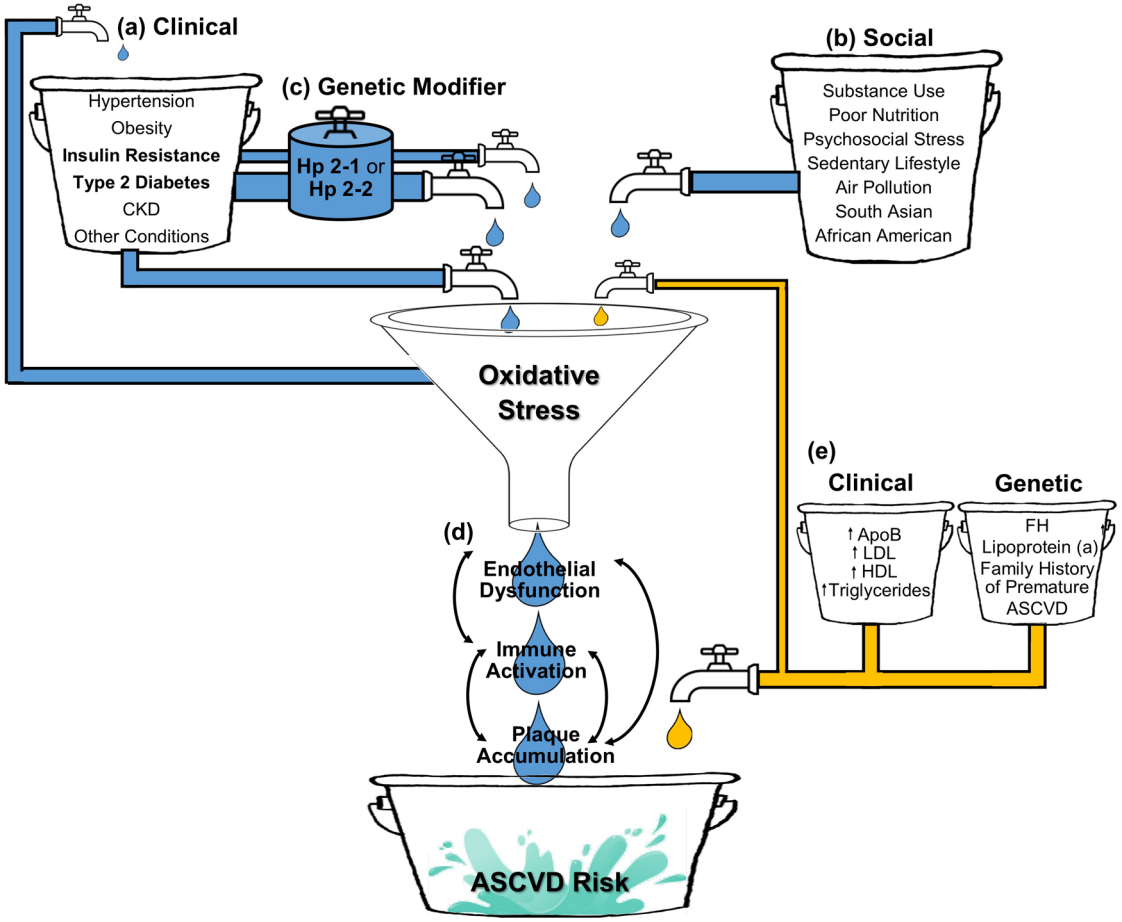

Figure 2. Oxidative stress mediating the accumulation of ASCVD risk.
Abbreviations: ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein, Hp, Haptoglobin; LDL, low-density lipoprotein.

high-sensitivity *C*-reactive protein (hs-CRP), insulin resistance (IR), type 2 diabetes (T2D), chronic kidney disease (CKD), and other chronic conditions (Figure 2(a)). Each of these contributions is described in turn.

Hypertension. First, OS plays a role in the development and worsening of HTN, a well-established risk factor of ASCVD.[17] The underlying OS may result from exogenous or endogenous processes, including psychological or physical stress, injury, infection, or environmental pollution.[4] ROS increase blood pressure by preventing NO action, a potent vasodilator, and by not inhibiting angiotensin II, an opposing vasoconstrictor.[6,17] Specifically, peroxynitrite production stems from OS, inhibiting eNOS and eventual eNOS uncoupling, preventing NO and leading to superoxide production.[4] Furthermore, angiotensin II increases nicotinamide adenine dinucleotide phosphate (NADPH), further increasing OS.[4] These ROS lead to vascular remodeling and endothelial dysfunction, worsening HTN and ASCVD risk.[17] Conversely, HTN causes increased expression and activity of ROS, mainly through NADPH, endoplasmic reticulum stress, and NO synthase uncoupling, all increasing OS.[18,19] Therefore, HTN develops in part from OS but also contributes to OS, providing an example of the feedback loop that can occur between OS and clinical risk factors.

Obesity. Obesity, whether general or visceral, increases incident ASCVD by approximately 68%.[20] Obesity, whether in isolation or combination with other metabolic diseases, provides another example of the reciprocal relationship between risk factor and OS, with obesity both causing and resulting from OS.[21] Obesity is associated with lower adiponectin. Adiponectin regulates glucose metabolism, preserves insulin sensitivity (preventing T2D), and exhibits anti-inflammatory and cardioprotective benefits.[22] Obesity is also associated with higher leptin levels, a hormone responsible for regulating satiety and hunger.[7] Increased leptin is pro-inflammatory, even activating cytokines in endothelial cells. Paradoxically, ROS also increase obesity through increasing and differentiating adipocytes and growth hormones, compounding OS potential in obesity.[7] Patel et al[23] found that individuals with obesity produced and sustained more postprandial ROS. Additionally, the higher caloric intake often associated with obesity increases OS through mitochondrial overload, increasing ROS.

Insulin resistance/Type 2 diabetes. Next, T2D and IR also exhibit a reciprocal relationship with OS. IR develops at least 5 to 12 years before T2D diagnosis.[24,25] IR occurs when insulin is less effective in tissues, predominantly muscle cells, leading to compensatory hyperinsulinemia.[26] Hyperglycemia results when the pancreatic beta cells can no longer keep up with this insulin demand. Results from the National Health and Nutrition Examination Survey (NHANES) found individuals with IR have an approximately 3-fold higher risk of coronary artery disease than individuals without IR.[27] Dal Canto et al.[28] iterate that T2D acts as a continuous variable ASCVD risk factor similar to blood pressure and cholesterol. Additionally, being diagnosed with T2D is equivalent to aging approximately 15 years, meaning individuals with T2D develop ASCVD 15 years earlier than those without T2D.[29]

IR and T2D induce the activity of ROS and decreased activity of antioxidants, adversely affecting the balance of prooxidants, and antioxidants.[6] Elevated cellular glucose ultimately leads to superoxide production from increased nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$).[30] Decreased adiponectin in T2D worsens IR, reduces the anti-inflammatory activity of this hormone, and is associated with lower high-density lipoprotein (HDL) cholesterol levels and higher low-density lipoprotein (LDL) cholesterol levels.[7,21] Furthermore, IR inhibits NO and increases endothelin-1 production, causing vasoconstriction and endothelial dysfunction.[31] Conversely, OS decreases insulin production and further impairs glucose uptake into muscle cells, worsening insulin resistance and glycemia.[32] The mounting ROS in IR, T2D, and the related conditions prevents phosphorylation of insulin receptor substrate-1.[10] This prevents glucose transporter 4 migration to the muscle cell membrane, which allows glucose uptake into the muscle cell, thereby worsening glycemia. T2D-associated OS is worsened with higher glycemia and related conditions such as obesity, CKD, and HTN.

Chronic kidney disease. CKD itself is an independent risk factor for ASCVD,[33,34] largely attributable to its association with OS.[35] CKD causes a reduction of antioxidants and increased ROS production.[36] CKD-associated OS decreases eNOS and increases renin, contributing to impaired glomerular circulation through angiotensin II, endothelin 1, and renin-induced vasoconstriction.[35] Additionally, ROS weaken the structural integrity of the glomerulus.[35] This imbalance of anti- and prooxidants impairs vasodilation and causes endothelial dysfunction and vascular smooth muscle cell spasms,[36] a crucial early step of atherosclerosis. The OS in CKD also worsens HTN through sodium retention and inflammation, increasing ASCVD.[35] Individuals with CKD often have other co-morbidities (eg, HTN, obesity, and T2D), compounding the amount of OS and ASCVD risk. The OS accelerates the progression of CKD, worsening the cycle of OS, CKD, and ASCVD.

Other conditions. Other clinical conditions increase an individual's ASCVD risk through OS. These conditions include but are not limited to, preeclampsia, premature menopause, obstructive sleep apnea, depression, autoimmune diseases, chronic infection (eg, hepatitis, HIV, or dental pathogens), hyperuricemia, and hyperhomocysteinemia.[37-45] These conditions also have a reciprocal relationship between the disease and OS.

Social risk factors mediated by oxidative stress

Social risk factors that increase ASCVD risk through OS can be categorized as either modifiable or nonmodifiable (Figure 2 [b]). Potentially modifiable social risk factors include substance use, poor nutrition, psychosocial stress, and air pollutants. One nonmodifiable social risk factor is South Asian ancestry, encompassing individuals from India, Pakistan, Nepal, Sri Lanka, Bangladesh, Bhutan, and the Maldives.[46-48] Further African Americans (AA) in the United States (US) have increased ASCVD risk.[49] Other less understood factors of racism; discrimination; and access to healthcare, housing, or food also may be related to race/ethnicity and therefore be nonmodifiable, depending on the individual's circumstances and broader structural determinants of health.

Substance use. Substance abuse includes alcohol overuse and tobacco or illicit substance use. Alcohol promotes ROS and prevents an individual's innate antioxidant activity against ROS through multiple mechanisms.[50] Specifically, as alcohol is converted to acetaldehyde then acetate, increased oxygen consumption (causing alcohol-induced tissue hypoxia), and ROS formation results.[50] Elevations in cellular free iron generate ROS and increases endothelial dysfunction.[50] Additionally, alcohol decreases ATP production from mitochondrial damage.[50,51] ROS and reactive nitrogen species cause this damage, but this damage leads to more ROS production.[51]

Tobacco use is a well-appreciated ASCVD risk factor. Tobacco smoking directly causes cardiovascular mitochondrial OS, increasing endothelial permeability and preventing vasodilation.[52] The tobacco smoking-induced OS hails from many mechanisms, primarily from increasing mitochondrial metabolism and ROS release.[52] Specifically, individuals who smoke tobacco have more production of F_2-isoprostanes, a biomarker for OS. F_2-isoprostanes are produced in response to free radicals inducing peroxidation of arachidonic acid.[53] These effects are dose-dependent of tobacco smoking. Tobacco smoking reduces NO production, preventing endothelial relaxation, and endogenous antioxidant production.[52]

The abuse of other illicit substances, including amphetamines, cannabinoids, cocaine, and opioids, has been associated with higher rates of ASCVD, especially among individuals with premature ASCVD.[54-57] Use of these substances leads to an increased hyperadrenergic state with impaired parasympathetic activity, OS, and procoagulation.[57] Furthermore, brain astrocytes

and microglia respond to drug-induced neuroinflammation and tissue damage.[54] These cells eventually cause ROS production, increasing OS inflammatory cytokine production. With substance abuse, these cytokines activate the astrocytes and microglias' ultimate production of OS. Substances shown to exhibit this self-perpetuating cycle include amphetamines, cannabinoids, cocaine, opioids, and nicotine.[54] Amphetamines and tobacco specifically have been shown to impair blood-brain-barrier integrity from increased OS.[58] Alarmingly, neuroinflammation may last months after drug exposure.[54]

Poor nutrition. In a recent analysis of the Global Burden of Disease Study 2017, which included 195 countries, an unhealthy diet was the leading contributor to ischemic heart disease deaths.[59] Foods high in saturated fat, trans fat, or sodium; processed and red meats; processed carbohydrates; and sugar-sweetened beverages and foods contribute to OS and ASCVD.[21,46,60] Specifically, van Oostrom et al.[61] found postprandial increases in neutrophils, cytokines, and hydroperoxides after participants were given high fat, high glucose, and mixed fat and glucose meals. These inflammatory changes highlight some of the underlying pathophysiology of poor nutrition and ASCVD.

In this article, poor nutrition is purposefully classified as a social risk factor. This perspective allows appreciation of how culture and social determinants of health (SDOH), such as food insecurity, food deserts, socioeconomic status, education level, and environment, contribute to an individual's regular food intake, the variety of foods available, and the choices made from that selection. However, poor nutrition could be viewed as a clinical factor, as it is not always influenced by SDOH. Poor nutrition can originate from a conscious choice to consume unhealthy foods regularly.

Psychosocial stress. Psychosocial stress can include various social situations within an individual's lived experience, such as the following: early adverse childhood experiences, lower socioeconomic status or financial instability, lower education, abuse/neglect, racism or discrimination, lack of employment or chronic work stress, access to healthcare or safe or secure housing, social isolation, and mental illness. Specifically, Powell-Wiley et al[62] highlighted the following biological consequences of chronic stress: increased central nervous system activation, cortisol and glucocorticoid receptor resistance, inflammatory cytokines, and accelerated aging through DNA methylation and shortening of telomere length. Chronic stress also leads to redox imbalance, which prevents the body's antioxidant defense mechanisms from neutralizing the ROS effects.[63] Each of these pathophysiologic mechanisms increases OS and inflammation, increasing ASCVD.

Air pollution. One emerging ASCVD risk factor is air pollution. Air pollution contains and produces ROS and activates cytokine-mediated inflammation and hemostasis pathways, increasing OS.[64] Sources of air pollution may include fossil fuel combustion from vehicles and commercial and residential heating units, road dust, windblown pollution, and smokestacks.[64] Areas at higher risk include developing countries, specifically urban areas with high population density, exposing a social disparity of ASCVD risk.[65] Acute and long-term exposure carries a higher risk of ASCVD events.[64] The OS associated with air pollution impairs ATP synthesis, causes mitochondrial dysfunction and DNA methylation, and activates transcription factors that express genes related to inflammation and endothelial dysfunction.[5]

Ancestry/race. South Asians and AAs (in the US), a nonmodifiable risk factor in this conceptual model, experience higher OS. South Asians have a higher prevalence and mortality from ASCVD.[47] This is likely not from different pathology but rather from the significantly higher prevalence of IR, T2D, and visceral adiposity.[47] Other Asian groups (ie, Chinese, Japanese, and Korean) have lower ASCVD risk; therefore, correct appropriation of risk is essential for accurate ASCVD risk estimation. AAs in the US also have a higher prevalence of obesity, T2D, HTN, hyperlipidemia, and ASCVD.[49] When compared to matched non-Hispanic Whites, inflammatory biomarkers are consistently higher.[66-68]

Genetic oxidative stress modification based on haptoglobin genotype

While many genetic modifiers are likely present—for a brief review, see Malakar et al[69] haptoglobin (Hp) genotype is particularly related to OS and ASCVD risk (Figure 2(c)). Hp is an acute-phase reactant protein released in response to physiologic or pathologic erythrocyte lysis (ie, physiologic red blood cell turnover, inflammation, infection, trauma, or hemolytic anemia). The Hp protein functions mainly to bind free hemoglobin (Hb).[70] Unbound Hb increases oxidative stress and vascular endothelial dysfunction through decreased NO production and increased free radical release.[70-72] Specifically, free heme iron (in the form of Hb) induces oxidative stress through the Fenton reaction ($H_2O_2 + Fe^{2+} \rightarrow OH\bullet + OH^- + Fe^{3+}$).[73] This means that endogenous hydrogen peroxide (H_2O_2) reacts with ferrous iron (Fe^{2+}) and catalyzes the production of reactive hydroxyl radicals ($OH^{\bullet}$), hydroxide (OH^-), and ferric iron (Fe^{3+}).[74,75] The resulting endothelial dysfunction and permeability trigger the macrophage endocytosis and cascade of foam cells to create atherosclerotic plaque, as previously discussed. Therefore, the Hp protein has antioxidant properties by clearing free Hb from circulation (Figure 1B).

Three main Hp genotypes exist with 2 alleles, which affect the antioxidant capability of the Hp protein. The Hp genotype determines the shape and size of the Hp protein. Specifically, the Hp 1-1 protein is a linear dimer, the Hp 2-1 protein is a linear polymer, and the Hp 2-2 protein is a cyclical polymer.[71,75,76] Because of these differences, the Hp protein from the Hp 1-1

genotype most efficiently enters tissues and the extravascular space to clear free hemoglobin; the Hp 2-1 protein is intermediate; and the Hp 2-2 protein is least efficient, making this genotype more associated with OS.[76,77]

Once the Hp protein binds the free Hb, the Hp-Hb complex exits circulation through the CD163 receptor on the liver's Kupfer cells.[78,79] However, the Hp 2-2 genotype's CD163 receptors do not endocytose the Hb-Hp complexes as quickly as Hp 1-1; therefore, these complexes remain in circulation longer.[76,80] Additionally, Asleh et al[81] reported more than twice the half-life of the Hp-Hb complexes in individuals with the Hp 2-2 genotype and T2D. These individuals also have fewer CD163 receptors to clear these complexes, increasing their time in circulation.[81] The prolonged exposure of Hp-Hb complexes in circulation oxidizes HDL through inappropriately binding to the apolipoprotein A-1 receptor on the HDL.[72,81,82] This change in HDL function from antiatherogenic to proatherogenic reduces HDL's cholesterol efflux function approximately 30% to 40%.[81] In the presence of T2D, the Hp 2-2 genotype also significantly increases (and Hp 2-1 to a lesser extent) ASCVD risk through increased OS from glycosylated Hb having more oxidative activity, which the Hp cannot prevent as effectively.[80]

Notably, Levy et al[83] found individuals with T2D and Hp 2-2 genotype have a 5 times higher risk of ASCVD than those with the Hp 1-1 genotype. Studies have not specifically examined the relationship between Hp genotype and ASCVD in individuals with IR. However, because IR is on a spectrum of dysglycemia, with glycosylated Hb, one can hypothesize that the Hp genotype may increase the risk of ASCVD, albeit to a lesser degree. Apart from T2D, a higher prevalence of resistant HTN, peripheral artery disease, more severe myocardial infarction, heart failure, and kidney disease has been associated with the Hp 2-2 genotype.[70,71,84]

Risk factors less mediated by oxidative stress

While this article proposes that the majority of ASCVD risk factors primarily exude their pathophysiologic influence through OS, clinical and genetic risk factors of ASCVD exist that are less clearly mediated by OS. Abnormal levels of lipoproteins, including LDL, HDL, and triglycerides, are independent ASCVD risk factors. Although present, these lipoproteins and triglycerides increase OS less significantly.

Elevated LDL has been associated with elevated ROS release.[85] Araujo et al[86] reported that patients with hyperlipidemia have higher OS from leukocytes producing ROS in addition to less effective antioxidant defenses. More impactful to the process of ASCVD development, if OS occurs, is the fact that oxidation of these lipoproteins accelerates the ASCVD pathology. Abnormal cholesterol primarily contributes to ASCVD once the lipoproteins are oxidized.

HDL particles exert antiatherogenic properties, including secreting antioxidant enzymes and reverse transport of LDL cholesterol.[87,88] HDL's antioxidant function helps to inhibit LDL oxidation.[87] HDL particle structure differs significantly in antioxidant and antiatherogenic capacity due to its varying size, metabolism, and cholesterol efflux ability.[87] Karabacak et al[89] reported higher OS levels in individuals with low HDL cholesterol levels compared to those with normal HDL cholesterol levels. Lower HDL cholesterol levels have less antioxidant ability and are often associated with higher ASCVD risk.

Elevated triglycerides are commonly associated with IR, T2D, obesity, and poor nutrition. Therefore, while hypertriglyceridemia is often associated with OS, other related risk factors may influence some of the attributable ASCVD risk. However, high postprandial triglycerides acutely induce OS and inflammation, and the accumulation of these exposures increases ASCVD risk.[90,91]

Description of the Conceptual Model

This conceptual model (Figure 2) broadly depicts an individual's accumulation of ASCVD risk by interacting with multifaceted risk factors. Here, we use an analogy of overflowing buckets to illustrate cumulative risk. Each bucket contains clinical, social, or genetic ASCVD risk factors whereby a few, many, or all may apply to a specific individual. Some of these are well-established risk factors described in the literature (eg, HTN, T2D, and hyperlipidemia).[46] We also have added some specific, proposed risk factors, with emerging evidence being provided to support their inclusion. These additional risk factors are included predominantly from their same mechanism of action on ASCVD risk (ie, OS). However, these lists are not comprehensive, especially for structural, genetic, and SDOH factors proposed to increase ASCVD. Other factors may be added as knowledge grows in this area.

Each risk category bucket has a pipe leading it to a faucet. Based on the number or severity of the risk factor(s) in each bucket, the faucet may be turned on higher, signifying more risk attribution from that category. A funnel is used to depict the mediation of the clinical, social, and genetic risk factors that contribute to ASCVD risk through OS. Using the funnel encourages the reader to change their perspective of the biological underpinnings of how these risk factors are connected to ASCVD pathology. For example, instead of obesity being viewed in terms of inactivity and excess caloric intake, it becomes associated with higher inflammatory biomarkers and OS.[7] This illustration purposefully focuses the reader on the central tenet of inflammation from OS being the connection of these risk factors to ASCVD pathology and development.

A pipe stems from the OS funnel, emptying back into the clinical risk factor bucket. Increased OS triggers or worsens clinical ASCVD risk factors, including HTN, obesity, IR, T2D, and autoimmune diseases. Consequently, these conditions contribute to more OS, illustrating the iterative and reciprocal relationship between OS and clinical ASCVD risk factors.

Under the bottom of the funnel of OS depicts the simplified ASCVD pathology (Figure 2(d)) of OS that causes endothelial dysfunction. Endothelial dysfunction activates the immune system from oxidized LDL and macrophages entering the intima, which eventually leads to plaque accumulation. Plaque accumulation perpetually activates the immune system, accelerating atherosclerosis. This pathologic process directly influences ASCVD risk. Essentially, the more OS one has (from multiple risk factors), the more ASCVD pathology is activated.

This conceptual model also depicts the hypothesized association of Hp 2-1 and Hp 2-2 genotypes increasing ASCVD risk through increasing OS in combination with IR. Essentially, Hp 2-1 and 2-2 genotypes act as an accelerant attached to the pipes connected to IR and T2D, increasing OS to a larger extent (hence, the larger pipe diameter) in individuals with T2D than those with IR.

Discussion

Despite great efforts, ASCVD remains the leading cause of death worldwide. Approximately half of all heart attacks occur in people with normal cholesterol and blood pressure and without a history of smoking or diabetes.[92,93] This alarming residual risk necessitates a more individualized and comprehensive ASCVD risk assessment with a better understanding of how risk factors contribute to ASCVD.

The conceptual model proposed in this article depicts how the accumulation of ASCVD risk goes far beyond traditional risk factors. This model could be used for clinician and patient education and in patient care settings to discuss ASCVD risk and develop treatment plans to address residual risk factors. Further, this model expands the perspective of an individual's ASCVD risk to appreciate additional clinical, social, and genetic factors which may alter the treatment plan. This approach contrasts with the traditional ASCVD risk assessment method. Without applying a more comprehensive lens, less appreciated yet still significant ASCVD risk factors (eg, IR, adverse SDOH, ethnicity, and Hp genotype) will be missed.

Clinical considerations to address oxidative stress

Because OS is an accumulation of internal and external prooxidants compared to antioxidants, clinicians should aim to address individualized, underlying causes of OS to reduce ASCVD risk. Healthcare must move beyond the current cholesterol-centric model of ASCVD, not devaluing the importance of cholesterol control but appreciating the significant impact of OS and inflammation on ASCVD risk. In turn, clinicians should educate patients on how their ASCVD risk factors contribute to their ASCVD disease risk or progression, then match interventions to reduce their risk factors. Addressing and reversing the risk factors proposed in the conceptual model (Figure 2) could reduce the OS associated with each risk factor, reducing ASCVD.

Lifestyle interventions. Over two-thirds of CAD deaths worldwide could be prevented by transitioning to a healthy diet rich in fiber, fruits, vegetables, legumes, nuts, whole grains, and fish.[59] These dietary changes impact blood pressure, lipids, IR, and glucose, in addition to reducing OS from the typical unhealthy nutrition patterns in developed countries. Clinicians should be aware of community or online resources to educate and support culturally appropriate lifestyle changes. Clinicians should offer referrals to services, programs, or specialists (eg, social work, community organizations, support groups, food banks, and registered dieticians) to address the complexities of nutrition risk factors.

Time-restricted eating, a version of intermittent fasting, reduces body weight and fat mass (improving insulin sensitivity), decreases the number and amount of remnant cholesterol postprandial effects, blood pressure, demand on pancreatic beta cells, and markers of OS (8-isoprostane).[94] Time-restricted eating includes a fasting window of typically 14 to 20 hours and an eating window of 4 to 10 hours. During the fast, individuals do not consume any calories or artificial sweeteners, but plain coffee or tea and abundant water are allowed.[94] Time-restricted eating may be a more approachable plan for nutrition change as it does not *require* changing what or how much an individual eats. Instead, it changes the timing, which has been found to lower total caloric intake.[94] Clinicians can discuss this intervention with patients, start with a shorter fasting window, and work toward a longer one over time. Cell phone applications are available to log the last food intake and inform the individual when their food window begins. Varady et al[95] report adjusting to an intermittent fasting plan can take up to 2 weeks and that patients should be reminded to stay well-hydrated to prevent potential side effects (eg, headache and constipation).

A socially controversial yet ASCVD-relevant topic to address with patients is alcohol consumption. Current ASCVD prevention guidelines recommend no more than 2 alcohol-containing drinks per day (with a maximum of 14 per week) for men and no more than 1 alcohol-containing drink per day (with a maximum of 7 per week) for women.[46] Previous observational studies have supported and even in some instances encouraged moderate alcohol consumption as an intervention to lower ASCVD risk. However, a recent large cohort study of 463 participants demonstrated moderate alcohol consumption was associated with a healthier lifestyle, confounding the correlation between cardioprotection and alcohol consumption.[96] Biddinger et al[96] ultimately found that when controlling for the healthy lifestyle factors present in individuals that consumed alcohol, all levels of habitual alcohol intake were associated with a nonlinear increased ASCVD risk, with an exponential increase in risk in moderate to heavy alcohol intake. Reducing alcohol can also lower triglycerides, blood sugar, obesity, and hepatic inflammation in patients with these conditions.

South Asian ancestry ASCVD risk estimation. Clinicians should investigate the country of origin of Asian patients. Specifically,

South Asians have a higher risk of ASCVD than other Asian groups (eg, Japanese, Korean, and Chinese).[46,47] Therefore, when combining all Asians into one category, the ASCVD risk appears to be less than other ethnic groups. However, clinicians could better assess and more aggressively treat the underlying insulin resistance in South Asians to reduce their ASCVD risk.[47] For example, using the International Diabetes Federation's cutoff for ethnicity-specific waist circumference is culturally appropriate and more clinically accurate to identify individuals with visceral adiposity or metabolic syndrome.[97] The Framingham Risk Score, American Heart Association/American College of Cardiology ASCVD risk calculator, and the United Kingdom Prospective Diabetes Study (UKPDS) risk engine have not been validated for use in South Asians.[47] Therefore, clinicians should consider using the UK QRISK3 calculator for estimating ASCVD risk in South Asians, appreciating the potential limitations of generalizability since this calculator is based on South Asians in the United Kingdom.[98]

Haptoglobin genotyping. This conceptual model proposes that individuals with IR and Hp genotype 2-1 or 2-2 have increased OS. Further research is needed to clinically support this theory since IR is part of the central pathology of developing T2D. One can hypothesize a smaller gain yet still increased OS with the Hp 2-1 and 2-2 genotype and IR when compared to T2D. Patients with Hp 2-2 genotype and T2D experienced a 51% reduction in myocardial infarction and a 54% reduction in cardiovascular disease death when using vitamin E daily.[99] However, ASCVD harm was experienced in those with Hp 1-1 and Hp 2-1 genotypes.[99] Furthermore, because vitamin E in HDL is significantly reduced, which is not synonymous with serum vitamin E, supplementing vitamin E may improve the cholesterol efflux of the HDL cholesterol.[82] This may account for some ASCVD reduction in individuals with the Hp 2-2 genotype. Hp genotype is a one-time test with significant ASCVD risk reduction potential available through commercially available laboratories. This genotype-specific intervention can be tested using this conceptual model for those with IR.

Limitations. This conceptual model's limitations include not depicting every ASCVD risk factor. It also introduces Hp genotype into ASCVD risk accumulation and hypothesizes a higher risk in patients with IR versus normal glycemia, which has yet to be established. However, this relationship is supported by the higher OS observed in patients with IR, although lesser than those with T2D. Additionally, the authors appreciate some ASCVD risk factors may be unknown, preventing comprehensive risk assessment. This article does not discuss every intervention to reduce OS but instead highlights a few for clinicians to consider. Furthermore, more research is needed for interventions to objectively reduce OS for primary, secondary, and tertiary prevention of ASCVD.

Conclusion

This conceptual model challenges the status quo and expands the influence of individualized ASCVD risk factors. It demonstrates OS as the main biological mechanism connecting most risk factors to ASCVD risk. With many of the risk factors, a reciprocal positive feedback relationship exists wherein the risk factor increases OS, and the OS worsens the risk factor. This conceptual model also specifically avows the nuance and crucial role of social factors on ASCVD that are typically unaddressed. With more accurate ASCVD risk estimation, risk factor-tailored interventions can be developed to address clinical, genetic, and social risk factors.

Acknowledgements

The authors would like to thank Mr. Curtis Roby, MA, for his editorial assistance in the preparation of this manuscript.

Author Contributions

Emily Mewborn conceptualized, designed, drafted, and edited the manuscript. Ansley Stanfill designed, drafted, and edited the manuscript.

ORCID iD

Emily Mewborn https://orcid.org/0000-0002-7830-8756

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update. *Circulation*. 2021;143:e254-e743.
2. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. *Circulation*. 2019;139:e1162-e1177.
3. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev*. 2017;2017:8416763.
4. Barrows IR, Ramezani A, Raj DS. Inflammation, immunity, and oxidative stress in hypertension-partners in crime? *Adv Chronic Kidney Dis*. 2019;26:122-130.
5. Rui W, Guan L, Zhang F, Zhang W, Ding W.PM2.5-induced oxidative stress increases adhesion molecules expression in human endothelial cells through the ERK/AKT/NF-κB-dependent pathway. *J Appl Toxicol*. 2016;36:48-59.
6. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J Clin Biochem*. 2015;30:11-26.
7. Pérez-Torres I, Castrejón-Téllez V, Soto ME, Rubio-Ruiz ME, Manzano-Pech L, Guarner-Lans V. Oxidative stress, plant natural antioxidants, and obesity. *Int J Mol Sci*. 2021;22:1786.
8. Kalyanaraman B. Teaching the basics of redox biology to medical and graduate students: oxidants, antioxidants, and disease mechanisms. *Redox Biol*. 2013;1:244-257.
9. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. *Curr Atheroscler Rep*. 2017;19:42.
10. Bale BF, Doneen AL, Leimgruber PP, Vigerust DJ. The critical issue linking lipids and inflammation: clinical utility of stopping oxidative stress. *Front Cardiovasc Med*. 2022;9:1042729.
11. Bentzon JF, O'tsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114:1852-1866.
12. Wong ND, Amsterdam EA, Toth PP. *ASPC Manual of Preventive Cardiology*. Humana Press; 2021.
13. Doran AC, Meller N, McNamara CA. Role of smooth muscle cells in the initiation and early progression of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2008;28:812-819.
14. Bale BF, Doneen AL, Vigerust DJ. High-risk periodontal pathogens contribute to the pathogenesis of atherosclerosis. *Postgrad Med J*. 2017;93:215-220.
15. Marchio P, Guerra-Ojeda S, Vila JM, Aldasoro M, Victor VM, Mauricio MD. Targeting early atherosclerosis: a focus on oxidative stress and inflammation. *Oxid Med Cell Longev*. 2019;2019:8563845-8563932.

16. Vergallo R, Crea F. Atherosclerotic plaque healing. *New Engl J Med*. 2020;383:846-857.
17. Rodrigo R, González J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. *Hypertens Res*. 2011;34:431-440.
18. Touyz RM, Rios FJ, Alves-Lopes R, Neves KB, Camargo LL, Montezano AC. Oxidative stress: a unifying paradigm in hypertension. *Can J Cardiol*. 2020;36:659-670.
19. Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative stress and hypertension. *Circ Res*. 2021;128:993-1020.
20. Bakhtiyari M, Kazemian E, Kabir K, et al. Contribution of obesity and cardiometabolic risk factors in developing cardiovascular disease: a population-based cohort study. *Sci Rep*. 2022;12:1544.
21. Rani V, Deep G, Singh RK, Palle K, Yadav UC. Oxidative stress and metabolic disorders: pathogenesis and therapeutic strategies. *Life Sci*. 2016;148:183-193.
22. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci*. 2017;18:1321.
23. Patel C, Ghanim H, Ravishankar S, et al. Prolonged reactive oxygen species generation and nuclear factor-kappaB activation after a high-fat, high-carbohydrate meal in the obese. *J Clin Endocrinol Metab*. 2007;92:4476-4479.
24. Robertson R. Pathogenesis of type 2 diabetes mellitus. *UpToDate*. Published online 2021. Accessed May 14, 2021. https://www-uptodate-com.ezproxy.uthsc.edu/contents/pathogenesis-of-type-2-diabetes-mellitus?search=insulin%20resistance&topicRef=1762&source=see_link
25. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. *Diabetes Care*. 2009;32 Suppl 2:S151-S156.
26. Abdul-Ghani MA, DeFronzo RA. Pathogenesis of insulin resistance in skeletal muscle. *J Biomed Biotechnol*. 2010;2010:476279-476319.
27. Adeva-Andany MM, Martínez-Rodríguez J, González-Lucán M, Fernández-Fernández C, Castro-Quintela E. Insulin resistance is a cardiovascular risk factor in humans. *Diabetes Metab Syndr Clin Res Rev*. 2019;13:1449-1455.
28. Dal Canto E, Ceriello A, Rydén L, et al. Diabetes as a cardiovascular risk factor: an overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol*. 2019;26:25-32.
29. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006;368:29-36.
30. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. *Metab Syndr Relat Disord*. 2015;13:423-444.
31. Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. *Endocr Rev*. 2019;40:1447-1467.
32. Luc K, Schramm-Luc A, Guzik T, Mikołajczyk T. Oxidative stress and inflammatory markers in prediabetes and diabetes. *J Physiol Pharmacol*. 2019;70:809-824.
33. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation*. 2003;108:2154-2169.
34. Sarnak MJ, Amann K, Bangalore S, et al. Chronic kidney disease and coronaryartery disease: JACC Ssate-of-the-art review. *J Am Coll Cardiol*. 2019;74:1823-1838.
35. Podkowińska A, Formanowicz D. Chronic kidney disease as oxidative stress- and inflammatory-mediated cardiovascular disease. *Antioxidants*. 2020;9:752.
36. Daenen K, Andries A, Mekahli D, Van Schepdael A, Jouret F, Bammens B. Oxidative stress in chronic kidney disease. *Pediatr Nephrol*. 2019;34:975-991.
37. Agarwal A, Doshi S. The role of oxidative stress in menopause. *J Mid Life Health*. 2013;4:140-146.
38. Eisele HJ, Markart P, Schulz R. Obstructive sleep apnea, oxidative stress, and cardiovascular disease: evidence from human studies. *Oxid Med Cell Longev*. 2015;2015:608438-608439.
39. Faraci FM, Lentz SR. Hyperhomocysteinemia, oxidative stress, and cerebral vascular dysfunction. *Stroke*. 2004;35:345-347.
40. Hassan EA. The relation between homocysteine, oxidative stress, and atherosclerosis disease. *Indian J Public Health Res Dev*. 2019;10:537-542.
41. Ivanov AV, Bartosch B, Isaguliants MG. Oxidative stress in infection and consequent disease. *Oxid Med Cell Longev*. 2017;2017:3496043.
42. Liu N, Xu H, Sun Q, et al. The role of oxidative stress in hyperuricemia and xanthine oxidoreductase (xor) inhibitors. *Oxid Med Cell Longev*. 2021;2021:1470380.
43. Raijmakers MT, Dechend R, Poston L. Oxidative stress and preeclampsia: rationale for antioxidant clinical trials. *Hypertension*. 2004;44:374-380.
44. Smallwood MJ, Nissim A, Knight AR, Whiteman M, Haigh R, Winyard PG. Oxidative stress in autoimmune rheumatic diseases. *Free Radic Biol Med*. 2018;125:3-14.
45. Vargas HO, Nunes SO, de Castro MR, et al. Oxidative stress and inflammatory markers are associated with depression and nicotine dependence. *Neurosci Lett*. 2013;544:136-140.
46. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of Cardiovascular Disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;140:e563-e595.
47. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e1-e34.
48. WorldAtlas. *The Countries of South Asia*. WorldAtlas. Published 2022. Accessed May 20, 2022. https://www.worldatlas.com/articles/the-population-and-economy-of-the-south-asian-countries.html
49. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e393-e423.
50. Wu D, Cederbaum A. *Alcohol, Oxidative Stress, and Free Radical Damage*. National Institute on Alcohol Abuse and Alcoholism. Published 2004. Accessed September 10, 2022. https://pubs.niaaa.nih.gov/publications/arh27-4/277-284.htm
51. Tan HK, Yates E, Lilly K, Dhanda AD. Oxidative stress in alcohol-related liver disease. *World J Hepatol*. 2020;12:332-349.
52. Dikalov S, Itani H, Richmond B, et al. Tobacco smoking induces cardiovascular mitochondrial oxidative stress, promotes endothelial dysfunction, and enhances hypertension. *Am J Physiol-Heart Circ Physiol*. 2019;316:H639-H646.
53. Morrow JD, Frei B, Longmire AW, et al. Increase in circulating products of lipid peroxidation (f2-isoprostanes) in smokers: smoking as a cause of oxidative damage. *New Engl J Med*. 1995;332:1198-1203.
54. Berríos-Cárcamo P, Quezada M, Quintanilla ME, et al. Oxidative stress and neuroinflammation as a pivot in drug abuse. A focus on the therapeutic potential of antioxidant and anti-inflammatory agents and biomolecules. *Antioxidants*. 2020;9:830.
55. Mahtta D, Ramsey D, Krittanawong C, et al. Recreational substance use among patients with premature atherosclerotic cardiovascular disease. *Heart*. 2021;107:650-656.
56. Rezkalla S, Kloner RA. Cardiovascular effects of marijuana. *Trends Cardiovasc Med*. 2019;29:403-407.
57. Singh A, Saluja S, Kumar A, et al. Cardiovascular complications of marijuana and related substances: a review. *Cardiol Ther*. 2018;7:45-59.
58. Sajja RK, Rahman S, Cucullo L. Drugs of abuse and blood-brain barrier endothelial dysfunction: a focus on the role of oxidative stress. *J Cereb Blood Flow Metab*. 2016;36:539-554.
59. Dai H, Much AA, Maor E, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990-2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes*. 2022;8:50-60.
60. Shikany JM, Safford MM, Newby PK, Durant RW, Brown TM, Judd SE. Southern dietary pattern is associated with hazard of acute coronary heart disease in the reasons for geographic and racial differences in stroke (REGARDS) study. *Circulation*. 2015;132:804-814.
61. van Oostrom AJ, Sijmonsma TP, Verseyden C, et al. Postprandial recruitment of neutrophils may contribute to endothelial dysfunction. *J Lipid Res*. 2003;44:576-583.
62. Powell-Wiley TM, Baumer Y, Baah FO, et al. Social determinants of cardiovascular disease. *Circ Res*. 2022;130:782-799.
63. Horn SR, Leve LD, Levitt P, Fisher PA. Childhood adversity, mental health, and oxidative stress: a pilot study. *PLoS One*. 2019;14:e0215085.
64. Franchini M, Mannucci PM. Thrombogenicity and cardiovascular effects of ambient air pollution. *Blood*. 2011;118:2405-2412.
65. Leni Z, Künzi L, Geiser M. Air pollution causing oxidative stress. *Curr Opin Toxicol*. 2020;20-21:1-8.
66. Albert MA, Ridker PM. Inflammatory biomarkers in African Americans: a potential link to accelerated atherosclerosis. *Rev Cardiovasc Med*. 2004;5 Suppl 3:S22-S27.
67. Carroll JF, Fulda KG, Chiapa AL, et al. Impact of race/ethnicity on the relationship between visceral fat and inflammatory biomarkers. *Obesity*. 2009;17:1420-1427.
68. Velásquez-Mieyer PA, Cowan PA, Pérez-Faustinelli S, et al. Racial disparity in glucagon-like peptide 1 and inflammation markers among severely obese adolescents. *Diabetes Care*. 2008;31:770-775.
69. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. *J Cell Physiol*. 2019;234:16812-16823.
70. MacKellar M, Vigerust DJ. Role of haptoglobin in health and disease: a focus on diabetes. *Clin Diabetes*. 2016;34:148-157.
71. Langlois MR, Delanghe JR. Biological and clinical significance of haptoglobin polymorphism in humans. *Clin Chem*. 1996;42:1589-1600.
72. Somer S, Levy AP. The role of haptoglobin polymorphism in cardiovascular disease in the setting of diabetes. *Int J Mol Sci*. 2020;22:287.

73. Sadrzadeh SM, Graf E, Panter SS, Hallaway PE, Eaton JW. Hemoglobin. A biologic fenton reagent. *J Biol Chem*. 1984;259:14354-14356.
74. Sadrzadeh SMH, Bozorgmehr J. Haptoglobin phenotypes in health and disorders. *Pathol Patterns Rev*. 2004;121:S97-S104.
75. Wassell J. Haptoglobin: function and polymorphism. *Clin Lab*. 2000;46: 547-552.
76. Levy AP, Asleh R, Blum S, et al. Haptoglobin: basic and clinical aspects. *Antioxid Redox Signal*. 2010;12:293-304.
77. Melamed-Frank M, Lache O, Enav BI, et al. Structure-function analysis of the antioxidant properties of haptoglobin. *Blood*. 2001;98:3693-3698.
78. Graversen JH, Madsen M, Moestrup SK. CD163: a signal receptor scavenging haptoglobin-hemoglobin complexes from plasma. *Int J Biochem Cell Biol*. 2002;34:309-314.
79. Shih AW, McFarlane A, Verhovsek M. Haptoglobin testing in hemolysis: measurement and interpretation. *Am J Hematol*. 2014;89:443-447.
80. Asleh R, Marsh S, Shilkrut M, et al. Genetically determined heterogeneity in hemoglobin scavenging and susceptibility to diabetic cardiovascular disease. *Circ Res*. 2003;92:1193-1200.
81. Asleh R, Blum S, Kalet-Litman S, et al. Correction of HDL dysfunction in individuals with diabetes and the haptoglobin 2-2 genotype. *Diabetes*. 2008;57: 2794-2800.
82. Goldenstein H, Levy NS, Ward J, Costacou T, Levy AP. Haptoglobin genotype is a determinant of hemoglobin adducts and vitamin e content in HDL. *J Diabetes Res*. 2018;2018:6125420.
83. Levy AP, Hochberg I, Jablonski K, et al. Haptoglobin phenotype is an independent risk factor for cardiovascular disease in individuals with diabetes: the Strong Heart Study. *J Am Coll Cardiol*. 2002;40:1984-1990.
84. Delanghe JR, Duprez DA, De Buyzere ML, et al. Haptoglobin polymorphism and complications in established essential arterial hypertension. *J Hypertens*. 1993;11:861-867.
85. Csonka C, Sárközy M, Pipicz M, Dux L, Csont T. Modulation of hypercholesterolemia-induced oxidative/nitrative stress in the heart. *Oxid Med Cell Longev*. 2016;2016:3863726-3863823.
86. Araujo FB, Barbosa DS, Hsin CY, Maranhão RC, Abdalla DS. Evaluation of oxidative stress in patients with hyperlipidemia. *Atherosclerosis*. 1995;117: 61-71.
87. Kontush A, de Faria EC, Chantepie S, Chapman MJ. A normotriglyceridemic, low HDL-cholesterol phenotype is characterised by elevated oxidative stress and HDL particles with attenuated antioxidative activity. *Atherosclerosis*. 2005;182: 277-285.
88. Ouimet M, Barrett TJ, Fisher EA. HDL and reverse cholesterol transport. *Circ Res*. 2019;124:1505-1518.
89. Karabacak M, Varol E, Türkdoğan AK, Kahraman F, Özaydın M. Low HDL cholesterol situations is characterised by elevated oxidative stress. *J Am Coll Cardiol*. 2013;62:C181.
90. Le NA. Lipoprotein-associated oxidative stress: a new twist to the postprandial hypothesis. *Int J Mol Sci*. 2014;16:401-419.
91. Le NA. Postprandial triglycerides, oxidative stress, and inflammation. In: Waisundara Y, Jovandaric V, Z, M, eds. *Apolipoproteins, Triglycerides and Cholesterol*. IntechOpen;2020:1-12.
92. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *New Engl J Med*. 1997;337: 1360-1369.
93. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated *C*-reactive protein. *New Engl J Med*. 2008;359:2195-2207.
94. Gabel K, Cienfuegos S, Kalam F, Ezpeleta M, Varady KA. Time-restricted eating to improve cardiovascular health. *Curr Atheroscler Rep*. 2021;23:22-29.
95. Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Cardiometabolic benefits of intermittent fasting. *Annu Rev Nutr*. 2021;41:333-361.
96. Biddinger KJ, Emdin CA, Haas ME, et al. Association of habitual alcohol intake with risk of cardiovascular disease. *JAMA Netw Open*. 2022;5:e223849.
97. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. *Published online* 2006. Accessed March 9, 2023. https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html
98. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:1-21.
99. Blum S, Vardi M, Brown JB, et al. Vitamin E reduces cardiovascular disease in individuals with diabetes mellitus and the haptoglobin 2-2 genotype. *Pharmacogenomics*. 2010;11:675-684.