Cardiovascular Disease as a Result of the Interactions Between Obesity, Climate Change, and Inflammation: The COCCI Syndemic

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Obesity and climate change conspire to create an environment in which subclinical vascular inflammation leads to progressive atherosclerosis, which contributes to the number 1 cause of global mortality: cardiovascular disease. The syndemic model requires 2 or more diseases or contributors to disease (such as obesity and climate change) clustering within a specific population in addition to the associated societal and social factors, ultimately creating an environment supportive of a greater adverse interaction. This article explores the syndemic of obesity and climate change as a driver for cardiovascular disease.

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Numerous breakthroughs in medicine and technology over the past half century have addressed risk factors for and management of cardiovascular disease (CVD); yet, despite these successes, CVD remains the number 1 cause of mortality in both men and women.1 The evidence base for treating patients with major CVD risk factors, such as hyperlipidemia, hypertension, and cigarette smoking, have resulted in both robust improvements and national guidelines.2-5 Therapeutic and preventive interventions have continued to improve cardiovascular (CV) outcomes, such that the most recent lipid-lowering trials have demonstrated continued benefits from lowering low-density lipoprotein cholesterol (LDL-C) to levels far below the targets elicited from current guidelines.6-10 However, even with the significant benefits associated with aggressive LDL-C lowering, there remains a considerable residual risk in both primary and secondary CV risk populations (Figure 1).

Historical Perspective on CVD

Cardiovascular disease steadily increased through the first half of the 20th century, peaking around 1968, when the annual growth flattened.11,12 Since that time, CVD mortality rates have decreased from 507/100,000 to 254/100,000—a 50% decrease; yet, given the growth of the population and especially people aged 65 years or older, CVD remains the number 1 cause of mortality.11 Had the trend from 1900 to 1968 continued, it is estimated that an additional 1 million CVD deaths likely would have occurred in 2014.12
CV Risk Factors

Starting in the 1950s and then escalating into the 1960s was a concern over the steep rise in CV events and mortality in the United States. To that end, several public health initiatives contributed to the plateauing of CV mortality, such as the Surgeon General’s 1964 report *Smoking and Health*, the 1977 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, and the 1988 National Cholesterol Education Program Adult Treatment Panel report, all of which recommended more aggressive approaches to CV risk factors. As a component of these guidelines, the traditional risk factors of age, gender, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, systolic blood pressure, smoking history, and diabetes were incorporated into the Framingham Risk Score and later in the Global Risk Assessment for Primary Prevention to predict CV risk. Starting in 1984, the self-reported risk factor status from the Behavioral Risk Factor Surveillance System incorporated 5 CV risk factors: total blood cholesterol greater than or equal to 240 mg/dL, hypertension, BMI greater than or equal to 30, hemoglobin A1c greater than or equal to 6.5%, and current smoker. These risk factors accounted for approximately half of the deaths due to CV events in 2009-2010.

After adjusting for the Behavioral Risk Factor Surveillance System CV risk factor cut-points, there remains considerable residual risk. Recent trials suggest that if more robust cut-points were implemented for these 5 CV risk factors, the residual risk would still persist, albeit further reduced.

Other CV and metabolic risk factors include high serum glucose, high triglyceride, and low HDL-C levels. Individually, these risk factors have not demonstrated similar significant CVD risk reductions as found with LDL-C reduction, blood pressure lowering, and cigarette smoking cessation and, therefore, have not promulgated similar guidelines indicating therapeutic targets for the management and/or prevention of CVD.
Residual CV Risk and Metabolic Syndrome

In the Third Report of National Cholesterol Education Program Adult Treatment Panel III, the diagnostic criteria for metabolic syndrome were defined as the presence of at least 3 of the following 5 risk factors: abdominal obesity, elevated triglyceride level, decreased HDL-C level, elevated blood pressure, and elevated fasting glucose level. When the metabolic panel of glucose, triglycerides, and HDL-C are evaluated collectively for metabolic syndrome, the residual risk for CVD is increased independent of body mass index (BMI). This increase in CVD risk with metabolic syndrome may explain, in part, the significant residual risk that remains, as shown in Figure 1, when traditional risk factors for CVD are improved. Additionally, when more than 3 of the metabolic syndrome risk factors are combined, there is a continuous trend of increasing CVD risk.

Other risk factors, including insulin resistance, pro-inflammatory state, and pro-thrombotic state, were also noted in the definition of metabolic syndrome but were not included in the diagnostic criteria because these risk factors could not be easily identified by routine clinical evaluation. However, these additional metabolic risk factors are most notably associated with obesity.

Residual CV Risk and Obesity

The Canadian guidelines for the diagnosis and management of dyslipidemia and the prevention of CVD, as well as those from the American College of Clinical Endocrinologists for management of dyslipidemia and prevention of CVD, have used the International Diabetes Foundation (IDF) definition for metabolic syndrome. In the IDF model, central obesity (waist circumference, 31 inches in women and 35-37 inches in men, depending on ethnicity) is an essential criterion and requires the addition of 2 of the other metabolic risk factors to complete the criteria defining the metabolic syndrome (Table). People with a BMI of 30 or greater without metabolic risk factors represent a subgroup with normal insulin sensitivity, absent of diabetes, dyslipidemia, or hypertension, and designated as metabolically healthy obese (MHO). The definition of MHO varies somewhat, with the most common being overweight or obese without the presence of metabolic syndrome. Using that definition, the prevalence of MHO generally ranges from 20% to 30% of the obese/overweight population. Compared with metabolically healthy normal-weight people, metabolically healthy overweight and MHO people tend to progressively increase CV risk as their weight increases when followed up for more than 10 years. This finding suggests that an increase in residual CV risk may occur as weight increases in people who are MHO such that about half will transition from metabolically healthy to unhealthy over the next decade. However, the trials investigating MHO did not control for other metabolic risk factors, such as insulin resistance and pro-inflammatory state; thus, people who transition from metabolically healthy to

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Waist Circumference</th>
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<tbody>
<tr>
<td>ATP III, AHA, ACC</td>
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<tr>
<td>Men</td>
<td>≥102 cm (40 in)</td>
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<tr>
<td>Women</td>
<td>≥88 cm (35 in)</td>
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<tr>
<td>IDF (European, US, Canada, Middle Eastern, Sub-Saharan African)</td>
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<tr>
<td>Men</td>
<td>≥94 cm (37 in)</td>
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<tr>
<td>Women</td>
<td>≥80 cm (31 in)</td>
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<tr>
<td>IDF (South Asian, Japanese, Chinese, Ethnic South and Central Americans)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥90 cm (35 in)</td>
</tr>
<tr>
<td>Women</td>
<td>≥80 cm (31 in)</td>
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**Table. Waist Circumference Criteria for Metabolic Syndrome**

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation.
unhealthy may represent a modified version of metabolic syndrome. In addition, Ortega et al\textsuperscript{30} included the level of fitness into the MHO definition and demonstrated that those with high fitness who had MHO represented a subgroup with no apparent additional CV risk.

Residual CV Risk and Normal Weight

The converse of MHO is normal-weight obesity, or people who are of normal weight (BMI <25) but with metabolic syndrome or insulin insensitivity.\textsuperscript{28,31} People with normal-weight obesity have been shown to demonstrate an increased CV risk independent of BMI.\textsuperscript{28,29} Another definition of normal-weight obesity includes those with a normal BMI but increased waist circumference or waist/hip ratio when defining CV risk.\textsuperscript{33}

In the IDF guidelines, the waist circumference criteria were modified by both gender and ethnicity, defining waist circumference differently depending on the ethnic populations (Table). In the Multi-Ethnic Study of Atherosclerosis and the Mediators of Atherosclerosis in South Asians Living in America trials, cardiometabolic risk factors for nonwhite populations (specifically Chinese Americans, blacks, Hispanics, and South Asian Americans) demonstrated greater CV risk and risk factors compared with white populations at a BMI of 18 to 25.\textsuperscript{19} When the BMI fell into overweight and obese categories, the loss of the disproportionate increase in metabolic risk in nonwhite groups essentially disappeared, as it aligned with the CV risk in the white population.\textsuperscript{19}

Residual CV Risk and Emerging Risk Factors

Defining CV risk usually involves the risk from the traditional risk factors of age, gender, total cholesterol, and HDL-C levels, systolic blood pressure, smoking history, and diabetes. However, once these risk factors are accounted for, a residual risk remains that may be associated with a host of other proposed CV risk factors, such as remnant lipid, LDL-C, and HDL-C particle size and number, lipoprotein(a), lipoprotein-associated phospholipase-A2, homocysteine, uric acid, sitosterols, and subclinical inflammation.\textsuperscript{33} The 2013 American College of Cardiology and American Heart Association (ACC/AHA) guidelines, as well as the Reynold Risk Score, evaluated many potential risk factors and determined, to date, that these guidelines have insufficient evidence to be included in the primary analysis for CV risk.\textsuperscript{2,34,35} In the future, some if not many of these risk factors may eventually be shown to merit inclusion among the traditional risk factors.

Other modifiable risk factors, such as socioeconomic status, health care access, discrimination and bias, sedentary lifestyle, and lack of fitness may likewise affect CV outcomes.\textsuperscript{16,36} It is beyond the scope of this review to detail all of these novel risk factors, and we therefore focus on the unique interactions associated with air pollution, dysmetabolic obesity, and their interface with socioeconomic factors as they relate to CV risk.

Residual CV Risk and Subclinical Inflammation

In the 2013 ACC/AHA guideline on the treatment of blood cholesterol, a group of biomarkers and noninvasive tests were recommended for consideration in people for whom the decision to treat remained unclear.\textsuperscript{2} Additional CVD risk factors include family history of premature CVD, high-sensitivity CRP (hs-CRP) greater than or equal to 2 mg/L, ankle brachial index less than 0.9, coronary artery calcium score greater than or equal to 300 Agatston units or greater than or equal to the 75th percentile for age, gender, and ethnicity.

Pertinent to this discussion was the inclusion of the inflammatory biomarker hs-CRP.\textsuperscript{2} The added CV risk from subclinical inflammation as measured by hs-CRP has been shown in both men and women to significantly improve global CV risk prediction.\textsuperscript{35,37} Results from the Canakinumab Anti-Inflammatory Thrombosis
Outcomes Study (CANTOS) demonstrated a significant decrease in CV events in participants with a history of myocardial infarction who also had an hs-CRP greater than 2 mg/L by reducing inflammation using the selective interleukin 1β (IL-1β) inhibitor, canakinumab. The CANTOS is the first such trial to focus on decreasing subclinical inflammation as an independent risk factor for reducing CV events. The CANTOS used baseline hs-CRP as a downstream surrogate marker for upstream inflammation as a result of IL-1β activation.

Given the significance of inflammation demonstrated by the CANTOS, those risk factors most significantly attributed to increasing inflammation via activation of the IL-1β pathway may be viewed as potential therapeutic targets to reduce the residual CV risk. Weighted multiple logistic regression analysis of CV risk factors adjusted for age and race identified obesity as the risk factor most strongly associated with elevated hs-CRP levels.

Residual CV Risk Associated With Air Pollution and Climate Change

Air pollution, especially smaller particulate matter (PM) less than 2.5 μm (PM2.5), has been shown to produce an inflammatory response that induces macrophage release of IL-1α, IL-1β, and IL-33 signaling pathways, activating the adaptive immune system via the nucleotide-binding oligomerization domain–like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome. Activation of NLRP3 results in further production of IL-1β, with consequent downstream effects driving the inflammatory process by signaling the production of IL-6 and hs-CRP. The inflammatory cascade provoked by PM2.5 is similar to the one instigated in metabolically unhealthy obese patients, in whom metabolically unhealthy adipose tissue is characterized by increased NLRP3 inflammasome activation. It appears that the type of adipose (metabolically unhealthy vs metabolically healthy) may induce inflammation and dysmetabolic outcomes, thus increasing the overall risk as a function of the type of adipose. A mechanistic pathway has been proposed by which PM2.5 induces oxidative stress and inflammation, resulting in acute, subacute, and chronic responses promoting atherosclerosis and CV events.

In an analysis of 36 epidemiologic studies evaluating population-attributable acute triggers for myocardial infarction, traffic exhaust was found to be the single most serious preventable cause to the general public. Both short-term and long-term exposure to PM2.5 have been associated with progressive atherosclerosis, CV events, and mortality. In 2015, the impact of air pollution as designated by ambient PM2.5 was the fifth-ranking mortality risk factor globally, resulting in an estimated 4.2 million deaths and 103 million disability-adjusted life years.

The Harvard Six Cities Study reported that the PM2.5 averaged between 11 and 29.6 μg/m³ and demonstrated a 28% increase in CV events for each 10 μg/m³ increase in PM2.5. In an extended 30-year follow-up, these pollutants were reduced in all 6 cities to less than 18 μg/m³, with an estimated reduction in CV mortality by 30% to 40%.

Today, more carbon dioxide is being released into the atmosphere and, as a consequence, the oceans are warming and acidifying. The combination of increasing ocean temperature and acidity diminishes the ocean’s capacity to absorb carbon dioxide emissions at its current level, thus resulting in more PM remaining in the atmosphere and further exacerbating this problem. In the United States, exposure to atmospheric nitric oxide and PM2.5 is 38% higher in communities predominately inhabited by Hispanics, blacks, and people in the lowest socioeconomic strata. This increased exposure to pollutants in the atmosphere is implicated in glucose dysregulation and insulin resistance, and it may help explain the epidemics in both obesity and diabetes in these communities. The far-reaching global health effects of pollution fall most heavily on the world’s poor communities, where more than 90% of pollution-related deaths occur in low-income and middle-income countries.
greatly affected by household air pollution and contaminated drinking water, while rapidly developing countries are affected by emerging environmental hazards, such as ambient air pollution, toxic chemicals, and pesticides.55

The COCCI Syndemic

The syndemic model requires evidence that 2 or more diseases or contributors to disease (such as obesity and climate change) clustering within a specific population, in addition to the associated societal and economic factors, ultimately creates an environment that supports an adverse interaction in a given population. The classic example of a syndemic is the concurrent infections of HIV and Mycobacterium tuberculosis, which result in worsening symptoms, enhanced disease progression, and increased pathogenic load.56 To that end, the emergence of (1) the obesity epidemic coincided with (2) changes in climate and air quality as a result of PM and atmospheric carbon dioxide surpassing 300 particles per million, both starting in the late 1960s and early 1970s.57

Another intervention occurring at that time was an attempt to address one of the perceived risk factors for coronary heart disease—saturated fat—by replacing dietary fat with carbohydrates.58,59 At the same time, high-fructose corn syrup was moving into the marketplace as a sweeter and cheaper food additive. In a historical analysis by Kearns et al,59 it was noted that at the time of these recommendations, the epidemiologic and mechanistic studies associating sucrose with coronary heart disease were available, albeit somewhat less robust than those for saturated fat, resulting in a recommendation to only recommend reducing cholesterol by substituting polyunsaturated fat for saturated fat.58,59

As an unintended consequence of prioritizing the reduction of fat in the diet, carbohydrate intake, especially fructose consumption, tripled, contributing greatly to the obesity epidemic.60,61

Figure 2.

Particulate matter (PM$_{2.5}$) inducing at-risk adipose cells to acute, subacute, and chronic systemic oxidative stress and inflammation. Abbreviations: ACS, acute coronary syndrome; IL, interleukin; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor 1; TG, triglyceride; TNF-$\alpha$, tumor necrosis factor $\alpha$; WBC, white blood cell.
The Global Burden of Disease Study analyzed 79 behavioral, environmental, and metabolic risks from 1990-2015 in 195 countries and territories. This study revealed that over the past 25 years, there were 4 risk factors that both increased exposure to the given risk factor and resulted in more than 100 million disability-adjusted life years. The leading risk factor was obesity followed by blood glucose and systolic blood pressure. The fourth risk factor, which demonstrated both increased exposure plus increased disability, was ambient PM. Thus, the industrialization of our planet has resulted in an increased risk for the development of CVD.

The concept of the additive CV risk as a result of combining obesity, metabolic syndrome, inflammation, and climate change has been reviewed previously. However, the proposed COCCI (CVD, Obesity, Climate Change, and Inflammation) syndemic highlights this interaction using a different model by also focusing on the biosocial complex, further demonstrating the intensification of CVD beyond that noted by any component individually (Figure 3).

Socioeconomic and Environmental Impact on the COCCI Model

In the syndemic model, certain segments of the population seem to be more susceptible to adverse outcomes than otherwise anticipated for that specific population. The concept of syndemics goes beyond comorbidity, as it encompasses social, environmental, and economic factors that contribute to further detrimental effects. In the COCCI syndemic, the obesity epidemic is more prevalent in the Hispanic and black populations than in the non-Hispanic white and Asian populations. From the COCCI perspective, PM$_{2.5}$ exposure seems to induce adverse risk to a greater degree in children, elderly people, racial minorities, and persons in a lower income strata. Globally, the attributable deaths and disability-adjusted life years from noncommunicable diseases are increasing to a great degree, owing to rising levels of PM$_{2.5}$ in the most populated low- and middle-income countries in east and south Asia.

In a recent comprehensive review, the Lancet Commission on Pollution and Health concluded that pollution of land, water, and air is the largest environmental cause of disease and premature death globally and is responsible for approximately 16% of all deaths worldwide. In the Lancet Commission report, it is estimated that nearly 92% of pollution-related deaths disproportionally occur in low- and middle-income countries. However, even in countries at a higher-income strata, pollution-induced disease and death still occurs and is noted predominately among minorities and marginalized members of society.

The 25-year trends from the Global Burden of Disease Study mortality rankings place air pollution fifth and high BMI, seventh. What may be even more disconcerting relative to the COCCI syndemic is that as much as one-third of overweight people may meet criteria for increased waist circumference and that the harmful impact on public health and the environment may persist in a linear fashion to PM$_{2.5}$ levels well below our current national safety standard of 12 µg/m$^3$. Using these expanded criteria, these 2 risk factors may indicate a CV risk greater than reported and present a plausible explanation as to why a significant residual CV risk persists after accounting for the traditional CV risk factors.
Discussion

The COCCI syndemic has affected the entire planet and appears to be growing despite all of our current efforts. This growth is promulgated in any region or population with concurrent environmental and/or socioeconomic stresses. Wealthy energy-consuming nations are generally responsible for many, if not most, of these stresses, while many of the poorer countries may be the recipient of much of the increased risk. So what can we, as health care professionals, do to help decrease CVD caused by the interaction between dysmetabolic obesity and climate change/air pollution and inflammation?

On May 10, 2017, the World Obesity Federation presented a case that “early diagnosis and treatment of childhood obesity could be considered similar to vaccination,” using the rationale that preventing a disease can occur through proactive public policy. The World Obesity Federation argued that as infectious diseases have been effectively controlled by changes to the environment, such as improved sanitation to reduce the levels of communicable diseases, the obesity epidemic could be controlled by changes to the environment to reduce the mediators causing obesity. Such changes would require collaboration between governments, health care professionals and their organizations, environmental authorities, and the food industry, among others. However, patients with obesity are also confronted by implicit and explicit bias, which often results in stigmatization, adverse health outcomes, and health care disparities, which together create an obstacle for positive interventional efforts.

A similar argument has been made by the American College of Physicians who, in 2016, published an urgent call for action by the medical community to address climate change. This statement encourages physicians to become educated about climate change and its effect on health and how best to respond. The Center for Climate Change and Health, in partnership with the California Medical Association Foundation, the Network of Ethnic Physician Organizations, and the National Medical Association, created a resource, The Physician’s Guide to Climate Change, Health and Equity, to help address how the medical community can respond to this growing concern. This guide is a resource and reference that investigates the complex and multifaceted connections between climate change/air pollution and its disproportionate burden on health equity.

Given the significant residual risk for CVD after traditional risk factors have been addressed and the resultant continuation of CVD as the number 1 cause of mortality across the globe, it behooves the health care system to reevaluate and then readdress this crisis. These concerns are exacerbated in low-income populations that are disproportionately affected by an increased prevalence of obesity, increased consumption of carbohydrates, especially those associated with high fructose corn syrup, and issues with transportation systems, zoning laws, and industrial policies that further increase their PM2.5 exposure.

Conclusion

We put forward a hypothesis that a syndemic model including CVD, obesity associated with metabolic syndrome, and climate change/air pollution may create an opportunity for novel approaches to improve the CVD epidemic. However, there is wide belief among physicians that much of the public health and societal issues germane to this syndemic are not under their purview and therefore “not my job.” The result of such an approach skirts the complexity of this issue and, ultimately, results in a disconnect between managing a symptom rather than the root cause. The COCCI syndemic highlights the importance for the health care community to rise to the challenge to address this complex issue as both a social justice issue and a priority for overall public health and well-being.

References


57. Scott R. Healthy response to climate change. BMJ. 2006;332(7554):1385-1387. doi:10.1136/bmj.332.7554.1385


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