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Review

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Long-Term Exposure to Ambient Air Pollution and Metabolic Syndrome and Its Components

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Ambient air pollution is a serious public health issue worldwide. A growing number of studies has highlighted the negative effects of air pollution on metabolic syndrome (MetS) and its components, including abdominal obesity, disorders of lipid metabolism, elevated blood pressure, and impaired fasting blood glucose. This review provides a brief overview of epidemiological and genetic interaction studies of the links between chronic exposure to ambient air pollution and MetS and its components, as well as plausible mechanisms underlying these relationships. The cumulative evidence suggests that long-term exposure to air pollution, especially particulate matter, increases the risk of MetS and its components. These associations can be partly modified by baseline characteristics, lifestyle, and health conditions. Gene-by-air-pollution interaction studies, limited to candidate genes in the past, have recently been conducted at an expanded genome-wide level. However, more such studies are needed to comprehensively understand the genetics involved in the association between air pollution and MetS. Mechanistic evidence suggests potential biological pathways, including inflammation, oxidative stress, and endothelial dysfunction.

Key words: Air pollution, Association, Gene-environment interaction, Inflammation, Metabolic syndrome, Oxidative stress

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INTRODUCTION

Ambient air pollution, including particulate matter (PM), is a global burden causing multiple human diseases. The World Health Organization (WHO) estimates that, in 2019, approximately 4.2 million premature deaths worldwide were caused by ambient air pollution. South Korea is no exception. According to a report by the Organization for Economic Cooperation and Development (OECD), the number of premature deaths caused by ambient air pollution in South Korea reached 359 per million individuals in 2010, and that figure is expected to more than triple to 1,100 per million individuals by 2060.[1] Most of those deaths are linked to acute cardiovascular events such as stroke and myocardial infarction.[2] However, prolonged exposure to air pollution can result in broader risks.[3] For example, much evidence demonstrates that long-term exposure to air pollution is implicated in metabolic syndrome (MetS) and its components, i.e., abdominal obesity (defined by the waist-to-height ratio), lipid metabolism disorders, elevated blood pressure (BP), and elevated fasting blood glucose levels, leading to premature all-cause mortality.[4,5] Additional studies have reported an association between long-term exposure to air pollution and MetS in subgroup analyses.[6-8]

MetS and its components are complex diseases that result from genetic predisposition, multiple environmental factors, and their interactions. In other words, even under continuous exposure to the same concentration of air pollutants, health outcomes vary among individuals because genetic susceptibility to metabolic traits varies, and that susceptibility can be accounted for in part by gene-by-air-

pollution interactions. Gene-environment interaction studies are important because they provide insights into the genetics and biological mechanisms underlying the relationships between air pollution and metabolic traits. Because of recent developments in genotyping technology, significant interaction results for a few candidate genes have been reported, along with results from genome-wide interaction studies.

This review discusses the associations between long-term exposure to air pollution and MetS (and its components) and investigates possible biological mechanisms underlying those relationships. In addition, this review mentions several genes that are plausibly involved in metabolic traits through interactions with air pollution.

AMBIENT AIR POLLUTION

Ambient air pollution refers to air pollution in outdoor environments and includes PM ≤ 2.5 μm in diameter ($PM_{2.5}$), PM ≤ 10 μm in diameter (PM_{10}), carbon monoxide, nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). The International Agency for Research on Cancer has classified PM as a causal carcinogenic agent (group 1 carcinogen). Air quality standards vary from country to country, depending on air pollution levels and socioeconomic status, among other factors. For example, the annual average concentration standard for $PM_{2.5}$ is about 15 μg/m^3 in South Korea, the United States, and Japan, but it is much higher, about 35 μg/m^3, in China. By contrast, the WHO guideline recommends that the annual average concentration not exceed 5 μg/m^3.[9] The standards in the WHO guideline are stringent because they represent the ultimate goal of reducing the enormous global health burden caused by exposure to air pollution. According to OECD Health at a Glance 2017, most OECD countries have unsafe levels of air pollution. Population exposure to $PM_{2.5}$ is relatively high in Türkiye, Korea, Poland, and Hungary, and it is below the OECD average in New Zealand, Canada, Australia, Finland, and Iceland.[10] The overall trend in air pollution concentrations has been decreasing since 1990, but the levels remain dangerously high. Considering its negative effects on human health, ambient air pollution has become a social problem worldwide.

EPIDEMIOLOGY OF METABOLIC DISORDERS DURING LONG-TERM EXPOSURE TO AMBIENT AIR POLLUTION

Association between air pollution and MetS

MetS is defined as a cluster of metabolic abnormalities such as abdominal obesity, elevated BP, hyperglycemia, high serum triglycerides, and low serum high-density lipoprotein (HDL). The results of previous epidemiological studies regarding the association between ambient air pollution and MetS have mostly been consistent (Table 1). The direct association between MetS and ambient air pollution was first investigated in 2015.[5] A study of Swiss adults found that 10 years of exposure to ambient PM_{10} increased the odds of MetS, and that association was stronger in individuals with vigorous physical activity (PA) levels, ever-smokers, and nondiabetics. Since then, most related association studies have been conducted in the adult Chinese population, and the results have consistently shown that exposure to air pollution is associated with an increased risk of MetS.[6-8,11-15] Negative effects of long-term exposure to air pollution on MetS have also been found in children and adolescents.[16,17] Interestingly, in both children and adults, males were found to be more vulnerable than females to MetS due to air pollution.[7,8,17] In addition, the impacts of air quality on MetS are modified by several potential factors, including smoking, alcohol consumption, PA, and obesity status.[6-8] PM is known to have a stronger negative effect on human diseases as the particle size decreases. Therefore, epidemiological studies have investigated exposure to PM_{10}, $PM_{2.5}$, and even PM ≤ 1 μm in diameter,[4,6-8,14,15,18,19] and more recent studies have expanded the list of pollutants to constituents of $PM_{2.5}$ (e.g., sulfate ion [SO_4^{2-}], nitrate [NO_3^-], and ammonium [NH_4^+]).[11,12,16]

Air pollution and obesity

Overweight and obesity, known risk factors for a variety of health outcomes, are becoming a major public health problem worldwide and are estimated to reduce life expectancy by 0.9 to 4.2 years. Given concerns about the obesity epidemic, numerous studies have investigated the causes of obesity, and ambient air pollution has been reported as one of them.[20-23] The relevant review literature reports that long-term exposure to ambient air pollution is associated with

Table 1. Summary of associations between long-term exposure to ambient air pollution and MetS

Author (year)	Population (cohort)	Exposure	Duration	Outcome	Subgroups	Key findings
Eze et al. (2015)[5]	Adults in Switzerland (SAPALDIA), n = 3,769	PM_{10} and NO_2	10-year average concentrations	MetS and its components (IFG, low HDL, HTG, hypertension, and AO)	Age, sex, diabetes status, smoking status, and PA	Air pollution is associated with inflammation, cardiovascular problems, and an elevated risk of MetS, particularly in ever-smokers, non-diabetics, and people with high PA. The most pronounced effects are IFG, hypertension, and AO, suggesting that the cardio-metabolic effects of air pollution result from disrupted glucose homeostasis and increased visceral fat.
Wallwork et al. (2017)[19]	Older males in the United States (NAS), n = 587	$PM_{2.5}$	Annual average concentrations	MetS and its components (AO, FBG, low HDL-C, hypertension, and HTG)	-	Air pollution and temperature can affect MetS and its components, such as elevated FBG and HTG. A slight increase in $PM_{2.5}$ or a 1 °C increase in annual temperature can heighten the risks.
Yang et al. (2018)[8]	Adults in China (33CCHS), n = 15,477	PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3	Annual average concentrations	MetS	Age, sex, smoking status, alcohol consumption, PA, income bracket, frequent soft drink intake, and dietary control	Long-term exposure to various ambient air pollutants increases the risk of MetS, particularly among males, young to middle-aged adults, low-income individuals, and those with unhealthy lifestyles.
Hou et al. (2020)[6]	Adults in China (Henan Rural Cohort Study), n = 39,089	PM_1, $PM_{2.5}$, PM_{10}, and NO_2	3-year average concentrations	MetS	PA	Long-term exposure to ambient air pollutants increases the risk of MetS in rural Chinese adults. Although PA reduces this risk, its protective effect diminishes as pollutant concentrations increase.
Zhang et al. (2021)[17]	Children and adolescents in China, n = 9,897	PM_1, $PM_{2.5}$, PM_{10}, and NO_2	2-year average concentrations	MetS and components (AO and FBG)	Sex, weight status, PA, and sugar-sweetened beverage intake	Long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 is associated with a high prevalence of MetS in Chinese children and adolescents, particularly males. This association is linked to AO and elevated FBG.
Guo et al. (2022)[12]	Middle-aged and older adults in China (CHARLS), n = 13,418	$PM_{2.5}$ and its constituents (BC, NH_4^+, NO_3^-, OM, and SO_4^{2-})	Annual average concentrations	MetS	Age, sex, urbanicity, smoking status, alcohol consumption, and obesity status	$PM_{2.5}$ and its components, especially BC, are associated with an increased risk of MetS. This risk is higher in females, individuals younger than 60, city residents, smokers, alcohol drinkers, and obese individuals.
Liu et al. (2022)[14]	Elderly adults in China (HABCS), n = 1,755	$PM_{2.5}$	3-year average concentrations	MetS and its components (AO, FBG, hypertension, HTG, and HDL-C)	Age, sex, and urbanicity	Each 10 μg/m^3 increase in $PM_{2.5}$ increases the risks of AO and MetS by 1.19 and 1.16 times, respectively, and decreases that of HDL-C by 1.14 times. The associations between $PM_{2.5}$ and MetS, AO, high FBG, and lower HDL-C were significant only in rural areas.
Wang et al. (2022)[7]	Adult residents in China (WCDCS), n = 10,253	$PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3	3-year average concentrations	MetS	Age, sex, smoking status, alcohol consumption, and fruit intake	Exposure to PM_{10}, $PM_{2.5}$, and O_3 is associated with a higher risk of MetS in China, whereas NO_2 and SO_2 did not show a clear link. The risk is higher in males, smokers, alcohol drinkers, and those who consume fruits only occasionally.

(*Continued to the next page*)

Table 1. Continued

Author (year)	Population (cohort)	Exposure	Duration	Outcome	Subgroups	Key findings
Zheng et al. (2022)[15]	Adults and elderly in China (Chronic Disease and Risk Factors Surveillance), n = 6,628	$PM_{2.5}$, PM_{10}, SO_2, NO_2, and O_3	2-year average concentrations	MetS and its components (AO, HTG, HDL-C, hypertension, and FBG)	Age, sex, smoking status, alcohol consumption, PA, BMI, grain consumption, vegetable and fruit consumption, and red meat consumption	A 10 μg/m^3 increase in the 2-year average $PM_{2.5}$ exposure is associated with higher risks of MetS, elevated FBG, and HTG. Long-term exposure to $PM_{2.5}$ is associated with MetS, dyslipidemia, and impaired fasting glucose.
Chen et al. (2023)[4]	Participants in Taiwan (MJ Health Database), n = 93,771	$PM_{2.5}$ and NO_2	Annual average concentrations	MetS and its components (AO, TG, HDL-C, BP, and FBG)	Age and sex	$PM_{2.5}$ is associated with higher TG, lower HDL-C, increased BP, higher FBG, and MetS in both sexes. In males, $PM_{2.5}$ is significantly linked to AO, whereas in females, it is more strongly associated with high BP. All age groups show positive associations between $PM_{2.5}$ and higher TG, BP, and FBG, with younger people at higher risk. NO_2 does not exhibit any significant effects on MetS or its components based on age or sex.
Li et al. (2023)[16]	Children and adolescents in China, n = 10,066	$PM_{2.5}$ and its constituents (BC, NO_3^-, OM, SO_4^{2-}, and SOIL)	Annual average concentrations	MetS and its components (AO, BP, TG, FBG, and HDL-C)	Sex, obesity status, PA, sugar-sweetened beverage intake, parental smoking status, and parental alcohol consumption	Long-term exposure to $PM_{2.5}$ and its constituents, especially BC, is linked to an increased risk of MetS in Chinese children and adolescents.
Liu et al. (2023)[13]	Adults in China (CHARLS), n = 14,097	PM_1, $PM_{2.5}$, PM_{10}, and NO_2	3-year average concentrations	MetS and its components (AO, BP, TG, FBG, and HDL-C)	Age, sex, health status, and alcohol consumption	Long-term exposure to NO_2 and PM is associated with higher rates of MetS and its components, including central obesity, high BP, increased fasting glucose, and low HDL-C, in Chinese adults.
Cai et al. (2024)[11]	Adults in China (YBDS), n = 48,148	$PM_{2.5}$ and its constituents (BC, NH_4^+, NO_3^-, OM, and SO_4^{2-})	3-year average concentrations	MetS and its components (AO, FBG, TG, BP, and HDL-C)	Serum uric acid	$PM_{2.5}$ and its constituents, especially ammonium and sulfate, increase the risk of MetS, partially mediated by serum uric acid. Ammonium is linked to high BP and low HDL-C; sulfate is associated with high fasting glucose; nitrate is connected to high TG; and organic matter is linked to increased waist circumference.

MetS, metabolic syndrome; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; PM_{10}, particulate matter 10 μm or less in diameter; NO_2, nitrogen dioxide; IFG, impaired fasting glycemia; HDL, high-density lipoprotein; HTG, hypertriglyceridemia; AO, abdominal obesity; PA, physical activity; NAS, Normative Aging Study; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; 33CCHS, 33 Communities Health Study; PM_1, particulate matter 1 μm or less in diameter; SO_2, sulfur dioxide; O_3, ozone; CHARLS, China Health and Retirement Longitudinal Study; BC, black carbon; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; SO_4^{2-}, sulfate; HABCS, Chinese Longitudinal Healthy Longevity Survey: Healthy Aging and Biomarkers Cohort Study; WCDCS, Wuhan Center for Disease Control & Prevention Study; BMI, body mass index; BP, blood pressure; TG, triglyceride; SOIL, soil particles; YBDS, Yunnan Behavior and Disease Surveillance.

an increased risk of obesity, primarily defined by body mass index (BMI), in all age groups (children, young adults, and older adults), although the size of the effect varies across studies.[24-26] In particular, previous association studies in adults have shown a stronger link between air pollution and obesity among females.[27,28] Traffic-related $PM_{2.5}$ exposure is closely related to an increased likelihood of obesity in Mexican-American females but not males.[28] A similar result was found in a rural Chinese population.[27] However, the findings about abdominal obesity are limited and unclear. Li et al.[29] found that subjects living 60 m from the nearest major roadway had 78.4 cm^3 more subcutaneous adipose tissue and 41.8 cm^3 more visceral adipose tissue than those living 440 m away. Outdoor air pollution exposure was also associated with waist circumference-defined central obesity and the visceral adiposity index in a middle-aged and older Chinese population.[30] However, no associations were observed between various abdominal adiposity traits and ambient air pollution in Korean adults.[31] Abdominal obesity, especially visceral fat accumulation, plays a crucial role in the pathogenesis of metabolic dysfunction.[32] In this context, further studies are needed to determine the effects of air pollution on abdominal obesity.

Air pollution and blood pressure/hypertension

Numerous epidemiological studies have demonstrated that long-term exposure to ambient air pollution is associated with increased BP and a higher incidence of hypertension. Elevated BP due to air pollution has been reported in adolescents,[33,34] pregnant women,[35-37] general adults,[38-42] and older adults.[43,44] Moreover, several lifestyle and health conditions have been shown to modify the relationship between air pollution and BP.[45-49] In a Chinese study, high-volume and vigorous-intensity PA was found to reduce the risk of hypertension at low $PM_{2.5}$ exposure levels ($< 59.8\ \mu g/m^3$) but not at high $PM_{2.5}$ exposure levels ($\geq 59.8\ \mu g/m^3$).[49] Another recent Chinese study showed that a healthy eating pattern that includes fresh fruits, vegetables, and whole grains can reduce the risk of hypertension caused by $PM_{2.5}$ and its components, emphasizing dietary interventions to prevent stage 1 hypertension.[47] In addition, obesity has been reported to intensify the effects of air pollution on increased BP levels and prevalent hypertension in the Chinese population.[46] In adult Korean males, in particular, the modifying effect of obesity on the association between PM_{10} exposure and hypertension was more pronounced in those with greater mass of abdominal visceral fat than abdominal subcutaneous fat.[48]

Air pollution and gestational diabetes mellitus/insulin resistance/type 2 diabetes mellitus

About one-fifth of the disease burden of type 2 diabetes mellitus (T2DM) is due to air pollution, with 13.4% attributable to ambient $PM_{2.5}$ pollution alone. Particularly high burdens have been estimated in Asia and South America.[50] The relationship between air pollution and diabetes has been reported in numerous epidemiological studies, mainly focusing on gestational diabetes mellitus (GDM).[18,51-54] A meta-analysis reported that, among the pollutants tested, only NO (pooled effect estimate [EE] = 1.04; 95% confidence interval [CI], 1.03 to 1.06) and SO_2 (pooled EE = 1.39; 95% CI, 1.04 to 1.73) had statistically significant EE. The most vulnerable pregnancy period was the second trimester.[55] A more recent meta-analysis demonstrated significant associations between GDM and maternal exposure to several air pollutants, including $PM_{2.5}$, PM_{10}, SO_2, and O_3.[56] These effects might be modulated by health issues such as anemia or high BP.[18] In addition, long-term exposure to ambient air pollution is linked to increased odds of insulin resistance and T2DM.[57-60] A recent meta-analysis of 10 studies reported that each 1 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10} concentration led to changes of 0.40% (95% CI, −0.03 to 0.84) and 1.61% (95% CI, 0.243 to 2.968), respectively, in the homeostasis model assessment of insulin resistance (HOMA-IR) level.[59] This effect of PM on HOMA-IR was maintained even after adjusting for visceral fat, which is a risk factor contributing to the development of insulin resistance.[60] Previous studies on T2DM found traffic-related air pollutants such as $PM_{2.5}$, NOX, and NO_2 to be associated with the incidence or risk of T2DM.[57,61] PM_{10} exposure was also related to prevalent diabetes in a population-based Swiss cohort.[58] Notably, the harmful effects of air pollutants were stronger among people with high PA levels.[57,58]

Air pollution and lipid profiling

A multiethnic study (i.e., White, Black, Hispanic, and Chinese) from 2017 found that medium-term (3 months before examination) $PM_{2.5}$ exposure was inversely associated with the HDL partial number but not HDL cholesterol.[62] However, in a recent study

based on the general population of Spain, each interquartile range increase in PM_{10}, $PM_{2.5}$, and NO_2 was significantly associated with 3.3%, 3.3%, and 3% reductions in HDL cholesterol, respectively.[63] A similar result was found in young adult Korean males.[64] Moreover, those effects were stronger in males and people with obesity.[63,65] Gaio et al.[66] proposed abdominal obesity as a mediator in the relationship between PM_{10} exposure and increased blood triglyceride levels. Furthermore, ambient PM_{10} exposure and abdominal adiposity had significant interactions with low-density lipoprotein (LDL) cholesterol in visceral fat but not subcutaneous fat.[67] In addition to the lipid profile, the risk of lipid disorders such as dyslipidemia and hypercholesterolemia increased with exposure to ambient air pollution.[68]

GENE-BY-AIR-POLLUTION INTERACTION

MetS and its components are complex diseases influenced by multiple genes, environmental factors, and interactions between them. In the past, the interactive effects of air pollution have been identified for a small number of candidate genes chosen based on prior hypotheses about underlying disease mechanisms.[69,70] In particular, studies on short- rather than long-term exposure mainly investigated genes associated with respiratory or cardiovascular diseases.[71-73] In relation to MetS and its components, interactions with long-term air pollution exposure have been reported for BP/hypertension and T2DM (Table 2).[74-79] In 2016, a Swiss cohort study demonstrated that a genetic risk score covering 63 T2DM genes modified the association between PM_{10} exposure and T2DM, particularly insulin resistance-related variants rather than β-cell function variants.[74] However, Jabbari et al.[75] reported that a genetic variant related to β-cell function in the melatonin receptor 1B (*MTNR1B*) gene, rs10830963, was associated with an increased risk of T2DM by interacting with long-term PM_{10} exposure. In a study of BP and hypertension, Levinsson et al.[78] observed no interaction between genetic polymorphisms in the GST genes (glutathione S-transferase π1 [*GSTP1*], glutathione S-transferase θ1 [*GSTT1*], and glutathione S-transferase C-terminal domain [*GSTCD*]) and long-term NO_2 exposure. In addition, Kim et al.[76] found that an intronic variant in *CDH13*, rs750059, strengthens the relationship between PM_{10} exposure and increased BP or hypertension in adult Korean males. Recently, Kim et al.[77] performed the first genome-wide interaction study for BP and found that the association between PM_{10} exposure and BP can be modified by multiple susceptibility loci, including nuclear receptor subfamily 2 (*NR2F2*). Moreover, a recent UK biobank study identified that a polygenic risk score and long-term exposure to air pollution had a combined effect that increased the risk of hypertension.[79] In addition to genetic polymorphisms, DNA methylation was reported to modify the link between air pollution and MetS, but that study was excluded from this review.

MECHANISMS

Although the biological mechanisms underlying the association between air pollution and MetS remain unclear, several hypotheses have been proposed (Fig. 1). Among them, systemic inflammation is the most plausible. Inhaled pollutants can penetrate the bloodstream through the lungs and circulate throughout the body, leading to systemic inflammation that eventually results in MetS and related disorders. Persistent exposure to air pollutants stimulates the production of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, via activated monocytes/macrophages.[80] Such cytokines are mainly released by adipocytes, especially visceral fat.[81] In a mouse model of diet-induced obesity, ambient $PM_{2.5}$ exposure strengthened visceral inflammation and insulin resistance.[82] In adipose tissue, inflammation inducers such as TNF-α and lipopolysaccharide can damage mitochondrial function, and that is associated with impaired lipolysis in adipocytes and decreased energy consumption. Such changes in energy digestion can reduce the absorption of LDL particles in the blood.[83] Furthermore, impairment of early mitochondrial function in energy metabolism can activate insulin secretion, leading to metabolic disorder.[83] Liao et al.[84] reported that exposure to air pollutants increases free fatty acid levels through adipose lipolysis and stress hormones, and that leads to changes in metabolic pathways and inflammation that result in metabolic disorders such as obesity and dyslipidemia. Epidemiological studies in humans have reported that visceral fat accumulation accelerates the negative effects of air pollution on various outcomes, including high LDL-cholesterol and hypertension.[48,67] $PM_{2.5}$ exposure activates the nuclear factor

Table 2. Gene-environment interactions: insights from candidate gene and GWISs

Author (year)	Population (cohort)	Exposure	Duration	Study design	Outcome	Key findings
Levinsson et al. (2014)[78]	Adults in West Sweden (INTERGENE/ADONIX), n = 3,614	NO_2	Annual average concentrations	Candidate gene study (*GSTT1*, *GSTP1*, and *GSTCD*)	Gene-air pollution interactions (cardiovascular health, hypertension)	Long-term exposure to NO_2 from air pollution is significantly associated with an increased risk of AMI. Variants in the *GSTP1* gene are also significantly associated with increased hypertension risk.
Eze et al. (2016)[74]	Adults in Switzerland (SAPALDIA), n = 1,524	PM_{10}	10-year average concentrations	Candidate gene study (63 T2DM-related genes)	Gene-air pollution interactions (T2DM)	The association between air pollution and T2DM is examined using GRS covering 63 T2DM-related genes. Higher levels of PM_{10} are associated with an increased risk of T2DM, particularly among individuals with a higher GRS.
Kim et al. (2019)[76]	Adult males in Korea, n = 1,868	PM_{10}	Annual average concentrations	GWIS (SNPs of *CDH13*)	Gene-air pollution interactions (BP, hypertension)	The gene variant rs7500599 in the *CDH13* gene interacts with air pollution (specifically PM_{10}) to affect blood pressure in Korean males. Those with the GG genotype exhibited higher systolic and diastolic blood pressure in response to PM_{10} exposure than those with the TT or GT genotypes. Hypertension risk increased in those with the GG genotype upon exposure to high PM_{10} levels, indicating a distinct gene-environment interaction.
Jabbari et al. (2020)[75]	Adults in Tehran, Iran (Tehran Cardiometabolic Genetic Study), n = 2,428	PM_{10}	3-year average concentrations	Candidate gene study (SNPs of *MTNR1B*)	Gene-air pollution interactions (T2DM)	Independent effects of air pollution and the rs10830963 polymorphism on the incidence of T2DM were observed. Long-term exposure to PM_{10} increases the risk of diabetes, with this effect being more pronounced in people with the rs10830963 gene mutation. These findings suggest that vulnerability to air pollution can be modulated by the genetic risk of T2DM.
Weng et al. (2022)[79]	Adults in the UK (UK Biobank), n = 391,366	$PM_{2.5}$, PM_{10}, NO_2, and NO_x	Annual average concentrations	GWIS (SNPs related to hypertension)	Gene-air pollution interactions (hypertension)	Both air pollution and genetic risk factors significantly increase hypertension likelihood, with their combined effects being more substantial.
Kim et al. (2023)[77]	Adult males in Korea, n = 1,868	PM_{10}	Annual average concentrations	GWIS (six variants for SBP and five for DBP)	Discover unique genetic loci for BP	The association between PM_{10} exposure and BP levels might be partially determined by newly discovered genetic loci, particularly mutations near the *NR2F2* gene (rs12914147). This research is the first to confirm such interactions through a GWIS, contributing to a better understanding of air pollution-gene interactions.

GWIS, genome-wide interaction study; INTERGENE/ADONIX, Interplay Between Genetic Susceptibility and Environmental Factors for the Risk of Chronic Diseases in West Sweden/Adult-onset Asthma and Exhaled Nitric Oxide; NO_2, nitrogen dioxide; *GSTT1*, glutathione S-transferase θ1; *GSTP1*, glutathione S-transferase π1; *GSTCD*, glutathione S-transferase C-terminal domain; AMI, acute myocardial infarction; SAPALDIA, Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults; PM_{10}, particulate matter 10 μm or less in diameter; T2DM, type 2 diabetes mellitus; GRS, genetic risk score; SNP, single-nucleotide polymorphism; *CDH13*, cadherin 13; BP, blood pressure; *MTNR1B*, melatonin receptor 1B; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter; NO_x, nitrogen oxide; SBP, systolic blood pressure; DBP, diastolic blood pressure; *NR2F2*, nuclear receptor subfamily 2.

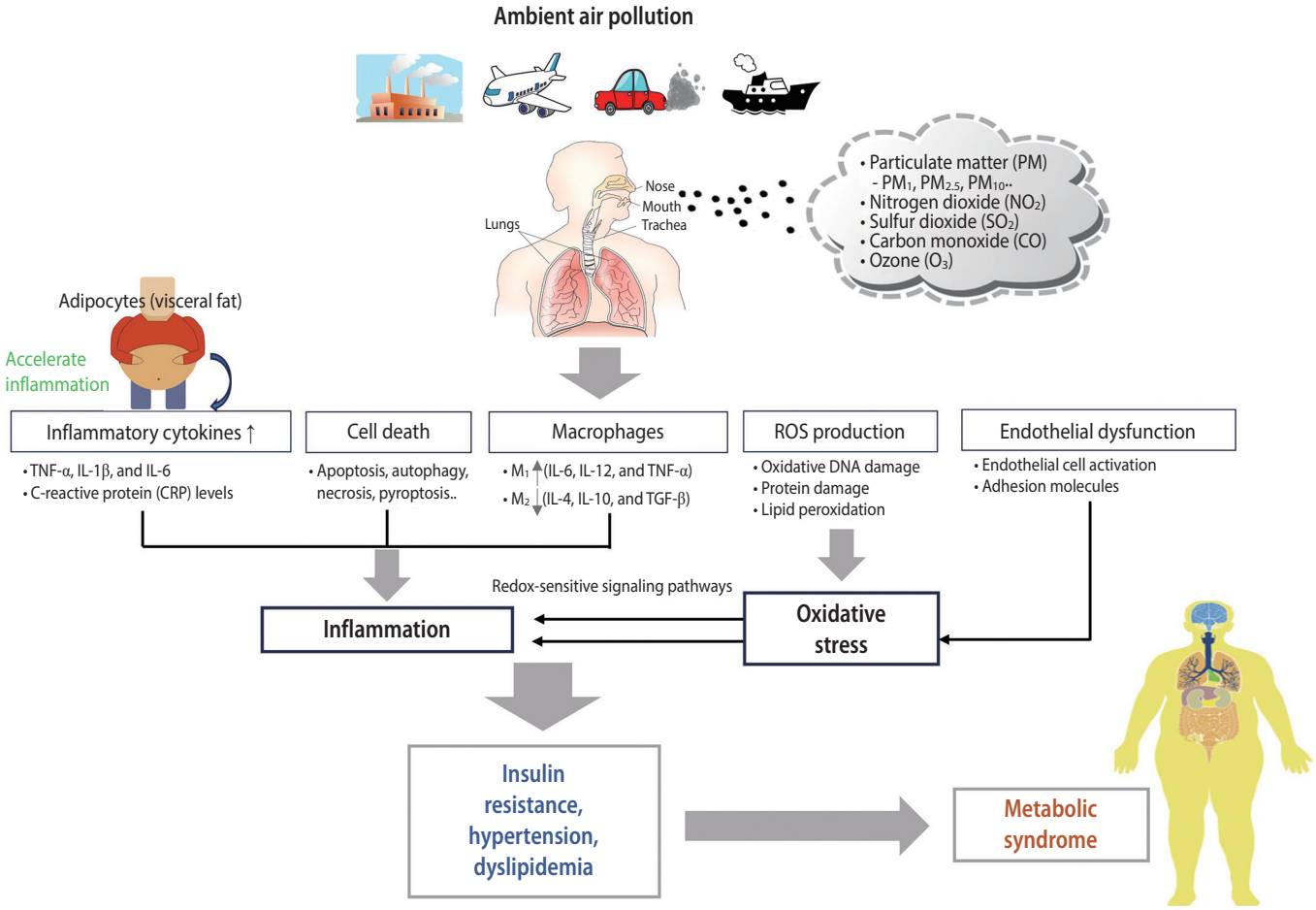

Figure 1. Possible mechanisms underlying the link between air pollution and metabolic syndrome. PM_1, particulate matter 1 μm or less in diameter; $PM_{2.5}$, particulate matter 2.5 μm or less in diameter; PM_{10}, particulate matter 10 μm or less in diameter; TNF-α, tumor necrosis factor-α; IL, interleukin; TGF-β, transforming growth factor-β; ROS, reactive oxygen species.

κB (NF-κB) and Toll-like receptor 4 (TLR4) inflammation pathways and inhibits insulin receptor substrate 1-mediated signal transduction. This inflammatory response can cause abnormal glucose tolerance and insulin resistance.[85] Moreover, chronic exposure to $PM_{2.5}$ is closely related to increased levels of C-reactive protein (CRP), a biomarker for inflammation.[86] In 2022, the China Health and Retirement Longitudinal Study reported that high CRP concentrations strengthened the relationship between air pollution and MetS.[87] In addition, PM exposure leads to multiple types of cell death, including apoptosis, autophagy, necrosis, pyroptosis, and ferroptosis.[88,89] Cell death has been recognized as a major cause of inflammatory reactions.[90] Macrophages also play an important role in regulating inflammation.[91] Depending on environmental changes, they are polarized into pro-inflammatory M1 macrophages or anti-inflammatory M2 macrophages. Chronic exposure to PM triggers the production of more M1 cytokines (e.g., IL-6, IL-12, and TNF-α) and the suppression of M2 cytokines (e.g., IL-4, IL-10, IL-13, and transforming growth factor-β).[92] The oxidative stress response is another key pathway for the association between ambient air pollution and metabolic disease. Inhaled PM and gas pollutants are potent pro-oxidants that can increase the production of reactive oxygen species (ROS).[93] In other words, exposure to air pollution contributes to oxidative damage via ROS generation, which causes oxidative DNA damage, protein damage, vasoconstriction, and lipid peroxidation.[94] Oxidative stress can induce redox-sensitive signaling pathways involved in cell death or inflammation. Air pollution-induced HDL dysfunction is caused by decreased apoA-I, an increased HDL oxidation index, oxidized LDL, and malondialdehyde.[95] Higher levels of air pollution also reduce cholesterol efflux capacity, antioxidant activity, and production of nitric oxide.[96] Furthermore, ex-

posure to air pollutants, especially $PM_{2.5}$, is closely related to endothelial injury, leading to decreased levels of pro-angiogenic growth factors (e.g., epithelial growth factor, soluble CD40 ligand, platelet-derived growth factor, and vascular endothelial growth factor) and increased levels of anti-angiogenic (e.g., TNF-α and interferon-gamma-inducible protein 10) and pro-inflammatory cytokines (e.g., monocyte chemoattractant protein-1, IL-6, and IL-1β).[97] Endothelial dysfunction causes vascular damage and metabolic disorders such as insulin resistance, hypertension, and dyslipidemia.[94,98] In addition, PM that accumulates in the lungs can rapidly induce autonomic nervous system (ANS) imbalance, which can increase BP. ANS imbalance can further affect the activation of vascular oxidative stress, which triggers β-cell dysfunction.[99] Not only are activated ROS directly involved in β-cell damage, particularly structural destruction of mitochondria, but they can also interfere with the insulin signaling pathway.[85] In addition, PM exposure activates endoplasmic reticulum stress and the unfolded protein response in lung and liver tissue, leading to apoptosis of islet β-cells, which is one cause of insulin secretion disorders and diabetes.[85,100] Further research is required to elucidate the mechanisms linking air pollution and MetS.

CONCLUSION

This review summarized the epidemiological relationship, genetic interactions, and possible mechanisms between long-term exposure to ambient air pollution and MetS and its components. The harmful effects of air pollutants, especially PM, on metabolic disorders have been reported, along with several factors that could mediate those effects. Not only does exposure to air pollution increase the risk of obesity (defined by BMI), obesity in turn modifies the risk of other metabolic conditions caused by air pollution. However, the association between air pollution and abdominal adiposity, measured by computed tomography, is unclear. Long-term exposure to ambient air pollution has been reported to be linked to increased BP and hypertension in a variety of age groups. Those associations could be modified by changes in vigorous-intensity PA and healthy eating habits. The association between air pollution and diabetes has been reported primarily in GDM, and the association can vary with health issues such as anemia and high BP. Air pollution exposure is closely related to dyslipidemia and hypercholesterolemia, in addition to decreased HDL cholesterol levels and increased triglycerides, and abdominal obesity might be involved in those associations. Recently, novel genetic loci that interact with air pollutants have been discovered at the genome-wide level, but additional genetic interaction studies are needed to gain a better understanding of the genetics and biological pathways that influence the association between exposure to pollution and MetS.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: HJK and JHP; acquisition of data: HJK and JH; analysis and interpretation of data: HJK; drafting of the manuscript: HJK and JH; critical revision of the manuscript: JHP; obtained funding: HJK and JHP; administrative, technical, or material support: HJK; and study supervision: JHP.

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