Ambient Fine Particulate Matter, Outdoor Temperature and Risk of Metabolic Syndrome

ABSTRACT

Ambient air pollution and temperature have been linked with cardiovascular morbidity and mortality. Metabolic syndrome and its components—abdominal obesity, elevated fasting blood glucose, low high-density lipoprotein cholesterol, hypertension and hypertriglyceridemia—predict cardiovascular disease, but the environmental causes are understudied. This study prospectively examined the long-term associations of air pollution, defined as fine-particulate matter with diameter ≤2.5μm ($PM_{2.5}$), and temperature on the development of metabolic syndrome and its components. Using covariate-adjusted Cox-models, we estimated associations of annual mean $PM_{2.5}$ and temperature with incident risk of metabolic dysfunctions in 587 elderly Normative Aging Study men (mean (SD), 70 (7) years) between 1993-2011. A 1-μg/m3 annual $PM_{2.5}$ increase was associated with higher risk of developing metabolic syndrome (Hazard ratio [HR]=1.27, 95% Confidence Interval (CI): 1.06, 1.52), elevated fasting blood glucose (HR=1.20, 95%CI: 1.03, 1.39) and hypertriglyceridemia (HR=1.14, 95%CI:1.00, 1.30). Metabolic syndrome and high fasting blood glucose findings remained significant in $PM_{2.5}$ levels below the U.S. Environmental Protection Agency's limit (12-μg/m3). A 1-Cº annual temperature increase was associated with greater elevated fasting blood glucose risk (HR=1.33, 95%CI: 1.14, 1.56). Men living in neighborhoods with worse air quality—i.e., with higher $PM_{2.5}$ levels and/or warmer than average—showed increased risk of developing metabolic dysfunctions

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Glossary:

Body mass index	BMI
Confidence Interval	CI
C-reactive protein	CRP
Hazard ratio	HR
High-density Lipoprotein	HDL
Homeostatic model assessment of insulin resistance	HOMA-IR
Interleukin 6	IL-6
Metabolic Equivalent hours	MET-hr
Moderate Resolution Imaging Spectroradiometer	MODIS
Nitric oxide	NO
Nitric oxide synthetase	NOS
Nitrogen dioxide	NO2
Normative Aging Study	NAS
Particulate matter	PM
Particulate matter with diameter under 2.5 μm	$PM_{2.5}$
Particulate matter with diameter under 10 μm	PM_{10}
Plasminogen activator inhibitor type 1	PAI-1
Reactive Oxygen Species	ROS
Standard Deviation	SD
Tumor necrosis factor-α	TNFα
Very-low-density lipoprotein	VLDL
Veteran Affairs	VA
White blood cell	WBC

Introduction:

Definition and Utility of Metabolic Syndrome

Metabolic syndrome is an urgent public health concern. It affects 10-25% of the global population and is associated with increased risk of total mortality; cardiovascular disease; cardiovascular disease-related mortality; type-2 diabetes mellitus; chronic kidney disease; liver disease; asthma; sleep apnea; and selected malignancies.[1,2,3,4,5]

Initially, several professional organizations endorsed slightly different diagnostic criteria for metabolic syndrome, causing inconsistency across studies.[6,7,8] In 2009, a joint interim task force, comprising representatives from the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity, convened to unify the diagnostic criteria.[9]

For the purposes of this paper, metabolic syndrome is defined in accordance with the unified criteria agreed upon by the joint interim task force. Diagnosis of metabolic syndrome is established by having at least three of the following five conditions: abdominal obesity (waist circumference ≥102 cm for men); hypertriglyceridemia (≥150 mg/dl or drug treatment for elevated triglycerides); reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dl for men or drug treatment for low HDL cholesterol); hypertension (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or drug treatment for elevated blood pressure); and high fasting blood sugar (≥100 mg/dl or drug treatment for elevated blood glucose) (TABLE 1).[8,9]

The confluence of three of these conditions increases cardiovascular and type-2 diabetes mellitus risk, over and above the risk associated with the individual disorders alone.[10] Specifically, metabolic syndrome carries a five-fold greater type-2 diabetes mellitus risk and a two-fold higher cardiovascular disease risk within five-ten years.[9] Compared to individuals without metabolic syndrome, individuals with metabolic syndrome are two-four times more likely to have a stroke; three-four times more likely to

suffer a myocardial infarction; and twice as likely to die from a cardiovascular episode, even controlling for previous cardiovascular event history.[11]

Despite these findings, the predictive value of metabolic syndrome compared to its individual components is controversial.[12] Several studies cast doubt on its relative prognostic utility. For example, the San Antonio Heart Study, a cohort study of 2,815 subjects, demonstrated similar cardiovascular disease and all-cause mortality risk among individuals with metabolic syndrome (HR: 2.53; 95% CI: 1.74 to 3.67, HR: 1.47; 95% CI: 1.13 to 1.92, respectively) and individuals with impaired fasting blood glucose (HR: 2.87; 95% CI: 1.96 to 4.20, HR: 1.89; 95% CI: 1.41 to 2.52, respectively) when controlling for age, gender and ethnic group.[13] Additionally, in a prospective study of 5128 men aged 40 to 59 without history of cardiovascular disease or type-2 diabetes mellitus, the Framingham Risk Calculator outperformed metabolic syndrome in predicting coronary heart disease and stroke.[14] Arguably, metabolic syndrome's main utility is not its prognostic value, but rather, its grouping of conditions with a shared underlying pathophysiology that exert effects through common metabolic pathways.[12] As a result, metabolic syndrome is a useful concept for gaining a better understanding of the pathophysiology of the metabolic dysfunction that confers heightened cardiovascular disease and mortality risk.

Metabolic Syndrome Epidemiology

Many factors are believed to modify metabolic syndrome risk, including: genetics; diet; activity level; smoking status; family history of diabetes mellitus; education; sex; age; race; ethnicity; socioeconomic status; and urban versus rural environment.[11] Metabolic syndrome increases with age, with 18.3% of individuals aged 20-39 years and 46.7% of those over 60 years meeting diagnostic criteria.[15] In the United States, metabolic syndrome affects an estimated 47-68 million people, with males 60 years or older among those at greatest risk.[16,17,18] Metabolic syndrome also varies slightly by race/ethnicity. Hispanics have the highest prevalence (35.4%; 95% CI, 34.2%-36.6%), followed by non-Hispanic whites (33.4%; 95% CI, 32.6%-34.2%) and blacks (32.7%; 95% CI, 31.5%-33.9%).[15]

Metabolic Syndrome Pathogenesis

Low-grade inflammation is thought to contribute both to the pathogenesis of metabolic syndrome and to the subsequent development of cardiovascular disease.[19,20] Several large population-based cohort studies, including the Framingham Heart Study; the Atherosclerosis Risk in Communities Study; and the Women's Health Initiative Observational Study support this link by demonstrating associations between inflammatory markers, such as elevated white blood cell count, and increased long-term cardiovascular disease risk.[21,22,23]

Since evidence supports the role of low grade inflammation in the genesis of metabolic syndrome, it is unsurprising that various risk factors appear to increase metabolic syndrome risk by inducing an inflammatory state. For example, one hypothesized mechanism by which obesity enhances metabolic syndrome risk is the release of pro-inflammatory cytokines.[20,24] Visceral fat is thought to have endocrine function by secreting bioactive substances called adipocytokines.[20,25] In healthy states, pro-inflammatory and anti-inflammatory cytokines are intricately balanced. In obese states, adipocytes undergo hypertrophy and hyperplasia.[20] As the adipocytes enlarge, blood supply may be compromised, leading to hypoxia. In turn, hypoxia causes cell necrosis and macrophage infiltration into the adipose tissue, creating an inflammatory state. Excess visceral adipose tissue causes dysregulation of the careful balance between pro- and anti-inflammatory cytokines. The visceral adipocytes overproduce pro-inflammatory cytokines, including tumor necrosis factor-α (TNFα); plasminogen activator inhibitor type 1 (PAI-1); and heparin binding epidermal growth factor-like growth factor; and underproduce anti-inflammatory cytokines, such as adiponectin.[25] This dysregulation in favor of an inflammatory state is thought to contribute to the development of insulin resistance, metabolic syndrome and cardiovascular disease.[25]

How do these cytokines contribute to metabolic syndrome? Evidence suggests that TNFα, one of the pro-inflammatory cytokines overproduced by visceral adipocytes in obesity, has paracrine activity, reducing insulin sensitivity in surrounding adipocytes by

inhibiting the insulin receptor substrate 1 signaling pathway.[11] This inhibition of insulin signaling could directly contribute to insulin resistance. Research in mice showing that neutralization of TNFα with a soluble TNFα receptor leads to greater insulin sensitivity further supports this conclusion.[26] Although TNFα neutralization in humans has not been shown to improve insulin sensitivity, the above results indicate TNFα and other inflammatory mediators are likely involved in the generation of insulin resistance.[11] The positive association between plasma TNFα and body mass index (BMI), white blood cell count and triglycerides, and the negative association between plasma TNFα and HDL cholesterol, provides additional evidence of TNFα's role in metabolic syndrome.[11]

Interleukin 6 (IL-6), which is secreted by adipose tissue and skeletal muscle cells, has several important systemic actions that also increase metabolic syndrome risk. Elevated levels of IL-6 have been associated with higher BMI; reduced HDL cholesterol; elevated fasting insulin; and increased risk of type-2 diabetes mellitus.[11] IL-6 likely exerts its effects through several mechanisms. It acts on the hypothalamus to regulate appetite and energy intake, and is involved in hepatic production of C-reactive protein (CRP), an acute phase reactant that is released in inflammatory states.[11] Additionally, IL-6 suppresses lipoprotein lipase, the rate-limiting enzyme that removes triglycerides from circulation. IL-6-induced lipoprotein lipase suppression may partially explain metabolic syndrome's elevated triglycerides and low HDL cholesterol, since other defects that cause lipoprotein lipase deficiency have been associated with severe hypertriglyceridemia; increases in chylomicrons and very-low-density lipoproteins (VLDLs); and low HDL cholesterol levels.[27]

Not only do TNFα and IL-6 directly induce inflammatory states; they also indirectly increase inflammation by inhibiting adiponectin.[11] Adiponectin, an anti-inflammatory cytokine, is a marker of insulin sensitivity. Low adiponectin levels are associated with insulin resistance; increased BMI; dyslipidemia; hypertension; elevated inflammatory markers; and greater cardiovascular disease risk.[28,29] IL-6 and TNFα therefore increase

metabolic syndrome risk by directly exerting their own disruptive effects and by decreasing the protective effects of adiponectin.

Reactive oxygen species—oxygen free radicals formed as byproducts of mitochondrial oxidative metabolism and through several other mechanisms—are also implicated in metabolic syndrome risk. Reactive oxygen species are important signaling molecules and are part of the immune system's antimicrobial defenses. However, their excess production can damage cells. High levels of reactive oxygen species are seen in chronic diseases.[30] Research now suggests that reactive oxygen species may induce the production of inflammatory cytokines.[30] Reactive oxygen species have also been implicated in worsening insulin resistance by activating protein kinases, c-Jun N-terminal kinase (JNK) and IKKβ, which are thought to be key contributors to the development of insulin resistance in obesity and diabetes mellitus.[31]

Reactive oxygen species can also lead to hypertension by increasing vascular tone due to the inhibition of nitric oxide (NO), an important mediator of vasodialation. NO bioavailability is decreased by superoxide radical overproduction, because NO binds to the superoxide radical to generate peroxynitrate.[32] (Insulin resistance also exacerbates NO reduction, since inhibition of Akt, an intermediate in the insulin pathway, leads to inhibition of nitric oxide synthetase (NOS) TNF-α further inhibits NOS expression).[32] Decreased NO bioavailability increases vascular tone and decreases vascular reactivity. Reactive oxygen species are additionally implicated in dyslipidemia, by causing increased very low-density lipoprotein secretion from the liver.

Other metabolic syndrome risk factors appear to act through similar mechanisms. Studies suggest that a high-fat diet, another metabolic syndrome risk factor, may similarly increase metabolic syndrome risk through inflammation and reactive oxygen species. In one study, following an overnight fast, Aljada et al. (2004) gave an experimental group of nine normal-weight participants a 900-calorie meal from a fast-food restaurant and a control group of eight normal-weight participants 300 ml of water.[24] They then measured the level of reactive oxygen species and inflammation in

blood samples at zero, one, two and three hours after the meal. Among those who had consumed the high-calorie meal, they found significant increases in reactive oxygen species generation and inflammation via greater expression of C-reactive protein and the pro-inflammatory transcription factor, nuclear factor kappa-beta (NFκB). There was no change in reactive oxygen species or inflammatory markers among subjects who drank 300 ml of water.

In another, similar study, a 75-g glucose challenge was associated with increased leukocyte production of superoxide, a reactive oxygen species.[33] Conversely, decreasing macronutrient intake in obese subjects by 1000 kcal/day for one month resulted in decreased mediators of oxidative stress and inflammation.[34] Importantly, unlike an isocaloric fast-food meal, a 900-kcal meal based on the American Heart Association Step 2 Diet, which is rich in fruit and fiber, does not cause oxidative stress and inflammation.[35] Therefore, diets high in fat and low in fruits and fiber may increase metabolic syndrome risk by increasing systemic inflammation and reactive oxygen species production.

Taken together, it appears that multiple metabolic syndrome risk factors, including obesity and high-fat diets, induce a pro-inflammatory state. This pro-inflammatory state causes insulin resistance, a condition that underlies and drives metabolic syndrome. Although over-nutrition and obesity are likely the most important factors in the development of metabolic syndrome, other factors that induce inflammation may also play a role.

Metabolic Syndrome and the Environment

Metabolic syndrome rates are increasing worldwide and show geographical variations, largely due to lifestyle, socioeconomic, and ethnic differences.[36,37,38] However, local environmental conditions might also contribute to variations in metabolic syndrome rates.[39] Air pollution—including atmospheric particulate matter with diameter ≤2.5 μm ($PM_{2.5}$)—and outdoor temperature are two essential environmental factors that have

been shown in in-vitro and experimental studies to affect cellular and systemic metabolic processes.[40,41]

$PM_{2.5}$ is generated via combustion reactions, including automobile exhaust; wood and coal combustion; and industrial emissions. Due to $PM_{2.5}$ particles' small size, they penetrate deep into the lungs and cause inflammation, and are thought to be of greater health significance than larger air particles.[42,43] According to a systemic analysis for the Global Burden of Disease Study 2010, assessing the comparative risk of 67 risk factors, ambient particulate matter pollution is ranked ninth as a contributing factor to the overall global burden of disease.[44]

Several epidemiological studies indicate possible associations between air pollutants and components of metabolic syndrome.[45,46,47,48,49,50] In one of the first studies of the topic, Brook et al. (2008) investigated the link between diabetes mellitus prevalence and nitrogen dioxide (NO2), a marker of traffic-related air pollution.[45] After controlling for age, body mass index, and neighborhood income, the data showed a significant association between NO2 exposure and diabetes in women, but not in men. This study supports the association between exposure to traffic-related air pollutants and the prevalence of diabetes mellitus in women.

Further research by Brook and colleagues examined whether long-term exposure to ambient particulate matter (PM) increases risk of diabetes-associated mortality.[51] Using a prospective cohort analysis of 2.1 million Canadian adults from the 1991 Canadian census mortality follow-up study, the researchers gathered mortality information from the Canadian Mortality Database from 1991-2001. Long-term $PM_{2.5}$ exposure was estimated from satellite data. The data revealed a relationship between long-term $PM_{2.5}$ exposure and increased diabetes-related mortality. Specifically, a 10-μg/m3 $PM_{2.5}$ exposure increase was associated with a 1.49 increase in the risk for diabetes-related mortality (95% CI, 1.37–1.62).

Research suggests that $PM_{2.5}$ may increase the risk of developing other components of metabolic syndrome as well. One case-control study examined the serum lipid levels of 236 policemen, half of whom performed traffic-related duties and half of whom worked in an office.[52] The groups were matched on age and length of service. The policemen who were exposed to traffic had significantly worse HDL cholesterol and triglyceride levels than the control group that worked in an office. This study supports the hypothesis that $PM_{2.5}$ exposure may increase the risk of dyslipidemia.

Another research group analyzed health data from the Taiwanese Survey on Prevalence of Hyperglycemia, Hyperlipidemia, and Hypertension (TwSHHH) to determine whether acute PM smaller than 10 μm (PM_{10})-exposure levels were associated with metabolic dysfunction.[46] The data indicated that one-day PM_{10} levels were negatively associated with HDL-cholesterol and positively associated with systolic blood pressure. Average PM_{10} levels three days prior to the assessment were positively associated with Hemoglobin A1c levels, but not with fasting glucose.[46] These data support the link between PM exposure and several components of metabolic syndrome, including dyslipidemia, hypertension and insulin resistance.

Animal studies further support the causal relationship between $PM_{2.5}$ exposure and metabolic dysfunction. In one such experiment, Sun et al. (2005) exposed apolipoprotein E-null mice on a high-fat diet to either concentrated $PM_{2.5}$ or filtered air for six months.[53] The high-fat diet mice exposed to $PM_{2.5}$ vs. filtered air had a 1.5-fold increase in atherogenesis; showed signs of endothelial dysfunction, including exaggerated vasoconstriction in response to phenylephrine challenge; and displayed evidence of vascular inflammation—all key elements suggesting metabolic dysfunction.

To elucidate the mechanism by which PM might contribute to the development or worsening of cardiovascular disease, several studies examined the association between PM and inflammatory markers. Inflammatory markers were chosen, because inflammation appears to be an important factor in the development of atherosclerosis, which is the primary cause of cardiovascular disease, as detailed in the above section.[54]

Several studies report associations between short-term ambient PM elevations and elevated inflammatory markers, including white blood cell (WBC) count and C-reactive protein.[54,55,56] Additionally, Chen & Schwartz (2008) found a graded-association between long-term PM exposure and inflammatory markers, as evidenced by increased WBC count.[57]

Experimental studies conducted in mice nicely demonstrate the association between $PM_{2.5}$ exposure and inflammation. Sun et al. (2009) advanced their initial research by demonstrating that long-term $PM_{2.5}$ exposure leads to systemic inflammation; increased visceral adiposity; and insulin resistance in male mice on a high-fat diet.[58] Circulating TNFα, PAI-1, and IL-6 levels were increased in the mice exposed to $PM_{2.5}$, indicating that $PM_{2.5}$, like obesity (as discussed above), may mediate metabolic syndrome risk through these cytokines. $PM_{2.5}$ exposure also caused several signaling abnormalities associated with insulin resistance in the mice, including impaired insulin signaling and elevated protein kinase C expression. The same researchers showed that long-term $PM_{2.5}$ exposure causes up-regulation of genes involved in lipogenesis; lipolysis; adipocyte differentiation; and lipid droplet formation in mouse adipose tissue.[59] A recent study demonstrated similar results. Cui et al. (2015) exposed male mice to intranasal-distilled PM for one month.[60] Levels of serum TNF-α and intracellular reactive oxygen species formation were then obtained. The researchers found that PM exposure significantly increased reactive oxygen species production and circulating TNF-α levels, providing additional evidence of the role of oxidative stress and inflammation in $PM_{2.5}$-induced metabolic syndrome risk. Taken together, these studies suggest possible mechanisms for how $PM_{2.5}$ might induce metabolic dysfunction.

$PM_{2.5}$ likely increases metabolic syndrome risk through other mechanisms, in addition to inflammation. Endothelial dysfunction is another pathway by which ambient air pollution may exacerbate metabolic syndrome risk. Plasma nitrite, the oxidation product of NO, is a known marker of endothelial dysfunction. Rutgers University researchers found that students exposed to higher levels of $PM_{2.5}$ in the 24 hours preceding blood collection

had higher plasma nitrite concentrations.[61] Acute $PM_{2.5}$ exposure appears to induce endothelial dysfunction, as evidenced by elevated NO. Other studies further support these results. In one double-blind, randomized, cross-over study, 30 healthy men inhaled either dilute diesel exhaust or filtered air for one hour.[62] The subjects had impaired regulation of vascular tone and endogenous fibrinolysis after exposure to dilute diesel exhaust. This endothelial dysfunction may contribute to the development of hypertension.

Indeed, acute exposure to $PM_{2.5}$ appears to elevate blood pressure. In a study of 23 healthy adults, researchers found that acute exposure to ambient particles mixed with ozone induced a 6-mmHg increase in diastolic blood pressure.[63] A similar study of 62 adults with heart disease demonstrated a direct positive relationship between increased blood pressure and ambient PM levels.[64] Although several mechanisms may contribute to this association, $PM_{2.5}$-induced endothelial dysfunction likely plays a role.

The sympathetic nervous system may also be involved in $PM_{2.5}$-induced metabolic syndrome risk. In one study, 25 healthy, rural-dwelling adults were exposed to urban air pollution for four to five hours/day on five consecutive days.[65] Participants' insulin sensitivity was assessed seven days prior to urban pollution exposure; on day five of the exposure; and seven days after the final exposure day. Sympathetic nervous system activity was assessed by heart rate variability (decreased variability indicates a shift in balance towards sympathetic activity and away from parasympathetic activity). $PM_{2.5}$ levels were obtained at the urban exposure site and at monitors near subjects' homes. Study results demonstrated that a 10 $\mu g*m^{-3}$ increase in sub-acute $PM_{2.5}$ exposures was associated with increased insulin resistance, as assessed by the homeostatic model assessment of insulin resistance (HOMA-IR), and reduced heart rate variability. Further analysis indicated that the association between $PM_{2.5}$ and insulin sensitivity is partially explained by lower heart rate variability. These results support the hypothesis that the connection between air pollution and metabolic syndrome may be partially explained by parasympathetic withdrawal/sympathetic activation.

Induction of hypothalamic inflammation is also a possible mechanism by which $PM_{2.5}$ may exert its influence. Hypothalamic inflammation has been implicated in dysfunction in sensing fuel; controlling energy intake; and expending energy in diet-induced obesity.[66]

In research conducted by Liu et al. (2014), mice that were genetically susceptible to type-2 diabetes mellitus were exposed to four-to-eight weeks of concentrated $PM_{2.5}$ or filtered air.[66] During this period, the mice received either no treatment; intra-cerebroventricular TNFα antibody (infliximab); or intra-cerebroventricular IKKβ inhibitor (IMD-0354). IKKβ is an enzyme involved in triggering immune response in the hypothalamus. Accordingly, inhibition of IKKβ blocks this inflammatory response.

During the study period, Liu et al. (2014) evaluated glucose tolerance; insulin sensitivity; and energy homeostasis, operationalized as oxygen consumption and heat production.[66] At the conclusion of the study, the mice were sacrificed and blood, spleen, visceral adipose tissue and the hypothalamus were collected to measure inflammatory cells. Consistent with prior research, $PM_{2.5}$ exposure was shown to induce hyperglycemia; insulin resistance; and elevated hypothalamic IL-6, TNFα and IKKβ mRNA expression. Mice who received intra-cerebroventricular IKKβ inhibitor (IMD-0354) displayed improved glucose tolerance; insulin sensitivity; energy homeostasis; and decreased peripheral inflammatory response to $PM_{2.5}$. Intra-cerebroventricular TNFα inhibition provided no such benefits.

A recent study found similar results for the protective effect of IKK inhibition in preventing $PM_{2.5}$-exacerbated cardiac damage in mice with type-2 diabetes mellitus.[67] These studies support the hypothesis that PM's inflammatory effects—specifically, the hypothalamic inflammatory response—may represent one mechanism by which PM causes metabolic dysfunction. Research also indicates that individuals with specific baseline metabolic dysfunctions—including obesity;[68,69,70] hypertension;[54,71,72] and diabetes mellitus[72,73]—may be particularly vulnerable to PM-induced cardiac disease.

Temperature is another environmental factor that has been associated with increased cardiac morbidity and mortality.[74] Prior studies have not explored the relationship between temperature and metabolic syndrome. However, studies have examined the association between temperature and individual components of metabolic syndrome. The Diabetes study, a nationwide, population-based, cross-sectional study conducted in Spain, used temperature data from the National Meteorology Agency from 1971-2000; clinical, demographic and lifestyle surveys; physical exams; and blood sampling to assess the association between ambient temperature and obesity.[75] After controlling for demographic and lifestyle variables, there was a statistically significant positive association between ambient temperature and obesity, with higher ambient temperature positively correlated to higher obesity levels. Higher ambient temperature has also been associated with significantly lower circulating HDL and higher circulating LDL.[76] In this study, temperature did not correlate with circulating triglyceride or total cholesterol levels. However, a prior experimental study did demonstrate that elevated temperature caused a 14% increase in plasma cholesterol.[76,77] Conversely, other research suggests fasting blood glucose and blood pressure are inversely related to temperature.[78,79]

Giorgini and colleagues (2015) used a cross-sectional observational study to determine whether short-term ambient $PM_{2.5}$ and temperature had an effect on cardiopulmonary exercise test results of 2078 patients undergoing cardiac rehabilitation at the University of Michigan.[74] The researchers found that short-term $PM_{2.5}$ and temperature elevations were associated with poorer aerobic exercise capacity. This result supports the hypothesis that elevated temperature, like PM, can worsen underlying cardiovascular disease.

Temperature may impact metabolic syndrome risk through adipose tissue's role in body temperature homeostasis. When temperature decreases, adipocytes release fatty acids to generate heat and maintain body temperature. Specifically, brown adipose tissue is involved in burning energy to produce heat. Brown adipose tissue appears to regulate whole-body metabolism and may improve insulin sensitivity and decrease weight gain risk.[80] Evidence suggests that individuals with a greater percentage of brown adipose

tissue are protected from diabetes mellitus and obesity.[41,80,81,82] Outdoor air temperature has been negatively associated with the amount and glucose-uptake activity of brown adipose tissue.[41] Therefore, those who are exposed to relatively warmer temperatures burn fewer calories to maintain their body temperature; have a lower percent of brown adipose tissue; and may be at greater risk for metabolic syndrome.

Purpose and Importance of the Present Study

Despite the intriguing data presented above, the possible relationship of local $PM_{2.5}$ levels and temperature with metabolic syndrome is still under-investigated in human populations. Previous epidemiology studies have investigated the relationship of single exposures with individual metabolic components, rather than with the entire complex of metabolic alterations that compose metabolic syndrome.[75,76,83,84,85] Furthermore, previous human studies have mainly focused on the associations between short-term temperature exposure and metabolic outcomes, which may reflect transient modifications that are not necessarily related to long-term risks.[76,77] To date, no studies reported an incident analysis on the topic.

The current study prospectively examined the association of the average levels of ambient $PM_{2.5}$ and temperature at the participant's address with the development of metabolic syndrome, as well as with the individual conditions that compose metabolic syndrome. We leveraged prospective data from Veteran Affairs (VA) Normative Aging Study (NAS) participants, a cohort of older men living across Eastern Massachusetts; Southern New Hampshire; and Southern Maine. We hypothesized that exposure to higher levels of $PM_{2.5}$ ambient air pollution would increase the risk of developing metabolic syndrome. The longitudinal, prospective design of this study has the potential to produce strong evidence for a causal link between pollution exposure and metabolic syndrome, because pollution exposure can be shown to predate the metabolic syndrome phenotype. This research could help inform future policy decisions regarding environmental pollution regulations and help target public health interventions to those individuals most at risk of developing metabolic syndrome.

METHODS

Study population

The present analysis included 587 men who were active participants in the longitudinal NAS between 1993-2011 (Table 2).[86] All participants included in the analysis were free of metabolic syndrome at the first visit (baseline) during the study period and received comprehensive outpatient medical evaluations every 3-7 years. During the visits, participants provided detailed information about their lifestyle, dietary habits, activity levels and demographic factors. In each diagnosis-specific analysis, we excluded participants who met pathological criteria for that disorder at the baseline visit (Table 2, Table 3). All participants gave written informed consent in accordance with the VA Boston Healthcare System Institutional Review Board and the Institutional Review Boards of all participating institutions.

Spatio-temporal resolved modeling of particulate matter (PM) level

To assign exposure we used a recently published validated spatiotemporal hybrid model, developed by our research group, to estimate daily $PM_{2.5}$ level (in μg/m3) across the study area.[87] We used the average $PM_{2.5}$ level during the year prior to each visit at each participant's residential address to assess the long-term association of air pollution with metabolic dysfunction. The model incorporates previously reported fine scale local land use regression and satellite aerosol optical depth.[87] This hybrid model provides address-level resolution for long-term $PM_{2.5}$ measurements collected between May 2000 and December 2011. Due to limitations in data availability, we used a similar hybrid satellite based Moderate Resolution Imaging Spectroradiometer (MODIS) model albeit at a lower spatial resolution of 10x10 km grid for May 2000-October 2003 and on a 1x1 km grid for October 2003-December 2011.[87,88] Missing observations on the 1x1 km grid over the period October 2003-December 2011 were also replaced with measures from 10x10 km grid. Out-of-sample cross validation showed good fit of the 10x10 km model (R2=0.81), and an excellent fit of 1x1 km the model (R2 = 0.87).[87,88]

Time- and space-resolved modeling of temperature level

We used the average daily temperature during the year before each visit at 1x1 km resolution as a proxy of the temperature at the participant's address in order to assess the long-term association of outdoor temperature with metabolic dysfunction. Daily temperature with 1x1 km resolution was predicted using a spatio-temporally resolved satellite based model similar to that used for $PM_{2.5}$.[89,90] Daily estimates were averaged to produce annual average temperatures. A ten-fold out of sample cross validation was used to validate the accuracy of the predictions and it showed good fit (mean out-of-sample R2 = 0.94).[89,90]

Assignment of $PM_{2.5}$ and temperature levels.

In this analysis, we defined as baseline the first NAS visit conducted prior to May 2000, i.e., the first month with available $PM_{2.5}$ and temperature estimates. We used as exposure metrics the average of $PM_{2.5}$ or temperature levels at each participant's address in the year before each subsequent follow-up visit, as a proxy for exposure between visits. The 1-year average was selected because it correlates well with averages of $PM_{2.5}$ over longer time windows (e.g., 2-5 years) in this study population (Table 4) and was available for a higher number of visits than the 2-5 year averages, because it could be calculated for follow-up visits conducted between 2-5 years after the inception of the model used to estimate $PM_{2.5}$.

Clinical measures

At each visit, anthropometric measures were performed with participants in undershorts and socks. Waist circumference was measured in centimeters at the umbilical level, perpendicular to the axis of the upper body.[91] Participants were considered to have abdominal obesity if their waist circumference was ≥102 cm. At each visit, fasting blood glucose and lipid levels were measured on blood drawn on the morning of the medical evaluation. In keeping with metabolic syndrome diagnostic criteria, high blood sugar was defined as a fasting blood glucose ≥100 mg/dl or drug treatment for elevated blood glucose, low HDL was any value <40 mg/dl or drug treatment for low HDL cholesterol and hypertriglyceridemia was any triglyceride measure ≥150 mg/dl or drug treatment for elevated triglycerides. Individuals were diagnosed with hypertension if their systolic

blood pressure ≥130 mm Hg or diastolic blood pressure was ≥85 mm Hg or they were taking drug treatment for elevated blood pressure. Participants who met three or more of the above diagnostic criteria for abdominal obesity, high fasting blood glucose, low HDL, hypertension or hypertriglyceridemia were considered to have metabolic syndrome.[8,92] A structured in-person questionnaire was used to collect information about lifestyle and dietary habits, including physical activity, smoking status, alcohol consumption and average dark fish consumption.

Statistical analysis

The risk of future metabolic dysfunction associated with 1-year average ambient $PM_{2.5}$ or temperature estimated at the participant's address was evaluated using the Cox proportional model. This method's ability, to handle censored data and time-dependent covariates, makes it well suited for this analysis.[93] Metabolic syndrome and five individual measures of metabolic function—waist circumference, fasting blood glucose, HDL cholesterol levels, blood pressure and triglycerides— were modeled separately.

Each model included time dependent variables - the participant's age at the time of the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (never, former, current) and physical activity (<12, 12|-30, ≥ 30 metabolic equivalent hours (MET-hr] per week) – and variables at the baseline visit – education as a proxy for socioeconomic status (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous). Statin, antihypertensive and diabetes medications were included in the model for metabolic syndrome as a whole and were considered as time dependent variables. $PM_{2.5}$ models were adjusted for 1-year average temperature levels and vice-versa. Each model included strata for variables that did not meet the Cox proportional hazard assumptions. We additionally represented the significant associations and verified graphically that $PM_{2.5}$ and temperature levels did not show major departures from the linear association with the outcomes (Figures 1-2).

We also reanalyzed each $PM_{2.5}$ model after restricting the analysis to observations with $PM_{2.5}$ levels lower than 12 μg/m3, which is the primary annual fine particle standard set by U.S. Environmental Protection Agency for public health protection.[94] As a sensitivity analysis, we excluded outliers for $PM_{2.5}$ and temperature levels for all models and we excluded physical activity from the list of covariates, because including them may have resulted in over-adjustment. We further investigated the interaction between air pollution and ambient temperature in relation to metabolic syndrome and its individual components. We additionally evaluated changes in each cardio-metabolic measure over time relative to air pollution and temperature using linear model with repeated observations for each participant. The analysis was subsequently stratified for participants with and without metabolic syndrome at the baseline. We used SAS® statistical package version 9.3 (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA) and R for all models.[95,96,97]

RESULTS

Descriptive statistics

Table 3 shows demographic and clinical data for all participants. At baseline, out of the 587 NAS participants 191 (33%) had abdominal obesity, 294 (50%) had high blood glucose, 261 (44%) had low HDL, 471 (80%) had hypertension, 271 (46%) had hypertriglyceridemia and 316 (53%) met metabolic syndrome criteria and were excluded from the corresponding analysis. Participants were 70 years old on average at baseline and attended up to 6 visits (average = 2.2). Most participants were Caucasian (88%), had at least a college degree (71%) and were permanent residents of the greater Boston area (86%). Most men reported low physical activity (58%), light or lower alcohol consumption (77%) and were former smokers (65%). Twenty-four percent of the participants used statins, 5% used diabetes drugs, and 49% used antihypertensive medications. Percentage of prescribed medications and number of participants varied across the data subsets used for analysis of individual metabolic syndrome components.

Ambient air pollution and temperature associations

Estimated $PM_{2.5}$ levels ranged between 4.2- 13.6 μg/m3 (mean (SD), 10.5 (1.4) μg/m3). A 1 μg/m3 annual $PM_{2.5}$ increase was significantly associated with a 27% increased risk of developing metabolic syndrome (Hazard Ratio (HR) = 1.27; 95% Confidence Interval (CI): 1.06, 1.52, P=0.01), as well as some of its components, i.e. 20% increased risk of developing elevated fasting blood glucose (HR = 1.20; 95% Confidence Interval (CI): 1.03, 1.39, P=0.02), and a 14% increased risk of hypertriglyceridemia (HR = 1.14, 95% CI: 1.00, 1.30, P=0.05) (Table 5, Figure 1). Estimated annual temperature levels ranged between 7.5-18.8 Cº (mean (SD), 11.4 (1.1) Cº). A 1 Cº annual temperature increase was associated with a 33% increased elevated fasting blood glucose risk (HR = 1.33, CI: 1.14, 1.56, P<0.001) (Table 5, Figure 2). However, temperature level was not significantly associated with the risk of metabolic syndrome as a whole (HR = 0.99, 95% CI: 0.82, 1.21, P=0.95).

After restricting the analysis only to observations with 1-year average $PM_{2.5}$ less than 12 μg/m3 (Table 6), $PM_{2.5}$ results for the metabolic syndrome and high fasting blood glucose analyses remained significant and showed stronger associations, i.e. 40% increased risk of developing metabolic syndrome (HR = 1.40, CI: 1.11, 1.77, P=0.005) and 31% increased risk of elevated fasting blood glucose (HR = 1.31, CI: 1.05, 1.63, P=0.02).

The 1-year average $PM_{2.5}$ and temperature included outliers, defined as having an absolute deviation of three standard deviations from the mean. Analysis excluding the 33 outliers confirmed results for $PM_{2.5}$ and temperature on metabolic syndrome and fasting blood glucose (Table 7). Only HDL Cholesterol levels were (negatively) associated over time with temperature levels (Table 8).

Results from analysis excluding physical activity from the list of covariates were consistent with previous findings (Table 9). Additionally there were no significant interactions between PM and temperature in any of the models (Table 10).

Increased temperature was significantly associated with increasing waist circumference over time (Table 8).

DISCUSSION

The present study showed associations of long-term exposure to ambient $PM_{2.5}$ and outdoor temperature levels with increased risk of developing several components of metabolic dysfunction. $PM_{2.5}$ was associated with increased risk of metabolic syndrome and some of its individual metabolic components, i.e., elevated fasting blood glucose and triglycerides; temperature was associated with increased elevated fasting blood glucose risk. To our knowledge, this is the first study that prospectively examined both $PM_{2.5}$ and temperature exposure in relation to risk of metabolic syndrome, as well as of its individual components. Our results indicate that individuals who lived in neighborhoods with worse air quality, as reflected in higher $PM_{2.5}$ levels, and/or that were warmer than average, had a greater risk of developing metabolic syndrome components. The associations of $PM_{2.5}$ with metabolic syndrome and fasting blood glucose remain significant when restricting the analysis to observations below the U.S. Environmental Protection Agency's threshold for primary annual fine particles. This finding may support the need for more stringent measures to further reduce $PM_{2.5}$ levels, as well as to begin considering ambient temperature—an environmental variable that has become key for climate change predictions—as a novel risk factor for long term metabolic risk.

Our results are consistent with recent research into the biological mechanisms through which high levels of $PM_{2.5}$ and temperature exposure may affect metabolic regulation. $PM_{2.5}$ exposure may predispose individuals to metabolic dysfunction through the generation of oxygen free radicals, which can disrupt insulin signaling and impair vasorelaxation, thus contributing to insulin resistance and vascular disease.[98,99] $PM_{2.5}$ has recently been shown to increase reactive oxygen species (ROS), which have been associated with metabolic dysfunction.[100,101,102] Additionally, $PM_{2.5}$ exposure may contribute to metabolic syndrome risk by activating cell signaling pathways implicated in

metabolic dysfunction. Sun et al. (2009) demonstrated that long-term $PM_{2.5}$ exposure leads to systemic inflammation, increased visceral adiposity and insulin resistance in male mice on a high fat diet.[58] Air pollution exposure caused several signaling abnormalities associated with insulin resistance in the mice, including decreased Akt/protein kinase B and endothelial nitric oxide synthase phosphorylation in endothelial cells and elevated protein kinase C expression. The same group showed that long-term $PM_{2.5}$ exposure causes up-regulation of genes involved in lipogenesis, lipolysis, adipocyte differentiation and lipid droplet formation in mouse adipose tissue.[59] These studies are highly supportive of our findings and suggest possible mechanisms for $PM_{2.5}$-induced metabolic dysfunction. Future research should further explore the mechanisms by which PM2.5 exposure induces metabolic dysfunction in humans and whether interventions to attenuate the response mitigate metabolic syndrome risk.

The temperature-high-blood-sugar relationship that we identified may be due to adipose tissue's role in adapting to temperature differences, which is consistent with prior obesity research.[103] Indeed, in the presence of colder temperature, fat stored in adipocytes is mobilized and used to produce heat to keep body temperature constant. Brown adipose tissue, in particular, burns energy and glucose to generate heat and individuals with higher proportions of brown adipose tissue are protected from diabetes and obesity.[41,80,81,82] Individuals exposed to comparatively higher temperatures burn fewer calories to maintain body temperature, have less brown adipose tissue, and therefore, as shown in our analysis, may be more prone to developing insulin resistance.

Interestingly, neither $PM_{2.5}$ nor temperature was significantly associated with abdominal obesity, low HDL cholesterol or hypertension, key components of metabolic syndrome that are often presented as underlying and/or preceding the other components and cardiovascular morbidity.[104,105,106] This finding may be due to the high prevalence of those conditions already present at the baseline and/or it may indicate that $PM_{2.5}$ and temperature activate metabolic mechanisms, such as inflammation, which might increase the risk of elevated fasting blood glucose and hypertriglyceridemia without

substantially increasing the risk of abdominal obesity, low HDL cholesterol and hypertension. On the other hand, the lack of association with abdominal obesity indicate that our findings were not confounded by possible correlations with obesity-associated lifestyles, such as those resulting in high calorie diet or low physical activity, which would be expected to also significantly increase obesity risk.

In the present study, the estimated effect size of the association between $PM_{2.5}$ and metabolic syndrome is relatively larger than other studies of cardiovascular events or death. Older individuals are especially susceptible to pollution-triggered morbidity and mortality.[107] The risk of developing metabolic syndrome increases with age. Metabolic syndrome affects approximately 24% of the US adult population, and the prevalence increases dramatically in older adults (≥ 50 year/old) to 44%.[16,92] Therefore, the Normative Aging Study participants represent a particularly vulnerable population, as it is composed of older male participants (average age of 70 years, SD=7). Previous studies suggested that metabolic syndrome is a precursor for coronary heart disease, and it contributes to the risk of cardiovascular mortality.[108,109] Increased risk for developing metabolic syndrome in response to air pollution might serve as one of the primary intermediate outcomes contributing to air pollution-related cardiovascular disease events.[16] We used validated space- and time-resolved models to estimate $PM_{2.5}$ at each participant's home address and temperature with 1x1 km resolution. All the NAS participants lived in the same metropolitan area, which is relatively cool and with a low penetrance of air conditioning.[110] However, 1-year averages of both $PM_{2.5}$ and temperature levels showed wide variations across participants, mostly due to differences in residential address characteristics such as proximity to roadways or water, and amounts of green space and concrete. In our study, we were also able to control for variables related to personal and residence-based characteristics, which should limit residual confounding by those factors. Finally, our results included a substantial number of observations; each of our 587 participants completed 2.2 study visits on average.

Some limitations could affect our study. The study sample is over 88% white and all male, which limits the generalizability of our results to other races and to women. Other possible sources of bias should be considered in the interpretation of our results, including the use of exposure estimates based on residential address of 1x1 km resolution, which may misclassify personal exposure levels. Measurement error of air pollution and temperature is a common limitation of epidemiologic studies, which usually leverage $PM_{2.5}$ and temperature measurements of ambient particulate concentrations and temperature, respectively, from stationary monitors to obtain estimates of study participants' exposure. The difference between the ambient estimate and a participant's average personal exposure is a potentially important source of bias, for both air pollution and temperature measures. This bias is unlikely to alter our conclusions on statistically significant findings, because using the ambient concentration misclassification is most likely to attenuate statistical associations.[111] It is possible, however, that measurement error is responsible for the lack of association observed with some metabolic components. Additionally, participants likely control the temperature inside their homes and may not have much exposure to ambient air temperature, which could also attenuate our temperature findings. Furthermore, because the NAS is a largely retired cohort, level estimates at the participant's' address or with 1x1 km resolution are expected to correlate well with personal exposures due to the lack of commuting to work.[112]

SUMMARY

Our results add evidence that long-term $PM_{2.5}$ and temperature exposures increase metabolic dysfunction risk. People living in neighborhoods with worse air quality, in terms of higher $PM_{2.5}$ levels, and/or warmer than average, showed an increased risk of developing metabolic dysfunctions. These metabolic associations may represent intermediates to explain the link between increased exposure to $PM_{2.5}$ and higher temperature with cardiovascular morbidity and long-term mortality risks. Our findings may indicate the need for more stringent control of ambient $PM_{2.5}$ levels and for revising estimates of the health impact of climate changes to account for long-term risk of metabolic dysfunction and its sequelae.

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Table 1.Clinical Identification of the Metabolic Syndrome and its Components and Number of Events Over Time in the Analysis.

ATP III/NHLBI Clinical Identification	Cut point	Number of events
Abdominal Obesity	≥102 cm (men)	107
High Fasting Blood Glucose	≥100 mg/dL or medication	118
Low HDL cholesterol	<40 mg/dL (men) or medication	165
Hypertension	≥130/≥85 mm Hg or medication	82
Hypertriglyceridemia	≥ 150 mg/dL or medication	154
Metabolic Syndrome	any 3 of the previous	140

Abbreviations: HDL: High-density Lipoprotein.

Table 2. Eligible and Non-Eligible Participants in NAS Data With at Least one Measurement on and After May 2000.

Units Selected from Sampling Frame	Number of participants
Respondent, total	759
Eligible respondent with missing measures or data	
Participants with only 1 visit and/or disease at the first visit	95
Missing covariates	15
Missing $PM_{2.5}$ estimates	56
Missing temperature estimates	6
Eligible respondents with non-missing data for main analysis, total	587

Abbreviations: $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.

Table 3: Descriptive Statistics at the Baseline Visit, According to the Metabolic Syndrome and its Individual Components.

Analysis	Entire population	Subsets used in each analysis					
		Abdominal Obesity	High Fasting Blood Glucose	Low HDL Cholesterol	Hypertension	Hypertrigly ceridemia	Metabolic Syndrome
Number of participants	587	396	293	326	116	316	271
Number of excluded participants		191	294	261	471	271	316
Number of visit, Mean (Max)	2.2 (6)	2.3 (6)	2.1 (6)	2.1 (6)	2.1 (6)	2.1 (6)	2.1 (6)
Age, Mean (SD)	70.4 (6.9)	70.8 (6.8)	70.5 (6.9)	70.5 (7.1)	68.4 (7.6)	70.8 (7.1)	70.4 (7.3)
Nonwhite (% of census tract), Mean (SD)	11.9 (13)	12 (12.6)	11.2 (11.9)	12.5 (13.6)	10.8 (11.6)	12.2 (13.3)	12.1 (12.9)
Education (years), N (%)							
≤12 years	171 (29.13)	116 (29.29)	86 (29.35)	89 (27.3)	33 (28.45)	86 (27.22)	72 (26.57)
12-16 years	294 (50.09)	196 (49.49)	138 (47.10)	166 (50.92)	54 (46.55)	161 (50.95)	134 (49.45)
>16 years	122 (20.78)	84 (21.21)	69 (23.55)	71 (21.78)	29 (25.00)	69 (21.84)	65 (23.99)
Physical Activity (MET-hr/week), N (%)							
<12	342 (58.26)	206 (52.02)	152 (51.88)	192 (58.9)	59 (50.86)	191 (60.44)	140 (51.66)
12–30	149 (25.38)	111 (28.03)	87 (29.69)	86 (26.38)	42 (36.21)	79 (25.00)	85 (31.37)
≥30	96 (16.35)	79 (19.95)	54 (18.43)	48 (14.72)	15 (12.93)	46 (14.56)	46 (16.97)
Smoking status, N (%)							
Never	169 (28.79)	121 (30.56)	95 (32.42)	94 (28.83)	36 (31.03)	94 (29.75)	87 (32.1)
Former	384 (65.42)	253 (63.89)	184 (62.8)	211 (64.72)	69 (59.48)	202 (63.92)	165 (60.89)
Current	34 (5.79)	22 (5.56)	14 (4.78)	21 (6.44)	11 (9.48)	20 (6.33)	19 (7.01)
Alcohol Consumption, N(%)							
(<2 drinks/day)	453 (77.17)	311 (78.54)	230 (78.50)	235 (72.09)	92 (79.31)	243 (76.9)	206 (76.01)
(≥2 drinks/day)	134 (22.83)	85 (21.46)	63 (21.50)	91 (27.91)	24 (20.69)	73 (23.10)	65 (23.99)

Table 3 continues on the following page

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Consumed Dark Fish (times/week), N (%)							
<1	507 (86.37)	335 (84.60)	245 (83.62)	285 (87.42)	99 (85.34)	270 (85.44)	231 (85.24)
≥1	80 (13.63)	61 (15.40)	48 (16.38)	41 (12.58)	17 (14.66)	46 (14.56)	40 (14.76)
Not Permanent Resident, N (%)							
No	514 (87.56)	346 (87.37)	254 (86.69)	286 (87.73)	100 (86.21)	280 (88.61)	237 (87.45)
Yes	73 (12.44)	50 (12.63)	39 (13.31)	40 (12.27)	16 (13.79)	36 (11.39)	34 (12.55)
Statin intake, N(%)							
No	449 (76.49)	288 (72.73)	217 (74.06)	326 (100)	91 (78.45)	316 (100)	262 (96.68)
Yes	138 (23.51)	108 (27.27)	76 (25.94)	0 (0)	25 (21.55)	0 (0)	9 (3.32)
Diabetes medicine intake, N(%)							
No	560 (95.40)	379 (95.71)	293 (100)	316 (96.93)	114 (98.28)	307 (97.15)	268 (98.89)
Yes	27 (4.60)	17 (4.29)	0 (0)	10 (3.07)	2 (1.72)	9 (2.85)	3 (1.11)
Hypertensive medicine intake, N(%)							
No	300 (51.11)	209 (52.78)	166 (56.66)	185 (56.75)	116 (100)	177 (56.01)	179 (66.05)
Yes	287 (48.89)	187 (47.22)	127 (43.34)	141 (43.25)	0 (0)	139 (43.99)	92 (33.95)

Abbreviations: HDL: High-density Lipoprotein; Max: Maximum; N: Number; SD: Standard Deviation.

Table 4. Correlation Coefficients Between 1-Year $PM_{2.5}$ Exposure Levels and $PM_{2.5}$ Exposure Levels With Different Time Windows.

Exposure level	Pearson Correlation coefficients with $PM_{2.5}$ 1-year	*P* [a]	Number of observations
$PM_{2.5}$ 1 year			1811
$PM_{2.5}$ 2 years	0.94	<.0001	990
$PM_{2.5}$ 3 years	0.91	<.0001	854
$PM_{2.5}$ 4 years	0.87	<.0001	702
$PM_{2.5}$ 5 years	0.86	<.0001	619

Abbreviations: $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.
[a] Two sided *P*.

Table 5: Association of 1-year $PM_{2.5}$[a] and Temperature[b] Levels exposure with Risk of Individual Components and Composite Diagnosis of Metabolic Syndrome.

Association with	N participants	N observations	N events	$PM_{2.5}$			Temperature		
				Hazard Ratio	95% CI	*P*[e]	Hazard Ratio	95% CI	*P*[e]
Abdominal Obesity[c]	396	857	107	1.00	(0.86, 1.16)	1.00	1.06	(0.86, 1.31)	0.58
High Fasting Blood Glucose[c]	293	562	118	1.20	(1.03, 1.39)	0.02	1.33	(1.14, 1.56)	<0.001
Low HDL Cholesterol[c]	326	625	165	0.98	(0.85, 1.13)	0.76	1.01	(0.85, 1.20)	0.90
Hypertension[c]	116	207	82	1.20	(0.97, 1.49)	0.09	1.14	(0.86, 1.50)	0.37
Hypertriglyceridemia[c]	316	598	154	1.14	(1.00, 1.30)	0.05	1.07	(0.92, 1.24)	0.36
Metabolic Syndrome[c,d]	271	517	140	1.27	(1.06, 1.52)	0.01	0.99	(0.82, 1.21)	0.95

Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; N: Number; $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.

[a] $PM_{2.5}$ (for each 1 ug/m^3) was 1-year average from daily estimates including AOD data from the 1x1 km model and 10x10 km model.

[b] Temperature (for each 1ºC) was 1-year average from daily estimates including AOD data from the 1x1 km model.

[c] Variables included in the model: time dependent variables-age at the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (current, former, never), physical activity (<12, 12|-30, ≥ 30 metabolic equivalent hours (MET-hr) per week)- and variables at the baseline-education (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous).

[d] Included medications varying over time: diabetes medication (no/yes), statin (no/yes) and antihypertensive medication(no/yes).

[e] Two sided *P*.

Table 6: Association of 1-Year $PM_{2.5}$[a] Levels with Risk of Individual Components and Composite Diagnosis of Metabolic Syndrome in Observations with $PM_{2.5}$ Levels Lower Than 12 μg/m^3.

Association with	N participants	N observations	N events	$PM_{2.5}$ Hazard Ratio	$PM_{2.5}$ 95% CI	$PM_{2.5}$ *P*[d]
Abdominal Obesity[b]	368	753	102	1.12	(0.94, 1.34)	0.21
High Fasting Blood Glucose[b]	261	484	101	1.31	(1.05, 1.63)	0.02
Low HDL Cholesterol[b]	287	536	141	0.98	(0.83, 1.16)	0.85
Hypertension[b]	101	179	67	1.36	(0.81, 2.29)	0.24
Hypertriglyceridemia[b]	282	515	135	1.14	(0.96, 1.35)	0.12
Metabolic Syndrome[b,c]	243	441	125	1.40	(1.11, 1.77)	0.005

Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; N: Number; $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.

[a] $PM_{2.5}$ (for each 1 ug/m^3) was 1-year average from daily estimates including AOD data from the 1x1 km model and 10x10 km model.

[b] Variables included in the model: time dependent variables-age at the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (current, former, never), physical activity (<12, 12|-30, ≥ 30 metabolic equivalent hours (MET-hr) per week), 1-year average temperature levels- and variables at the baseline-education (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous).

[c] Included medications varying over time: diabetes medication (no/yes), statin (no/yes) and antihypertensive medication(no/yes).

[d] Two sided *P*.

Table 7. Sensitivity Analysis Excluding Outliers for $PM_{2.5}$ and Temperature. Effect of 1-Year $PM_{2.5}$[a] and Temperature[b] Levels Exposure on Risk of Individual Components and Composite Diagnosis of Metabolic Syndrome in NAS Participants Since May 2000.

Effect on	N participants	N observations	N events	$PM_{2.5}$			Temperature		
				Hazard Ratio	95% CI	*P*[e]	Hazard Ratio	95% CI	*P*[e]
Abdominal Obesity[c]	390	834	107	0.99	(0.85, 1.15)	0.88	1.12	(0.88, 1.42)	0.36
High Fasting Blood Glucose[c]	287	547	113	1.23	(1.05, 1.44)	**0.01**	1.38	(1.12, 1.71)	**0.003**
Low HDL cholesterol[c]	317	603	161	1.00	(0.86, 1.15)	0.95	1.06	(0.85, 1.31)	0.61
Hypertension[c]	112	200	79	1.18	(0.95, 1.47)	0.14	1.03	(0.74, 1.44)	0.84
Hypertriglyceridemia[c]	303	571	147	1.18	(0.98, 1.42)	0.09	1.23	(0.93, 1.63)	0.14
Metabolic Syndrome[c,d]	263	498	135	1.50	(1.07, 2.09)	**0.02**	1.06	(0.71, 1.60)	0.77

Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; N: Number; $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.

[a] $PM_{2.5}$ (effect for each 1 ug/m^3) was 1-year average from daily estimates including AOD data from the 1x1 km model and 10x10 km model.

[b] Temperature (effect for each 1ºC) was 1-year average from daily estimates including AOD data from the 1x1 km model.

[c] variables included in the model: time dependent variables-age at the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (current, former, never), physical activity (<12, 12|-30, ≥ 30 metabolic equivalent hours (MET-hr) per week)- and variables at the baseline-education (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous).

[d] included medications varying over time: diabetes medication (no/yes), statin (no/yes) and antihypertensive medication(no/yes).

[e] Two sided *P*.

Table 8: Association of 1-year $PM_{2.5}$[a] and Temperature[b] Levels exposure with the Change Over Time in the Individual Conditions of the Metabolic Syndrome for all participants (N=587) and Progression of Each Condition for Participants With and Without the Metabolic Syndrome at the Baseline.

Association	All participants (N=587)			On participants without metabolic syndrome at the baseline (N=271)			On participants with metabolic syndrome at the baseline (N=316)			*P** for interaction
	Est.	95% CI	*P**	Est.	95% CI	*P**	Est.	95% CI	*P**	
PM2.5										
Waist circumference[c]	2.05	(-1.22; 5.32)	0.22	1.60	(-1.66; 4.85)	0.34	1.74	(-1.05; 5.75)	0.18	0.24
Fasting Blood Glucose[c,d]	0.10	(-0.44; 0.65)	0.71	-0.19	(-0.74; 0.35)	0.49	0.28	(-0.27; 0.83)	0.32	0.004
HDL Cholesterol[c,e]	0.16	(-0.17; 0.49)	0.35	0.07	(-0.32; 0.47)	0.71	0.17	(-0.16; 0.51)	0.30	0.28
Systolic Blood Pressure[c,f]	0.34	(-0.16; 0.84)	0.18	0.36	(-0.17; 0.89)	0.18	0.27	(-0.19; 0.87)	0.20	0.83
Diastolic Blood Pressure[c,f]	0.16	(-0.17; 0.49)	0.35	0.25	(-0.1; 0.6)	0.16	0.18	(-0.22; 0.47)	0.48	0.26
Triglycerides[c,e]	-0.74	(-2.90; 1.42)	0.50	-1.14	(-3.18; 0.91)	0.28	1.12	(-2.76; 1.62)	0.61	0.42
Temperature										
Waist circumference[c]	5.22	(0.05; 10.39)	**0.05**	5.02	(0.07; 9.97)	**0.05**	2.68	(-0.76; 9.74)	0.09	0.47
Fasting Blood Glucose[c,d]	0.01	(-0.92; 0.93)	0.99	0.02	(-0.8; 0.84)	0.96	0.46	(-1.31; 0.49)	0.37	0.004
HDL Cholesterol[c,e]	0.28	(-0.23; 0.80)	0.28	0.22	(-0.32; 0.77)	0.43	0.32	(-0.41; 0.83)	0.51	0.87
Systolic Blood Pressure[c,f]	-0.53	(-1.34; 0.28)	0.20	-0.51	(-1.33; 0.31)	0.22	0.44	(-1.38; 0.35)	0.24	0.73
Diastolic Blood Pressure[c,f]	-0.07	(-0.72; 0.57)	0.82	-0.02	(-0.64; 0.61)	0.96	0.32	(-0.58; 0.65)	0.91	0.71
Triglycerides[c,e]	-0.56	(-3.01; 1.89)	0.66	-0.81	(-3.17; 1.56)	0.50	1.23	(-3.45; 1.37)	0.40	0.79

Abbreviations: 95%CI: 95% Confidence Interval; Est: Estimate, HDL: High-density Lipoprotein, $PM_{2.5}$: Particulate matter with diameter < 2.5μm.
* Two sided *P.*

[a] $PM_{2.5}$ (for each 1 ug/m^3) was 1-year average prior the baseline visit from daily estimates including AOD data from the 1x1 km model and 10x10 km model.
[b] Temperature (for each 1ºC) was 1-year average prior the baseline visit from daily estimates including AOD data from the 1x1 km model.
[c] Variables included in the model: time dependent variablesthe participant's age at the time of the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (never, former, current) and physical activity (<12, 12|-30, ≥ 30 metabolic equivalent hours [MET-hr] per week) – and variables at the baseline visit – education as a proxy for social economic status (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous).
[d] Included medications varying over time: diabetes medication (no/yes).
[e] Included medications varying over time: statin (no/yes).
[f] Included medications varying over time: antihypertensive medication(no/yes).

Table 9: Association of 1-year $PM_{2.5}$[a] and Temperature[b] Levels exposure with Risk of Individual Components and Composite Diagnosis of Metabolic Syndrome, Excluding the Physical Activity variable.

Association with	N participants	N obs	N events	N (%) obs Moderate PA	N (%) obs High PA	$PM_{2.5}$ Hazard Ratio	$PM_{2.5}$ 95% CI	$PM_{2.5}$ P[e]	Temperature Hazard Ratio	Temperature 95% CI	Temperature P[e]
Abdominal Obesity[c]	396	857	107	229 (26)	165 (19)	1.01	(0.88; 1.17)	0.85	1.03	(0.84; 1.27)	0.77
High Fasting Blood Glucose[c]	293	562	118	157 (27)	110 (19)	1.20	(1.03; 1.40)	0.02	1.30	(1.12; 1.52)	0.001
Low HDL Cholesterol[c]	326	625	165	161 (25)	95 (15)	1.03	(0.89; 1.20)	0.66	1.03	(0.86; 1.25)	0.74
Hypertension[c]	116	207	82	73 (35)	31 (15)	1.19	(0.96; 1.48)	0.11	1.14	(0.87; 1.49)	0.33
Hypertriglyceridemia[c]	316	598	154	150 (24)	87 (14)	1.14	(1,00; 1.30)	0.04	1.06	(0.91; 1.22)	0.46
Metabolic Syndrome[c,d]	271	517	140	151 (28)	95 (18)	1.28	(1.03; 1.58)	0.02	1.03	(0.82; 1.29)	0.80

Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; N: Number; PA: Physical Activity; $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.

[a] $PM_{2.5}$ (for each 1 ug/m^3) was 1-year average from daily estimates including AOD data from the 1x1 km model and 10x10 km model.
[b] Temperature (for each 1ºC) was 1-year average from daily estimates including AOD data from the 1x1 km model.
[c] Variables included in the model: time dependent variables-age at the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (current, former, never) - and variables at the baseline-education (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous).
[d] Included medications varying over time: diabetes medication (no/yes), statin (no/yes) and antihypertensive medication(no/yes).
[e] Two sided *P*.

Table 10: Association of interaction term of 1-year $PM_{2.5}$[a] and Temperature[b] Levels exposure with Risk of Individual Components and Composite Diagnosis of Metabolic Syndrome.

Association with	N participants	N observations	N events	Interaction Temperature-$PM_{2.5}$		
				Hazard Ratio	95% CI	*P*[e]
Abdominal Obesity[c]	396	857	107	0.94	(0.81; 1.1)	0.44
High Fasting Blood Glucose[c]	293	562	118	0.97	(0.84; 1.12)	0.70
Low HDL Cholesterol[c]	326	625	165	0.99	(0.87; 1.12)	0.87
Hypertension[c]	116	207	82	1.15	(0.93; 1.42)	0.18
Hypertriglyceridemia[c]	316	598	154	1.02	(0.91; 1.15)	0.70
Metabolic Syndrome[c,d]	271	517	140	0.96	(0.81; 1.13)	0.62

Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; N: Number; $PM_{2.5}$: Particulate matter with diameter under 2.5 μm.

[a] $PM_{2.5}$ (for each 1 ug/m^3) was 1-year average from daily estimates including AOD data from the 1x1 km model and 10x10 km model.

[b] Temperature (for each 1ºC) was 1-year average from daily estimates including AOD data from the 1x1 km model.

[c] Variables included in the model: time dependent variables-age at the visit (continuous), dark fish consumption (<once a week, ≥once a week), alcohol consumption (<2 drinks/day, ≥2 drinks/day), smoking status (current, former, never), physical activity (<12, 12|-30, ≥ 30 metabolic equivalent hours (MET-hr) per week)- and variables at the baseline-education (<12, 12|–|16, >16 years), an indicator for whether the participant was a part-time resident of the greater Boston area (yes/no), percentage of the participant's census tract that is nonwhite (continuous).

[d] Included medications varying over time: diabetes medication (no/yes), statin (no/yes) and antihypertensive medication(no/yes).

[e] Two sided *P*.

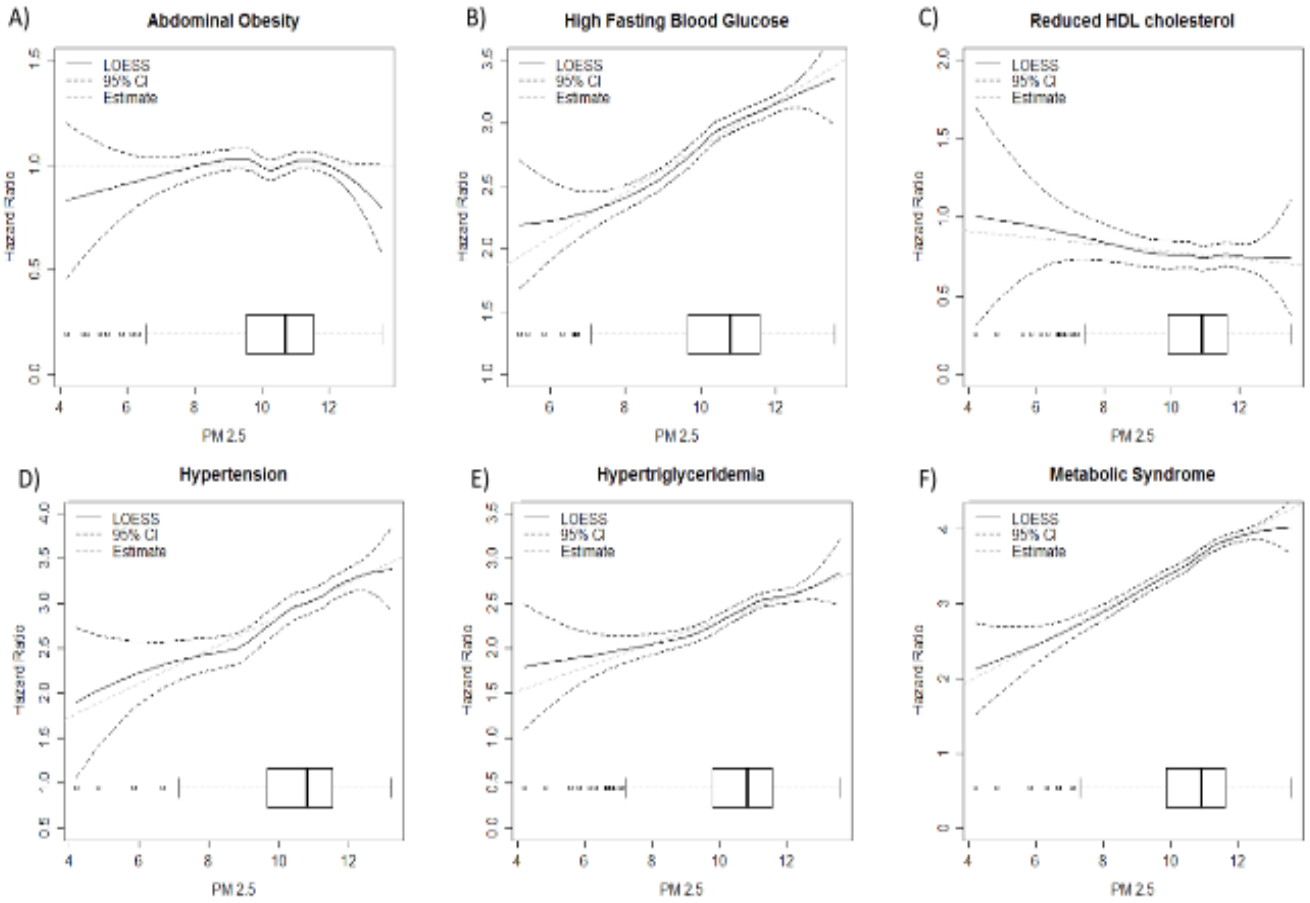

Figure 1 Legend: Level of exposure to fine particulate matter $PM_{2.5}$ and the hazard ratio for each individual component and composite diagnosis of metabolic syndrome in NAS participants since May 2000. Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; LOESS: locally weighted scatterplot smoothing; $PM2_{.5}$: Particulate matter with diameter under 2.5 μm.

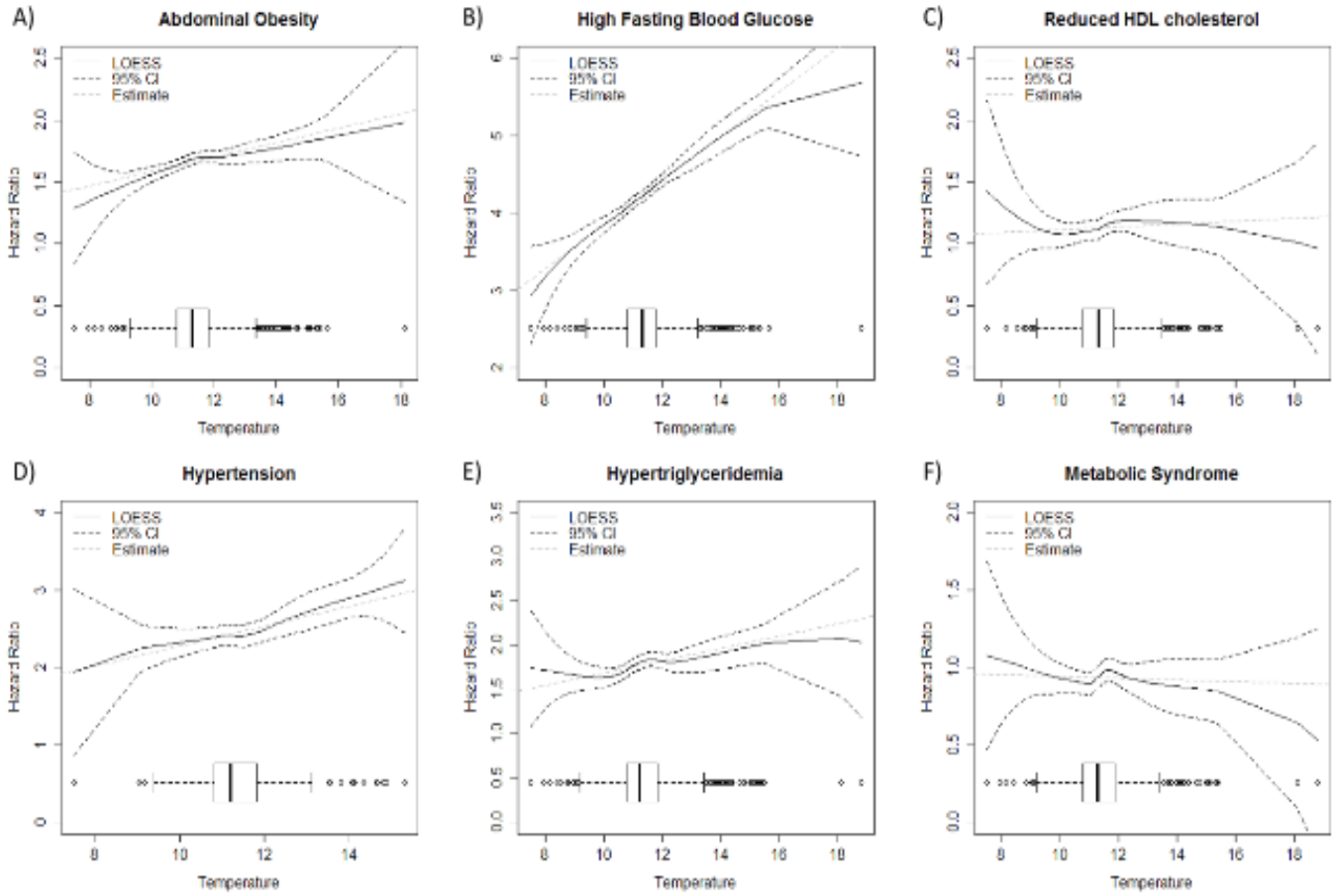

Figure 2 Legend. Level of exposure to temperature and the hazard ratio for each individual component and composite diagnosis of metabolic syndrome in NAS participants since May 2000. Abbreviations: 95%CI: 95% Confidence Interval; HDL: High-density Lipoprotein; LOESS: locally weighted scatterplot smoothing.