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REVIEW ARTICLE

Inflammation Describes and Explains the Adverse Effects of Aerosol Optical Depth-Particulate Matter on Cardiovascular Outcomes: A Literature Review Since 2012

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ABSTRACT

The success of remote sensing methodology to accurately estimate ambient particulate matter (PM) on the earth's surface has resulted in the increased use of aerosol optical depth (AOD) AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 concentration level fused surfaces in cardiovascular epidemiologic and hypothesis-testing of inflammatory physiologic studies. AOD-PM fused surfaces have served as proxies for ambient PM monitor measurements in economically developed and developing counties as well as in urban and rural areas. Since 2012, 45 published studies have evaluated the association between increased AOD-PM concentration level readings and adverse cardiovascular outcomes. Fifteen surveillance studies used inflammation as a descriptive physiologic mechanism and another 20 investigations used the inflammatory physiologic mechanism to explain how AOD-PM exposure changes the cardiovascular system. Among the remaining ten studies, nine mentioned another description and one referred to another explanation. Analyses of the published studies showed: 1) There was 81% agreement between AOD-$PM_{2.5}$ readings and ambient $PM_{2.5}$ monitor measurements. 2) Developing countries had higher AOD-$PM_{2.5}$ readings than developed countries. 3) Descriptive physiologic inflammatory studies found positive associations between higher AOD-PM readings and more acute myocardial infarction, cardiovascular disease, and heart failure outcomes. 4) Higher AOD-PM readings were associated with abnormal blood glucose, c-reactive protein and lipids in studies that cited the inflammatory physiologic mechanism as an explanation. 5) The percentage of specific outcomes increased as the number of identified risk factors also went up only if the AOD-$PM_{2.5}$ readings were higher and decreased if the AOD-$PM_{2.5}$ readings were lower. 6) The inflammation description AOD-$PM_{2.5}$ readings mean (43.4 $\mu g/m^3$) did not differ from the inflammation explanation AOD-$PM_{2.5}$ mean (32.0 $\mu g/m^3$). Study results were used to update the physiologic inflammatory mechanism as a mediator of the effects of AOD-PM exposure on the cardiovascular system. The full extent of the adverse effects of AOD-PM exposure on the cardiovascular system only becomes evident when cardiovascular and other pathophysiological changes are also considered and evaluated. This review paper aims to demonstrate why AOD-PM and cardiovascular system studies are a new and useful source of information about how ambient PM exposure adversely impacts the cardiovascular system in diverse populations in different countries.

Keywords: Aerosol Optical Depth, Particulate Matter, Cardiovascular Disease, Risk Factors, Inflammation

Abbreviations

Acute MI=acute myocardial infarction
ALS=allostatic load
ANOVA=analysis of variance
AOD=aerosol optical depth
ATS=carotid artery intima-media thickness
AU=Australia
BG=blood glucose
CA=chronological age
CI=95% confidence interval
CKD=chronic kidney disease
CN=China
CRP=c-reactive protein
CVD=cardiovascular disease
DM2=diabetes mellitus 2
DTCAT3: chronic disease risk group
GEN=gender
GEO=geography
HF=heart failure
HS=hemorrhagic stroke
HTD=hypertensive disease
ID=inflammation description
IDN=Indonesia
IE=inflammation explanation
IHD=ischemic heart disease
IL=Israel
IR=Iran
IS=ischemic stroke
IT=Italy
LIP=lipids
MX=Mexico
OD=other description
OE=other explanation
OTCAT3=other risk group
PE=Peru
PG=participant group
PLC=platelet count
PM=particulate matter
PM_{1}=≤1.0 μg/m^3
$PM_{2.5}$=≤2.5 μg/m^3
PM25CAT: AOD-$PM_{2.5}$ group
PM_{10}=≤10 μg/m^3
PME=physiologic mechanism
RTCAT3=combined risk group
S=stroke
SA=Saudi Arabia
TW=Taiwan
US=United States
WT=weight

1. Introduction

In the last decade, the methodology used to quantify the contribution of air pollution, especially particulate matter (PM), to cardiovascular disease has included remote sensing and on-the-ground ambient PM monitors. [1-3] PM monitors can accurately measure PM concentration levels within a limited radius of about 20 km around the air monitor, and the PM measurements are only available at discrete time intervals of about every three days. [3] A significant improvement in PM remote sensing is the availability of uniform space-time aerosol optical depth (AOD)-PM concentration level fused surfaces anywhere on the earth's surface. [4] With regards to the adverse effects of PM exposure on the cardiovascular system, current study results from diverse populations and environments can increase our understanding of how PM exposure can produce adverse health outcomes, especially to the cardiovascular and circulatory systems, the heart, brain, kidneys, pancreas, and adipose tissue. [4-11]

A literature search of the National Library of Medicine PubMed database identified 45 different studies published since 2012 that used AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_{1} as proxies for ambient PM_{10}, $PM_{2.5}$, and PM_{1} monitor measurements to understand the adverse effects of acute and chronic PM exposure on the cardiovascular system. [12] Most publications mentioned inflammation in the Discussion to describe study results of conducted studies or to advance our understanding of inflammation as an intermediate physiologic mechanism. Study results often included assessments of AOD-$PM_{2.5}$ accuracy by quantifying the correlation between AOD-$PM_{2.5}$ concentration level readings and ambient $PM_{2.5}$ monitor measurements, or by using another AOD-PM evaluation procedure. The retrieved publications also provided AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_{1} measurements for different geographic areas, which included urban-rural locations in economically developed and economically developing countries. Study outcomes included other cardiovascular chronic diseases or laboratory- and clinical-specific dependent measures of AOD-PM-produced inflammation within the cardiovascular and circulatory systems and the terminal organs connected to the heart through the circulatory system. Another helpful source of information generated by these remote sensing studies included risk factors that identify geographic locations, characteristics of study participants and diverse climatic conditions where acute or chronic AOD-PM exposure contributes to the subsequent occurrence of pathophysiological changes to the cardiovascular system.

The purpose of this literature review was to evaluate AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_{1} and cardiovascular studies published between 2012-2023, summarize study results that used inflammation descriptively versus other studies that

attempted to undertake investigations that increased our understanding of the inflammatory physiologic mechanism. The former group of publications, consisting primarily of AOD-PM and cardiovascular epidemiologic studies, is identified with the inflammation description (ID) acronym. In contrast, the latter group of publications is identified with the inflammation explanation (IE) acronym. A smaller subset of published reports did not mention inflammation but used other statements to describe (OD) or explain (OE) the obtained results. Fine-grain analyses of ID and IE, as well as OD and OE, as intermediate processes in AOD-PM and cardiovascular studies, will be undertaken to address these issues: 1) Do AOD-$PM_{2.5}$ fused surfaces accurately represent ambient $PM_{2.5}$ monitor measurements? 2) Are AOD-$PM_{2.5}$ concentration level readings accurate estimates of ambient $PM_{2.5}$ monitor measurements in different countries? 3) What pathophysiological cardiovascular changes occur in persons exposed to elevated AOD-PM concentration level readings? 4) What are the cardiovascular and other risk factors that occur after study participants are exposed to elevated AOD-PM concentration level readings? A final objective was to utilize results from this literature review to update the role of the inflammatory physiological mechanism as an intermediate outcome operating between AOD-PM exposure and the subsequent occurrence of pathophysiological changes to the cardiovascular system.

2. Methods

2.1. IDENTIFIED PUBLICATIONS

The National Library of Medicine PubMed database was used to search for remote sensing studies, specifically AOD publications, to evaluate the adverse effects of increased ambient PM concentration level readings to the cardiovascular system, circulatory system, and related terminal organs. [12] All search strategies utilized specific search words or word phrases included in the title and abstract fields of the published studies: The first search strategy contained "particulate matter" as a search phrase; the second utilized "satellite," "remote sensing," and "aerosol optical depth" as search terms with the logical operator "or"; the third included the search words of "cardiovascular," "hypertension," "acute myocardial infarction," and "heart failure"; the fourth had "cerebrovascular," "stroke," "diabetes," "kidney," and "weight,"; "lipids," "platelet count," "hyperlipidemia," and "risk factors" were search terms in the last search strategy. The logical operator "and" was used to combine the first two search strategies. The result of concatenating the first and second search strategies was the outcome that contained published studies that utilized AOD-PM. Subsequent search runs used the identified AOD-PM studies (search strategies #1 and #2 combined) with other search words and terms in the other three search strategies. The logical operator "and" concatenated the AOD-PM studies with the 3rd through the 5th search strategies. Each remaining search strategy (#3, #4, #5) was undertaken as a separate search.

Unduplicated articles were selected if remote sensing methodology was utilized to evaluate the association between AOD-PM_{10}, AOD-$PM_{2.5}$, or AOD-PM_1 and the cardiovascular system, circulatory system, or interconnected organs such as the heart, brain, liver, kidneys, or adipose tissue. The PubMed literature search was conducted between December 30, 2022, and February 6, 2023, a temporal search window that lasted about one month.

In all, 45 different articles were identified. Twenty-four of the articles were epidemiologic studies that mostly used inflammation descriptively, ID. Twenty-one reports evaluated the inflammatory physiologic mechanism; these were IE publications. Thus, this latter group of articles often used inflammation as an explanatory physiologic mechanism. The 45 articles reviewed in this report were included in 2 tables. These two tables are in the Appendix: Table A1 mostly contained ID studies, and Table A2 usually had IE publications.

The same information was abstracted from all studies in the two tables. The table columns (variables), from the left margin, included: study identifier; general cardiovascular outcome category; country where the investigation was undertaken; several variables in the Methods and Results column (study design; square of the correlation coefficient expressed as a percentage (a concordance measure between AOD-PM readings and monitor PM measurements); AOD-PM particle size (10, 2.5, and 1 measured in $\mu g/m^3$); AOD-PM concentration also recorded in $\mu g/m^3$ units; ↑=higher, or ↓=lower AOD-PM concentration level reading; specific cardiovascular outcome; number of study participants in the specific outcome/number of participants in the entire study; and, direction/significance of the association between AOD-PM exposure and the specific cardiovascular outcome measure (↑=significantly higher, ↓=significantly lower (protective in some instances), and ↔=not significant; risk measures (geographic, age, gender, cardiovascular risk factors such as weight extremes or smoking, and

non-cardiovascular risk factors such as ambient temperature extreme (^=higher value for a variable, e.g., Age^=older persons; ᵛ=lower value for a variable, e.g., Ageᵛ=younger persons); ↑=significantly higher, ↓=significantly lower (protective under some conditions). The last column documents how the study utilized the inflammatory physiologic mechanism (PME) to describe (ID) or explain (IE) study results. Studies that did not refer to the inflammatory physiologic mechanism were identified using two additional acronyms, which included another description (OD) or another explanation (OE).

2.2. ANALYSES OF STUDY VARIABLES

Descriptive (number of observations, mean, the mean's 95% confidence interval, CI) and inferential (Chi-Square, X^2; *t*-test for two groups; multi-group unbalanced analysis of variance, ANOVA) statistical analyses were utilized to answer the scientific questions included at the end of the Introduction. All descriptive and inferential statistical analyses were undertaken using the analytical procedures in Base SAS [13,14] and SAS/STAT. [15] The Base SAS Procedures Guide's Proc MEANS [13] was used to compute descriptive statistics on continuous variables (number of observations, mean, CI). The Base SAS statistical procedures' Proc FREQ [14] was used to evaluate categorical variables (cell frequencies and associated percentages) and the relationship between two (or more) categorical variables. Proc FREQ [14] was also utilized to determine if cell totals in one categorical variable were independent of cell totals in another categorical variable. This type of discrete-variable analysis was accomplished using the Chi-Square test, X^2. The Pearson Chi-Square Test Exact was used when the expected cell frequency in one cell was less than 5. The SAS/STAT Proc TTEST (t-test) was used to determine if two groups differed on the same continuous outcome measure. The SAS/STAT Proc GLM analytical method was used to evaluate the differences between the three or more levels of a single grouping variable or two or more independent variables on the same outcome measure, i.e., ANOVA for unbalanced data. [15] The mean and CI were used to identify the group means that were either below the CI's lower limit or above the CI's upper limit of the reference group mean. [13] These two outcomes identified a significant difference between a comparison group mean and the reference group mean, $p \leq 0.05$. When the comparison group mean was within the CI's lower and upper limits of the reference group's mean, this outcome was not significant, $p > 0.05$. The null hypothesis was rejected when a statistical test's probability was $p \leq 0.05$, i.e., a statistically significant outcome.

3. Results and Discussion

The 45 studies in Table A1 (n=24) and Table A2 (n=21) were completed in 11 countries. In descending order, 17 (37.8%) publications were conducted in China (CN), 12 (26.7%) in the United States (US), 5 (11.1%) in Taiwan (TW), 3 (6.7%) in Israel (IL), 2 (4.4%) in Mexico (MX) and one (2.2%) each in Australia (AU), Indonesia (IDN), Iran (IR), Italy (IT), Peru (PE), and Saudi Arabia (SA). There were no significant differences between the 24 (53.3%) studies in Table A1 and the 21 (46.7%) publications in Table A2 ($X^2(1)<1$, $p>0.05$). About one-fourth of the 45 studies (n=11, 24.4%) were published between 2012-2017, and about three-fourths (n=34, 75.6%) were published between 2018-2023 ($X^2(1)=11.76$, $p \leq 0.01$). Stated differently, significantly more AOD-PM and cardiovascular studies were published during the most recent six-year interval than during the first six-year interval. The Table by Year analysis was not significant ($X^2(1)<1$, $p>0.05$): 17 (37.8%) of the studies in Table A1 and 17 (37.8%) of the published papers in Table A2 appeared in print during the most recent six-year interval, 2018-2023. Similarly, 7 (15.6%) of the studies in Table A1 and 4 (8.9%) in Table A2 were published during the first six-year interval, 2012-2017.

There were significant differences in the number of times the inflammatory physiologic mechanism or some other description/explanation was used in the AOD-PM and cardiovascular studies ($X^2(3)=17.84$, $p \leq 0.01$). Fifteen (33.3%) of the studies utilized inflammation to describe the obtained results, while 20 of the studies (44.4%) used inflammation to explain the results. The other descriptive (OD) category was used to describe the results in nine (20.0%) studies, and the other explanation (OE) appeared in one (2.2%) published paper. The Table by Inflammation category analysis was also significant (Pearson Chi-Square Test Exact, $X^2(3)=37.61$, $p \leq 0.01$): 15 (33.3%) papers in Table A1 used ID, and no report in Table A2 used ID. Conversely, 19 (42.2%) publications in Table A2 used IE, and only one (2.2%) article in Table A1 used IE. Eight (17.8%) studies in Table A1 mentioned OD. The two remaining studies in Table A2 infrequently mentioned OD (n=1, 2.2%) or OE (n=1, 2.2%).

For the 45 studies in both tables, there were significant differences in study design ($X^2(3)=21.58$, $p \leq 0.01$). The prospective cohort design was used in 22 (48.9%) studies, cross-

sectional in 15 (33.3%), case-control in six (13.3%), and retrospective cohort in two (4.4%). The Table by Design analysis was not significant (Pearson Chi-Square Test Exact, $X^2(3)=5.27$, $p>0.05$).

All studies in both tables were significantly different in the use of ambient air monitors or another statistical procedure to validate the accuracy of AOD-$PM_{2.5}$ concentration level readings ($X^2(2)=12.50$, $p\leq0.01$): 22 (61.1%) used $PM_{2.5}$ monitors, 7 (19.4%) used another gold standard instead of $PM_{2.5}$ air monitor measurements, and another 7 (19.4%) did not validate the utilized AOD-$PM_{2.5}$ concentration level readings. The Table by Monitor analysis was not significant (Pearson Chi-Square Test Exact, $X(2)<1$, $p>0.05$).

3.1. AOD-$PM_{2.5}$ MONITOR VALIDATION

Thirty-six of the 45 studies (80.0%) utilized AOD-$PM_{2.5}$, eight (17.8%) used AOD-PM_{10}, and one (2.3%) used AOD-PM_1. The validation analysis was only completed for studies that utilized AOD-$PM_{2.5}$ because this group had the largest sample size. A shared variance statistic was used in the AOD-$PM_{2.5}$ fused surface validation assessment. The correlation (r) between AOD-$PM_{2.5}$ concentration level readings with ambient $PM_{2.5}$ monitor concentration level measurements, or another reference source, was computed in the published studies. The shared variance statistic (r^2) is obtained by first calculating the correlation between the AOD-$PM_{2.5}$ concentration level readings and ambient $PM_{2.5}$ monitor measurements, raising this concordance value to the second power, and then expressing r^2 as a percentage ($r^{2\%}$).

For 29 studies, the $r^{2\%}$ mean (CI) was 81.0% (74.3%-82.4%). Stated differently, 81.0% of the AOD-$PM_{2.5}$ concentration level readings resembled the monitor $PM_{2.5}$ measurements or another reference source, within a 95% accuracy boundary of 74.3% to 82.4%. There were no significant $r^{2\%}$ differences between the 22 studies that used ambient air monitor $PM_{2.5}$ concentration level measurements to validate the AOD-$PM_{2.5}$ concentration level readings (76.9%) versus the other seven studies that used another procedure to assesses the validity of the AOD-$PM_{2.5}$ concentration level readings (82.8%; Satterthwaite unequal variance method, $t(24.2)=1.87$, $p>0.05$). A two-way ANOVA was used to assess the Table by Monitor and the interaction between these two predictors for $r^{2\%}$. The Table ($F(1)<1$, $p>0.05$), Monitor ($F(1)=1.34$, $p>0.05$) and the Table*Monitor interaction ($F(1)<1$, $p>0.05$) were not significant.

3.2. AOD-$PM_{2.5}$ READINGS

For all publications, the mean (CI) for AOD-$PM_{2.5}$ concentration level readings was 34.5 (25.8-43.2) $\mu g/m^3$. There were no significant differences between the 21 studies in Table A1 and the 15 studies in Table A2 in AOD-$PM_{2.5}$ concentration level readings ($t(34)<1$, $p>0.05$). For Table A1 studies, the AOD-$PM_{2.5}$ concentration level readings were significantly lower when ambient $PM_{2.5}$ air monitors were not used (n=4, 10.4 $\mu g/m^3$) than when the ambient $PM_{2.5}$ air monitors were used (n=12, 48.6 $\mu g/m^3$; Satterthwaite unequal variance, $t(11.1)=-4.84$, $p\leq0.01$). When the same analysis was completed by including Table A2 studies, the mean of the AOD-$PM_{2.5}$ concentration level readings for the three reports that did not use ambient $PM_{2.5}$ air monitor measurements (31.9 $\mu g/m^3$) was not significantly different from the AOD-$PM_{2.5}$ mean of the ten publications that used ambient $PM_{2.5}$ air monitors (34.1 $\mu g/m^3$; $t(11)<1$, $p>0.05$). When the AOD-$PM_{2.5}$ concentration level readings were evaluated by using the six-year category predictor variable, the seven studies published between 2012-2017 had significantly lower AOD-$PM_{2.5}$ concentration level readings (12.6 $\mu g/m^3$) than the AOD-$PM_{2.5}$ concentration level readings for the 22 studies that were completed between 2018-2023 (44.2 $\mu g/m^3$; Satterthwaite unequal variance, $t(25.9)=-5.16$, $p\leq0.01$).

Next, the AOD-$PM_{2.5}$ mean for each country was compared to the mean (CI) for all studies in both tables (i.e., reference mean and CI: n=36, mean=34.5 $\mu g/m^3$, CI: 25.8 $\mu g/m^3$-43.2 $\mu g/m^3$). If the country comparison mean was below the reference mean's CI lower level of 25.8 $\mu g/m^3$, then the comparison mean was significantly lower than the reference mean (34.5 $\mu g/m^3$; $p\leq0.05$). If the country mean was above the CI's upper level (43.2 $\mu g/m^3$), then the comparison mean was significantly higher than the reference mean ($p\leq0.05$). But, if the country mean was within the CI's lower and higher levels, then the comparison mean was not significantly different from the reference mean ($p>0.05$). Five countries had AOD-$PM_{2.5}$ concentration level readings that were significantly lower than the reference mean (AU, n=1, 6.4 $\mu g/m^3$; IDN, n=1, 14.4 $\mu g/m^3$; MX, n=2, 23.3 $\mu g/m^3$; PE, n=1, 20.9 $\mu g/m^3$; US, n=12, 11.5 $\mu g/m^3$) and three countries had AOD-$PM_{2.5}$ concentration level reading means that were significantly higher than the reference mean (CN, n=12, 62.6 $\mu g/m^3$; IR, n=1, 45.3 $\mu g/m^3$; SA, n=1, 87.9 $\mu g/m^3$). The TW mean (n=5, 26.1 $\mu g/m^3$) was not significantly different from the reference mean.

3.3. INFLAMMATION DESCRIPTION STUDIES

Table A1 summarizes the results of studies that evaluated the association between AOD-$PM_{2.5}$ concentration level readings and cardiovascular chronic disease-specific outcomes. Twenty-four different studies contributed a total of 59 specific outcomes. In each subsection below, the results of analyses of the general cardiovascular outcomes will be summarized. The cardiovascular chronic disease summary will include mean AOD-$PM_{2.5}$ concentration level reading differences between countries, statistical evaluation of the relationship between AOD-$PM_{2.5}$ and the specific outcome, identified risk factors, and how inflammation was used. For the 59 specific outcomes there were 42 (71.2%) ID's, 13 (22.0%) OD's, and 4 (6.8%) IE's ($X^2(2)=40.10$, $p \leq 0.01$). A one-way ANOVA was used to determine if the three levels of the inflammation variable differed on mean AOD-$PM_{2.5}$ concentration level readings. The outcome was not significant ($F(2)<1$, $p>0.05$): ID, 37.0 $\mu g/m^3$; IE=21.6 $\mu g/m^3$; and OD=29.8 $\mu g/m^3$.

3.3.1. Acute Myocardial Infarction (Acute MI). Eight studies [16-23] completed in 4 countries (CN, IR, IT, and US) reported nine specific outcomes. Mean AOD-$PM_{2.5}$ concentrations level readings were higher in CN (n=2, 59.9 $\mu g/m^3$) and in IR (n=1, 45.3 $\mu g/m^3$) than in the US (n=4, 11.7 $\mu g/m^3$). All specific outcomes showed a significant positive association between higher AOD-$PM_{2.5}$ concentration level readings and higher Acute MI-specific outcomes. Persons living in rural areas in IT (n=2) and in the US (n=1) were at significantly higher risk than those persons living in urban areas. But Iranians living in rural areas had a significantly lower risk (protective) than Iranians residing in urban areas (n=1). The sample size for the Iranian acute MI-specific outcome (n=73) was smaller than the sample sizes of the IT (n=321,768) and US (n=4,745) acute MI-specific outcomes. Other risk factors included higher ambient temperature (n=1), male gender (n=1), and diabetes mellitus 2 (n=1). Regarding inflammation, ID was mentioned for six and OD for three specific outcomes.

3.3.2. Cardiovascular Disease (CVD). The eight studies [16-19,24-27] that reported the nine CVD-specific outcomes were completed in CN, in IR, in IT, and in the US. Mean AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=3, 55.8 $\mu g/m^3$) and in IR (n=1, 45.3 $\mu g/m^3$) than in the US (n=3, 11.8 $\mu g/m^3$). All nine CVD-specific outcomes showed a significantly positive association between increased AOD-PM_{10} (IT) or AOD-$PM_{2.5}$ concentration level readings and higher CVD-specific outcomes. Living in a rural area (n=3) or another geographic area (n=1), older age (n=6), male gender (n=2), and diabetes mellitus 2 (n=1) were significant CVD risk factors. ID was mentioned for eight CVD-specific outcomes, and OD was stated for the remaining CVD-specific outcome.

3.3.3. Hypertensive Disease (HTD). Eight studies [24,28-34] provided results for nine HTD-specific outcomes completed in CN, in TW, and in the US. Mean AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=5, 56.8 $\mu g/m^3$), lower in the US (n=1, 10.5 $\mu g/m^3$), and intermediate in TW (n=2, 26.8 $\mu g/m^3$). AOD-PM_{10} (99.4 $\mu g/m^3$) was used with one HTD-specific outcome [28] completed in CN. Seven of the nine HTD-specific outcomes had significantly positive associations between higher AOD-PM_{10} or AOD-$PM_{2.5}$ concentration level readings and more HD-specific outcomes. The US study [34] with the non-significant outcome had the smallest number of participants (n=116). Significant HTD-specific risk factors included living in a rural area (n=1) or another geographic area (n=1), older age (n=3), and increased weight (n=3). Eight of the HTD-specific outcomes included ID, and one referred to OD.

3.3.4. Heart Failure (HF). Three studies [19,22,23], one from IT and two from the US evaluated four HF-specific outcomes. The AOD-$PM_{2.5}$ concentration level reading mean for the two HF-specific outcomes completed in the US was 12.5 $\mu g/m^3$. All four outcomes showed a significantly positive association between elevated AOD-PM_{10} (IT) or AOD-$PM_{2.5}$ concentration level readings and increases in HF-specific outcomes. Important risk factors included living in a rural area (n=1) and higher ambient temperature (n=1). ID was mentioned for two, and OD was stated for the other two HF-specific outcomes.

3.3.5. Hemorrhagic Stroke (HS). Two studies [17,35], one from CN and the other from IL, evaluated three HS-specific outcomes. The IL study used AOD-PM_{10} (54.8 $\mu g/m^3$) and AOD-$PM_{2.5}$, while the CN study only reported AOD-$PM_{2.5}$. The AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=1, 52.3 $\mu g/m^3$) than in IL (n=1, 21.6 $\mu g/m^3$). All three AOD-PM and HS-specific outcome associations were not significant. Smaller study sample sizes could be one reason for the non-significant outcomes in the IL findings. [35] Each IL HS-specific outcome only included 512 participants. The CN investigation utilized 7,684 HS patients but had a non-significant outcome. Significant risk factors included lower age (n=2) and lower

ambient temperature (n=2). The IL study mentioned IE, while the CN publication referred to ID.

3.3.6. Ischemic Heart Disease (IHD). Seven studies [17,19,26,36-39] provided results for nine IHD-specific outcomes completed in CN, in IDN, in IT, in PE, in SA, and in the US. Seven specific IHD outcomes utilized AOD-$PM_{2.5}$, one AOD-PM_{10} (IT), and the other AOD-PM_1 (CN, 66.0 µg/m³). The mean AOD-$PM_{2.5}$ concentration level readings were higher in SA (n=1, 87.9 µg/m³) and in CN (n=2, 67.2 µg/m³), lower in IDN (n=1, 14.4 µg/m³) and in the US (n=1, 11.9 µg/m³), and intermediate in PE (n=1, 20.9 µg/m³). Five of the IHD-specific outcomes were significantly positive, and four were not significant. The IDN study [37] with a non-significant outcome only included 74 participants. Living in a rural area (n=2) in IT was a significant risk factor. ID was mentioned for six and OD for three IHD-specific outcomes.

3.3.7. Ischemic Stroke (IS). Three studies [17,19,35] contributed results for five IS-specific outcomes, completed in CN, in IL, and in IT. The AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=1, 52.3 µg/m³) and lower in IL (n=1, 21.6 µg/m³). There were three significant outcomes, one in CN and two in IT. The two IS-specific outcomes completed in IL were not significant: one utilized AOD-PM_{10} (54.8 µg/m³), and the other used AOD-$PM_{2.5}$. The IL study [35] also reported significant risk factors for lower age (n=2) and lower ambient temperature (n=2). ID was mentioned for three, and IE for two IS-specific outcomes.

3.3.8. Stroke (S). Ten studies [16-18,24-26,36-39] contributed results for 11 S-specific outcomes completed in CN, in IDN, in IR, in PE, in SA, and in the US. One S-specific outcome completed in CN utilized AOD-PM_1 (66.0 µg/m³), while the other ten used AOD-$PM_{2.5}$. Mean AOD-$PM_{2.5}$ concentration level readings were higher in SA (n=1, 87.9 µg/m³), in CN (n=4, 62.3 µg/m³), and in IR (n=1, 45.3 µg/m³), lower in IDN (n=1, 14.4 µg/m³) and in the US (n=2, 10.8 µg/m³), and intermediate in PE (n=1, 20.9 µg/m³). Seven of the 11 S-specific outcomes were significant. All four non-significant specific outcomes had smaller sample sizes: 589 and 342 (CN), 92 (IR), and 20 (IDN). Older age (n=3), diabetes mellitus 2 (n=1), and hypertension (n=1) were significant risk factors while living in a rural area (n=1) and demonstrating higher physical activity (n=1) were protective, i.e., they were associated with lower S-specific risk. ID was mentioned for eight and OD for three S-specific outcomes.

3.3.9. Summary of Inflammation Description Study Results. Table A1 epidemiologic studies that utilized inflammation descriptively showed AOD-PM exposure leads to the subsequent occurrence of acute myocardial infarction, cardiovascular disease, hypertensive disease, heart failure, hemorrhagic stroke, ischemic heart disease, ischemic stroke, and the more general stroke diagnostic category. The relationship between AOD-PM concentration level readings and the eight cardiovascular chronic diseases was significant (Pearson Chi-Square Test Exact, $X^2(7)=19.32$, $p \leq 0.01$). In this analysis of 59 specific cardiovascular outcomes 44 (74.6%) were significant and 15 (25.4%) were not significant. These are the percentages for the number of significant outcomes relative to the total number of outcomes, listed in descending order: 1) Acute MI, 100.0% (significant n's=9, total n's=9); 2) CVD, 100.0% (significant=9, total=9); 3) HF, 100.0% (significant=4, total=4); 4) HD, 77.8% (significant=7, total=9); 5) S, 63.6% (significant=7, total=11); 6) IS, 60.0% (significant=3, total=5); 7) IHD, 55.6% (significant=5, total=9); 8) HS, 0.0% (significant=0, total=3).

It is possible to utilize these significant outcome percentages to arrive at a tentative conclusion about the effectiveness of utilizing AOD-PM concentration level readings in epidemiologic studies of cardiovascular chronic diseases. Factual confidence in these AOD-PM and cardiovascular chronic disease associations can be established by first forming three cardiovascular chronic disease categories and then observing the percentage of significantly positive outcomes in each confidence group: strong confidence, 76.0%-100.0%; suggestive, 26%-75.0%; and insufficient evidence, 0.0%-25.0%. The highest percentage tier included Acute MI, CVD, HF, and HD. For these four cardiovascular chronic diseases there is strong confidence that elevated AOD-PM concentration level readings contributed to the occurrence of more adverse cardiovascular-related health events. The intermediate percentage category included S, IS, and IHD. For these three cardiovascular chronic diseases there is suggestive evidence that higher AOD-PM concentration level readings are associated with more adverse cardiovascular hospital events. HS is the only cardiovascular chronic disease to be included in the lowest tier, identified with the label of insufficient evidence. Notice also that HS has the smallest number of specific outcomes – only three. There were four HF-

cardiovascular disease specific outcomes, but all of them were significant. In addition, the mean number of HS-specific outcome observations was 2,902.7, while the mean number of observations for all cardiovascular chronic diseases, including HS, was much higher, 238,126.9. The sample sizes for the three HS- specific outcomes may not have been large enough for the statistical test used to detect the effect size for the association between elevated AOD-PM concentration level readings and increased HS-specific chronic disease events.

An analysis of the total number of observations for specific cardiovascular outcomes showed a significant association between smaller sample sizes and non-significant associations between AOD-$PM_{2.5}$ exposure and adverse cardiovascular outcomes. Section 3.5., below, provides additional information about sample size and significant outcomes. Under some circumstances, enrolling the optimal number of study participants with specific cardiovascular chronic diseases may not be possible.

3.4. INFLAMMATION EXPLANATION STUDIES

Nearly-all studies in Table A2 were designed to understand how exposure to higher AOD-PM concentration level readings is expressed as an inflammatory physiologic response that can be documented as changes in the selected inflammatory-related laboratory and clinical measures, structural changes to the circulatory system, worse cardiovascular chronic disease outcomes, including the occurrence of risk factors. Table A2 variables were formatted and displayed in the same way as Table A1 variables. The Table A2 general outcome acronyms do not always correspond to the specific outcome acronyms. Another difference is that most Table A2 studies referred to the inflammatory physiologic mechanism to evaluate and later explain how elevated AOD-PM concentration level readings resulted in the subsequent occurrence of adverse cardiovascular outcomes.

Among the 73 specific outcomes in Table A2, there were significant differences between the three levels of the inflammation variable ($X^2(2)=97.51$, $p \leq 0.01$): 64 (87.7%) IE's, 7 (9.6%) OE's, and 2 (2.7%) OD's. A one-way ANOVA was used to evaluate differences between the three physiologic mechanism inflammatory categories and mean AOD-$PM_{2.5}$ concentration level readings. The outcome of this ANOVA analysis of the three levels of the inflammation variable was significant ($F(2)=4.80$, $p \leq 0.01$): The OD inflammation level had the highest mean AOD-$PM_{2.5}$ concentration level reading of 56.0 µg/m^3, OE had the lowest (12.2 µg/m^3), and IE had an intermediate value of 32.4 µg/m^3. Between-mean comparisons based on the use of the Tukey-Kramer adjusted multiple comparisons test showed that OE was significantly lower than either OD or IE.

3.4.1. Allostatic load (ALS). ALS is a composite measure of inflammation. One study [40], completed in CN, utilized AOD-PM_{10} (72.6 µg/m^3), AOD-$PM_{2.5}$ (41.8 µg/m^3), and AOD-PM_1 (27.6 µg/m^3) to document observed changes to ALS-specific outcomes. There were significantly positive associations between ALS and AOD-PM_{10} and AOD-$PM_{2.5}$. Important risk factors for the two significant ALS outcomes were older age (n=2), lower educational attainment (n=2), lower income (n=2), and increased alcohol use (n=2); being a member of an ethnic minority (n=2) was protective. Significant risk factors for the non-significant ALS-specific outcome included lower educational attainment (n=1) and increased alcohol use (n=1); persons who identified with a recognized ethnic group (n=1) also had decreased risk. IE was mentioned for all three ALS-specific outcomes.

3.4.2. Carotid Artery Intima-Media Thickness (ATS). Two different studies, one from AU [41] and the other from CN [42], reported three ATS-specific outcomes, one from AU and two from CN. The AOD-$PM_{2.5}$ concentration level readings were higher in CN (62.6 µg/m^3) and lower in AU (6.4 µg/m^3). There were two significant positive associations between higher AOD-$PM_{2.5}$ concentration level readings and increased carotid artery intima-media thickness and a significant but inverse association between higher AOD-$PM_{2.5}$ concentration level readings and decreased brachial-flow mediated dilation. Carotid artery intima-media thickness risk factors included living in a specific geographic area (n=1), older age (n=1), male gender (n=1), elevated low-density lipoprotein cholesterol (n=1), higher diastolic (n=1) and systolic (n=1) blood pressure values and smoking (n=1). The three brachial flow mediated dilation risk factors were protective: older age (n=1), male gender (n=1), and higher diastolic blood pressure (n=1). IE was mentioned for all three ATS-specific outcomes.

3.4.3. Blood Glucose (BG). The three studies [34,43,44] that reported on four BG-specific outcomes were completed in IL and in the US. The mean AOD-$PM_{2.5}$ concentration level readings were higher in IL (n=1, 22.3 µg/m^3) and lower in the US (n=2, 10.6 µg/m^3). The other IL BG-specific

outcome used AOD-PM_{10} (54.1 µg/m^3). All four BG-specific outcomes were significant and positive. Important risk factors were diabetes mellitus 2 (n=2), higher ambient temperature (n=2), and lower risk for intracellular adhesion molecule 1. IE was mentioned for all four BG-specific outcomes.

3.4.4. Chronic Kidney Disease (CKD). Three studies, two from CN [45,46] and one from the US [47], reported five CKD-specific outcomes. Four CKD-specific outcomes utilized AOD-$PM_{2.5}$, and one from CN also used AOD-PM_1 (46.8 µg/m^3). Mean AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=2, 56.8 µg/m^3) and lower in the US (n=2, 11.8 µg/m^3). All five AOD-$PM_{2.5}$ and AOD-PM_1 and CKD-specific outcomes were significant. Significant risk factors included living in an urban or in a rural area (n=2), younger age (n=2), female gender (n=4), and lower weight (n=2). IE was mentioned for all five CKD-specific outcomes.

3.4.5. C-Reactive Protein (CRP). Five CRP-specific outcomes were reported in one CN study [48] and in two TW publications. [49,50] Mean AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=1, 54.0 µg/m^3) and lower in TW (n=2, 25.4 µg/m^3). The CN study also included AOD-PM_{10} (91.1 µg/m^3) and AOD-PM_1 (43.7 µg/m^3). All five CRP-specific outcomes were significant and positive. Significantly higher risk factors included older age (n=1), higher income (n=1), and CVD (n=3). Higher exercise capacity (n=1) was protective, i.e., indicative of decreased CRP risk. IE was mentioned for all five CRP-specific outcomes.

3.4.6. Diabetes Mellitus 2 (DM2). Five studies were completed in CN [30,51], in MX [52], in SA [39], and in the US [25] reported results for five DM2-specific outcomes. Mean AOD-$PM_{2.5}$ concentration level readings were higher in SA (n=1, 87.9 µg/m^3) and in CN (n=2, 56.3 µg/m^3), lower in the US (n=1, 9.6 µg/m^3), and intermediate in MX (n=1, 24.1 µg/m^3). Of the five DM2-specific outcomes, four were significant. The non-significant outcome occurred in MX. The MX study sample size was limited to 121 participants. Important risk factors included living in a rural area (n=2), female gender (n=2), and lower education (n=1). IE was mentioned for three and OD for two DM2-specific outcomes.

3.4.7. Lipids (LIP). Eleven studies, five completed in CN [30,45,46,53,54], one each in IL [43] and in MX [55], and 4 in the US [34,47,56,57], reported on 41 LIP-specific outcomes. Mean AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=7, 44.9 µg/m^3), lower in the US (n=11, 11.9 µg/m^3), and intermediate in MX (n=4, 22.5 µg/m^3) and in IL (n=3, 22.3 µg/m^3). AOD-PM_{10} concentration level readings were also higher in CN (n=4, 72.1 µg/m^3) than in IL (n=3, 54.1 µg/m^3). One CN study also used AOD-PM_1 (42.5 µg/m^3). There were 26 significantly positive, 13 significantly negative (protective in some cases), and two non-significant LIP-specific outcomes. Risk factors included living in a rural area (n=2) or another geographic area (n=2) and older age (n=9). Of the 41 LIP-specific outcomes, 34 mentioned IE, and 7 included OE.

3.4.8. Platelet Count (PLC). PLC was evaluated in one study [58] completed in TW. The reported AOD-$PM_{2.5}$ concentration level reading was 26.5 µg/m^3. There was a significantly positive association between elevated AOD-$PM_{2.5}$ concentration level readings and the PLC-specific outcome. Significant risk factors included older age (n=1) and female gender (n=1). IE was mentioned for the one PLC-specific outcome.

3.4.9. Weight (WT). Four studies completed in CN [30,59], in IL [60], and in the US [34] contributed six WT-specific outcomes. The mean AOD-$PM_{2.5}$ concentration level readings were higher in CN (n=3, 58.1 µg/m^3), lower in the US (n=1, 10.5 µg/m^3), and intermediate in IL (n=1, 21.8 µg/m^3). The IL study also used AOD-PM_{10} (63.2 µg/m^3). There were five significantly positive associations and one significantly negative (protective) association between the AOD-PM_{10} and AOD-$PM_{2.5}$ concentration level readings and the WT-specific outcomes. Risk factors for the significantly positive results included older age (n=1), lower dyslipidemia (n=1), lower hypertension (n=1), and leptin (n=1). Risk factors for one significantly negative specific outcome included living in a rural area (n=1), lower education (n=1), smoking (n=1), and hypertension (n=1). IE was cited for all six WT-specific outcomes.

3.4.10. Summary of Inflammation Explanation Study Results. Table A2 publications demonstrated that established laboratory and clinical outcome measures can be used with AOD-PM concentration level readings to advance our understanding of how the inflammatory physiologic mechanism explains the adverse effects of ambient PM exposure on the cardiovascular system. Specific lipid outcomes included total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total glycerides, and

estimated glomerular filtration rate. Other laboratory measures of inflammation included c-reactive protein, blood glucose and platelet count.

There was not a significant difference in the number of the three specific outcomes (significantly positive, significantly negative, and not significant) for each of the nine cardiovascular-related specific categories (Pearson Chi-Square Test Exact, $X^2(16)=17.14$, $p>0.05$). Out of the 73 specific outcomes, only four (5.5%) were not significant. ALS included one non-significant outcome (33.3%) out of three specific outcomes. DM2 also had one non-significant outcome (20.0%) out of five specific outcomes. LIP had two non-significant outcomes (4.9%) out of 41 total specific outcomes. More of the statistical outcomes between AOD-PM concentration level readings and the specific cardiovascular outcomes were significantly positive (n=54, 74.0%). The significantly negative (protective in some instances) results included 15 specific outcomes with a percentage value of 20.6%. Among the 15 significantly negative outcomes, ALS had one (total=3, 33.3%), WT also had one (total=6, 16.7%) and LIP had 13 (total=41, 31.7%).

Because LIP-specific outcomes included laboratory measures of inflammation such as LDL and HDL, in some cases, a significantly negative association does not represent a protective outcome or lower risk. To illustrate, a significantly negative association between higher AOD-PM concentration level readings and lower HDL indicates an adverse cardiovascular inflammatory outcome as does a significantly positive association between higher AOD-PM concentration level readings and increased LDL. Both cardiovascular specific outcomes represent the presence of an inflammatory physiologic response following acute or chronic exposure to higher ambient PM, measured as higher AOD-PM concentration level readings.

If the same factual confidence criteria that were first described in Section 3.3.9., above, are now applied to the results for the nine general outcome groups formed to evaluate inflammation explanation studies and included in Sections 3.4.1. through 3.4.9., eight of the nine general outcome groups had significantly positive or negative AOD-PM and cardiovascular specific outcome association percentages that were high enough to be included in the strong confidence tier (ATS, BG, CKD, CRP, DM2, LIP, PLC, WT) while the ALS general outcome group had to be placed in the suggestive confidence tier because of its lower percentage value. Notice that for these cardiovascular laboratory and clinical measures of inflammation there was no cardiovascular-related specific outcome to be placed in the insufficient factual evidence tier.

3.5. SAMPLE SIZE AND SIGNIFICANCE

In some cases, non-significant associations occurred with smaller sample sizes. For all studies, in Tables A1 and A2, there was a significant association between the median split (20,905 or fewer subjects versus more than 20,905 subjects, Low and High Participant Groups, PG, respectively) of the total number of observations included in the specific cardiovascular outcome samples and reported significance between AOD-PM concentration level readings and adverse cardiovascular specific outcomes ($X^2(2)=10.52$, $p\leq0.01$). Of the 98 (74.2%) Table A1 and Table A2 specific outcomes that were significant, there were 54 (55.1%) in the PG High Group, and 44 (44.9%) in the PG Low Group. Among the 19 (14.4%) non-significant outcomes, there were 16 (84.2%) in the PG Low Group and 3 (15.8%) in the PG High Group. When this same analysis was carried out for the specific cardiovascular outcomes in each Table separately, the results were significant for the 59 specific outcomes in Table A1 ($X^2(1)=10.50$, $p\leq0.01$) but not significant for the 73 specific outcomes in Table A2 (Pearson Chi-Square Test Exact, $X^2(2)<1$, $p>0.05$). In Table A1, the most extreme difference was for the 15 (25.4%) non-significant outcomes out of the 59 specific outcomes: There were 14 (93.3%) non-significant outcomes in the PG Low Group and only one (6.7%) non-significant outcome in the PG High Group. Among the 44 significant outcomes, 24 (54.6%) were in the PG High Group and 20 (45.4%) in the PG Low Group.

3.6. RISK FACTORS

Risk factors were included in Tables A1 and A2. The individual risk factors were combined into discrete groups to permit a statistical analysis of their characteristics and relationships with other cardiovascular and non-cardiovascular variables, with particular emphasis on AOD-$PM_{2.5}$ concentration level reading differences between countries. The newly formed risk groups included geography (GEO), chronological age (CA), gender (GEN), cardiovascular chronic disease risk total (DTCAT3), other non-cardiovascular disease risk total (OTCAT3), and all cardiovascular and non-cardiovascular risks combined (RTCAT3).

3.6.1. Geography (GEO). There were significant differences between the three levels of the geographic variable ($X^2(2)=7.46$, $p\leq0.05$). Living in a rural area (n=15, 57.7%) or another

geographic area (n=7, 26.9%) was associated with increased risk. The Country by GEO analysis was significant (Pearson Chi-Square Test Exact, $X^2(8)=27.04$, $p\leq0.01$). Living in a rural area was a significant risk factor in CN (n=7, 26.9%), in IT (n=6, 23.1%), and in the US (n=2, 7.7%). Living in another geographic area was also a significant risk factor in AU (n=1, 3.8%), in CN (n=3, 11.5%), and in the US (n=3, 11.5%). The GEO by Table analysis was not significant (Pearson Chi-Square Test Exact, $X^2(2)=3.42$, $p>0.05$). The GEO by the median split of the AOD-$PM_{2.5}$ concentration level readings (PM25CAT) was not significant (Pearson Chi-Square Test Exact, $X^2(2)=3.63$, $p>0.05$). ANOVA results showed non-significant differences between the three levels of the GEO variable used as the predictor and the AOD-$PM_{2.5}$ concentration level readings as the outcome measure ($F(2)<1$, $p>0.05$).

3.6.2. Chronological Age (CA). Age was a significant risk factor ($X^2(2)=13.35$, $p\leq0.01$). Older persons were either at higher (n=27, 58.7%) or lower (n=9, 19.6%) risk, while younger participants (n=10, 21.7%) were only at higher risk. The Table by CA analysis was not significant (Pearson Chi-Square Test Exact, $X^2(2)=3.48$, $p>0.05$). The CA by the PM25CAT analysis was significant (Pearson Chi-Square Test Exact, $X^2(2)=7.63$, $p\leq0.05$). There were 22 (73.3%) age risk factors in the PM25CAT High Group and eight (26.7%) in the Low Group. Older age as a risk factor occurred more often (n=18, 60.0%) than younger age as a risk factor (n=8, 26.7%) or older age associated with lower risk (n=4, 13.3%).

3.6.3. Gender (GEN). The various gender outcomes differed significantly from each other ($X^2(3)=15.55$, $p\leq0.01$). Under different study conditions, females were at higher (n=15, 51.7%) or lower (n=9, 31.0%) risk; similarly, males were also at higher (n=4, 13.8%) or lower (n=1, 3.4%) risk. The Table by GEN analysis was significant (Pearson Chi-Square Test Exact, $X^2(3)=20.91$, $p\leq0.01$). There were 26 (89.7%) gender-related risk factors in Table A2 and only three (10.3%) in Table A1. In Table A1, only males showed higher risk. In Table A2, females were either at higher (n=15, 51.7%) or lower (n=9, 31.0%) risk; likewise, males were at higher (n=1, 3.4%) or lower (n=1, 3.4%) risk. The GEN by PM25CAT analysis was not significant (Pearson Chi-Square Test Exact, $X^2(3)=3.24$, $p>0.05$).

3.6.4. Chronic Disease Total (DTCAT3). The DTCAT3 analysis was significant ($X^2(2)=57.85$, $p\leq0.01$): 83 (62.8%) specific outcomes had no chronic disease risk; 36 (27.3%) had one disease risk; and 13 (9.8%) had two or more disease risks. The Table by DTCAT3 analysis was significant ($X^2(2)=16.10$, $p\leq0.01$). The number and percentage of specific outcomes identified as risks were higher in Table A2 (n=73, 55.3%) than in Table A1 (n=59, 44.7%). The PM25CAT by DTCAT3 analysis was also significant ($X^2(2)=11.07$, $p\leq0.01$). The PM25CAT High Group had a higher total (percentage) of specific outcomes for two or more cardiovascular risk factors (n=10, 10.1%) than the PM25CAT Low Group (n=1, 1.0%), while the PM25CAT Low Group had a higher total (percentage) of specific outcomes without a cardiovascular risk factor present (n=41, 41.4%) than the PM25CAT High Group (n=26, 26.3%). The two PM25CAT Groups had a similar number (percentage) of specific outcomes with one cardiovascular risk factor: Low Group: n=9, 9.1%; High Group: n=12, 12.1%. Figure 1 shows the specific outcome cardiovascular risk factor percentages in the two PM25CAT Groups stratified by the three DTCAT3 levels: 0, 1, or 2+ cardiovascular risk factors.

3.6.5. Other Total (OTCAT3). The same analysis that was completed above for the cardiovascular only risk factors was also undertaken for the remaining non-cardiovascular risk factors. There were significant differences between the number of non-cardiovascular risk factors in the three levels of the OTCAT3 variable ($X^2(2)=118.34$, $p\leq0.01$). In descending order of occurrence, there were 102 (77.3%) specific outcomes without risk factors, 24 (18.2%) with one risk factor, and six (4.6%) with two or more risk factors. The Table by OTCAT3 analysis was not significant (Pearson Chi-Square Test Exact, $X^2(2)=1.55$, $p>0.05$). The PM25CAT by OTCAT3 analysis was also not significant (Pearson Chi-Square Test Exact, $X^2(2)=3.40$, $p>0.05$).

3.6.6. Total Risk Factors (RTCAT3). The analysis of all risk factors, cardiovascular and other risk factors combined, was significant ($X^2(2)=12.41$, $p\leq0.01$). In descending order, specific outcomes with two or more risk factors occurred most often (n=55, 41.7%), followed by specific outcomes with no risk factor (n=52, 39.4%), and specific outcomes with one risk factor occurred less often than the first two (n=25, 18.9%). The Table by RTCAT3 analysis was significant ($X^2(2)=7.74$, $p\leq0.05$). Table A2 had a higher number of 2+ risk factors (n=36, 27.3%) than Table A1 (n=19, 14.4%). Table A2 also had fewer no risk factors (n=21, 15.9%) than Table A1 (n=31, 23.5%). The PM25CAT by RTCAT3 analysis was also significant ($X^2(2)=10.07$, $p\leq0.01$). While the PM25CAT High Group had more 2+ risk factors (n=25, 25.2%) than the

PM25CAT Low Group (n=11, 11.1%), the PM25CAT High Group had fewer specific outcomes without a risk factor (n=17, 17.2%) than the PM25CAT Low Group (n=31, 31.3%). When one risk factor was present, the number (percentage) for the PM25CAT Low Group (n=9, 9.1%) was similar to the number (percentage) for the PM25CAT High Group (n=6, 6.1%).

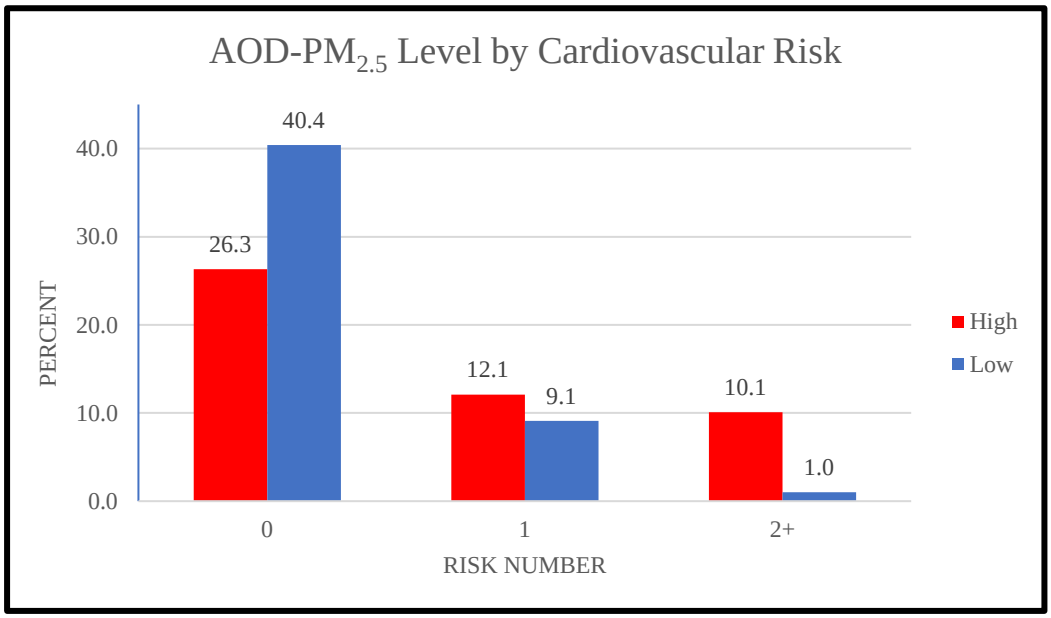

Figure 1. The percentage of specific cardiovascular outcomes in the High (red hue bars) and Low (blue hue bars) PM25CAT Groups by increasing number of cardiovascular risk factors (DTCAT3: 0, 1, 2+).

Figure 2 shows changes in the percentage of specific outcomes in the PM25CAT Low and High Groups as a function of increasing number of total risk factors (0, 1, 2+). As the number of total risks increased from 0 to 2+, the percentages also increased, but only in the PM25CAT High Group. In the PM25CAT Low Group, increases in total risks, from 0 to 2+, were associated with decreases in specific outcome percentages, especially for 0 risk versus 2+ risks.

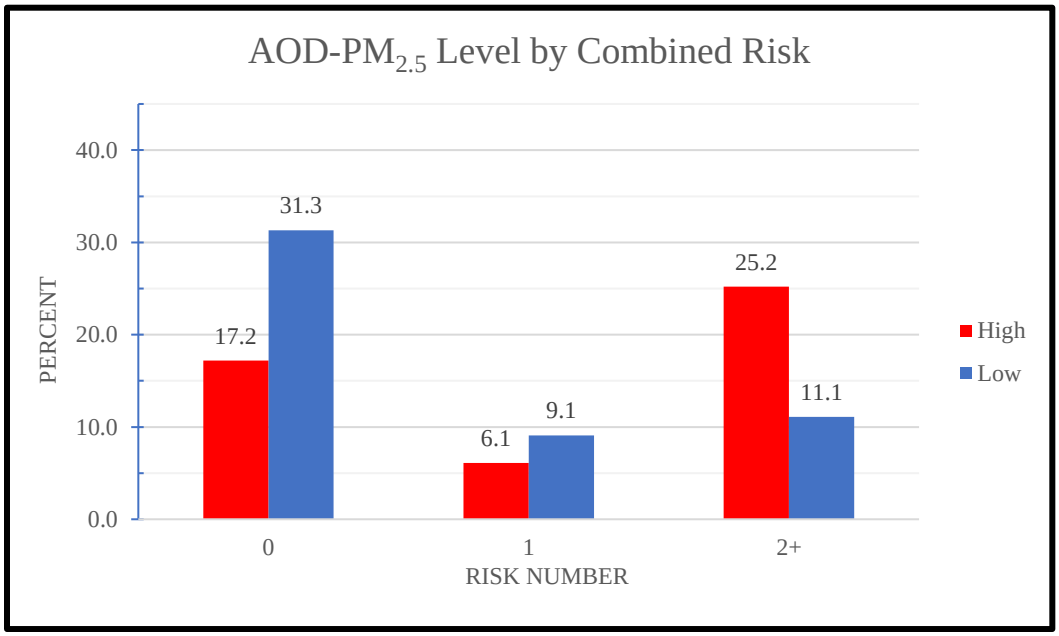

Figure 2. The percentage of specific outcomes for all risk factors in the PM25CAT High (red hue bars) and Low (blue hue bars) Groups by increasing number of cardiovascular and other risk factors combined (RTCAT3: 0, 1, 2+).

3.6.7. Inflammation. The cell frequencies for the four inflammation categories included in the physiologic mechanism (PME) variable were significantly different ($X^2(3)=69.88$, $p\leq0.01$): IE occurred most often (n=68, 51.5%); ID had the second highest frequency of occurrence (n=42, 31.8%); OD was third (n=15, 11.4%); and OE had the lowest frequency of occurrence (n=7, 5.3%). The Table by the PME physiologic mechanism category analysis was significant (Pearson Chi-Square Test Exact, $X^2(3)=109.76$, $p\leq0.01$). The most salient difference was the higher cell totals for ID in Table A1 (n=42, 31.8%) and its absence in Table A2 (n=0, 0.0%). The IE cell totals were higher in Table A2 (n=64, 48.5%) than in Table A1 (n=4, 3.0%). The PM25CAT by PME analysis was also significant (Pearson Chi-Square Test Exact, $X^2(3)=11.55$, $p\leq0.01$). The ID cell totals were higher in the PM25CAT High Group (n=22, 22.2%) than in the PM25CAT Low Group (n=12, 12.1%). The IE cell totals were similar in the PM25CAT Low Group (n=22, 22.2%) and in the PM25CAT High Group (n=21, 21.1%). Follow-up analyses using ANOVA confirmed significant differences in the AOD-$PM_{2.5}$ concentration level reading means among the four PME inflammation categories ($F(3)=4.01$, $p\leq0.01$). The AOD-$PM_{2.5}$ concentration level reading means were, in descending order of magnitude: ID (43.4 µg/m^3) first; OD (33.3 µg/m^3) second; IE (32.0 µg/m^3) third; and OE (12.2 µg/m^3) last. Follow-up comparisons among the four AOD-$PM_{2.5}$ concentration level reading means with the Tukey-Kramer adjusted multiple comparison test confirmed that the ID mean was significantly higher than the OE mean.

4.0. Comments on Inflammation Used to Describe or Explain Study Results

This literature review identified 45 articles published between 2012-2023 that evaluated the contribution of AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 concentration level readings to cardiovascular chronic diseases and other circulatory-related adverse health outcomes that were completed in urban-rural areas within economically developed and economically developing countries. Validation results confirmed that AOD-$PM_{2.5}$ concentration level readings were reliable and accurate estimates of ambient $PM_{2.5}$ monitor concentration level measurements. Most published studies utilized the inflammation physiologic mechanism to describe or explain their results on the contribution of higher AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 concentration level readings to different adverse cardiovascular outcomes. Many of the publications in Table A1 used inflammation descriptively. Most of the research articles in Table A2 used inflammation to explain their results. Together, these AOD-PM concentration level readings and cardiovascular disease publications provide a new and unexpectedly helpful source of factual information about the characteristics and adverse consequences of exposure to higher AOD-PM concentration level readings to the cardiovascular system.

4.1. RISK FACTORS

The analyses of risk factors provide new information about the characteristics of persons more susceptible to elevated AOD-PM exposure and the subsequent occurrence of cardiovascular chronic diseases or atypical changes in laboratory and clinical measures indicative of inflammation. [4,6,61-64] The reviewed studies also provided new information about the importance of geography as a risk factor for AOD-PM exposure and related cardiovascular disorders. [4,8] Where persons live, work, and spend their free time are also associated with other risk factors that can include role stratification (i.e., ethnicity in CN, and race in the US, for example), educational under- or over-attainment, available disposable income, and other patient attributes such as chronological age, gender, smoking, and alcohol use. Concentrations of older or younger persons in a specific geographic area, as well as the preponderance of total males versus total females, smoking and alcohol abuse rates may also differ geographically.

Geography as a risk factor can also include local environmental and climatic conditions that can increase the adverse effects of exposure to higher AOD-PM concentration level readings, as shown by studies completed in China, Israel, and Saudi Arabia. Climatic conditions can include temperature extremes in summer and in winter and strong winds that can disperse soil particles, fertilizers, pesticides, and other environmental hazards. Anticipated future climate change effects should increase the likelihood of extreme climatic events occurring more often. Even today, exposure to higher AOD-PM concentration level readings, especially in economically developing countries, is still a significant risk factor for the increased occurrence of cardiovascular chronic diseases.

4.2. UPDATED CONCEPTUAL PHYSIOLOGIC INFLAMMATORY MECHANISM

The 45 reviewed AOD-PM and cardiovascular chronic disease studies provide sufficient information to develop an updated conceptual model demonstrating how inflammation, as an

established physiologic mechanism, mediates the contribution of higher ambient AOD-PM concentration level readings to the subsequent occurrence of cardiovascular chronic diseases. Figure 3 illustrates how AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 exposure can adversely impact the cardiovascular system. When fine particulates ($PM_{2.5}$ and PM_1) are inhaled through the mouth and nose, they enter the lungs, and from there, can translocate tissue barriers in the lungs and enter the circulatory system. [4,11,52,61-68] The brain is especially vulnerable to fine PM's adverse effects because fine PM's detrimental effects can be expressed by translocation of particulates from the lungs into the circulatory system (first exposure route) and also directly from the nose to the brain (second exposure route). [4,10,11]

Once fine PM has entered the circulatory system, it can travel to (and accumulate) in the heart, brain, kidneys, liver, and adipose tissue. [9,62,63,65-67] Increased concentration of fine PM in terminal organs also results in elevated oxidative stress. The inflammatory response starts once the accumulation of free radicals exceeds the capacity of cells in an impacted organ to mitigate the fine PM-produced oxidative stress response. This sequence of events begins with the occurrence of local inflammation within one affected organ and is later followed by the development of general inflammation in two (or more) impacted organs.

The adverse effects of increased exposure to fine PM on the cardiovascular system include both the development of inflammation in the target organ (heart) and at least one other organ (e.g., brain, or adipose tissue). Stated differently, preliminary evidence suggests a positive association between elevated AOD-$PM_{2.5}$ and AOD-PM_1 concentration level readings and the future occurrence of two or more cardiovascular-related chronic diseases. Other publications have emphasized adverse cardiovascular effects occurring from exposure to even lower ambient PM levels. [69,70]

To accurately assess the full impact of AOD-PM exposure on the cardiovascular system, the selected primary cardiovascular chronic disease (Acute MI and heart) has to be evaluated along with at least another affected cardiovascular-related chronic illness (diabetes mellitus 2 and the kidneys). Whenever other cardiovascular-related chronic diseases besides those implicating the heart are excluded from the analysis, the full extent of the AOD-PM effects on a cardiovascular chronic illness may be underestimated.

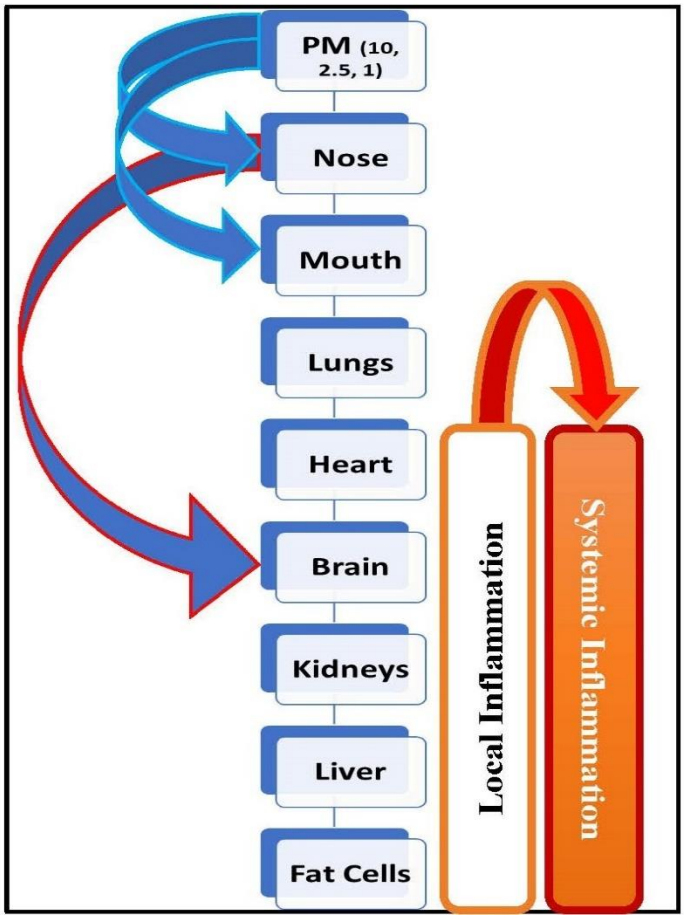

Figure 3. Illustration of the hypothesized effects of increased AOD-PM(10, 2.5 and 1) concentration level readings on the cardiovascular system based on the results of the 45 reviewed publications. Ambient AOD-$PM_{2.5}$ and AOD-PM_1 exposure results in the translocation of fine PM directly into the circulatory system. From there, fine particulates can accumulate in different target organs besides the heart. In this conceptual representation of the underlying physiologic inflammatory mechanism, accumulation of adipose tissue mass in various locations in the body of the impacted person is structurally and functionally equivalent to a traditionally viewed organ such as the heart or liver. In the case of the brain, there is another route for fine PM exposure besides through the circulatory system – from the nose directly to the brain. [4,10,11] Excessive accumulation of reactive oxygen species in one target organ can result in local inflammation. Systemic inflammation occurs when inflammation has developed in at least two organs, the heart and the pancreas or kidneys, for example.

4.3. GENERALIZATION OF FINDINGS

The aim of this review paper was to demonstrate the contribution of published studies that have utilized AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 as proxies for the effects of ambient PM_{10}, $PM_{2.5}$, and PM_1 monitor measurements on the cardiovascular system. Three technical issues limit the generalization of the conclusions reached in this review paper. The 45 articles selected and reviewed only represent a convenience sample and do not constitute all published studies evaluating the association between AOD-PM and cardiovascular outcomes. Second, only one source was used to search for the published studies [12], and only English-language publications were selected. A third limitation was the duration of the temporal search window which was about one month. For these reasons, there could be more published articles on the association between AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 and the cardiovascular system than the 45 publications found and included in this review paper. Even considering these caveats, this review paper was still able to demonstrate that 45 publications have evaluated the association between AOD-PM concentration level readings and the adverse cardiovascular outcomes within a span of only 12 years and that the total number of retrieved published studies was higher between 2018-2023 and lower between 2012-2017.

4.4. ADDITIONAL ID AND IE DIFFERENCES

By working through the issues identified in the analysis of the AOD-PM and adverse cardiovascular outcomes publications, it is now possible to further differentiate the use of the inflammation physiologic mechanism to describe or explain study results. As a starting point in this fine-grain analysis, it would be useful to consider similarities and differences between the studies included in Table A1 and in Table A2. One noticeable difference is that the studies in Table A1 were epidemiologic studies that evaluated the contribution of AOD-PM exposure to chronic cardiovascular diseases. Table A2 studies also utilized AOD-PM as the exposure source, but many outcome measures were clinical and laboratory in nature. These observations suggest that the type of outcome measure selected is related to the use of the inflammatory physiologic mechanism to describe the obtained results in greater detail, as was the case with most of the studies in Table A1, as opposed to designing and implementing studies that add new information about the inflammatory physiologic mechanism, as was the case with the studies in Table A2.

To further refine the difference between inflammation as a description and inflammation as an explanation, we need to consider the single epidemiologic study in Table A1 that used inflammation as an explanation. [35] This publication's purpose was to undertake an epidemiologic study in order to assess the contribution of AOD-PM_{10} and AOD-$PM_{2.5}$ to the occurrence of hemorrhagic stroke by generating new information about the inflammatory physiologic mechanism operating as an intermediate process between exposure and outcome. Even though there was not a study in Table A2 that used the inflammatory physiologic mechanism descriptively, what we know so far is that how inflammation is used depends on how the author(s) of the published paper designed the study and what scientific question(s) the study was expected to answer.

Note should be taken of the fact that other researchers who read and utilize the results based on inflammation as an explanation can only use the study's findings (and interpretations) descriptively. To illustrate, the updated conceptual schematic of the inflammatory physiologic mechanism included in this paper (please refer to Figure 3 above) relied on results from publications in Table A2 and the one study in Table A1 that used inflammation as an explanation. But the conceptual inflammatory physiologic mechanism developed in this publication is only a description and not an explanation of the fine PM-produced inflammation on the cardiovascular system.

5. Conclusions

This review paper evaluated published articles on the association between AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 concentration level readings and adverse cardiovascular outcomes that were published between 2012 and 2023. The identified publications were stratified on the physiologic mechanism of inflammation to describe or explain study results. The former group articles utilized epidemiologic methods to evaluate the contribution of increased AOD-PM_{10}, AOD-$PM_{2.5}$, and AOD-PM_1 concentration level readings to the subsequent occurrence of cardiovascular chronic diseases and other cardiovascular-related adverse health outcomes. Most of these published papers cited inflammation as a descriptive underlying physiologic mechanism to further understand the obtained results. The research questions and methods utilized in these papers were not intended to evaluate inflammation as a physiologic mechanism. In contrast, the latter group of articles used established laboratory and clinical outcome

measures of inflammation, and sometimes also included traditional epidemiologic methods and outcomes, to assess the inflammatory physiologic mechanism as a mediator between exposure to elevated AOD-PM concentration level readings and the subsequent occurrence of adverse cardiovascular outcomes; these studies advanced our understanding of the inflammatory mechanism, i.e., inflammation explanation.

The combined Results and Discussion section of this review paper included a fine-grain analysis of study results from different countries. Findings from most of these studies demonstrated consistent associations between higher AOD-$PM_{2.5}$ concentration level readings and worse cardiovascular outcomes. Living in rural areas was also a risk factor in developing and developed countries. Other significant risk factors included age, gender, smoking, and excessive alcohol use. Higher AOD-$PM_{2.5}$ concentration level readings were associated with more cardiovascular only risks and all risk factors (cardiovascular and non-cardiovascular) combined. Results from the reviewed studies were subsequently used to develop an updated conceptual version of the inflammatory physiologic mechanism to account for the adverse cardiovascular outcomes that result from acute or chronic AOD-PM exposure.

6. Conflicts of Interest

The author is the President and Director of Research at the Diablo Analytical Institute,
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9. APPENDIX

Table A1: Published Studies from Different Countries Reporting on the Association Between Aerosol Optical Depth-Particulate Matter (AOD-PM: 10, 2.5, 1) Concentration Level Fused Surfaces and Cardiovascular Outcomes, Including Risk Factors: Inflammation Description.

STS[1]	OUT[2]	CO[3]	METHODS AND RESULTS[4]	RISK[5]	PME[6]
16	AMI	CN	[PC, 95.0^{M}] AOD-$PM_{2.5}$ [67.4]↑:AMI [879/116,972]↑	No	ID
17	AMI	CN	[PC, 84.0^{M}] AOD-$PM_{2.5}$ [52.3]↑:AMI [4,604/512,689]↑	No	ID
18	AMI	IR	[PC, NA] AOD-$PM_{2.5}$ [45.3]↑:AMI [73/3,081]↑	R↓, M↑, DM2^↑, ACT^↓, LDL^↑, SMK^↑	ID
19	AMI	IT	[CS, 75.0^{M}] AOD-PM_{10} [NA]↑:AMI [321,768/2,154,810]↑	R↑	ID
19	AMI	IT	[CS, 80.0^{M}] AOD-$PM_{2,5}$[NA]↑:AMI [321,768/2,154,810]↑	R↑	ID
20	AMI	US	[CC, 85.0] AOD-$PM_{2.5}$ [9.4]↑:AMI [4,467/9,072]↑	No	ID
21	AMI	US	[PC, NA] AOD-$PM_{2.5}$ [12.4]↑:AMI [704/5,679]↑	No	OD
22	AMI	US	[CC, NA] AOD-$PM_{2.5}$ [10.5]↑:AMI [60,939/18,2817]↑	No	OD
23	AMI	US	[CC, 62.1^{M}]: AOD-$PM_{2.5}$[14.4]↑:AMI [4,745/14,276]↑	R↑, AT^↑	OD
16	CVD	CN	[PC, 95.0^{M}] AOD-$PM_{2.5}$ [67.4]↑:CVD [5,760/116,972]↑	R↑, AGE^↑, SMK^↓	ID
24	CVD	CN	[PC, 81.0^{M}] AOD-$PM_{2.5}$ [47.6]↑:CVD [1,575/14,331]↑	UR↑, AGE^↑, SMK^↑	ID
17	CVD	CN	[PC, 84.0^{M}] AOD-$PM_{2.5}$ [52.3]↑:CVD [148,030/512,689]↑	M↑, INC^, FUEL^↑	ID
18	CVD	IR	[PC, NA] AOD-$PM_{2.5}$ [45.3]↑:CVD [441/3,081]↑	R↓, M↑, AGE^↑, HP^, DM2^↑, SMK^↑	ID
19	CVD	IT	[CS, 75.0^{M}] AOD-PM_{10} [NA]↑:CVD [2,154,810/2,154,810]↑	R↑, AGE^↑	ID
19	CVD	IT	[CS, 80.0^{M}] AOD-$PM_{2.5}$ [NA]↑:CVD [2,154,810/2,154,810]↑	R↑, AGE^↑	ID
25	CVD	US	[CS, 85.0] AOD-$PM_{2.5}$ [9.6]↑:CVD [621,787/621,787]↑	No	ID
26	CVD	US	[CC, 81.0] AOD-$PM_{2.5}$ [11.9]↑:CVD [3,028,857/3,028,857]↑	No	ID
27	CVD	US	[CS, NA] AOD-$PM_{2.5}$ [14.0]↑:CVD [44,610/44,610]↑	AGE^↑, B↑, ED^↓, INC^↓	OD
28	HTD	CN	[CS, 81.0^{M}] AOD-PM_{10} [99.4]↑: HTD [5,783/43,745]↑	WT^↑	ID
29	HTD	CN	[PC, 79.0^{M}] AOD-$PM_{2.5}$ [77.7]↑:HTD [13,981/59,456]↑	AGE^{V}↑, WT^↑	ID
28	HTD	CN	[CS, 86.0^{M}] AOD-$PM_{2.5}$ [60.1]↑:HTD [5,783/43,745]↔	No	ID
30	HTD	CN	[CS, NA] AOD-$PM_{2.5}$ [33.4]↑:HTD [4,383/19,236]↑	R↑, AGE^, ED^{V}↑, WT^↑, ET^↑, EXE^{V}↑	ID
24	HTD	CN	[PC, 81.0^{M}] AOD-$PM_{2.5}$ [47.6]↑:HTD [953/14,331]↑	AGE^↑	ID
31	HTD	CN	[PC, 95.0^{M}] AOD-$PM_{2.5}$ [65.4]↑:HTD [38,094/99,084]↑	UR↑, WT^{V}↑, DM2^{V}↑, HC^{V}↑	OD
32	HTD	TW	[PC, 68.9^{M}] AOD-$PM_{2.5}$ [26.7]↑HTD [15,587/125,913]↑	WT^↓	ID
33	HTD	TW	[PC, 68.9^{M}] AOD-$PM_{2.5}$ [26.8]↑:HTD [14,356/134,978]↑	AGE^↓, WT^↓	ID
34	HTD	US	[PC, 87.0] AOD-$PM_{2.5}$ [10.5]↑:HTD [116/587]↔	No	ID
19	HF	IT	[CS, 75.0^{M}] AOD-PM_{10} [NA]↑:HF [471,042/2,154,810]↑	No	ID
19	HF	IT	[CS, 80.0^{M}] AOD-$PM_{2.5}$ [NA]↑:HF [471,042/2,154,810]↑	No	ID
22	HF	US	[CC, NA] AOD-$PM_{2.5}$ [10.5]↑:HF [114,137/342,411]↑	No	OD
23	HF	US	[CC, 62.1^{M}] AOD-$PM_{2.5}$ [14.4]↑: HF [6,919/20,427]↑	R↑, AT^↑	OD
17	HS	CN	[PC, 84.0^{M}] AOD-$PM_{2.5}$ [52.3]↑:HS [7,684/512,689]↔	No	ID
35	HS	IL	[CC, 79.0] AOD-PM_{10} [54.8]↑:HS [512/4,837]↔	AGE^{V}↑, AT^{V}↑	IE
35	HS	IL	[CC, 72.0] AOD-$PM_{2.5}$ [21.6]↑:HS [512/4,837]↔	AGE^{V}↑, AT^{V}↑	IE
36	IHD	CN	[CS, 75.0^{M}] AOD-$PM_{2.5}$ [82.0]↑:IHD [477/24,845]↔	No	ID
17	IHD	CN	[PC, 84.0^{M}] AOD-$PM_{2.5}$ [52.3]↑:IHD [50,323/512,689]↔	No	ID
36	IHD	CN	[CS, 71.0^{M}] AOD-PM_{1} [66.0]↑:IHD [477/24,845]↑	No	ID
37	IHD	IDN	[CS, 52.1^{M}] AOD-$PM_{2.5}$ [14.4]↑:IHD [74/2,324]↔	No	OD
19	IHD	IT	[CS, 75.0^{M}] AOD-PM_{10} [NA]↑:IHD [511,027/2,154,810]↑	R↑	ID
19	IHD	IT	[CS, 80.0^{M}] AOD-$PM_{2.5}$ [NA]↑:IHD [511,027/2,154,810]↑	R↑	ID
38	IHD	PE	[CS, 70.0^{M}] AOD-$PM_{2.5}$ [20.9]↑:IHD [5,134/71,984]↔	No	OD

39	IHD	SA	[CS, 91.0ᴹ] AOD-$PM_{2.5}$ [87.9]↑:IHD [138,041/138,041]↑	No	OD
26	IHD	US	[CC, 81.0] AOD-$PM_{2.5}$ [11.9]↑:IHD [1,198,199/1,198,199]↑	No	ID
17	IS	CN	[PC, 84.0ᴹ] AOD-$PM_{2.5}$ [52.3]↑:IS [50,174/512,689]↑	No	ID
35	IS	IL	[CC, 79.0] AOD-PM_{10} [54.8]↑:IS [4,325/4,837]↔	AGEᵛ↑, ATᵛ↑	IE
35	IS	IL	[CC, 72.0] AOD-$PM_{2.5}$ [21.6]↑:IS [4,325/4,837]↔	AGEᵛ↑, ATᵛ↑	IE
19	IS	IT	[CS, 75.0ᴹ] AOD-PM_{10} [NA]↑:IS [329,702/2,154,810]↑	No	ID
19	IS	IT	[CS, 80.0ᴹ] AOD-$PM_{2.5}$ [NA]↑:IS [329,702/2,154,810]↑	No	ID
36	S	CN	[CS, 75.0ᴹ] AOD-$PM_{2.5}$ [82.0]↑:S [589/24,845]↔	No	ID
16	S	CN	[PC, 95.0ᴹ] AOD-$PM_{2.5}$ [67.4]↑:S [3,540/116,792]↑	No	ID
24	S	CN	[PC, 81.0ᴹ] AOD-$PM_{2.5}$ [47.6]↑:S [342/14,331]↔	AGE^	ID
17	S	CN	[PC, 84.0ᴹ] AOD-$PM_{2.5}$ [52.3]↑:S [5,722/512,689]↑	No	ID
36	S	CN	[CS, 71.0ᴹ] AOD-PM_{1} [66.0]↑:S [589/24,845]↑	No	ID
37	S	IDN	[CS, 52.1ᴹ] AOD-$PM_{2.5}$ [14.4]↑:S [20/2,324]↔	No	OD
18	S	IR	[PC, NA] AOD-$PM_{2.5}$ [45.3]↑:S [92/3,081]↔	R↓, AGE^↑, DM2^↑, HP^↑, ACT^↓	ID
38	S	PE	[CS, 70.0ᴹ] AOD-$PM_{2.5}$ [20.9]↑:S [10,239/71,984]↑	AGE^↑	OD
39	S	SA	[CS, 91.0ᴹ] AOD-$PM_{2.5}$ [87.9]↑:S [34,334/34,334]↑	No	OD
25	S	US	[CS, 85.0] AOD-$PM_{2.5}$ [9.6]↑:S [57,704/57,704]↑	No	ID
26	S	US	[CC, 81.0] AOD-$PM_{2.5}$ [11.9]↑:S [710,341/710,341]↑	No	ID

[1]STS=study number. [2]OUT=outcome: AMI=Acute MI, CVD=cardiovascular disease, HF=heart failure, HS=hemorrhagic stroke, HTD=hypertensive disease, IHD=ischemic heart disease, IS=ischemic stroke, S=stroke. [3]CO=country: CN=China, IDN=Indonesia, IL=Israel, IR=Iran, IT=Italy, PE=Peru, SA=Saudi Arabia, TW=Taiwan, US=United States. [4]Methods and Results: [Study design: CC=case control, CS=cross sectional, PC=prospective cohort; r_{xy}^2=square of correlation coefficient percent; Superscript: M=Monitor, No superscript "M"=no Monitor; NA=not available]; AOD-PM_{10}= ≤10 μg/m^3, AOD-$PM_{2.5}$=≤2.5 μg/m^3, AOD-PM_1=≤1 μg/m^3. [AOD-PM concentration level reading in μg/m^3, NA=not available]. ↑=higher, or ↓=lower AOD-PM concentration level reading; right side of the colon (:) are the acronyms for the specific outcomes; they are the same abbreviations as the acronyms used for the general outcomes in the OUT variable that are listed in the column with the superscript "2." [left side of the "/": total observations for the specific outcome, right of the "/": total observations in study]. ↑=significant increase (p≤0.05), ↓=significant decrease (p≤0.05), or ↔=no significant change (p>0.05) in health outcome measure relative to the AOD-PM concentration level reading. [5]Risk=risk measures: ACT=physical activity, AGE=chronological age, AT=ambient temperature (also a risk factor for season), B=Black race, DM2=diabetes mellitus 2, ED=education, ET=ethnicity, EXE=exercise, FUEL=cooking fuel, HC=hypercholesterolemia, HT=hypertension, INC=income, LDL=low-density lipoprotein cholesterol, M=male gender, R=rural, SMK=smoking, UR=urban and rural geographic area, WT=body wight, and No=no risk identified. The symbols "^" and "V" that follow each continuous risk variable represent the higher-end or lower-end of the referenced risk variable continuum, respectively e.g., AGEᵛ=younger, while AGE^=older. Likewise, for a categorical measure such as DM2, DM2^=presence of diabetes mellitus 2, while DM2ᵛ=absence of diabetes mellitus 2. Significance and direction (positive or negative) of risk variable: ↑=significantly higher risk, ↓=significantly lower risk. [6]PME=physiologic mechanism: ID=inflammation description, IE=inflammation explanation, and OD=other description. In this table there was no instance of other explanation, OE.

Table A2: Published Studies from Different Countries Reporting on the Association Between Aerosol Optical Depth-Particulate Matter (AOD-PM: 10, 2.5, 1) Concentration Level Fused Surfaces and Cardiovascular Outcomes, Including Risk Factors: Inflammation Explanation.

STS[1]	OUT[2]	CO[3]	METHODS AND RESULTS[4]	RISK[5]	PME[6]
40	ALS	CN	[CS, 86.0] AOD-PM_{10} [72.6]↑:ALS [85,545/85,545]↑	AGE^↑, ETV↑, EDV↑, INCV↑, ALC^↑	IE
40	ALS	CN	[CS, 90.0] AOD-$PM_{2.5}$ [41.8]↑:ALS [85,545/85,545]↑	AGE^↑, ETV↑, EDV↑, INCV↑, ALC^↑	IE
40	ALS	CN	[CS, 77.0] AOD-PM_{1} [27.6]↑:ALS [85,545/85,545]↔	ETV↑, EDV↑, ALC^↑	IE
41	ATS	AU	[PC, 63.0[M]] AOD-$PM_{2.5}$ [6.4]↑:CIMT [1,063/1,063]↑	UR↑, SMK^↑	IE
42	ATS	CN	[CS, 81.0[M]] AOD-$PM_{2.5}$ [62.6]↑:CIMT [1,656/1,656]↑	AGE^↑, M↑, LDL^↑, DBP^↑, SBP^↑	IE
42	ATS	CN	[CS, 81.0[M]] AOD-$PM_{2.5}$ [62.6]↑:BFMD [1,656/1,656]↓	AGE^↓, M↓, DBP^↓	IE
43	BG	IL	[RC, 79.0] AOD-PM_{10} [54.1]↑:BG [26,223/73,117]↑	DM2^↑	IE
43	BG	IL	[RC, 72.0] AOD-$PM_{2.5}$ [22.3]↑:BG [26,223/73,117]↑	DM2^↑	IE
44	BG	US	[PC, 83.0] AOD-$PM_{2.5}$ [10.6]↑:BG [551/551]↑	ICAM-1^↓	IE
34	BG	US	[PC, 87.0] AOD-$PM_{2.5}$ [10.5]↑:BG [293/587]↑	AT^↑	IE
45	CKD	CN	[CS, 86.0] AOD-$PM_{2.5}$ [60.9]↑:Scr [2,546,047/2,546,047]↑	F↑	IE
46	CKD	CN	[PC, NA] AOD-$PM_{2.5}$ [52.7]↑:ESRD [207/1,979]↑	No	IE
45	CKD	CN	[CS, 82.0] AOD-PM_{1} [46.8]↑:Scr [2,546,047/2,546,047]↑	F↑	IE
47	CKD	US	[PC, NA] AOD-$PM_{2.5}$ [11.8]↑:CKD [1,585,827/2,482,737]↑	UR↑, F↑, AGEV↑, WTV↑	IE
47	CKD	US	[PC, NA] AOD-$PM_{2.5}$ [11.8]↑:ESRD [2,398,318/2,482,737]↑	UR↑, F↑, AGEV↑, WTV↑	IE
48	CRP	CN	[CS, 81.0] AOD-PM_{10} [91.1]↑:CRP [7,915/7,915]↑	CVD^↑	IE
48	CRP	CN	[CS, 86.0] AOD-$PM_{2.5}$ [54.0]↑:CRP [7,915/7,915]↑	CVD^↑, AGE^↑	IE
48	CRP	CN	[CS, 75.0] AOD-PM_{1} [43.7]↑:CRP [7,915/7,915]↑	CVD^↑, INC^↑	IE
49	CRP	TW	[PC, 68.9[M]] AOD-$PM_{2.5}$ [26.0]↑:CRP [30,034/30,034]↑	No	IE
50	CRP	TW	[PC, 68.9[M]] AOD-$PM_{2.5}$ [24.7]↑:CRP [40,209/40,209]↑	EXE^↓	IE
51	DM2	CN	[PC, 79.0[M]] AOD-$PM_{2.5}$ [79.1]↑:DM2 [6,439/88,397]↑	R↑, AGEV↑, F↑, WTV↑, HPV↑, SMKV↑	IE
30	DM2	CN	[CS, NA] AOD-$PM_{2.5}$ [33.4]↑:DM2 [755/19,236]↑	R↑, AGE^↑, F↑, WTA^↑, EDV↑, ALCV↑	IE
52	DM2	MX	[CC, 72.4] AOD-$PM_{2.5}$ [24.1]↑:DM2 [121/480]↔	No	OD
39	DM2	SA	[CS, 91.0[M]] AOD-$PM_{2.5}$ [87.9]↑:DM2 [6,1751/6,1751]↑	No	OD
25	DM2	US	[CS, 85.0] AOD-$PM_{2.5}$ [9.6]↑:DM2 [398,596/398,596]↑	No	IE
53	LIP	CN	[PC, NA] AOD-PM_{10} [72.1]↑:TC [67,305/67,305]↑	AGE^↑, WT^↑, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{10} [72.1]↑:LDL [67,305/67,305]↑	AGE^↑, F↑, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{10} [72.1]↑:HDL [67,305/67,305]↓	AGE^↓, F↓, WT^↓, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{10} [72.1]↑:TG [67,305/67,305]↑	AGE^↑, F↑, ETV↓	IE
45	LIP	CN	[CS, 86.0] AOD-$PM_{2.5}$ [60.9]↑:eGFR [2,546,047/2,546,047]↓	R↑, F↓, WTV↓, SMKV↓	IE
30	LIP	CN	[CS, NA] AOD-$PM_{2.5}$ [33.4]↑:HLIP [5,391/19,236]↓	R↓, AGE^↓, F↑, WT^↓, EDV↓, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-$PM_{2.5}$ [41.9]↑:TC [67,305/67,305]↑	AGEV↑, WT^↑, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-$PM_{2.5}$ [41.9]↑:LDL [67,305/67,305]↑	AGE^↑, F↑, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-$PM_{2.5}$ [41.9]↑:HDL [67,305/67,305]↓	AGE^↓, F↓, WT^↓, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-$PM_{2.5}$ [41.9]↑:TG [67,305/67,305]↑	AGE^↑, F↓	IE
46	LIP	CN	[PC, NA] AOD-$PM_{2.5}$ [52.7]↑:eGFR [1,979/1,979]↑	UR↑	IE
54	LIP	CN	[CS, 58.0[M]] AOD-PM_{1} [55.7]↑:TC [39,057/39,057]↑	AGE^↑, F↓	IE
54	LIP	CN	[CS, 58.0[M]] AOD-PM_{1} [55.7]↑:LDL [39,057/39,057↑	AGE^↑, F↓, WT^↑	IE
54	LIP	CN	[CS, 58.0[M]] AOD-PM_{1} [55.7]↑:HDL [39,057/39,057]↓	F↑	IE
54	LIP	CN	[CS, 58.0[M]] AOD-PM_{1} [55.7]↑TG [39,057/39,057]↓	AGE^↓, F↓, WT^↑	IE
45	LIP	CN	[CS, 82.0] AOD-PM_{1} [46.8]↑:eGFR [2,546,047/2,546,047]↓	R↑, AGE^↓, F↓, WTV↓, SMKV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{1} [28.1]↑:TC [67,305/67,305]↔	AGE^↓, WT^↑, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{1} [28.2]↑:LDL [67,305/67,305]↑	AGE^↑, F↑, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{1} [28.2]↑:HDL [67,305/67,305]↓	AGE^↓, F↓, WT^↓, ETV↓	IE
53	LIP	CN	[PC, NA] AOD-PM_{1} [28.2]↑:TG [67,305/673,05]↑	AGE^↑, F↑, ETV↓	IE

43	LIP	IL	[RC, 79.0] AOD-PM_{10} [54.1]↑:LDL [26,223/73,117]↑	DM2^↑	IE
43	LIP	IL	[RC, 79.0] AOD-PM_{10} [54.1]↑:HDL [26,223/73,117]↓	DM2^↓	IE
43	LIP	IL	[RC, 79.0] AOD-PM_{10} [54.1]↑:TG [26,223/73,117]↑	DM2^↑	IE
43	LIP	IL	[RC, 72.0] AOD-$PM_{2.5}$ [22.3]↑:HDL [26,223/73,117]↓	DM2^↓	IE
43	LIP	IL	[RC, 72.0] AOD-$PM_{2.5}$ [22.3]↑:LDL [26,223/73,117]↑	DM2^↑	IE
43	LIP	IL	[RC, 72.0] AOD-$PM_{2.5}$ [22.3]↑:TG [26,223/73,117]↑	DM2^↑	IE
55	LIP	MX	[PC, 74.0^{M}] AOD-$PM_{2.5}$ [22.5]↑:TC [465/465]↑	No	IE
55	LIP	MX	[PC, 74.0^{M}] AOD-$PM_{2.5}$ [22.5]↑:LDL [465/465]↑	No	IE
55	LIP	MX	[PC, 74.0^{M}] AOD-$PM_{2.5}$ [22.5]↑:HDL [465/465]↓	No	IE
55	LIP	MX	[PC, 74.0^{M}] AOD-$PM_{2.5}$ [22.5]↑:TG [465/465]↓	No	IE
56	LIP	US	[PC, 88.0^{M}] AOD-$PM_{2.5}$ [10.5]↑:eGFR [669/669]↓	No	OE
34	LIP	US	[PC, 87.0] AOD-$PM_{2.5}$ [10.5]↑:HDL [326/587]↔	No	IE
34	LIP	US	[PC, 87.0] AOD-$PM_{2.5}$ [10.5]↑:HG [316/587]↑	No	IE
47	LIP	US	[PC, NA] AOD-$PM_{2.5}$ [11.8]↑:eGFR [1,649,148/2,482,737]↑	UR↑, F↑, AGEV↑, WTV↑	IE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:TC [6,587/6,587]↑	No	OE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:LDLP [6,587/6,587]↑	No	OE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:LDL [6,587/6,587]↑	No	OE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:HDLP [6,587/6,587]↑	No	OE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:HDL [6,587/6,587]↑	No	OE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:TRLP [6,587/6,587]↑	No	OE
57	LIP	US	[CS, 84.0^{M}] AOD-$PM_{2.5}$ [12.5]↑:TG [6,587/6,587]↑	No	OE
58	PLC	TW	[PC, 68.9^{M}] AOD-$PM_{2.5}$:[26.5]↑:PLC [362,396/362,396]↑	F↑, AGE^↑	IE
59	WT	CN	[PC, 95.0^{M}] AOD-$PM_{2.5}$ [70.4]↑:BMI [77,609/77,609]↑	No	IE
59	WT	CN	[PC, 95.0^{M}] AOD-$PM_{2.5}$ [70.4]↑:$BMI_{\geq 25}$ [60,453/77,609]↑	AGE^↑, DYSV↑, DM2V↑, HPV↑	IE
30	WT	CN	[CS, NA] AOD-$PM_{2.5}$ [33.4]↑:WT [7,727/19,236]↓	R↑, EDV↑, SMK^↑, HP^↑	IE
60	WT	IL	[RC, 84.6] AOD-PM_{10} [63.2]↑:AT [712/712]↑	LEPTIN↑, OMIRS↑, CCL8↑, SCE2F1↓, OMrad↓	IE
60	WT	IL	[RC, 84.6] AOD-$PM_{2.5}$ [21.8]↑:AT [712/712]↑	SCLC3II↑, OMLC3II↑, SCE2F1↓, OMrad↓	IE
34	WT	US	[PC, 87.0] AOD-$PM_{2.5}$ [10.5]↑:MetS [271/587]↑	No	IE

[1]STS=study number. [2]OUT=outcome: ALS=allostatic load, ATS=carotid artery intima-media thickness, BG=blood glucose, CKD=chronic kidney disease, CRP=c-reactive protein, DM2=diabetes mellitus 2, LIP=lipids, PLC=platelet count, WT=weight. [3]CO=country: AU=Australia, CN=China, IL=Israel, MX=Mexico, SA=Saudi Arabia, TW=Taiwan, US=United States. [4]Results: [Study design: CS=cross sectional, PC=prospective cohort, RC=retrospective cohort; r_{xy}^2=square of correlation coefficient percent; Superscript: M=Monitor; Absence of "M"superscript=No monitor, NA=not available]. AOD-PM_{10}= ≤10 µg/m^3, AOD-$PM_{2.5}$= ≤2.5 µg/m^3, AOD-PM_1=≤1 µg/m^3. [AOD-PM concentration level reading measured in µg/m^3]. ↑=higher, or ↓=lower AOD-PM concentration level reading; right side of colon (:) are the specific outcomes: AT=adipose tissue, ALS=allostatic load, BFMD=brachial-flow mediated dilation, BG=blood glucose, BMI=body mass index, CIMT=carotid artery intima-media thickness, CKD=chronic kidney disease, CRP=c-reactive protein, DM2=diabetes mellitus 2, eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease, HDL=high-density lipoprotein cholesterol, HDLP=HDL particles, HG=hypertriglyceridemia, HLIP=hyperlipidemia, LDL=low-density lipoprotein cholesterol, LDLP=LDL particles, MetS=metabolic syndrome, PLC=platelet count, Scr=serum concentration, TC=total cholesterol, TG=total glycerides, TRLP=triglyceride particles, WT=weight. [left of the "/": total observations for specific outcome, right of the "/": total observations in study]. ↑=significant increase ($p \leq 0.05$), ↓=significant decrease ($p \leq 0.05$), or ↔=no significant change ($p > 0.05$) in health outcome measure relative to AOD-PM concentration level readings. [5]Risk=risk measures: AGE=chronological age, ALC=alcohol, AT=ambient temperature (also a risk factor for season), CCL8=OM-CCL8, CVD=cardiovascular disease, DM2=diabetes mellitus 2, DYS=dyslipidemia, ED=education, ET=Ethnicity, EXE=exercise, F=female gender, HP=hypertension, ICAM-1=intracellular adhesion molecule-1, INC=income, LDL=low density lipoprotein cholesterol, LEPTIN=human ornamental adipose tissue leptin, M=male gender, OMIRS=OM insulin receptor substrates, OMLC3II=OM microtubule-associated protein 1A/1B-light chain 3-II, R=rural, SBP=systolic blood pressure, SCE2F1=SC-transcription factor E2F2, SCLC3II=SC microtubule-associated protein 1A/1B-light chain 3-II, SMK=smoking, UR=urban and rural geographic area, WT=weight, and No=no risk identified. The symbols "^" and "V" that follow each continuous risk variable

represent the higher-end or lower-end of the referenced risk variable continuum, respectively e.g., AGE^{V}=younger while AGE$^{\wedge}$=older. Likewise, for a categorical measure such as DM2, DM2$^{\wedge}$=presence of diabetes mellitus 2 while DM2^{V}=absence of diabetes mellitus 2. Significance and direction (positive or negative) of risk variable: ↑=significantly higher risk, or ↓=significantly lower risk. [6]PME=Physiologic mechanism: IE=inflammation explanation, OD=other description, and OE=other explanation.