SPPH 502: Epidemiology Methods I

Major Written Assignment

Does Long-term Exposure to Traffic-Related Particulate Matter Air Pollution Increase the Risk of Coronary Artery Disease?

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Introduction:

Traffic-related air pollution levels have consistently been associated with increased overall mortality and morbidity (1). Effects of exposure to particulate matter (PM) on the heart have been of particular interest, as the elevation of fine particulates ($PM_{2.5}$) has shown strongest association with increased risk of myocardial infarction (2), as well as ischemic cardiovascular disease (1), possibly via accelerated atherosclerosis (3).

The objective of this paper is to gather currently available evidence on whether long-term exposure to elevated traffic-related $PM_{2.5}$ increases the risk of developing coronary artery diseases, as measured through indicators of atherosclerosis. The population of interest is urban adults who are not diagnosed with cardiovascular disease. Since the entire urban population is exposed to at least some level of $PM_{2.5}$, comparisons were made between individuals who were exposed to *different* levels of $PM_{2.5}$ on a continuous scale.

Methods

Literature Search Strategy

A search of three databases (MEDLINE through PubMed, Embase and Google Scholar) was performed using multiple combinations of keywords “air pollutants,” “particulate matter,” “coronary artery disease,” and “atherosclerosis”. In PubMed, the following MeSH query was used: *(Air Pollutants OR Particulate Matter) AND (Coronary Artery Disease OR Atherosclerosis).* Results were limited to full-text human studies published in English. Due to recent advances in pollution measurement techniques, publications older than five years were excluded.

Selection Criteria for Three Studies to Appraise in Full

Based on previously established PICO criteria, reviewed studies were further limited to those that included $PM_{2.5}$ as an exposure and at the very least reported carotid intima-media thickness or coronary artery calcification as clinical outcomes. Preference was given to studies that reported more clinical outcomes, included larger sample sizes, and were published in higher impact journals. The Inclusion of diverse pollution exposure data, representative of both developing and industrial countries was also a major consideration.

Assessment of Selected Studies

Full-texts of selected studies were evaluated individually and assessed based on a multitude of factors, including study design, the population, exposures and how exposures were measured/estimated, outcomes, results, and limitations. In doing that, *The Public health critical appraisal checklist* previously by Heller et al. (4) was used as a guideline.

Results

Synthesis of the Literature Search and Summary of Evidence

Initially, a total of 53 studies were identified and further analyzed in Excel. Abstracts were screened and articles related to other conditions (11/53, 21%), effects of smoking (9/53, 17%), acute effects (n=2/53, 4%), and non-clinical studies (4/53, 8%), as well as review articles (4/53, 8%) and commentaries (4/53, 8%) were excluded. Abstracts of the remaining 18 articles were further reviewed to select three papers to appraise in full.

Abstracts of included studies (n=18) were examined further and studies focused on exposures other than $PM_{2.5}$ (n=4), biomarker outcomes (n=3), racial and socioeconomic differences (n=2), and measurement methods (n=2) were excluded. Table 1 shows the list of studies that were excluded after an examination of abstracts and reasons for exclusion of each.

included abstracts are presented in Table 2. Overall, the abstracts suggest an association between exposure to traffic-related pollution, as measured through proximity to roadways or levels of $PM_{2.5}$, PM_{10}, or NO_x, and progression of subclinical coronary artery disease as demonstrated through elevated biomarker levels or progression of atherosclerosis indicators.

Selected Studies

Based on the criteria outlined in the Methods section, the cross-sectional study by Su et al. (5), and the prospective cohorts by Adar et al. (6), and Kaufman et al. (7) were selected for full appraisal. The first study is cross-sectional, and provides evidence in high pollution context of an Asian metropolitan area. The studies by Adar et al., and Kaufman et al., are both prospective cohorts with large and ethnically-diverse population samples. All studies have been published in high impact journals and met exposure and outcome specifications set in the Methods section. Specifications of these three studies have been outlined in Table 3.

Table 1 Excluded abstracts and reasons for exclusion

Study	Journal	IF	Design	Reason for Exclusion
Ghosh et al. (2016)	Environ Health Perspect.	8.4	Modelling	Outcome: The burden of near roadway air pollution using mathematical modelling.
Jones et al. (2015)	J Epidemiol Community Health.	3.2	Cross-Sectional (n=6347)	Focused on the effect of race.
Wu et al. (2015)	Chemosphere	3.1	Prospective Cohort (n=40)	Outcome: Biomarkers of oxidative stress.
Hajat et al. (2015)	Epidemiology	6.1	Prospective Cohort (n=6814)	Outcome: Biomarkers.
Leary et al. (2014)	Am J Respir Crit Care Med.	13.1	Prospective Cohort (n=3896)	Exposure: NO_2. Outcome: right ventricle function.
Kälsch et al. (2014)	Eur Heart J.	15.2	Retrospective Cohort (n=4238)	Outcome: thoracic aortic calcification.
Hajat et al. (2013)	Environ Health Perspect.	8.4	Prospective Cohort (n=6140)	Focused on the effect of socioeconomic status.
Rivera et al. (2013)	Environ Health Perspect.	8.4	Cross-Sectional (n=2780)	Exposure: NO_2.
Kaufman et al. (2012)	Am. J. Epidemiol.	5.5	Methods Paper	Methods Paper.
Allen et al. (2012)	Environ Health Perspect.	8.4	Methods Paper	Methods Paper.
Tonne et al. (2012)	Epidemiology	6.1	Retrospective Cohort (n=2348)	Exposure: PM_{10}.

Table 2 Final included abstracts

Study	Journal	IF	Design	Exposures	Outcomes	Notes
Kaufman et al. (2016)	Lancet	45.2	Prospective Cohort (n=6795)	$PM_{2.5}$, NO_X, Black Carbon	CAC, CIMT	US Data: MESA Air
McGuinn et al. (2016)	Environ Res.	3.1	Retrospective Cohort (n=5679)	$PM_{2.5}$	CAD Index	US Data: Duke Univ.
Su et al. (2015)	Environ Health Perspect.	8.4	Cross-Sectional (n=689)	$PM_{2.5}$, PM_{10}, NO_X	CIMT	Taiwan Data
Kim et al. (2014)	Am. J. Epidemiol.	5.5	Cross-Sectional (n=5488)	$PM_{2.5}$ Chemistries	CIMT	US Data: MESA
Sun et al. (2013)	Environ. Health.	2.7	Cross-Sectional (n=6256)	$PM_{2.5}$	CAC, CIMT	US Data: MESA
Adar et al. (2013)	PLoS Med.	13.6	Prospective Cohort (n=5276)	$PM_{2.5}$	CIMT	US Data: MESA
Krishnan et al. (2012)	J Am Coll Cardiol.	17.8	Prospective Cohort (n=3040)	$PM_{2.5}$	FMD, BAD	US Data: MESA

IF: Impact Factor. CAC: Coronary Artery Calcium. CIMT: Carotid Intima-Media Thickness. CAD: Coronary Artery Disease. FMD: Flow-Mediated Dilation. BAD: Baseline Arterial Diameter. MESA: The Multi-Ethnic Study of Atherosclerosis and Air Pollution.

Table 3 Characteristics of the Three Selected Studies

	Su et al. (2015)(5)	**Adar et al. (2013)**(6)	**Kaufman et al. (2016)**(7)
Study Design	Cross-Sectional	Prospective Cohort	Prospective Cohort (10 years) (n=6795)
Primary Objective	To evaluate association between CIMT and one-year average exposure to traffic-related pollution	To examine associations between long-term $PM_{2.5}$ concentrations and the progression of atherosclerosis	To assess association between long-term exposure to ambient air pollution and progression of coronary artery calcium and CIMT.
Population	35–65 years old adults without diagnosis of coronary heart disease, cerebrovascular disease, and heart failure, who had volunteered for a case-control cardiovascular study (n=689).	MESA participants with CIMT measurements in the first three clinical visits (n=5276). MESA study composed of 5660 adults aged 45–84 without clinical cardiovascular disease, from four ethnic groups (Hispanic, black, white, and Chinese) recruited from six locations across US.	MESA participants plus 257 additional recruitment from three new locations to add heterogeneity in pollution exposures.
Exposure	$PM_{2.5}$, $PM_{2.5sbs}$, PM_{10}, NO_2, and NO_X, as estimated using regression models developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE)(8)	$PM_{2.5}$ as measured for each participant using regressions based on monitoring stations data and study-specific air samples collected outside the homes and in the communities of participants	$PM_{2.5}$, NO_X, and Black Carbon, measured using regressions based on 27 long-term sites, 771 community snapshot locations, and outside 697 participants' homes in addition to EPA monitors.
Outcome	Carotid Intima-Media Thickness	Carotid Intima-Media Thickness	Coronary Artery Calcium and Carotid Intima-Media Thickness
Main Results	Average percentage increased in maximum left CIMT was 4.23% (95% CI: 0.32, 8.13) per 10-μg /m^3 increase in $PM_{2.5abs}$; 3.72% (95% CI: 0.32, 7.11) per 10-μg/m^3 increase in PM_{10}; 2.81% (95% CI: 0.32, 5.31) per 20-μg/m^3 increase in NO2; and 0.74% (95% CI: 0.08, 1.41) per 10-μg/m^3 increase in NO_x. The associations were not evident for right CIMT, and black carbon was not associated with the outcomes.	Higher average levels of residential $PM_{2.5}$ were associated with increased CIMT progression among people living in the same metropolitan area after adjusting for smoking and age. Each 2.5 mg/m^3 increase in $PM_{2.5}$ levels, was associated with 5.0 mm/year greater CIMT progression when compared to people living in less polluted regions of the same metropolitan area.	Pollutant exposures were associated with coronary calcium, but not intima-media thickness change. For each 5 μg $PM_{2.5}$/m^3 increase, coronary calcium progressed by 4.1 (95% CI 1·4–6·8) Agatston units per year. The estimate for the effect of a 5 μg/m^3 higher long-term exposure to $PM_{2.5}$ in intima-media thickness was –0.9 μm (95% CI –3.0 to 1.3) per year

EPA: Environmental Protection Agency. CIMT: Carotid Intima-Media Thickness.

Individual Study Assessments

The following sections discuss individual study assessments. Although some of the studies included several exposures, discussions here will be limited to exposure of interest, $PM_{2.5}$, and its black carbon component.

Study 1: Su et al. (2015)

The 2015 study by Su and colleagues (5) reported the cross-sectional association between long-term exposure to $PM_{2.5}$ and carotid intima-media thickness. The study used previously developed land-use regression models (8) to estimate one-year average exposure for individuals. A separate measure for $PM_{2.5}$ exposure called $PM_{2.5abs}$ – defined as absorbance level of $PM_{2.5}$ and measured through an evaluation of the blackness of the $PM_{2.5}$ filter – was also measured. The study found no association between intima-media thickness and $PM_{2.5}$ levels but reported an average increase of 4.23% (95% CI: 0.32-8.13) in the measurement of *maximum left* carotid intima-media thickness, with every $1x10^{-5}$/m increase in $PM_{2.5abs}$. A similar significant association, however, was not observed for *right* carotid artery measurement.

The strength of the study is that it explores the relationship between pollution and atherosclerosis in an Asian metropolitan setting, where pollution levels are consistently higher than Western European or North American cities. Su and colleagues report an estimated average annual $PM_{2.5}$ exposure of 27.34 μg/m³, which is almost three times recommended air quality threshold set by World Health Organization (5).

The study, however, suffers from several serious biases. The enrollment strategy of the study which relied on volunteers responding to an advertisement has a resulted in a volunteer bias, evident in the fact that 72% of participants are men. This puts the external validity of the study in question, as the sample does not seem to be representative of the general population in Taiwan. Another limitation is the lack of reporting on the proportion of employed participants, especially those in certain occupations that are associated with significantly increased exposure to pollution.

The analysis also seems to suffer from the Multiple Testing Problem. Instead of fitting the regression model based on a single carotid intima-media thickness score, maximum, mean, and

combined scores from both right and left common carotid arteries have been tested individually. While every single one of these measures seems to be a reasonable outcome, multiple testing of all of them with no *a priori* physiological justification is inappropriate, and could result in finding associations by chance.

Study 2: Adar et al. (2013)

In 2013, Adar and colleagues reported early results from MESA Air, a prospective cohort study of $PM_{2.5}$ exposure and surrogate indicators of atherosclerosis in adults without pre-existing cardiovascular conditions(6). In their analysis, the authors used mixed models to show that a 2.5 $\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with 5 µm/y (95% CI: 2.6-7.4) greater progression in carotid intima-media thickness among participants in the same metropolitan area. The model adjusted for age, gender, ethnicity, smoking status and socio-economic indicators as confounders. No significant association was found without adjustment for the metropolitan area.

Strengths of the study include prospective cohort design that allows for establishing a temporal relationship between exposure and outcome, large sample size (n=5660), and estimation of exposure using sophisticated hierarchical spatiotemporal models. The authors also report results of their mixed model at three different stages of development, each of which accounts for an increasing number of confounders. The transparency in systematic reporting of results from all stages of the model is re-assuring, as it shows that confounders were not selectively adjusted for, to produce the desired outcome. Further sensitivity analyses showed that the findings were robust to an increasing degree of control for an extended list of potential confounders. Likewise, stratified analysis of subgroups (See Figure 2 in Adar et al. (6)) showed no evidence of confounding.

The fact that each site used a different recruitment strategy makes a systematic enrollment bias less likely in this study, although it could introduce bias in centre-to-centre comparisons. One shortcoming in the paper is that recruitment strategies are not spelled out in detail, which prevents the proper assessment of a potential selection bias.

Approximately 94% of participants reached follow-up. Although the authors state that the probability of being lost to follow-up was unrelated to baseline outcome measures, it is unclear whether this has been checked or whether it is just being assumed.

Study 3: Kaufman et al. (2016)

Results of the MESA Air study were published in *Lancet* in early 2016(7). In the largest and longest study of its kind to date, 6795 subjects aged 45-84 years old were followed in a 10-year prospective cohort. Pollution exposures were measured at 27 long-term monitoring sites, 771 snapshot locations within communities, and outside 697 participants' residences. Individually resolved exposures were then estimated using community-specific spatiotemporal models. Lifestyle questionnaires, together with meteorology and outdoor particulate tracers were used to calculate $PM_{2.5iwa}$, a separate exposure variable for each participant that adjusted for the proportion of time spent indoors. Throughout the course of the study, coronary artery calcium and right common carotid artery intima-media thickness were repeatedly measured in subjects using CT and ultrasound, respectively. Association between progression of these surrogate atherosclerosis markers and long-term $PM_{2.5}$ and black carbon exposures were assessed using complex regression models adjusting for baseline age, gender, ethnicity, socio-economic status, cardiovascular risk factors, clinical site and CT scanner technology.

The study reported a positive correlation between an increase in $PM_{2.5}$ exposure and increased rate of coronary artery calcium progression. A 5 $\mu g/m^3$ increase in exposure was associated with 4.1 Agatston units per year (95% CI 1.4–6.8) increased rate of coronary artery calcium progression. $PM_{2.5}$ exposure, however, was not associated with increased progression of carotid intima-media thickness, as a 5 $\mu g/m^3$ increase in exposure was associated with a –0.9 µm per year (95% CI –3.0 to 1.3) change in carotid intima-media thickness. No significant association was found for either black carbon or $PM_{2.5iwa}$, although the latter may be due to limitations and inaccuracies in estimating $PM_{2.5iwa}$. Sensitivity analyses showed results to be robust to changes in stages of control for potential confounder variables.

The MESA Air study is a significant addition to the previous body of evidence on the association of particulate matter pollution and atherosclerosis, which previously comprised of cross-

sectional and short-term cohort studies. The ten-year follow-up period of MESA Air and its ethnically-representative population sample, as well as using sophisticated exposure models which enabled resolving within-city exposure contrasts at unprecedented levels, are amongst its main strengths.

Developed exposure prediction models explained an impressive 79% of the variation of $PM_{2.5}$ exposure in selected participants' homes (model fit R^2=0.79, with 95% CI: 0.54-0.85). Further, geographical distribution of participants' homes and the respective predicted pollutants levels are visualized efficiently using color coded city maps (See Figure 2 in Kaufman et al. (7)).

Similar to Study 2, the study was carried out in six different centres across the US, with each centre recruiting participants according to community-specific logistics and experience. While using centre-specific enrollment strategies reduces chances of facing a study-wide selection bias, one must be careful in interpreting city to city differences, as they may be attributable to differences in selection strategies.

An significant limitation of the study is lost to follow-up and potential biases caused by that. As the authors mention in the paper, carotid intima-media thickness analysis was limited to participants who returned for ultrasound scans; a population that was found to be, on average, two years younger, more educated and less likely to be diabetic when compared with those who were included in coronary calcium analysis. While the authors mention this potential source of bias as a limitation, they fall short of addressing it. Since "age" was found to be a confounder (See Figure 4 in Kaufman et al. (7)), it is possible that the effect of exposure on intima-media thickness has been hampered by the younger age of participants.

Another major limitation is that the study does not discuss patients who have been lost to follow-up due to incidents of cardiovascular disease, or cardiovascular-related death. The relatively long duration of study can potentially include transitions from subclinical to symptomatic atherosclerosis in a subset of the participants which needs to be accounted for. However, this type of bias would skew results towards the null hypothesis of no association. Concluded positive associations are thereby unaffected.

Discussion

Synthesis and Summary of Evidence

The three appraised studies analyze the association between long-term exposure to $PM_{2.5}$ and subclinical atherosclerosis. The method used for estimating exposure is in principle similar among studies, although inside city differences are reflected more accurately in Study 2 and Study 3. The method used to estimate exposures involves measuring pollution at the community level, followed by developing regressions to estimate exposure for individuals. The levels of exposure were relatively high in Study 1 ($PM_{2.5}$ IQR: 23.67-30.45 $\mu g/m^3$), which is consistent with exposure levels in many developing countries. Exposure levels in Study 2 ($PM_{2.5}$ IQR: 14.12-19.08 $\mu g/m^3$) and Study 3 ($PM_{2.5}$ IQR: 12.9-15.7 $\mu g/m^3$), were lower, which is consistent with exposure levels in advanced economies. For comparison, WHO guidelines recommend a maximum annual mean $PM_{2.5}$ exposure of 10 $\mu g/m^3$ (9).

While Study 1 and Study 2 use carotid intima-media thickness as the sole surrogate indicator for subclinical atherosclerosis, Study 3 reports both carotid intima-media thickness and coronary artery calcification. Of the three appraised studies, only Study 2 found a significant association between $PM_{2.5}$ and intima-media thickness. Such association, however, was not replicated in Study 3 which had a larger sample size, a significantly longer follow-up, and an improved exposure measurement. Study 1 found no association between $PM_{2.5}$ exposure and intima-media thickness but did find some association between the black carbon component of $PM_{2.5}$ and left carotid intima-media thickness. The association, however, is possibility an artifact of the Multiple Testing Problem, especially as it was not present for the *left* carotid artery, and was not replicated in Study 3. However, Study 3 found a strong association between $PM_{2.5}$ and coronary artery calcium progression, which was robust to stratified tests and sensitivity analysis.

Although using carotid intima-media thickness as a surrogate indicator of atherosclerosis is common in the literature (10), its usefulness has been questioned (11), especially when the *progression* of intima-media thickness is being studied (12). In contrast, both *presence* (13) and *progression* (14) of calcium plaques in coronary arteries are known to be a predictor of ischemic

vascular events. Coronary artery calcium has also been shown to be a much stronger predictor of coronary disease events compared with intima-media thickness (15).

Overall, it seems that progression in coronary artery calcium is a better surrogate indicator for atherosclerosis in cohort studies. Study 3 provides long-term prospective follow-up of an extraordinarily well-characterized population regarding both exposure and potential confounders and is the best evidence in the area. Study 3 is the first to report an association between $PM_{2.5}$ and coronary artery calcium progression, and its results provide strong biological support for the previously observed pollution-related increase in cardiovascular events.

Public Health and Policy Implications

A growing body of observational evidence suggests a strong relationship between long-term exposure to traffic-related particulate pollutants and developing cardiovascular disease. The findings are consistent with a causal relationship between traffic-related pollution and the risk of coronary artery disease, and support a global effort to reduce exposure to these pollutants, especially in developing countries where pollution levels have been particularly high.

Conclusion

The evidence suggests an association between increasing particulate pollution and subclinical atherosclerosis, demonstrated through an increase in the rate of progression of coronary artery calcium. This is consistent with the previous knowledge on association of long-term exposure to particulate pollution and increased risk of cardiovascular events. These findings add to the body of evidence for a causal relationship between particulate pollution and the risk of cardiovascular events by providing evidence of biological plausibility.

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