STATEMENT

Synopsis of Research Report 142

HEALTH EFFECTS INSTITUTE

# Air Pollution and Health: A European and North American Approach

## BACKGROUND

Over the past decade, scientists seeking to understand the role that air pollution might play in population health effects have relied heavily on epidemiologic studies known as time-series studies. Time-series studies use information on daily concentrations of air pollutants and daily measures of health impact (numbers of deaths or of admissions to hospitals), initially at the level of a single city. However, the wide range of methods used to assemble and analyze data from individual cities has made their findings difficult to interpret and has led to progressive efforts to combine information across multiple cities and ultimately, across geographic regions. The goal of these larger analyses has been to develop more reliable estimates of the potential acute effects of air pollution on human health, to provide a common basis for comparison of risks across geographic areas, and to increase the ability to discriminate between health effects that may truly be related to air pollution and those that may be attributable to other factors. Ultimately, the goal is to improve the scientific basis for decisions about whether and how to regulate air pollution.

To explore these issues, HEI sponsored a unique collaboration among investigators from Europe, the United States, and Canada, led by co-principal investigators Klea Katsouyanni, University of Athens and Jonathan Samet, then at the Johns Hopkins Bloomberg School of Public Health, and overseen by an external Scientific Oversight Group. The resulting project was called Air Pollution and Health: A European and North American Approach or APHENA. With access to data from three geographic areas, APHENA offered a much larger and diverse data set with which to address methodological as well as scientific issues about the relationships between $PM_{10}$, ozone, and mortality and morbidity that were the subject of lively debates at the time the project was first conceived in 1999.

The investigators undertook a rigorous examination of time-series methods used to model the relationship between daily $PM_{10}$ (particulate matter with an aerodynamic less than 10 micrometers) and ozone concentrations and daily mortality and hospital admissions. They sought to develop a standardized approach to the analysis of time series data at the city and regional level, to assess the consistency between relative rates of mortality and hospital admissions across Europe and North America when estimated using a common analytic protocol, and to explore possible explanations for any remaining variation in the results that analytic differences could not explain.

## APPROACH

The APHENA project was designed to take advantage of the largest databases available at the time. These had been developed by the three groups of investigators for earlier studies: 1) the *Air Pollution and Health: A European Approach* Phase 2 (APHEA2) study involving 32 cities; 2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest U.S. cities; and 3) multicity research on the health effects of air pollution in 12 Canadian cities.

Each database included air pollution monitoring data for particulate matter and ozone, health outcome data in the form of daily mortality for all ages, for persons younger than 75 years, and for persons 75 years or older (from all nonaccidental causes [all-cause]), cardiovascular disease, or respiratory disease) and daily hospital admissions for persons 65 years or older (for cardiovascular and respiratory disease). Other database variables used

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Klea Katsouyanni at University of Athens Medical School, Athens, Greece and by Dr. Jonathan M Samet at John Hopkins Bloomberg School of Public Health, Baltimore, MD and their colleagues. The complete report, *Air Pollution and Health: A European and North American Approach (APHENA)*, can be obtained from HEI or our Web site (see last page).

for APHENA included weather data and a number of socioeconomic and other variables known or suspected to influence mortality or hospital admissions. (These latter variables were considered potential *effect modifiers,* factors that can modify the main effect of air pollution on health and that may differ between study areas).

The decision to rely on the preexisting times-series databases had the advantage of lower costs and a more rapid start to the methodological work of the project. Also, the original published analyses of these datasets could serve as a baseline against which to explore the impact of the methodological choices made in APHENA. However, it had the disadvantage that inherent differences between the way air pollution or outcome data were collected by government agencies in different countries remained as a potential source of uncertainty. Furthermore, restrictions placed by various government agencies on the use of the data further limited evaluation of the datasets because the APHENA investigators could not create a central repository for the time-series data. This limitation precluded a full exchange of data sets, so quality assurance evaluations were based on an exchange of data from six cities.

The APHENA methods exploration followed the two-stage process typical of multicity studies, beginning with analysis of the data for individual cities. The APHENA investigators undertook careful analysis of: 1) the class of models to be used for analysis, including the data smoothing methods to control for potential confounding by seasonal or other temporal trends in the data; 2) the amount of control for these trends (that is, the amount of smoothing represented by the number of degrees of freedom associated with the smoothing method chosen); and 3) the suite of other variables to be included in the model.

On the basis of extensive sensitivity analyses and other evaluations, the investigators decided that they could not justify either fitting a single model for all cities or fitting separate models for each city — the most common approach at the time. They agreed instead on a common protocol involving a range of models and assumptions to be applied to all city-specific analyses of daily deaths and hospital admissions.

For the second stage of analysis, the APHENA investigators conducted a systematic comparison of the statistical approaches previously used by the NMMAPS and APHEA groups to pool the estimates across cities and to explore variations in the effect estimates for their regions. Although the HEI Scientific Oversight Group had encouraged selection of a single approach for the second stage, the investigators felt that their comparative analysis did not suggest a clear preference for one method over another, so each investigative group continued to apply its preferred method.

Having explored the sensitivity of the health effects estimates to analytic choices, the investigators then focused on trying to understand other factors that might explain the variation in the effect estimates between cities and regions. They evaluated potential modification of the effects of $PM_{10}$ on all-cause mortality by variables common to the data sets for those cities that had daily PM data — 22 cities in Europe and 15 in the United States. They investigated potential modification of the ozone effect on mortality in all three regions, including Canada. Although the investigators presented pooled estimates of $PM_{10}$ mortality effects for Europe and the United States and of ozone mortality effects across all three regions, too many differences existed among the databases to explore effect modification using the combined data sets.

**RESULTS**

The problem the APHENA investigators addressed in their substantial methodologic work was essentially one of model selection. They found that effect estimates remained fairly stable across a broad spectrum of model assumptions. In particular, they found that the amount of smoothing (numbers of degrees of freedom selected) for control of seasonal and temporal confounding was more important than the method of smoothing (for example, the use of natural or penalized splines in the models). This finding is important because it suggests that a relatively simple choice of method may usually be appropriate, but that investigators should explore several choices for the amount of smoothing. Coupled with the limitations arising from using large administrative databases that have been constructed for other purposes, a reasonable guideline for future investigators is to choose the simplest model that seems to capture the main variability in the data, and to explore in detail the sensitivity of the most scientifically relevant conclusions.

Using the standardized protocol developed from this work, the APHENA investigators largely confirmed the basic findings from previous independent analyses of the three data sets for both $PM_{10}$ and ozone, including the much higher effect estimates in Canada relative to the other two regions. The investigators reported small, but positive and statistically significant associations between a 10 $\mu g/m^3$ increase in $PM_{10}$ and all-cause and cardiovascular mortality in Canada,

Europe, and the United States. Effects of $PM_{10}$ on respiratory mortality were less consistent across region and model. Ozone showed a smaller, but generally positive association with all-cause and cardiovascular mortality in each of the three regions, but not with respiratory mortality. Quality control measures implemented during the project showed that the three teams produced essentially the same results when asked to analyze the same subset of data sets from the project.

Estimates of the effect of $PM_{10}$ on hospital admissions for cardiovascular and respiratory disease varied across the three centers. Daily increases in $PM_{10}$ were not associated with significantly increased risks of hospitalization for cardiovascular disease in Canada, but were in Europe and in the United States. The risks of admission for respiratory disease in the three regions were more uncertain, variable, and model dependent.

In contrast to estimates of the effect of ozone on cardiovascular mortality, the effects on cardiovascular hospital admissions were closer to zero and not statistically significant. The converse was observed with the respiratory effects; the effects of ozone on respiratory disease admissions were largely positive while respiratory mortality effects were close to zero. Effects on respiratory admissions were both higher and more uncertain in Canada than in Europe or the United States.

The exploration of effect modification was ultimately limited by the number of variables common to the data sets and the smaller number of cities (only those with daily pollutant data) included in the analyses. For $PM_{10}$, the most consistent evidence of effect modification was found for age and unemployment in Europe and the United States; a higher percentage of older people and a higher unemployment rate were each associated with a greater effect of $PM_{10}$ on all-cause mortality in both regions. The investigators found no consistent patterns of effect modification for $O_3$ across the three regions.

**DISCUSSION**

APHENA was an ambitious project undertaken by a highly qualified team of investigators from Europe, the United States, and Canada. It made substantial contributions to how multicity time-series studies should be designed and conducted. In particular, the APHENA investigators' careful development and application of a common analytic approach to city-level analyses was an important advance over other meta-analytical approaches, in common use prior to this study, which relied on published city-specific results. Furthermore, it demonstrated the importance of a well-reasoned strategy of sensitivity analyses, both to support model development and to provide a transparent presentation of the role of model choices on the estimates of health effects.

The investigators successfully demonstrated that methodological differences between the centers' approaches to the regional-level analyses were not the reason for variability observed in previous study findings of the three geographic areas. Although the decision to allow each center to continue to use separate methods was not the original plan, the HEI Review Committee found it reassuring that the APHENA investigators' extensive comparison of the APHEA and NMMAPS approaches indicated little reason to choose between the two methods. However, the Committee found that the information provided in the report was not sufficient to support an independent assessment of that conclusion.

The findings of small, but significant effects of $PM_{10}$ and ozone on daily death and, to varying degrees, on hospital admissions are important. They corroborate earlier findings on the health effects of daily air pollution and, coupled with the systematic analytic approaches and quality control measures used in the studies, demonstrate that the effect estimates can not be attributed solely to the vagaries of model choice.

The hope that the common analytic strategy might help reveal some of the other potential contributors to variations observed within and between the three regions was largely unfulfilled. Few new insights were possible given the limited number of potential effect modifiers that were common to the databases for the three regions, and also given the restriction of the analyses to the smaller number of cities with daily $PM_{10}$ and ozone data within regions. Some of the more puzzling differences between regions therefore remained largely unexplained — in particular the much higher effect estimates for $PM_{10}$ and ozone in Canada relative to Europe and the United States.

The APHENA study demonstrated the substantial challenges that face efforts to standardize and integrate data from different countries. Overcoming government agency reluctance or other impediments to establishing centralized databases might help, but some challenges remain beyond the control of investigators. Basic underlying disparities in the existing databases with respect to air pollutant monitoring methods and frequency, mortality and hospitalization records, and sociodemographic data are very difficult to fix retrospectively.

The authors suggest that periodic pooling of data, as in APHENA, should be considered both to explore methodological questions and to assess the progress of air pollution controls in reducing health impacts. The HEI Review Committee believes this recommendation should be evaluated cautiously. Studies like APHENA that use a well-reasoned, common analytic strategy, may offer the best approach for comparing and combining data across regions or countries. However, APHENA illustrated how the limitations of using existing data sets can impact the ability to make clear comparisons and to explain the health effects of air pollution — sometimes just as much as the technical details of model selection. For these limitations to be overcome in any future collaboration across international boundaries, thought needs to be given to substantially greater coordination and harmonization of the air pollution monitoring, health outcome, and covariate data collected in different countries. The costs of undertaking such exercises would need to be weighed against the expected advances in our understanding of air pollution and health effects.

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