

Long-Term Health Effects of Particulate and Other Ambient Air Pollution: Research Can Progress Faster If We Want It To

Nino Künzli¹ and Ira Bruce Tager²

¹Institute of Social and Preventive Medicine University Basel, Switzerland; ²School of Public Health, University of California Berkeley, Berkeley, California, USA

There is need for the assessment of long-term effects of outdoor air pollution. In fact, a considerable part of the large amount of U.S. research money that has been dedicated to investigate effects of ambient particulate pollution should be invested to address long-term effects. Studies that follow the health status of large numbers of subjects across long periods of time (i.e., cohort studies) should be considered the key research approach to address these questions. However, these studies are time consuming and expensive. We propose efficient strategies to address these questions in less time. Apart from long-term continuation of the few ongoing air pollution cohort studies in the United States, data from large cohorts that were established decades ago may be efficiently used to assess cardiorespiratory effects and to target research on detection of the most susceptible subgroups in the population, which may be related to genetic, molecular, behavioral, societal, and/or environmental factors. This approach will be efficient only if the available air pollution monitoring data will be used to spatially model long-term outdoor pollution concentrations across a given country for each year with available pollution data. Such concentration maps will allow researchers to impute outdoor air pollution levels at any residential location, independent of the location of monitors. Exposure imputation may be based on residential location(s) of participants in long-standing cardiorespiratory cohort studies, which can be matched to pollutant levels using geographic information systems. As shown in European impact assessment studies, such maps may be derived relatively quickly. **Key words:** exposure models, geographic information systems, GIS, long-term effects, outdoor air pollution, particulate matter. *Environ Health Perspect* 108:915–918 (2000). [Online 18 August 2000] <http://ehpnet1.niehs.nih.gov/docs/2000/108p915-918kunzli/abstract.html>

On both sides of the Atlantic, research advisory boards have emphasized the need for the investigation of long-term health effects of outdoor air pollution (1–3). Although air pollution-related health effects have received considerable attention and funding in the last two decades, efforts have focused primarily on short-term effects through controlled exposure studies and a variety of epidemiologic study designs (4–8).

A few longitudinal studies (9–11) and many cross-sectional studies have evaluated potential long-term health effects. However, additional epidemiologic studies are needed to evaluate potential long-term health effects of exposures to ambient air pollution. In particular, such studies should be able to provide reasonable estimates of past exposures that extend over many years, either for groups (populations) or individuals. These studies also are needed to better estimate the public health impact of air pollution and the benefit of air pollution control (12).

Apart from intervention studies (which usually are not suitable in environmental health), cohort studies (which follow the health history of the same people over long periods of time) remain the “gold standard” design used to assess the effects of air pollution on life expectancy or on the incidence, course, resistance, and remission of diseases. However, cohort studies have disadvantages

that stem both from inherent features of the exposures of interest as well as from the health outcomes. We will discuss these issues and propose efficient strategies to overcome the main problems and to facilitate optimal use of the substantial research money dedicated to investigate the health effects of particulate pollution (as one of the key surrogates of overall outdoor air pollution).

A Challenging Research Setting

In contrast to occupational or behavioral risk factors, exposure to outdoor ambient air pollution is ubiquitous. Lifetime exposures to outdoor air pollution, which are relatively homogeneously distributed across large areas [e.g., ozone and mass concentration of fine particulate matter, particulate matter ≤ 2.5 μm in aerodynamic diameter (PM_{2.5})], are mostly influenced by the outdoor air quality. For these pollutants as well as for those with local source spatial variation (e.g., nitrogen dioxide, carbon monoxide), residential location is one of the major personal determinants of exposure to outdoor air pollution. Moreover, in contrast to ozone, fine particles have the additional property of efficient penetration into indoor environments, which further increases the homogeneity of personal long-term exposure to PM_{2.5} from outdoor sources between people in the same

geographic area (13). From this perspective, the study of long-term effects of outdoor air pollution between populations, that is, comparison of health across different levels of exposure to outdoor air pollution, is thought to necessitate the study of subjects living in geographically (i.e., environmentally) distinct areas. To prevent area-specific or ecologic confounding, subjects should live in as many different areas as possible (14). However, the gain in statistical power through increasing the number of study sites often conflicts with financial and logistic limitations (15). As a consequence, the few air pollution studies that have been explicitly designed to assess long-term effects of air pollution have usually been restricted to a limited number of study sites (10,16,17).

Long-Term Health Effects: Lack of Disease Specificity

There is no specific air pollution disease; air pollution has to be considered a component cause for a variety of multifactorial health outcomes. Thus, cohort studies must be rather large for interpretable associations with outdoor air pollution to be observed and extracted. Furthermore, given progressive improvements in air quality in many developed countries, the range of long-term outdoor air pollution concentrations may be limited across geographic regions. As a consequence, to estimate long-term effects with reasonable precision, study population size may need to be considerable, and cohorts must be followed over long periods, usually decades.

This scenario (large numbers, long follow-up) is not attractive for funding agencies who prefer to fund projects with short time frames and limited budgets. Therefore, it is not surprising that, worldwide, only a few studies have been designed *a priori* as cohorts to investigate the long-term effects of ambient air pollution on morbidity and mortality. In the United States, only two studies, so far, have reached more than 15 years of follow-up time (9,10). The Swiss Study on Air Pollution and Lung Disease in Adults (SAPALDIA) (18) is

Address correspondence to N. Künzli, Institute of Social and Preventive Medicine University Basel, Steinengraben 49, 4059 Basel, Switzerland. Telephone: 41 61 267 60 66. Fax: 41 61 267 61 90. E-mail: nino.kuenzli@unibas.ch

Received 3 April 2000; accepted 18 May 2000.

currently organizing funding for the 10-year follow-up. Although it is a high priority to continue these key projects far into the new millennium, there also is a need for new and innovative approaches to confirm findings from these few studies and to address the remaining open questions (1,2); these approaches should be less subject to the constraints of long follow-up times and the logistical problems of large samples from multiple locations. Consequently, we propose quick and inexpensive solutions, which may well be applied in the United States as a way to efficiently invest some part of the large public research program dollars for the investigation of health effects of particulate pollution.

Optimize Exposure and Sample Size

The efficiency of the epidemiologic assessment of long-term health effects depends on the range and distribution (spread) of exposure across study participants. Both aspects of exposure may be optimized by sampling subjects from the entire outdoor concentration distribution across the United States. Thus, rather than selecting a finite number of study areas with clusters of people sharing similar long-term exposure, relatively small numbers of people from a broad range of areas may be selected (19). Such person-based sampling strategy may efficiently increase the range and spread of the exposure distribution. In the usual area-based sampling, these parameters are usually limited; for example, in the Harvard Six Cities Study, long-term exposure to outdoor air pollution across > 8,000 subjects is restricted to only six levels (10). There are only a few studies that have chosen such strategies so far (9,20,21).

Modeling—An Optimal Use of Monitor Data

Residential location is a useful predictor of outdoor air pollution exposure levels only if suitable objective measurements of outdoor air quality are available. For homogeneously distributed background outdoor air pollution (e.g., PM_{2.5}) a fixed-site outdoor monitor may well reflect the long-term average air quality across areas of several square kilometers. Therefore, existing air pollution cohort studies have been based on selection of populations from sites with available monitors. In fact, availability of monitoring data has been another key criterion that has restricted researchers to the selection of subjects from a few study sites rather than from any residential location. Thus, if the problem of having only a finite number of monitors can be resolved, subjects from residential locations with no pollutant monitors may no longer be excluded or lost to follow-up.

There is a straightforward solution: based on available monitoring data, annual mean values of several surrogates of outdoor air pollution such as particulate matter, ozone, or nitrogen dioxide, may be modeled spatially. Imputation of model-based values of long-term mean exposure to most residential location across the United States would be possible. The recent European impact assessment studies (22,23) successfully applied this strategy for Austria, France, and Switzerland. Modeling air pollutant distributions may most likely yield a sufficiently reliable annual mean estimate for the majority of populated regions in the United States. Values may be assigned to square kilometers, for example, in a geographic information system (GIS) format, which may be easily matched to coordinates or geocodes of any residential location of study populations. Such GIS exposure maps may be created both retrospectively (where an adequate historical database exists or they can be created from surrogates) and prospectively for each year. This would allow assignment of time-weighted averages of long-term cumulative exposures, even for residentially mobile subjects.

Models may be based either on concentration or emission data, if available (22). In the Swiss part of the recent European study (22), it was possible to derive annual mean concentrations of PM₁₀ (particulate matter ≤ 10 μm in aerodynamic diameter) for each square kilometer across Switzerland with the use of emission registry data. Dispersion models considered primary particulate emissions, formation of secondary particulates, and large-scale transboundary background levels. The advantage of emission-based modeling is the ability to create distributions of source-specific indicators of exposure rather than to use only distributions of total outdoor air pollution.

To date, no long-term air pollution epidemiology study has applied such exposure maps to impute exposure, although the great potential of the GIS and environmental epidemiology has been well acknowledged (24,25). A full-space GIS-based map may allow geocode-based matching of concentrations of any location for any subject. The approach may be considered an extension and generalization of the current gold standard of outdoor air pollution assignment (20,21,26), where imputation is based on distance-weighted averages of the closest monitors. The approach requires, however, identification of the closest monitoring stations for each subject and residence. Thus, a disadvantage of this approach is that imputation must be repeated separately for each research project.

There are a variety of applications and users of such GIS exposure data:

- **Environmental health scientists.** Investigators of the long-term air pollution health effects will benefit substantially because full data will be available for participants who change their residences one or more times. With progress in modeling, it may be feasible in the future to model spatial distribution of pollutants with higher within-area spatial variability. Thus, the additional effects of proximity to particular sources may be more efficiently investigated and the errors in exposure assignment may be elucidated.
- **Risk assessors.** Population exposure distributions, a requirement to estimate the public health impact of air pollution, may be easily derived from these maps (22,23).
- **Policy makers.** Availability of annual exposure distribution maps will allow continuous evaluation of the change over time in population exposure (e.g., the number of people exposed to levels above air quality standards). The population exposure will depend on both air quality and real estate planning strategies.
- **Abatement scenario evaluations.** The impact of potential emission reduction strategies on the population exposure distribution may be evaluated and used in cost-benefit analyses.
- **Monitoring optimization.** With improved modeling techniques of the classic criteria pollutant, it will be possible to reduce direct monitoring of these pollutants to a new primary goal—to repeatedly validate the modeling results rather than to provide measured point values across a dense network. Thus, financial resources will be available to measure additional indicators of air pollution that may be of further health or policy relevance, such as particle constituents, particle number, carcinogens, or other factors (1,2).

Given all these benefits of GIS-based exposure modeling, it is not surprising that modeling has been and will be supported by the national environmental agencies involved in the European impact assessment study (22). The same interest may be expected to apply for the U.S. Environmental Protection Agency, which could assign contractors to provide annual U.S.-wide exposure maps for the past one to two decades.

The Cohorts Already Exist

Large, already established, naturally aging cohorts developed for the study of respiratory and cardiovascular diseases could now be used to investigate associations of morbidity and life expectancy with long-term outdoor air pollution exposure. This approach has been successfully applied once so far, with the use of the American Cancer Society (ACS) cohort (11). However, because exposure maps were

not available to this study, cities without fine particulate data could not be included in the analyses. With the suggested maps at hand, the “piggy-back” approach should be intensified and modified by the suggested exposure imputation approach mentioned above. There clearly are some key candidate studies of interest: the MRFIT follow-up, the Nurses Health Study, the Health Professional Studies, the Physicians Health Study, the Atherosclerosis Risk in Communities Study, the Coronary Artery Risk Development in Young Adults, or the National Institutes of Health–National Heart, Lung, and Blood Institute-sponsored Lung Health Study, to name a few U.S. examples. As shown by Pope et al. (11), the use of existing cohorts may drastically increase not only the number of subjects but also the number of study sites involved, reaching, for example, 150 study sites in the ACS cohort. Participants of other well-established historic cohorts live across large parts or even the whole United States; thus, long-term outdoor air pollution exposure may, by default, spread across a broad range of exposure, fulfilling a key requirement of efficient epidemiologic research. In most cases, participants’ residential history will be known for several decades; thus time-weighted average exposures may be imputed and effects of outdoor exposure during specific periods may be addressed separately.

The use of established cohorts offers the possibility to investigate, within rather short time frames, the association between long-term outdoor air pollution exposure with health outcomes not yet considered in long-term studies, such as specific cardiovascular diseases. The few ongoing air pollution cohort studies developed a strong focus on respiratory health, whereas short-term air pollution studies indicate that the cardiovascular system may play an important pathophysiological role (27–30). Among some of the large cohorts, data that is already available may permit investigation of whether genetic, societal, behavioral, and environmental factors modify the susceptibility to long-term effects of outdoor air pollution, an area with clear need for intensified research (1–3). The required steps for such investigations are, in theory, easy to perform, are achievable within a short time (e.g., about 1 year to derive useful exposure maps), and will be relatively inexpensive as compared to establishment of new, full-scale air pollution cohort studies.

Problems To Be Addressed

The approach may appear simple at first glance. However, there are a number of important issues that should be addressed before studies of the type that we have suggested can be implemented with confidence.

Cohort study data. There are no centralized or standardized cohort study data systems available. Thus, as a first step, criteria for the identification of potentially useful cohort studies need to be established, for example, the minimum number of participants, minimum duration of follow-up, quality of residential histories, specificity of measured health outcomes, and potential confounders (including the measurement methods). The distribution of the key measures should be provided because they may be needed to estimate the power of the air pollution study. Finally, a compendium of existing cohort studies should be compiled and rated on each of the criteria. The relative suitability of given cohorts to address particular questions about long-term health effects would be based on objective criteria.

Exposure assignment. As recently reviewed, residential location is a useful measure of exposure (31). This is particularly true for long-term mean concentrations, whereas the short-term within- and between-person variability in exposure may be substantial due to the short-term variability in time–activity patterns across diverse microenvironments. Nevertheless, the proposed imputation of long-term exposure, although conceptually intriguing, requires further research that addresses precision and sources of error for the geographically imputed values. In a first step, the availability of concentration measures and emission data should be described, including measures of the geographic variability and time trends. Characteristics of monitoring stations, the density of monitoring networks, and the responsible agencies should be listed. Whereas valid imputed values may be readily available for pollutants with high spatial homogeneity and efficient indoor penetration, pollutants for which concentrations strongly depend on the proximity to sources, that is, mainly primary pollutants, may not easily be assigned without further research regarding the impact of small-scale time–activity patterns on long-term personal exposure profiles (32). One may expect that, based on validation studies, the exposure experts will make some restrictions for the user of the first generation of nationwide exposure maps. For example, the validity of assigned values may be questioned in areas with very influential small-scale topographic or weather conditions; the availability of retrospective time trend data may vary across regions; and geographically homogenous pollutants such as fine particulates or ozone will be assigned with higher confidence than source-specific pollutants (e.g., traffic exhaust related exposure) for which geographic imputation of exposure data may lack precision. These exposure-related issues, however, are inherent to air pollution epidemiology,

particularly in the field of short-term effect studies, and thus may not be an argument against the use of existing cohorts to assess long-term effects.

Collaboration. The proposed efficient approach will happen only if the pertinent interdisciplinary community of researchers, monitoring agencies, and policy makers are ready to collaborate. This may be the biggest hurdle in a scientific world where transdisciplinary collaboration has little tradition and a lack of funding structures. Thus, collaboration is unlikely to happen without a major concerted effort under the lead of a committed agency or institution. Sufficient funding will be required to trigger, organize, and manage the interdisciplinary and transproject collaboration. Skills must be shared to contribute to one common goal: to gain further insight into the long-term health effects of outdoor air pollution and its relevance on public health.

REFERENCES AND NOTES

- ESF. Scientists’ Recommendations: Environment and Health Research for Europe. An ESF Position Paper. Strasbourg, France:European Science Foundation, 1998.
- HEI. The Health Effects of Fine Particles: Key Questions and the 2003 Review. Report of the Joint Meeting of the EC and HEI, January 1999, Brussels, Belgium. Brussels, Belgium:Health Effects Institute; 1999.
- National Research Council. Research Priorities for Airborne Particulate Matter. II. Evaluating Research Progress and Updating the Portfolio. Washington, DC:National Academy Press, 1999.
- Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. *Am J Respir Crit Care Med* 153(1):3–50 (1996).
- Health effects of outdoor air pollution. Part 2. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. *Am J Respir Crit Care Med* 153(2):477–498 (1996).
- Holgate S, Samet JM, Koren HS, Maynard RL. Air Pollution and Health. San Diego, CA:Academic Press, 1999.
- Katsouyanni K, Touloumi G, Spix C. Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from times series data from the APHEA project. *Br Med J* 314:1658–1663 (1997).
- Wilson R, Spengler J. Particles in Our Air. Concentrations and Health Effects. Boston, MA:Harvard University Press, 1996.
- Abbey DE, Nishino N, McDonnell WF, Burchette RJ, Knutsen SF, Beeson WL, Yang JX. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am J Respir Crit Care Med* 159:373–382 (1999).
- Dockery DW, Pope AP, Xu X, Spengler JD, Wae JW, Fay M, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. Cities. *N Engl J Med* 329(24):1753–1759 (1993).
- Pope AC, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 151(3):669–674 (1995).
- Künzli N, Kaiser R, Medina S, Studnicka M, Chanel O, Filliger P, Herry M, Horak F Jr, Puybonnieux-Textier V, Quénel P, et al. Public health impact of outdoor and traffic-related air pollution: a tri-national European assessment. *Lancet* (in press).
- Mathys P, Oglesby L, Stern WB, Braun-Fahrlander C, Jantunen M, Künzli N. Traffic related PM_{2.5} efficiently penetrate from outdoor to indoor (Elemental Analyses Study EAS-EXPOLIS). *Epidemiology* 10(suppl 4):S50 (1999).

14. Piantadosi S, Byar D, Green S. The ecologic fallacy. *Am J Epidemiol* 127:893-904 (1988).
15. Navidi W, Thomas D, Langholz B, Stram D. Statistical methods for epidemiologic studies of the health effects of air pollution. *Res Rep Health Eff Inst* 86:1-50 (1998).
16. Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, Bongard JP, Brändli O, Domenighetti G, Elsasser S, et al. Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med* 155(1):122-129 (1997).
17. Navidi W, Thomas D, Stram D, Peters J. Design and analysis of multilevel analytic studies with applications to a study of air pollution. *Environ Health Perspect* 102(suppl 8):25-32 (1994).
18. Martin BW, Ackermann-Liebrich U, Leuenberger P, Künzli N, Stutz EZ, Keller R, Zellweger JP, Wutrich B, Monn C, Blaser K, et al. SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Disease in Adults. *Soz Präventivmed* 42(2):67-84 (1997).
19. Kinney P, Aggarwal M, Nikivorov SV, Nadas A. Methods development for epidemiological investigations of the health effects of prolonged ozone exposure. Part III. An approach to retrospective estimation of lifetime ozone exposure using a questionnaire and ambient monitoring data (U.S. sites). *Res Rep Health Eff Inst* 81:79-108 (1998).
20. Galizia A, Kinney PL. Long-term residence in areas of high ozone: associations with respiratory health in a nationwide sample of nonsmoking young adults. *Environ Health Perspect* 107:675-679 (1999).
21. Künzli N, Lurman F, Segal M, Ngo L, Balmes J, Tager IB. Association between lifetime ambient ozone exposure and pulmonary function in college freshman - results of a pilot study. *Environ Res* 72(1):8-23 (1997).
22. Filliger P, Puybonnieux-Textier V, Schneider J. PM10 Population Exposure; Technical Report on Air Pollution. Health Costs due to Road Traffic-related Air Pollution; An impact assessment project of Austria, France and Switzerland. Bern, Switzerland:Federal Department of Environment, Transport, Energy and Communications, Bureau for Transport Studies, 1999. Available: <http://www.who.dk/london99/transport04.htm> [cited 27 July 2000].
23. Sommer H, Chanel O, Vergnaud JC, Herry M, Sedlak N, Seethaler R. Monetary Valuation of Road Traffic Related Air Pollution. Health Costs due to Road Traffic-Related Air Pollution. An Impact Assessment Project of Austria, France and Switzerland. Prepared for the Third WHO Ministerial Conference of Environment & Health, London, 1999. Available: <http://www.who.dk/london99/transport04.htm> [cited 27 July 2000].
24. Croner CM, Sperling J, Broome FR. Geographic information systems (GIS): new perspectives in understanding human health and environmental relationships. *Stat Med* 15(17-18):1961-1977 (1996).
25. Vine MF, Degnan D, Hanchette C. Geographic information systems: their use in environmental epidemiologic research. *Environ Health Perspect* 105:598-605 (1998).
26. Abbey DE, Hwang BL, Burchette RJ. Estimated long-term ambient concentrations of PM10 and development of respiratory symptoms in a nonsmoking population. *Arch Environ Health* 50:139-152 (1995).
27. Peters A, Pery S, Döring A, Stieber J, Koenig W, Wichmann HE. Increases in heart rate during an air pollution episode. *Am J Epidemiol* 150(10):1094-1098 (1999).
28. Pope AC, Dockery DW, Kanner RE, Villegas GM, Schwartz J. Oxygen saturation, pulse rate, and particulate air pollution. *Am J Respir Crit Care Med* 159:365-372 (1999).
29. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? *J Air Waste Manage Assoc* 46:927-939 (1996).
30. Seaton A, Soutar A, Crawford V, Elton R, McNerlan S, Cherrie J, Watt M, Agius R, Stout R. Particulate air pollution and the blood. *Thorax* 54:1027-1032 (1999).
31. Huang YL, Betterman S. Residence location as a measure of environmental exposure: a review of air pollution epidemiology studies. *J Exp Anal Environ Epidemiol* 10:66-85 (2000).
32. Oglesby L, Künzli N, Rössli M, Braun-Fahrländer C, Mathys P, Stern W, Jantunen M, Kousa A. Validity of ambient levels of fine particles as surrogate for personal exposure to outdoor air pollution. *J Air Waste Assoc* 50:174-185 (2000).

Environmental Health Perspectives online at the



<http://ehp.niehs.nih.gov/>