

May 3, 2010

James E. Enstrom, Ph.D., M.P.H.
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Los Angeles, CA 09905-1772

Dear Dr. Enstrom,

The HEI Research Committee recently reviewed your Preliminary Application entitled *Criteria Pollutants and Mortality in California*, submitted under HEI RFPA 09-5 *Health Effects of Air Pollution*. I regret to inform you that the Committee declined to request a full application.

The Committee's decision was based on several considerations. While your application raised some interesting research questions, the Research Committee felt that it contained insufficient detail on your proposed methodology - even in this summary presentation - to understand how and whether research questions would be adequately addressed. There was also concern that one of the proposed cohorts, the CPS-I, was over 50 years old, and additional follow-up would not contribute significant additional information to answer questions raised in the application.

Finally, the Committee felt that, given other recent and ongoing work in this area, HEI is less interested in pursuing additional analyses until that work has been completed. Two California-specific studies that you did not cite in your application have been published: one by Dr. Michael Jerrett (LA-only analysis of the CPS-II cohort in HEI Report 140; originally in *Epidemiology* (2005; 16: 727-736) and the other by Dr. Bart Ostro of CalEPA (California Teacher's Study: Environmental Health Perspectives, volume 118, number 3, March 2010). In addition, the Committee understands that Dr. Jerrett is also completing, with funding from CARB, a statewide version of the analysis he conducted under HEI auspices for the LA area. Since the final results from that study are not yet available, the Committee was not convinced that additional state-specific research is a high priority for HEI until the scientific community has had the opportunity to see and review those results.

Thank you for submitting your Preliminary Application to HEI. Please let me know if you have any further questions.

With best wishes for your future research endeavors,



Kate Adams, Sc.D., HEI Staff Scientist

Health Effects Institute Preliminary Application RFPA 09-5

**CRITERIA POLLUTANTS AND MORTALITY IN
NIH-AARP DIET AND HEALTH STUDY COHORT**

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May 17, 2010

BACKGROUND AND RATIONALE

There is a major scientific controversy regarding the relationship between fine particulate air pollution (PM2.5) and mortality in California that needs to be addressed with additional epidemiologic research. This controversy is part of the larger issue of geographic variation and time trends in the mortality risk associated with criteria pollutants like PM2.5 and ozone. A full presentation of the controversy regarding the relationship between PM2.5 and mortality in California was given at the February 26, 2010 California Air Resources Board (CARB) Symposium "Estimating Premature Deaths from Long-term Exposure to PM2.5" (<http://www.cal-span.org/cgi-bin/archive.php?owner=CARB&date=2010-02-26>).

The controversy centers around the October 24, 2008 California Air Resources Board (CARB) Staff Report "Methodology for Estimating Premature Deaths Associated with Long-Term Exposures to Fine Airborne Particulate Matter in California" (http://www.arb.ca.gov/research/health/pm-mort/pm-mort_final.pdf). This report was used as the primary public health justification for the December 12, 2008 approval by CARB members of extremely expensive "STATEWIDE TRUCK AND BUS REGULATIONS" (<http://www.arb.ca.gov/regact/2008/truckbus08/truckbus08.htm>).

On December 10, 2008 I submitted public comments to CARB questioning the scientific basis for these regulations (http://www.arb.ca.gov/lists/truckbus08/897-carb_enstrom_comments_on_statewide_truck_regulations_121008.pdf). In addition, on July 11, 2008 other prominent scientists and I submitted additional criticisms of this relationship (http://www.arb.ca.gov/research/health/pm-mort/pm-mort_supp.pdf). Now there is epidemiologic evidence from eight different sources that there is no current relationship between PM2.5 and "premature deaths" in California and/or that there is geographic variation in PM2.5 mortality risk across the United States. This evidence is summarized below.

- 1) Figure 21 “Fine Particles and Mortality Risk” on page 197 of the 2000 HEI Reanalysis Report by Krewski et al. (Krewski 2000) shows “medium mortality” in California: “0.711<relative risk of mortality<0.919”. This finding is based the HEI reanalysis of 1982-1989 deaths in the ACS 1982 Cancer Prevention Study (CPS II) cohort. Figure 21 has been discussed in my CARB public comments cited above and in my June 1, 2006 *Inhalation Toxicology* response (<http://www.scientificintegrityinstitute.org/IT060106.pdf>).
- 2) Slide 46 in the July 23, 2001 EPA Clear Air Scientific Advisory Committee (CASAC) presentation by Dr. Lester D. Grant shows no relationship between PM_{2.5} and deaths in the “West” based on the 2000 HEI Reanalysis (ACS CPS II cohort). Details are given on pages S-10 and S-11 of the July 11, 2008 public comments by Jon M. Heuss (<http://www.scientificintegrityinstitute.org/Heuss071108.pdf>) and in the full EPA CASAC presentation by Grant (<http://www.scientificintegrityinstitute.org/Grant072301.pdf>).
- 3) My December 15, 2005 *Inhalation Toxicology* paper, “Fine Particulate Air Pollution and Total Mortality Among Elderly Californians, 1973-2002,” showed no relationship between PM_{2.5} and deaths in 11 California counties in the California Cancer Prevention Study (CA CPS I) cohort during 1983-2002 (<http://www.scientificintegrityinstitute.org/IT121505.pdf>).
- 4) The December 1, 2008 *Environmental Health Perspectives* paper by Drs. Scott L. Zeger, Francesca Dominici, Aidan McDermott, and Jonathan M. Samet, “Mortality in the Medicare Population and Chronic Exposure to Fine Particulate Air Pollution in Urban Centers (2000-2005)” found “no evidence of a positive association between ZIP code-level PM_{2.5} and mortality rates for the 640 urban ZIP codes in the western region [California, Oregon, and Washington]. This lack of association is largely because the Los Angeles basin counties (California) have higher PM levels than other West Coast urban centers, but not higher adjusted mortality rates.” (<http://www.ehponline.org/members/2008/11449/11449.pdf>).
- 5) My unpublished February 11, 2009 letter regarding the January 22, 2009 *New England Journal of Medicine* paper “Fine-Particulate Air Pollution and Life Expectancy in the United States” by Drs. C Arden Pope III, Majid Ezzati, and Douglas W. Dockery showed there was no relationship between reduction in PM_{2.5} concentrations during 1979-2001 and increase in life expectancy during 1980-1999 in 11 California counties with PM_{2.5} data or in the four California cities used in the *NEJM* paper itself (http://www.arb.ca.gov/lists/gmove09/1-carb_enstrom_comments_re_pm2.5_and_life_expectancy_052709.pdf) Further details by Stan Young of NISS presented at February 20, 2010 AAAS Symposium and summarized in February 26, 2010 CARB Symposium.
- 6) Table 33 in the 2009 HEI Research Report No. 140 by Krewski et al. shows that there has been a sharp decline in the nationwide relative risk (RR) relating PM_{2.5} to mortality based on 1979-1983 PM_{2.5} data and 1982-2000 deaths in the ACS CPS II cohort. The RR = 1.048 (1.022-1.076) during 1982-1989, 1.021 (1.002-1.041) during 1990-1998, and 1.014 (0.980-1.049) during 1999-2000 (<http://www.arb.ca.gov/research/health/pm-mort/enstrom.pdf>). Based on this recent HEI evidence, there may be no current relationship between PM_{2.5} and mortality in the US as a whole.

7) The November 1, 2009 *Environmental Health Perspectives* paper by Drs. Robin C. Puett, Jaime E. Hart, Jeff D Yanosky, Christopher Paciorek, Joel Schwartz, Helen Suh, Frank E Speizer, and Francine Laden “Chronic Fine and Coarse Particulate Exposure, Mortality, and Coronary Heart Disease in the Nurses’ Health Study” ([doi/10.1289/ehp.0900572](https://doi.org/10.1289/ehp.0900572)). This paper found a positive relationship between PM_{2.5} and mortality in the women from the Nurses’ Health Study living in metropolitan areas of the northeastern and midwestern United States. However, the paper suggested that the relationship may have been different in other parts of the United States, such as, California.

8) The February 26, 2010 CARB Symposium on “Estimating Premature Deaths from Long-term Exposures to PM_{2.5}” included a PPT presentation by Dr. Michael Jerrett “California-specific Studies on the PM_{2.5} Mortality Association” (<http://www.arb.ca.gov/research/health/pm-mort/jerrett.pdf>). Jerrett slides 12 and 26 present relative risk (RR) results for the CA CPS II cohort showing RR ~ 1.00 (0.97-1.03) for all causes of death during 1982-2000. The Jerrett result is in exact agreement with the Enstrom 2005 result for the CA CPS I cohort RR = 1.00 (0.98-1.02) for all causes of death during 1983-2002. Based on the CA CPS I and CA CPS II results, by far the two largest California-specific studies, the number of “premature deaths” associated with PM_{2.5} exposure is zero (http://www.arb.ca.gov/lists/offroad09/25-carb_enstrom_comments_on_pm2.5_mortality_in_ca_042110.pdf).

The above findings provide substantial evidence that there is both geographic and temporal variation in PM_{2.5} mortality risk in the United States, including no current relationship in California and declining risk nationally. In addition, there is recent evidence of no relationship between ozone and mortality in California (Jerrett 2009 and Smith 2009), with a mortality risk pattern for ozone in the US that appears to follow the same pattern seen for PM_{2.5} (Krewski 2000). Thus, it is very important to analyze the current national relationship between criteria pollutants and mortality in a detailed and transparent way using a large and relevant data base that provides new results that can be independently reproduced. Although the focus must be on PM_{2.5} and ozone, it is important to assess another criteria pollutants: PM₁₀, carbon monoxide, sulfur dioxide, and nitrogen dioxide. These analyses must address the concerns raised in recent reviews regarding PM_{2.5} (Moolgavkar, 2005) and ozone (McClellan, 2009). These analyses are quite timely given the currently ongoing assessment of criteria pollutants by the US Environmental Protection Agency (US EPA 2009).

PROJECT PLAN

The proposed new research is a detailed analysis of the relationship between criteria pollutants and mortality in the NIH-AARP Diet and Health Study. This constitutes one of the largest analyses ever conducted in the United States. The NIH-AARP Diet and Health Study was developed at the National Institutes of Health (NIH) to examine the relationship between diet and health (<http://dietandhealth.cancer.gov/>). During 1995-1996, 3.5 million dietary questionnaires were mailed to AARP members, aged 50-71 years, who resided in eight states, including California. A total of 566,407 individuals (339,671 males and 226,736 females) returned the

questionnaire, and a total of 334,910 of these completed a 1996-1997 risk-factor questionnaire (Schatzkin 2001). The NIH-AARP cohort has been followed for mortality during 1995-2005, with about 50,000 deaths identified through 2005. Additional follow-up has been conducted, including a 2004-2006 follow-up questionnaire (George 2009). This cohort has not been used for air pollution epidemiology, but individual lifestyle characteristics, including county of residence, are available on all subjects. This large cohort can provide important new evidence on criteria pollutants and mortality in California and the United States. Demographic characteristics of the NIH-AARP cohort include: 1) Age at entry: 50-54 = 73,790; 55-59 = 125,694; 60-64 = 159,071; 65-69 = 186,512; 70+ = 21,340; 2) State of residence: CA = 175,090; FL = 122,013; GA = 15,994; LA = 21,720; MI = 28,574; NC = 46,950; NJ = 71,068; PA = 84,998. Of the approximately 50,000 total deaths that occurred during 1995-2005, there were 4,700 from lung cancer, 9,600 from all other cancers, 19,600 from all circulatory diseases (15,900 from diseases of the heart and 2,500 from cerebrovascular diseases) and 3,500 from chronic obstructive pulmonary disease (<http://dietandhealth.cancer.gov/resource/>).

SPECIFIC AIMS

- 1) Obtain required permission from NIH to use NIH-AARP Health and Diet cohort database, with state and county of residence identification, for this research project. Initial query indicates use of this cohort for air pollution epidemiology research is acceptable to NIH.
- 2) Assemble available California and national county-level data since 1995 on criteria pollutants (PM_{2.5}, ozone, PM₁₀, carbon monoxide, sulfur dioxide, and nitrogen dioxide) from CARB and US EPA databases and merge it into the NIH-AARP database based on county of residence of subjects. Prepare SAS database for detailed analysis of NIH-AARP cohort.
- 3) Conduct analyses using Cox proportional hazards regression (PHREG) model that makes full use of the NIH-AARP cohort database and the existing 1995-2004 mortality follow-up data. Run this model using SAS Proc PHREG (SAS 2004) to provide relative risks for death for PM_{2.5}, ozone, and the other criteria pollutants. These analyses will be similar to those previously done (Enstrom 2005, Enstrom 2006, Jerrett 2009, and Krewski 2009). The analyses will include the confounding variables used by Enstrom 2005 and Krewski 2009, such as: age, sex, race, marital status, education, health status, body mass index, smoking history, alcohol consumption, diet, exercise, occupational exposure, and urbanization. The analyses will initially focus on deaths from all causes and will be conducted for residents in each of the eight states in the cohort, including California. Later analyses will be conducted for major causes of death, particularly cancer, respiratory diseases, and circulatory diseases. Additional details of the analysis plan need to be completed.
- 4) Make a detailed comparison of the relationships found in the NIH-AARP cohort with published results obtained in the CA CPS I cohort, the CPS II cohort, and other major US cohorts, as recently summarized by the US EPA Integrated Science Assessment (US EPA 2009).
- 5) Prepare and submit for publication a detailed manuscript(s) based on the results obtained from the above specific aims.

SIGNIFICANCE

Because of the importance of the health effects of criteria pollutants, it is valuable to analyze and reassess their relationship to mortality in a rigorous, detailed, and transparent way using a large and accessible data base, such as the NIH-AARP cohort. In particular, it is important to obtain recent, detailed, and transparent results specific to California and the United States for the relationship to mortality of PM_{2.5} and the other criteria pollutants: ozone, PM₁₀, carbon monoxide, sulfur dioxide, and nitrogen dioxide. These analyses will address the concerns raised in recent reviews regarding PM_{2.5} (Moolgavkar 2005) and ozone (McClellan 2009). These analyses are quite timely given the currently ongoing assessment of criteria pollutants by the US Environmental Protection Agency (US EPA 2009). This research has the potential to clarify and improve the regulation of criteria pollutants in California and the United States.

BUDGET

The budget is estimated to be approximately \$100,000 in total direct costs per year for three years, depending upon final proposal. This budget will be used to provide an appropriate level of funding for myself, a statistician, data base manager, a research assistant. Also, a small portion of the funding will be used to obtain expert assistance from potential scientific consultants, such as, Jan de Leeuw, Ph.D., UCLA; Frederick W. Lipfert, Ph.D., New York; Suresh Moolgavkar, M.D., Ph.D., Exponent; Richard L. Smith, Ph.D., University of North Carolina; and S. Stanley Young, Ph.D., National Institute of Statistical Sciences. These consultants still need to approve their participation in this project.

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July 6, 2010

James E. Enstrom, Ph.D., M.P.H.
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Dear Dr. Enstrom,

The HEI Research Committee recently reviewed your Preliminary Application entitled *Criteria Pollutants and Mortality in the NIH-AARP Diet and Health Study Cohort*, submitted under HEI RFPA 09-5 *Health Effects of Air Pollution*. I am pleased to inform you that the Committee decided to request a full application.

I have attached a copy of our Fall 2009 RFA Booklet which contains instructions on submitting your Full Application to HEI under RFPA 09-5. Information on full applications may be found on pages 15 and 16, with the Full Application instructions appearing on pages 23-26. Additionally, forms F1 through F10 are available on our website: <http://www.healtheffects.org/RFA/Forms/RFAforms.htm>

The Committee discussed several key issues which you should address in your full application. Specifically, in the section "Anticipated Results and Significance", under the Project Plan section, the Committee would expect to see a discussion of the literature on air pollution and mortality in the US and in California and how your proposed study will advance our understanding. As the NIH-AARP is a new cohort to the air pollution community, we will also need to see detailed descriptive statistics on the cohort population, as well as full details of availability of air quality data and other important design details, as would be the case with any such proposal. The Committee will also expect a letter granting access to data from the administrators of the NIH-AARP cohort and letters of commitment from any collaborators.

Please submit your application no later than September 3, 2010 if you hope to have it considered at the October 2010 Research Committee Meeting, as we send all such proposals out for external peer review prior to the Committee's own review. If you have any questions, feel

free to contact me via e-mail at kadams@healtheffects.org, or by phone at (617) 488-2330.

Regards,

A handwritten signature in black ink that reads "Kate Adams". The signature is written in a cursive, flowing style.

Kate Adams, Sc.D
HEI Staff Scientist

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July 5, 2011

James E. Enstrom, Ph.D., M.P.H.
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Sent by email to: jenstrom@ucla.edu

Dear Dr. Enstrom,

HEI recently received and reviewed your Full Application entitled *Criteria Pollutants and Mortality in the NIH-AARP Diet and Health Study Cohort*, submitted under HEI RFPA 09-5 *Health Effects of Air Pollution*. The HEI Research Committee discussed your full application at their June 24, 2011 meeting. The Research Committee was also provided with the additional information you sent us on June 20. I regret to inform you that the Research Committee has decided not to fund this study.

While the Committee noted that your choice of cohort was novel and interesting and that you do raise some important scientific questions regarding regional differences in long-term health effects of airborne particulate matter, they concluded that the study, as described relatively briefly in your application, would not address these issues adequately. The proposal provided insufficient scientific background for the study. The Committee was concerned that you do not yet have access to the cohort data (as requested in our letter of July 6, 2010), and that your application lacked detailed data handling and analysis plans. The Committee was also not clear which criteria pollutants you planned to link to which outcomes. Furthermore, the Committee felt that the proposal lacked information on your plan for implementing the exposure assignment methods necessary for this type of cumulative incidence study, such as the type and quality of air pollution data to be used, the time periods for defining the exposure, and the process by which exposures will be assigned.

I have attached the reviews of your application. These should help you understand the Committee's decision and we hope provide constructive criticism for your future work. If you have any questions, please feel free to contact me.

Regards,

A handwritten signature in black ink that reads "Kate Adams". The signature is written in a cursive, flowing style.

Kate Adams, Sc.D.,
HEI Staff Scientist

Cc: Dan Greenbaum, President, HEI
Rashid Shaikh, Director of Science, HEI

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Introduction:

The applicant plans to study an approximate 10%, non-random sample of the NIH-AARP Diet and Health Study conducted by NIH to provide additional data on the association, or lack thereof, between exposure to PM_{2.5} and pre-mature mortality.

Critique:

This application is so incomplete that an in-depth evaluation is not possible. The specific points of major concern are:

1. It is the applicants contention that the existing data do not support the mortality associations with PM_{2.5}. However, the application presents no coherent set of data to support the content. Instead, there are numerous website listing which reference the applicants testimony to various groups and some monographs. I assume that I was supposed to go to these and develop for myself the coherent argument that he needs to justify this application. I did not see that as my task. The applicant should have provided a coherent summary of his previous testimony and writing along with data to support the position that would then serve as the rationale for what he wants to do. Absent such a summary, I see no justification to fund it.
2. There is no information on the type and quality of air pollution data to be used and how exposures will be assigned. Since it appears that this is a cumulative incidence type of study, I would like to know how exposure periods will be defined and with what data.
3. The data analysis plan is so incomplete that, even if the applicant met the first criterion, I still would have no idea of how he plans to test his hypothesis. Moreover, PHREG in SAS does not allow for the complex spatio-temporal confounding that has to be addressed in a study such as this. Without know what endpoints will be considered, what other variables will be important, I have no idea if this study would have the power to provide any new insights. I strongly doubt that it would.
4. The sample of subjects is a non-random, ~10% sample, which undoubtedly has all kinds of selection bias relative to the target population. The possibility is never even considered as to what influence this would have on any results reported, all other things being done properly.

Some minor issues:

1. The discussion of resources is not adequate to determine if the investigator can handle the large datasets that will be needed. There is not data security plan and no QA/QC plan.

Recommendation: REJECT.

REVIEW #2

Enstrom application

In the face of clear and well-focussed criticism from the two reviewers, I am not going to attempt to make the case that this should be funded, but I also hope that it won't be dismissed out of hand, since I actually do think that Dr. Enstrom is on to something.

The controversy that Dr. Enstrom refers to repeatedly in his introduction amounts to the following: virtually all the air pollution studies for the US (NMMAPS for PM₁₀, NMMAPS for ozone, MCAPS for PM_{2.5} and ACS-II for PM_{2.5}, to name the four main ones) show a strong east-west gradient in the effect, the air pollution effect being less strong in the western part of the country. Many people have acknowledged this effect but there is no universal agreement about the explanation for it. Yet despite this apparent disparity, California has pursued the strongest air pollution regulations in the country. The question that Dr. Enstrom and others of like mind are asking is why this is justified. I would not pretend to know the answer myself, but I do think he is raising a real issue that deserves serious consideration.

Unfortunately, the proposal lacks a clear statement of the scientific issues involved – instead Dr. Enstrom has cited a series of public comments to CARB, which may or may not contain adequate scientific documentation (I haven't checked), but in any case, citations to the refereed literature or preliminary analyses of data should have been given. The spatial variability of the ozone-mortality coefficient from NMMAPS has been documented by Bell and Dominici (2008) and by Smith et al (2009) – Enstrom cites the latter paper but does not explain how it is relevant to his proposed study. In the case of MCAPS, the raw data are not publicly available but Dominici et al. have published the county-specific coefficients and standard errors, which would allow a spatial analysis similar to that done for ozone in the two papers just cited. For ACS-II, which is a cohort study similar to what Dr. Enstrom proposes here, it seems that nobody has done a comprehensive analysis of whether the PM_{2.5} effect is spatially variable, but there is indirect evidence in the HEI reanalysis report (Krewski et al, 2000) and there have been some independent calculations by Dr. Jerrett which are reported in the proposal. As a side comment, I am a little surprised that Dr. Enstrom didn't pursue his efforts to gain access to the ACS-II dataset, but perhaps he felt that he had more important battles to fight. In any case, the potential existence of a new dataset that could allow independent examination of the issues is an interesting development and indeed what prompted the HEI Research Committee to invite this full application.

What we would need to see now is a comprehensive data analysis plan. I don't think basic proportional hazards regression is sufficient to answer the questions of interest – at least we would need the random effects extension that has been developed by Krewski and Burnett, but preferably, a full spatial analysis. The problem is that Dr. Enstrom doesn't have a spatial statistical expert on his team. The role of the UCLA statistical consultant is not specified – there isn't even a CV. Moreover, there is no information at all about the work to be done by the two external consultants, Drs. Lipfert and Young, but I don't believe either of them is an expert in spatial statistics.

In summary, this proposal really takes us no further than the pre-proposal. Dr. Enstrom has a valid idea for a research project. He does not have a viable plan for pursuing it. Unless he can come up with such a plan, HEI cannot consider this proposal further.

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REVIEW #3

HEI Grant Review for J E. Enstrom

Budget Justification:

Minimal justification as to why the proposal requires 50% of his time. One major effort was listed as obtaining cooperation from NCI and NIH for use of the database. He was asked to obtain this cooperation at time of grant submission which he has failed to do. It would be inappropriate to provide funding without confirmed access to the database. Further, he lists the need for two senior consultants but states that details regarding their contributions "must be worked out". If he doesn't know how they will be used in the project it is inappropriate to request their assistance.

Other Support:

Has no active support and refuses to report Pending Support unless he is funded. Again this is an inappropriate response to usual needs for an agency to assess overlap.

Scholarship:

Publication record extremely limited and shows lack of research scholarship. Based on this limited record and lack of "back-up support" from well published investigators, I do not think the investigator has shown sufficient scientific progress to be awarded a grant as a PI.

Major issue:

This grant has not been submitted through a responsible University Office of Sponsored program. Because of this issue, technically the research proposal should be returned without review.

Hypothesis and Specific Aims:

The independent variables are PM2.5 and "other criteria pollutants". The investigator needs to provide specificity as to what specific criteria pollutants he is planning to use in the analysis. It appears from page six however that he plans to assess six but no description is provided as to time period, access to measurement data, sampling location, analysis of complex mixtures etc.

The outcome variable is "total mortality (premature death)". There is no operational definition provided for how this outcome will be measured or defined. What ICD codes will be included? Will premature death be defined by age and gender specific categories?

There are 4 aims listed on page 3 (5 aims on page4). The first aim is to obtain NIH approval for use of the database. This aim should have been completed prior to the grant submission. He has had about ten months to obtain approval since the letter sent from HEI on July 2010. This letter specifically requested that he obtained permission for use of the database prior to resubmission. He failed to follow directions and assure the funding agency that he had permission to use the database. Aim 2 and 3 is reliant on aim 1 i.e. access to the database. Since assurance was not provided for aim 1 then currently there is no

confidence aim 2 or 3 can be achieved. Aim 4 is not an aim. The role of an aim is to undertake specific activities that will test the hypothesis. Aim 4 states that a manuscript will be submitted. This is unfortunately not an aim.

Related Previous Studies:

Dr. Enstrom fails to describe his previous research but just cites only one paper, a response to a critique of his paper and numerous public comments.

Methods:

There is no description on how the investigator will assemble the CA and national county level data on criteria pollutants. There is no description on the extensive process of data management and organization this will require. How will the data be “prepared” and linked with mortality data. How will mixtures be considered? The investigator states that “additional details of the analysis plan need to be completed”. This is an understatement. The investigator has provided no details and no plans. Under methods aim 4 there is to be a detailed comparisons of cohorts. He mentions CA CPS I and II “and other major cohorts”. This is the first time these cohorts were discussed in the context of the AARP cohort. There are no research methods or approach provided. The lack of details for a complex data management and analysis task that will be necessary provides grave concerns that the investigator understands what is being proposed.

On a positive note, a brief description of the NIH-AARP was provided. The investigator stated that individual life style characteristics are available but fails to state whether or not some of the most important factors are included such as smoking/pack-years history, alcohol use, all residences where the individual has reside throughout the study, exercise patterns, and weight change over time. Giving us a web site to access does not provide any assurance that the investigator knows what should be considered or how the data should be related to interactions between exposure, external lifestyle factors and mortality events.

REVIEW #4

HEI: Enstrom Proposal

The proposal is straightforward: the aim is to examine the relationship between exposure to criteria pollutants and cause-specific mortality in the NIH-AARP cohort of middle-aged and older US residents (50-71 years) in 8 states, including California. The study is concisely and clearly written. The PI and co-investigators are well qualified to lead the proposed research and the environment well-suited to conduct the analyses of these existing data.

The results will update those of many major epidemiologic studies. No new hypotheses, or novel methods, are proposed. It would be interesting to assess whether the addition of GIS methods for improving individual level exposure assessment could be incorporated and thus make the proposal more exciting and innovative. The focus on criteria pollutants only will also limit some interpretation, although it is fully understandable why these are chosen.

The budget is reasonable as requested. The likelihood of results is high, though less likely to provide novel insights into PM related mortality.

Although diminished some by the above weaknesses, enthusiasm for the proposal is high.

Review #5

Review of NIH-AARP diet and health study cohort
HEI
Dr. James Enstrom

Scientific merit

The proposed work makes use of a large existing cohort, the NIH-AARP Diet and Health Study, of over 500,000 study subjects, with risk-factor questionnaires on over 300,000. The cohort has not previously been used in air pollution studies. The primary goal of this work is to use the cohort to examine the impact of criteria pollutants on mortality, cardiopulmonary disease, and lung cancer. Unfortunately, the proposal has severe limitations regarding the description of the rationale for the study, the methods, and the role of the various members of the research team. This proposal should not be funded.

The key strength of the proposed research is the use of a cohort that is a unique, large, high-quality dataset that has not previously been investigated for air pollution epidemiology. The benefits of this cohort, other than its novelty and sample size, are not explored in the proposal. No information is given on what will be new about this work as compared to the wealth of previous studies on criteria pollutants and health. As examples, the proposal correctly notes that individual lifestyle characteristics are available, but does not specify how these would be used in analysis. It also does not specify how exposure will be characterized for the cohort and whether location through time is known for this cohort. As written, the proposal implies that county of residence is available (page 5), but does not specify whether the location for each study subject was obtained only at one time point, or whether location of residence is known throughout time as study subjects moved. Residential mobility is important in this research as the key objective requires assessment of air pollution exposure. The potential limitations and structure of the cohort data are not discussed.

The proposal does not provide the necessary rationale for a research proposal. Instead the introduction states that a "controversy" exists for PM_{2.5} and mortality research, but does not describe this controversy or provide adequate links to peer-reviewed studies on this topic. The proposal states that there exists epidemiological evidence from 8 sources that there is no relationship between PM_{2.5} and premature mortality in California and/or that there is geographic variation in PM_{2.5}, but does not provide the references. The text muddles these two points: the lack of an association, and geographic heterogeneity in the association. That geographic variation exists is well understood. The proposal provides no information on how this research would help address that issue or explain why such variation exists. It also does not provide information on how the proposed project would be able to answer any scientific question in a better way than previous research. The scientific evidence that a relationship does exist is omitted entirely from the discussion. The proposal provides links to several public comments made by the PI, but text citing current literature is needed and would be more compelling. As yet another example, the author notes "I have now determined that there was sub geographic variation in PM_{2.5} risk across the United States, particularly in California, that was not properly revealed in [a report]. I am currently preparing this evidence for publication." This type of unsubstantiated statement is not acceptable. The link for this statement is not appropriate scientific evidence, but a newspaper clipping. The proposal should either provide a reference for published information, or present the preliminary findings briefly in the proposal. Given the numerous studies and wealth of information on PM_{2.5} and health, and the important remaining scientific questions on this topic, the authors should be able to provide a compelling argument for why a given research project is needed, but that was not done in this proposal. Further, as numerous large scale studies of mortality and PM have been conducted, the proposal must explain why this particular analysis, which uses standard methods, would provide any new evidence.

The methods description is highly inadequate. The authors refer to a previous study and note that methods are similar. They do not describe the methods in any detail. The confounders are not specified, although some example confounders are listed. The statistical methods are described only in very vague terms.

The related studies section does not provide the needed information. It does list two publications, work as a consultant making public comments, and the PI's career as an epidemiologist. While this information is relevant, a better proposal would describe in text how the proposed work builds on and advances the previously published work, not links to previous work. However, it is anticipated that the author could perform the epidemiological analysis, given his experience.

The specific pollutants that will be investigated are not specified. The proposal uses the language "criteria pollutants." Does this mean that all criteria pollutants will be investigated, and no other pollutants? Particulate matter chemical components would be of interest. The choice of exposure appears to have been given only brief thought.

The need to assemble national data on criteria pollutants is unclear given that the study area is a fraction of the U.S.

The proposal states that the PI will "obtain required permission" for cooperation of NCI and NIH regarding use of the dataset. It would be helpful to know how likely this cooperation will be, with supporting letters or other documentation from NCI and NIH. Without this cooperation, the project cannot go forward. However, the proposal does note that an initial inquiry to NIH indicates that the project will be acceptable.

On a minor point, the language that the results will be published, which is mentioned repeatedly in the proposal, is understood for scientific research. In future proposals, the authors may wish to omit this language in order to provide more useful information within length restrictions.

Personnel and facilities

The project is to be conducted by Dr. Enstrom and Dr. Tang, a statistician, with consultants of Dr. Lipfert and Dr. Young. The PI (Enstrom) has extensive experience in epidemiological research. His experience includes work in cancer epidemiology, analysis of large cohorts, and study of air pollution and human health.

The responsibilities of Dr. Enstrom and Dr. Tang are described. The responsibilities of the consultants (Drs. Lipfert and Young) are not specified at all. The proposal notes "Details regarding their specific contributions must be worked out." The roles of each researcher should be determined before a proposal is submitted.

Adequacy of research facilities

The description of resources is a very brief and a bit vague (computers with SAS and other software); however, it is anticipated that resources for the project are adequate and that research facilities will not be a problem. It would be helpful to have more information on the computing system as a large amount of data would need to be stored and analyzed.

Proposed cost

The budget includes \$30,000 for consulting fees, although the proposal notes that the roles of the consultants have not been determined. As the consultants' contribution is completely unknown, the budget seems arbitrary.

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