The correspondence section is a public forum and, as such, is not peer-reviewed. EHP is not responsible for the accuracy, currency, or reliability of personal opinion expressed herein; it is the sole responsibility of the authors. EHP neither endorses nor disputes their published commentary.

The Association between Air Pollution and Subclinical Atherosclerosis

http://dx.doi.org/10.1289/ehp.1307403

Rivera et al. (2013) investigated the association between air pollution and subclinical atherosclerosis by using carotid intima media thickness (IMT), ankle–brachial index (ABI), and several indicators of air pollution. As a main outcome, air pollution was positively associated with an ABI of > 1.3, and also with changes in IMT. In contrast, they observed no significant association between air pollution and an ABI of < 0.9.

I have some concerns about their study (Rivera et al. 2013). First, the study included a small number of subjects with ABIs < 0.9 and > 1.3 (56 and 116, respectively). The authors used multinomial logistic regression analysis; for the full-adjustment model, > 16 air pollution variables were used. There is a limitation in the number of independent variables appropriate for multiple logistic regression analysis (Novikov et al. 2010; Peduzzi et al. 1996), and enough events should be included to maintain statistical power for multivariate analysis. According to the criteria that at least 10 events per variable are required to keep stable estimates (Peduzzi et al. 1996), Rivera et al. (2013) needed ≥ 170 events with an ABI < 0.9 or > 1.3 for their analysis.

Second, Rivera et al. (2013) used systolic and diastolic blood pressure to adjust for the relationship between air pollution and indicators of atherosclerosis. But multicollinearity among independent variables should have been considered in the analysis (York 2012).

Finally, Rivera et al. (2013) could not clarify the lack of association between ABI < 0.9 and indicators of air pollution. An ABI of 0.9–1.0 is also associated with cardiovascular risk (Ono et al. 2003). Therefore, the association between air pollution and subclinical atherosclerosis should be evaluated by selecting a higher cut-off value of ABI, such as 1.0. This procedure will increase the number of events for multivariate analysis.

Other researchers have reported a significant association between air pollution and IMT (Bauer et al. 2010; Diez Roux et al. 2008). Lenters et al. (2010) also examined the association between air pollutants and indicators of vascular damage but observed no association between air pollution and IMT. Lenters et al. (2010) used nitrogen dioxide (NO_2), black smoke, particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$), and sulfur dioxide (SO_2) as indicators of air pollution, and they used pulse wave velocity and augmentation index in addition to IMT as indicators of vascular damage. Traffic intensity and proximity of residence to roads were also used as indicators of air pollution. Lenters et al. found significant associations only between NO_2 and pulse wave velocity and augmentation index and between SO_2 and pulse wave velocity. Because contradictory results for this association have been reported, further longitudinal studies are needed to assess this association.

The author declares he has no actual or potential competing financial interests.

Tomoyuki Kawada
Department of Hygiene and Public Health, Nippon Medical School, Tokyo, Japan
E-mail: kawada@nms.ac.jp

REFERENCES

Bauer M, Moebus S, Möhlenkamp S, Dragano N, Nonnemacher M, Fuchsluger M, et al. 2010. Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR (Heinz Nixdorf Recall) study. J Am Coll Cardiol 56:1803–1808.

Diez Roux AV, Auchincloss AH, Franklin TG, Raghunathan T, Barr RG, Kaufman J, et al. 2008. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 167:667–675.

Lenters V, Uiterwaal CS, Beelen R, Bots ML, Fischer P, Brunekreef B, et al. 2010. Long-term exposure to air pollution and vascular damage in young adults. Epidemiology 21:512–520.

Novikov I, Fund N, Freedman LS. 2010. A modified approach to estimating sample size for simple logistic regression with one continuous covariate. Stat Med 29:97–107.

Ono K, Tsuchida A, Kawai H, Matsuo H, Wakamatsu R, Maezawa A, et al. 2003. Ankle-brachial blood pressure index predicts all-cause and cardiovascular mortality in hemodialysis patients. J Am Soc Nephrol 14:1591–1598.

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. 1996. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49:1373–1379.

Rivera M, Basagaña X, Aguilera I, Foraster M, Agis D, de Groot E, et al. 2013. Association between long-term exposure to traffic-related air pollution and subclinical atherosclerosis: the REGICOR study. Environ Health Perspect 121:223–230; doi:10.1289/ ehp.1205146.

York R. 2012. Residualization is not the answer: rethinking how to address multicollinearity. Soc Sci Res 41:1379–1386.

The Association between Air Pollution and Subclinical Atherosclerosis: Rivera et al. Respond

http://dx.doi.org/10.1289/ehp.1307403R

We appreciate Kawada's interest in our study (Rivera et al. 2013). His letter focuses on some limitations of our study, which were already discussed in our article.

Kawada notes that the small number of participants with low ankle–brachial index (ABI) provided low power to detect an association; this is a limitation that we acknowledged in our article (Rivera et al. 2013). Kawada also points out that the number of covariates in the model exceeds the common rule of thumb of having at least 10 events per variable. We recognize that, with a small number of cases, one is inevitably faced with the trade-off between including all relevant confounders and keeping the number of covariates to a minimum. However, in our article we provided results from a minimally adjusted model including only five confounders and an interaction term. In this model, the number of events per variable was > 10, and the results were not significantly different from those of the fully adjusted model. Kawada suggests selecting a "higher cut-off value of ABI, such as 1.0" for low ABI given that "an ABI of 0.9–1.0 is also associated with cardiovascular risk (Ono et al. 2003)." The findings of Ono et al. were for patients on hemodialysis due to end-stage renal disease and thus cannot be extrapolated to healthy population samples such as the one considered in our study (i.e., with no history or current signs of cardiovascular disease). We selected a cut-off value of 0.9 for low ABI because of the strong evidence of increased risks of incident cardiovascular disease, morbidity, and mortality in individuals with ABI < 0.9 (Allison et al. 2008; Ankle Brachial Index Collaboration 2008; Lee et al. 2004; McDermott et al. 2005). A cut-off value of 0.9 is also more specific (Lee et al. 2004) and much more common in the literature, which allows comparison with other studies.

Kawada's second argument involves the consideration of multicollinearity in the fully adjusted model (model 2), in which systolic and diastolic blood pressure were included. Systolic and diastolic blood pressure were only moderately correlated (correlation coefficient, 0.62), and according to the variance inflation factor (VIF), there were no multicollinearity problems (VIF was 2.45 for systolic blood pressure and 1.98 for diastolic blood pressure).

Kawada points at "contradictory results" in the association between air pollution and carotid intima media thickness (IMT), mainly based on the null and weak associations found by Lenters et al. (2010) between several markers of air pollution [nitrogen dioxide, sulfur dioxide, $PM_{2.5}$ (particulate matter ≤ 2.5 μm in aerodynamic diameter), black smoke, and traffic intensity] and three indicators of vascular damage (IMT, pulse wave velocity, and augmentation index). We consider, however, that these do not constitute results contradictory to the positive

association between air pollution and sub-clinical markers of atherosclerosis found in the six studies thoroughly discussed in our article (Bauer et al. 2010; Diez Roux et al. 2008; Hoffmann et al. 2007, 2009; Künzli et al. 2005, 2010) as well as by Wilker et al. (2013). The study by Lenters et al. (2010) involved a cohort of young adults, on aver-age 28 years of age. Exposure to air pollution was estimated at the current address only. As the authors acknowledged, the young age of participants and the exposure mis-classification, which resulted from exposure estimated at the current address only, are likely explanations for their mixed results.

Finally, we agree with Kawada's closing remark on the need for longitudinal studies, as we concluded in our article.

The authors declare they have no actual or potential competing financial interests.

Marcela Rivera,[1] Xavier Basagaña,[2,3] Inmaculada Aguilera,[2,3,4] Maria Foraster,[2,3,4,5] David Agis,[2,3,4] Eric de Groot,[6] Laura Perez,[7,8] Michelle A. Mendez,[9] Laura Bouso,[2,3,4] Jaume Targa,[10] Rafael Ramos,[11,12] Joan Sala,[13] Jaume Marrugat,[14] Roberto Elosua,[4,14] and Nino Künzli[7,8]

[1]University of Montreal Hospital Research Centre (CRCHUM), Montreal, Quebec, Canada; [2]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; [3]Hospital del Mar Research Institute (IMIM), Barcelona, Spain; [4]CIBER Epidemiología y Salud Pública (CIBERESP), Spain; [5]Universitat Pompeu Fabra, Barcelona, Spain; [6]Department of Vascular Medicine, Academic Medical Centre, Amsterdam, the Netherlands; [7]Swiss Tropical and Public Health Institute, Basel, Switzerland; [8]University of Basel, Basel, Switzerland; [9]University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [10]4sfera Innova, Girona, Spain; [11]Research Unit, Family Medicine, Jordi Gol Institute for Primary Care Research (IDIAP Jordi Gol), Catalan Institute of Health, Catalunya, Spain; [12]Department of Medical Sciences, School of Medicine, University of Girona, Girona, Spain; [13]Servicio de Cardiología, Hospital Universitari Josep Trueta, Institut Català de la Salut, Girona, Spain; [14]Grupo de Epidemiología y Genética Cardiovascular, Hospital del Mar Research Institute (IMIM), Barcelona, Spain
E-mail: marcelaepi@gmail.com

REFERENCES

Allison MA, Hiatt WR, Hirsch AT, Coll JR, Criqui MH. 2008. A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life. J Am Coll Cardiol 51:1292–1298.

Ankle Brachial Index Collaboration. 2008. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality. JAMA 300:197–208.

Bauer M, Moebus S, Möhlenkamp S, Dragano N, Nonnemacher M, Fuchsluger M, et al. 2010. Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR (Heinz Nixdorf Recall) study. J Am Coll Cardiol 56:1803–1808.

Diez Roux AV, Auchincloss AH, Franklin TG, Raghunathan T, Barr RG, Kaufman J, et al. 2008. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 167:667–675.

Hoffmann B, Moebus S, Dragano N, Stang A, Möhlenkamp S, Schmermund A, et al. 2009. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. Environ Health Perspect 117:1302–1308; doi:10.1289/ehp.0800362.

Hoffmann B, Moebus S, Möhlenkamp S, Stang A, Lehmann N, Dragano N, et al. 2007. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 116:489–496.

Künzli N, Jerrett M, Garcia-Esteban R, Basagaña X, Beckermann B, Gilliland F, et al. 2010. Ambient air pollution and the progression of atherosclerosis in adults. PLoS ONE 5(2):e9096; doi:10.1371/journal.pone.0009096.

Künzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, et al. 2005. Ambient air pollution and athero-sclerosis in Los Angeles. Environ Health Perspect 113:201–206; doi:10.1289/ehp.7523.

Lee AJ, Price JF, Russell MJ, Smith FB, Van Wijk MCW, Fowkes FGR. 2004. Improved prediction of fatal myo-cardial infarction using the ankle brachial index in addi-tion to conventional risk factors: the Edinburgh Artery Study. Circulation 110:3075–3080.

Lenters V, Uiterwaal CS, Beelen R, Bots ML, Fischer P, Brunekreef B, et al. 2010. Long-term exposure to air pol-lution and vascular damage in young adults. Epidemiology 21:512–520

McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, et al. 2005. Ankle-brachial index and subclinical car-diac and carotid disease: the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 162:33–41.

Ono K, Tsuchida A, Kawai H, Matsuo H, Wakamatsu R, Maezawa A, et al. 2003. Ankle-brachial blood pressure index predicts all-cause and cardiovascular mortality in hemodialysis patients. J Am Soc Nephrol 14:1591–1598.

Rivera M, Basagaña X, Aguilera I, Foraster M, Agis D, de Groot E, et al. 2013. Association between long-term exposure to traffic-related air pollution and subclinical atherosclerosis: the REGICOR study. Environ Health Perspect 121:223–230; doi:10.1289/ ehp.1205146.

Wilker EH, Mittleman MA, Coull BA, Gryparis A, Bots ML, Schwartz J, et al. 2013. Long-term exposure to black car-bon and carotid intima-media thickness: the Normative Aging Study. Environ Health Perspect 121:1061–1067; doi:10.1289/ehp.1104845.