Differences in Heart Rate Variability Associated with Long-Term Exposure to NO₂

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BACKGROUND: Heart rate variability (HRV), a measure of cardiac autonomic tone, has been associated with cardiovascular morbidity and mortality. Short-term studies have shown that subjects exposed to higher traffic-associated air pollutant levels have lower HRV.

OBJECTIVE: Our objective was to investigate the effect of long-term exposure to nitrogen dioxide on HRV in the Swiss cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA).

METHODS: We recorded 24-hr electrocardiograms in randomly selected SAPALDIA participants ≥ 50 years of age. Other examinations included an interview investigating health status and measurements of blood pressure, body height, and weight. Annual exposure to NO₂ at the address of residence was predicted by hybrid models (i.e., a combination of dispersion predictions, land-use, and meteorologic parameters). We estimated the association between NO₂ and HRV in multivariable linear regression models. Complete data for analyses were available for 1,408 subjects.

RESULTS: For women, but not for men, each 10-µg/m³ increment in 1-year averaged NO₂ level was associated with a decrement of 3% (95% CI, –4 to –1) for the standard deviation of all normal-to-normal RR intervals (SDNN), –6% (95% CI, –11 to –1) for nighttime low frequency (LF), and –5% (95% CI, –9 to 0) for nighttime LF/high-frequency (HF) ratio. We saw no significant effect for 24-hr total power (TP), HF, LF, or LF/HF or for nighttime SDNN, TP, or HF. In subjects with self-reported cardiovascular problems, SDNN decreased by 4% (95% CI, –8 to –1) per 10-µg/m³ increase in NO₂.

CONCLUSIONS: There is some evidence that long-term exposure to NO₂ is associated with cardiac autonomic dysfunction in elderly women and in subjects with cardiovascular disease.

KEY WORDS: air pollution, autonomic nervous system, cardiovascular diseases, cohort study, heart rate variability, long-term exposure, nitrogen dioxide, sex. Environ Health Perspect 116:1357–1361 (2008). doi:10.1289/ehp.11377 available via http://dx.doi.org/ [Online 20 June 2008]

Numerous short-term studies and a few longer-term studies have linked higher air pollutant levels with increased daily morbidity and mortality from cardiovascular diseases (Forastiere et al. 2005; Hoffmann et al. 2007; Künzli et al. 2005; Le Terré et al. 2002; Rosenlund et al. 2006). These studies mostly described the effect of particulate matter (PM) on cardiovascular health; thus, information on the effect of other pollutants (i.e., gaseous pollutants) is scarce.

The underlying biologic mechanisms linking short- or long-term exposure to air pollutants with cardiovascular disease is still a subject of research. Several hypotheses have been proposed, including direct effects of pollutants on the cardiovascular system, blood, and lung receptors, and/or indirect effects mediated through pulmonary oxidative stress and inflammatory responses (Brook et al. 2004), potentially also leading to structural changes with lasting damage of the cardiovascular system. Heart rate variability (HRV) is a measure of cardiac autonomic tone and has been described as an intermediate factor between air pollution and cardiovascular morbidity (Dockery 2001; Donaldson et al. 2001; Pope et al. 2004; Utell et al. 2002).

Associations between nitrogen dioxide and HRV have been reported but, to our knowledge, only in short-term studies (Chan et al. 2005; Liao et al. 2004; Wheeler et al. 2006). Long-term exposure to NO₂ might lead to altered HRV through structural changes of the heart. The aim of this study was to test the hypothesis that long-term exposure to traffic-related air pollution, as measured by NO₂ concentrations, is negatively associated with HRV in the population-based Swiss cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA).

Materials and Methods

This study is part of the SAPALDIA cohort study, which was originally designed to assess health effects from long-term exposure to air pollutants in the Swiss adult population. Details of its design and objectives have been reported elsewhere (Ackermann-Liebrich et al. 2005; Felber Dietrich et al. 2006). In brief, a random sample of the Swiss population was recruited from the registries of eight distinct areas. In 1991, after written invitation, a total of 9,651 participants received intensive health examinations and a detailed health interview. In 2001–2003, we were able to reexamine 8,047 of the original participants. We assessed HRV in a random selection (n = 1,846; 955 women, 891 men) of the 4,417 participants ≥ 50 years of age by 24-hr electrocardiograms (ECGs) after an invitation by the fieldworkers at the study center. Exclusion criteria were general or spinal anesthesia within 8 days before the ambulatory ECG recording (n = 5), having had a myocardial infarction within 3 months before the examination (n = 2), and taking digitals (n = 6); no one had an artificial pacemaker.

Exposure to NO₂ in the Swiss cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA). HRV in the Swiss cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA).
Table 1. Characteristics of the study population.

| Characteristic                        | Men (n = 683) | Women (n = 725) |
|---------------------------------------|--------------|-----------------|
| NO₂, 1-year average (µg/m³)           | 22.7 ± 0.36  | 22.7 ± 0.36     |
| NO₂, same day (µg/m³)                 | 25.4 ± 0.82  | 24.5 ± 0.61     |
| PM₁₀, same day (µg/m³)                | 23.9 ± 0.68  | 23.4 ± 0.68     |
| PM₂.₅, same day (µg/m³)               | 20.0 ± 0.75  | 18.6 ± 0.71     |
| Exposed to environmental tobacco smoke [no. (%)] | 153 (22.4) | 144 (19.86) |
| Cook with gas [no. (%)]               | 45 (6.6)     | 57 (7.9)        |
| Age (years)                           | 60.2 ± 6.0   | 60.4 ± 6.3      |
| Tertiary education [no. (%)]          | 248 (36.3)   | 105 (14.5)      |
| Home-staying* [no. (%)]               | 230 (33.7)** | 402 (55.5)      |
| BMI (kg/m²)                           | 27.1 ± 3.5*  | 26.2 ± 4.9      |
| Systolic blood pressure (mmHg)        | 137 ± 19*    | 127 ± 19        |
| Diastolic blood pressure (mmHg)       | 84 ± 11      | 79 ± 10         |
| Have history of hypertension [no. (%)]| 367 (46.3)*  | 315 (43.5)      |
| Have self-reported diabetes [no. (%)] | 32 (4.7)     | 22 (3.0)        |
| Uric acid (µmol/L)                    | 385 ± 78*    | 285 ± 68        |
| Cholesterol (mmol/L)                   | 6.2 ± 0.0**  | 6.4 ± 0.0       |
| Exercise (> 1 hr/week)                | 337 (49.3)*  | 280 (38.6)      |
| Are current smokers [no. (%)]         | 205 (30.0)*  | 133 (18.3)      |
| Use beta blockers [no. (%)]           | 78 (11.4)    | 81 (11.2)       |
| Have known cardiac disease* [no. (%)] | 121 (17.7)   | 115 (15.9)      |
| Take diuretics, sympathomimetetics, calcium channel blockers, angiotensin-converting enzyme inhibitors | 92 (13.5) | 110 (15.2) |

Values shown are mean ± SD except where indicated.
*Unemployed, retired, or deceased persons.
†Self-reported medical examination/treatment because of cardiovascular problems in the 12 months before the ECG.
\*p < 0.001, and \**p < 0.01 for difference between sexes.
factors through enzymatic tests by the Institute of Clinical Chemistry of the UniversityHospital of Zürich (Hitachi Modular Autoanalyzer; Hitachi, Rotkreuz, Switzerland; assays from Roche Diagnostics, Mannheim, Germany).

Ethical approval for the study was given by the central Ethics Committee of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committees for each of the eight examination areas, and subjects signed an informed consent at the examination. We certify that we followed all applicable institutional and governmental regulations concerning the ethical use of human volunteers and the Declaration of Helsinki during this research.

Statistical methods. We assessed differences in proportions and means between sexes using the chi-square test and the Student’s t-test, respectively. Because an initial inspection suggested that the distribution of the residuals was skewed, we log-transformed HRV values for further analyses; the results are presented as percent differences between the exposure groups.

To estimate the effect of exposure to NO2 on HRV, we used a multivariable regression model adjusting for study site (random effects), age, education, self-reported diabetes, hypertension, smoking status, frequency of physical exercise, uric acid levels, and beta-blocker intake in the previous 30 days. Because we estimated exposure to NO2 for the participant’s home address, we also examined the association for subjects likely to spend more time at home, including unemployed, retired, or diseased persons. The literature has repeatedly reported higher susceptibility to air pollutants in subjects with existing cardiovascular disease (Holguin et al. 2003; Wheeler et al. 2006). We therefore also stratified our analyses according to the presence or absence of self-reported medical examination or treatment because of cardiovascular problems in the previous 12 months.

In sensitivity analyses, we included the average NO2 levels on the day of the Holter recording as a measure of short-term exposure to air pollution into the multivariable regression model because the associations between past exposure and HRV might be confounded by short-term effects. To focus more on the effect of traffic-related NO2 on HRV, we also adjusted for NO2 from sources other than traffic in another analysis.

We performed statistical analyses using Stata 9.2 (StataCorp, College Station, TX, USA) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows the characteristics of the study population. Men had on average more cardiovascular risk factors than women (i.e., higher BMI, blood pressure, uric acid levels, prevalence of self-reported diabetes and of current smoking), whereas history of cardiovascular disease did not differ significantly between sexes. On the other hand, educational level of men was on average higher than that of women, and they engaged more often in exercise. One-year average exposure to NO2 ranged from 7 to 50 µg/m3, with a median of 20 µg/m3 and a mean of 23 µg/m3. Compared with SAPALDIA participants ≥ 50 years of age who did not have an HRV measurement, participants of this study less frequently had hypertension (49% vs. 63%) and self-reported diabetes (3.6% vs. 5.7%), were less frequently current smokers (19% vs. 22%), and had a higher educational level (25% with tertiary education vs. 21%).

Covariate-adjusted regression coefficients of NO2 exposure for different indices of HRV are given in Table 2 [crude regression coefficients are presented in Supplemental Material, Table 1 (http://www.ehponline.org/members/2008/11377/suppl.pdf)]. These were adjusted for age, BMI, hypertension, frequency of exercise, beta blocker use, uric acid, self-reported diabetes, smoking status, educational level, and random area effects. Women, but not men, showed a consistent negative association between NO2 exposure and HRV. Among women, each 10-µg/m3 increment in 1-year averaged NO2 level was associated with a decrement of 3% [95% confidence interval (CI), –4 to –1] in SDNN, of 6% (95% CI, –11 to –1) in nighttime LF, and of 5% (95% CI, –9 to 0) in nighttime LF/HF. Removing 2.5% of observations at each end of the NO2 exposure range showed similar results [Supplemental Material, Table 2 (http://www.ehponline.org/members/2008/11377/suppl.pdf)].

To assess possible reasons for the observed difference between sexes and because women spend more time at home (Table 1), we further examined the association between exposure to NO2 and HRV for subjects likely to spend more time at their home address. Figure 1 shows the covariate-adjusted percent differences in SDNN per 10-µg/m3 increment in mean NO2 among home-staying and non–home-staying men and women. A significant association between exposure to NO2 at the home address and HRV can be seen only in home-staying women: 24-hr SDNN was 3% [95% CI, –6 to –0.4] lower per 10-µg/m3 increase in NO2, and TP was 9% [95% CI, –15 to –3] lower. Home-staying men showed no such association [for complete data, see Supplemental Material, Table 3 (http://www.ehponline.org/members/2008/11377/suppl.pdf)].

Stratification by cardiovascular disease showed that subjects who had a medical examination or treatment because of cardiovascular problems in the previous 12 months had a 4% (95% CI, –8 to –1) lower SDNN per 10-µg/m3 increase in NO2. Subjects without self-reported cardiovascular problems in the previous 12 months did not show a significant negative association between HRV and long-term exposure to NO2. When further stratifying by sex, this association was stronger in women than in men, but this difference was not statistically significant, with only 115 women and 121 men in this category (Figure 2).

Table 2. Adjusted regression coefficients* of annual home outdoor exposure to NO2 (by 10 µg/m3) in models of indices of HRV, by sex.

| Outcome variable | 24-hr Night | 24-hr Night | Females (n = 725) |
|------------------|-------------|-------------|------------------|
|                  | Coefficient (SE) | p-Value | Coefficient (SE) | p-Value | Coefficient (SE) | p-Value |
| ln(SDNN)         | 0.0008 (0.011)   | 0.946    | 0.0109 (0.014)   | 0.429   | –0.0268 (0.010) | 0.012 |
| ln(TP)           | 0.0137 (0.027)   | 0.617    | 0.0049 (0.030)   | 0.870   | –0.0545 (0.023) | 0.074 |
| ln(HF)           | 0.0131 (0.042)   | 0.759    | 0.0138 (0.045)   | 0.763   | –0.005 (0.043) | 0.910 |
| ln(LF)           | 0.0046 (0.031)   | 0.882    | –0.0112 (0.031)  | 0.721   | –0.0347 (0.030) | 0.261 |
| ln(LF)/HF        | –0.0079 (0.027)  | 0.768    | –0.0254 (0.027)  | 0.353   | –0.0253 (0.025) | 0.317 |

*Adjusted for age, BMI, hypertension, exercise, beta blockers, uric acid, self-reported diabetes, smoking status, educational level, and random area effects. *Adjusted over the previous year.

Figure 1. Estimated percent difference and 95% CI in SDNN per 10-µg/m3 increment in the annual mean NO2 stratified by time spent at home, adjusted for age, BMI, hypertension, exercise, beta blockers, uric acid, self-reported diabetes, smoking status, educational level, and random area effects.
Inclusion of short-term exposure to NO2 into the multivariable regression model (Table 3) did not change the results for long-term exposure to a relevant degree. Estimates of the short-term effect of NO2, PM10, or PM2.5 on HRV were all nonsignificant [see Supplemental Material, Tables 4–6 (http://www.epiconline.org/members/2008/113777/suppl.pdf)].

Additional controlling for NO2 from sources other than traffic at the home address did not change the results significantly (Table 4). Previous year’s PM10 did not show did not change the results significantly sources other than traffic at the home address Supplemental Material, Tables 4–6 (http://www.epiconline.org/members/2008/113777/suppl.pdf).}

We found a negative association between exposure to ambient NO2 and HRV in women, but not in men, that is not due to extreme observations. In the literature, findings on the modification of the effect of air pollution on cardiovascular health by sex are heterogeneous. Some earlier studies have pointed to a higher susceptibility to the effects of air pollution in females (Chen et al. 2005; Künzli et al. 2005; Rosenlund et al. 2006; Zeka et al. 2006), some did not find modification of the effect by sex (Cakmak et al. 2006; Forastiere et al. 2005; Krewski et al. 2005), and others found even a higher susceptibility in males (Hoffmann et al. 2006, 2007; Maheswaran and Elliott 2003). Having considered only resident exposure data, we examined whether our sex-specific results were confounded by behavioral differences. In subgroup analyses including only subjects likely to spend more time at their home address, we still found the association only in women, and not in men. However, studies in neighboring Germany have shown that elderly men spend less time at home than do elderly women because of gender-specific division of duties (Blanke et al. 1996; Küster 1998). Other differences between employed women and women who spend more time at home that might explain our results (e.g., level of stress) could not be addressed in this study, and we cannot rule out that these findings were due to chance.

Previous studies have suggested that subjects with underlying cardiovascular disease are at greater risk of severe events induced by air pollution (i.e., hospitalization for congestive heart failure, fatal coronary events, or adverse outcomes after myocardial infarction) (Forastiere et al. 2005; Schwartz et al. 2005; Wellenius et al. 2005; Zanobetti and Schwartz 2007). In subgroup analyses, we found an effect of long-term exposure to ambient NO2 only in subjects who had a medical examination or treatment because of cardiovascular problems in the previous 12 months.

Potential mechanisms supporting our findings, including the differences in males versus females, center around the fact that traffic exposure, for which NO2 is a marker, or even NO2 by itself, might lead to chronic autonomic dysfunction through the multiple pathways that have been associated with air pollution exposure (Brook et al. 2004). Specifically, chronically elevated pulmonary

### Table 3. Regression coefficients* of annual home outdoor exposure to NO2 by (10 μg/m3) in models of indices of HRV, adjusting for short-term exposure to NO2

| Outcome variable | Coefficient (SE) | p-Value | Coefficient (SE) | p-Value |
|------------------|-----------------|---------|-----------------|---------|
| ln(SDNN)         | –0.0200 (0.015) | 0.174   | –0.0076 (0.017) | 0.653   |
| ln(TP)           | –0.0458 (0.035) | 0.189   | –0.0167 (0.037) | 0.652   |
| ln(HF)           | –0.0486 (0.053) | 0.360   | –0.0281 (0.055) | 0.612   |
| ln(LF)           | –0.0421 (0.040) | 0.309   | –0.289 (0.042)  | 0.491   |
| ln(LF/HF)        | 0.0075 (0.034)  | 0.825   | 0.0200 (0.036)  | 0.932   |

*Adjusted for same-day average NO2 exposure, age, BMI, hypertension, exercise, beta blockers, uric acid, self-reported diabetes, smoking status, educational level, and random area effects. Averaged over the previous year.

### Table 4. Regression coefficients of annual home outdoor exposure to road-traffic–related NO2 by (10 μg/m3) in models of indices of HRV

| Outcome variable | Coefficient (SE) | p-Value | Coefficient (SE) | p-Value |
|------------------|-----------------|---------|-----------------|---------|
| ln(SDNN)         | 0.0053 (0.011)  | 0.631   | 0.0131 (0.013)  | 0.320   |
| ln(TP)           | 0.0181 (0.026)  | 0.579   | 0.0140 (0.029)  | 0.630   |
| ln(HF)           | 0.0199 (0.039)  | 0.622   | 0.0277 (0.043)  | 0.525   |
| ln(LF)           | 0.0162 (0.029)  | 0.581   | 0.0025 (0.031)  | 0.895   |
| ln(LF/HF)        | –0.0034 (0.026) | 0.894   | –0.0251 (0.026) | 0.337   |

*Adjusted for NO2 from non–road-traffic sources (household, industry, agriculture/off-road, and background) averaged over previous year, age, BMI, hypertension, exercise, beta blockers, uric acid, self-reported diabetes, smoking status, educational level, and random area effects.
and systemic inflammation may alter autonomic dysfunction. Elevated C-reactive protein has been linked to reduced HRV in the literature (Madsen et al. 2007; Park et al. 2005). Although one cannot rule out differences in physiologic responses to air pollution between sexes [differences between the sexes have been noted in response to cigarette smoking (Gan et al. 2006)], we believe that it is more likely that the main explanation for the effect differences by sex is that exposure misclassification for women who spend more hours at home is smaller than for men who travel.

Despite some limitations, our personal exposure assessment has several advantages compared with previously reported studies of long-term exposure to air pollution. Most earlier studies assigned exposure estimates to groups of individuals residing in the same city or close to the same pollution monitor, thus providing less differentiation. In a sensitivity analysis, we included short-term exposure to NO2 into the model. The results did not sizably change compared with the model without short-term NO2, indicating that the reported results reflect a further sensitivity analysis and found similar results as in the baseline analysis. If NO2 were serving primarily as a surrogate for ultrafine particles, then we would expect that removing the part of the NO2 association that is due to regional sources would increase the effect size. This was not the case, which suggests that the effect may be due to NO2 itself. Confounding by indoor sources of NO2 is also unlikely because controlling for environmental tobacco smoke or gas cooking did not modify the relation between NO2 and HRV.

Conclusions

We found some evidence that long-term exposure to NO2 is negatively associated with cardiac autonomic dysfunction in middle-age to elderly women and in subjects with cardiovascular disease. The different associations in men and women might be at least in part due to confounding by behavioral differences between the sexes.

References
Ackermann-Liebrich U, Kuna-Dibbert B, Probst-Hensch NM, Schindler C, Felber Dietrich D, Zemp Stutz E, et al. 2005. Follow-up of the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991–2003: methods and characterization of participants. Soz Praventivmed 50:1–18.
Blanke K, Eihing M, Schwarz N. 1996. Zeit im Blickfeld. Ergebnisse einer repräsentativen Zeitbudgeterhebung. Stuttgart: Gershoff Gammert. Available: http://www.ulb-tu-darmstadt.de/tox/5194855.pdf [accessed 11 September 2008].
Brook RD, Franklin B, Casicio W, Hong Y, Howard G, Lipselt M, et al. 2004. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109(21):2655–2671.
Cakmak S, Dalles RE, Judek S. 2006. Do gender, education, and income modify the effect of air pollution gases on cardiac disease? J Occup Environ Med 48(1):89–94.
Chan CC, Chuang KJ, Su TG, Lin LY. 2005. Association between nitrogen dioxide and heart rate variability in a susceptible population. Eur J Cardiovasc Prev Rehabil 12(6):580–586.
Chen LH, Knutsen SF, Shavlik D, Beeson WL, Petersen F, Ghamsary M, et al. 2005. The association between fatal coronary heart disease and ambient particulate air pollution: are females at greater risk? Environ Health Perspect 113:1723–1729.
Dockery DW. 2001. Epidemiologic evidence of cardiovascular effects of particulate air pollution. Environ Health Perspect 109(suppl 6):483–486.
Donaldson K, Stone V, Seaton A, MacNee W. 2001. Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ Health Perspect 109(suppl 6):523–527.
Dow S, Schindler C, Wu L, Kröl-D., Bayer-Ajesby L, Brutsche M, et al. 2007. Reduced exposure to PM2.5 and attenuated age-related decline in lung function. N Engl J Med 357(21):2338–2347.
Felber Dietrich D, Schindler C, Schwartz J, Barthelemy JC, Tschopp JM, Roche F, et al. 2006. Heart rate variability in an ageing population and its association with lifestyle and cardiovascular risk factors: results of the SAPALDIA study. European Heart J 27:521–529.
Forastiere F, Stafoggia M, Piccigotto S, Bellander T, D’Ippolito D, Lanki T, et al. 2005. A case–cross analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. Am J Respir Crit Care Med 172(12):1549–1555.
Gan GD, Man SF, Postma DS, Camp P, Sin DD. 2006. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res 7:52; doi:10.1186/1465-9921-7-52 [Online 29 March 2006].
Hoffmann B, Moebus S, Mohlenkamp S, Stang A, Lehmann N, Dragano N, et al. 2007. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 116(5):489–496.
Hoffmann B, Moebus S, Stang A, Beck EM, Dragano N, Mohlenkamp S, et al. 2006. Residence close to high traffic and prevalence of coronary heart disease. Eur Heart J 27(22):2696–2702.
Holguin F, Tellez-Rojo MM, Hernandez M, Cortez M, Chow JC, Watson JJ, et al. 2003. Air pollution and heart rate variability among the elderly in Mexico City. Epidemiology 14(5):521–527.
Krewski D, Burnett RT, Goldberg M, Hoover K, Siemiatycki J, Abramowicz M, et al. 2005. Reanalysis of the Harvard Six Cities Study, part II: sensitivity analysis. Inhal Toxicol 17(7–8):343–353.
Künzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, et al. 2005. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 113:201–206.
Küster C. 1998. Zeitverwendung und Wohnen im Alter. In: Wohnbedürfnisse, Zeitverwendung und soziale Netzwerke älterer Menschen. Expertiseband 1 zum Zweiten Altenbericht der Bundesregierung. Frankfurt am Main:Deutsches Zentrum für Altersfragen, 51–75.
Le Tertre A, Medina S, Samoli E, Forsberg B, Michelozzi P, Boumgard A, et al. 2002. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. J Epidemiol Community Health 56(10):773–779.
Liao D, Duan Y, Whitel EA, Zheng ZJ, Heiss G, Chinchilli VM, et al. 2004. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol 159(1):768–777.
Liu LJ, Curjic L, Keidel D, Heldstab J, Künzli N, Bayer-Oglesby L, et al. 2007. Characterization of source-specific air pollution exposure for a large population-based Swiss cohort (SAPALDIA). Environ Health Perspect 115:1638–1645.
Madsen T, Christensen JT, Toft E, Schmidt EB. 2007. C-reactive protein is associated with heart rate variability. Ann Noninvasive Electrocardiogr 12(3):216–222.
Maheshwara R, Elliott P. 2003. Stroke mortality associated with living near main roads in England and Wales: a geographical study. Stroke 34(12):2778–2780.
North American Society of Pacing and Electrophysiology. 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93(4):1043–1065.
Park SK, O’Neill MS, Vokonas PS, Sparrow D, Schwartz J. 2005. Effects of air pollution on heart rate variability: the VA Normative Aging Study. Environ Health Perspect 113:304–309.
Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109(1):71–77.
Rosenlund M, Berglund N, Pershagen GD, Halvqvist J, Jonzon T, Bellander T. 2006. Long-term exposure to urban air pollution and myocardial infarction. Epidemiology 17(4):383–390.
Schwartz J, Litonjua A, Suh H, Verrier M, Syring M, Zanobetti A, et al. 2005. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 60(8):455–461.
Staatsel J. 2004. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Ws 134(35):3514–3522.
Utell MJ, Frampton MW, Zareba W, Devlin RB, Cascio WE. 2002. Cardiovascular effects associated with air pollution: potential mechanisms and methods of testing. Inhal Toxicol 14(2):1231–1247.
Wellenius GA, Bateson TF, Mittleman MA, Schwartz J. 2005. Particulate air pollution and the rate of hospitalization for congestive heart failure among Medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol 161(11):1030–1038.
Wheeler A, Zanobetti A, Gold DR, Schwartz J, Stone P, SuH H. 2006. The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. Environ Health Perspect 114:568–566.
WHO. 1998. Hypertension control. Report of a WHO expert committee. WHO Technical Report Series 862. Geneva:World Health Organization.
Zanobetti A, Schwartz J. 2007. Particulate air pollution, progression, and survival after myocardial infarction. Environ Health Perspect 115(11):769–775.
Zeka A, Zanobetti A, Schwartz J. 2006. Individual-level modifiers of the effects of particulate matter on daily mortality. Am J Epidemiol 163(9):849–853.