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Cardio-Respiratory Effects of Air Pollution in a Panel Study of Outdoor Physical Activity and Health in Rural Older Adults

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Objective: To examine cardio-respiratory effects of air pollution in rural older adults exercising outdoors. **Methods:** Adults 55 and over completed measurements of blood pressure, peak expiratory flow and oximetry daily, and of heart rate variability, endothelial function, spirometry, fraction of exhaled nitric oxide and urinary oxidative stress markers weekly, before and after outdoor exercise, for 10 weeks. Data were analyzed using linear mixed effect models. **Results:** Pooled estimates combining 2013 ($n = 36$ participants) and 2014 ($n = 41$) indicated that an interquartile increase in the air quality health index (AQHI) was associated with a significant ($P < 0.05$) increase in heart rate (2.1%) and significant decreases in high frequency power (−19.1%), root mean square of successive differences (−9.5%), and reactive hyperemia index (−6.5%). **Conclusions:** We observed acute subclinical adverse effects of air pollution in rural older adults exercising outdoors.

Learning Objectives

- Discuss the rationale for and methods of the new study evaluating the effects of air pollution in older adults living in a rural area.
- Identify specific cardiorespiratory effects associated with air quality in rural older adults.
- Discuss the implications for recommendations on outdoor activity levels during times of high pollution levels for older adults in rural areas.

Numerous panel studies have been conducted examining the association between air pollution and cardiovascular and respiratory physiological parameters,[1–27] but most studies have been conducted in urban areas, and relatively little is known about the effects of outdoor air pollution in rural or smaller urban areas, particularly among older adults. Nonetheless, it is commonly recommended that individuals, particularly older adults or those with cardiac or respiratory disease, should reduce the duration and/or intensity of outdoor physical activity when air pollution concentrations are elevated.[28] Given the lack of evidence on effects of air pollution in rural areas, advice is based primarily on studies conducted in urban areas. In Canada, advice is provided through the air quality health index (AQHI) which is based on a weighted sum of concentrations of nitrogen dioxide (NO_2), ozone (O_3), and particulate matter of median aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$), where weights were derived from an analysis of air pollution and mortality in Canada's largest cities.[29] Owing to differences in the concentrations and mix of pollutants between large cities and smaller cities, or rural areas, the AQHI may not accurately predict health risks outside large urban centres. Air quality in these areas may be adversely affected by emissions from local industry, woodsmoke, or long range transport of regional secondary pollutants. Moreover, compared with urban residents, rural residents have poorer health status and greater potential for exposure as a result of greater time spent outdoors for work or recreation.[30,31]

In order to address these gaps, the primary objective of this study was to examine the cardio-respiratory effects of air pollution in a panel study of outdoor physical activity and health (OPAH) in rural older adults. We hypothesized that air pollution exposures/AQHI values in the hours or days prior to health measures would be associated with subclinical adverse effects (increased blood pressure, heart rate, urinary oxidative stress markers, fraction of exhaled nitric oxide and decreased oxygen saturation, pulmonary function, endothelial function, and heart rate variability). Some of the results of this study have been previously reported in an abstract.[32]

METHODS

The study was conducted in Kincardine, Ontario, a town of approximately 11,000. Data were collected during June through August of 2013 and 2014. Participants were recruited using advertisements. To avoid introducing bias, the study hypothesis was not disclosed, rather, subjects were told that the study pertained to outdoor physical activity and health. Participants had to be at least 55 years old, non-smokers, non-exposed at home to environmental tobacco smoke and without seasonal allergies. Subjects with unstable angina, atrial flutter, atrial fibrillation, paced rhythm, left bundle branch block or implanted cardioverter-defibrillator, and allergy to latex or adhesives were excluded. Presence of arrhythmias and conduction disturbances was determined through screening 12 lead electrocardiograms (ECG). The

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study was approved by Health Canada and Western University Research Ethics Boards and written consent was obtained from all subjects.

Continuous hourly measures of carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter of median aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), sulfur dioxide (SO_2) and temperature were collected using a dedicated Airpointer (Recordum Messtechnik GmbH, Vienna, Austria) monitor deployed at the same location both years, approximately 1.5 km and 1 km from the sites used for weekly health measures in 2013 and 2014, respectively. Missing values were filled using data from a nearby (~15 km) government monitor. The AQHI was calculated as follows:

$$\mathrm{AQHI} = \frac{10}{10.4} \times (100 \times [e^{0.000871 \times \mathrm{NO_2}} - 1 + e^{0.000537 \times \mathrm{O_3}} - 1 + e^{0.000487 \times \mathrm{PM_{2.5}}} - 1])$$

where all pollutants are entered as 3 hours moving average concentrations in ppb (NO_2, O_3) or $\mu g/m^3$($PM_{2.5}$).[29]

Demographic information, smoking history, presence of respiratory or cardiovascular disease, medications, and housing characteristics were determined at study enrollment using a baseline health questionnaire. Daily and weekly questionnaires documented recent medication use, outdoor activity, symptoms, and indoor exposures (cooking, burning, hobbies).

Participants completed daily measurements of blood pressure, peak expiratory flow rate (PEFR) and oximetry, and weekly measurements of heart rate variability (HRV), endothelial function, spirometry, fraction of exhaled nitric oxide (FeNO), and urinary oxidative stress markers before and after 30 minutes of prescribed outdoor activity. Participants were asked to engage in light outdoor exercise such as walking, at the same time and in the same location every day and to expend a similar level of effort each day. They were advised not to exercise outdoors when there was a severe weather warning (eg, thunderstorm) or an air quality advisory. Exercise was unsupervised but on days when participants underwent weekly measurements, prescribed walking routes were employed. Each subject was monitored for up to 10 weeks with weekly measurements carried out at the same time of day and day of the week. Heart rate variability was measured by recording ambulatory electrocardiograms for approximately 4 hours each study visit using three-channel (seven-lead) digital Holter monitors. Data were analyzed on a GE Medical Systems Information Technology workstation (MARS version 7.2, GE Healthcare, Chicago, IL). A 5-minute reading from the end of 15 minutes rest periods was examined before and at two intervals after exercise. Time domain measures of intervals between successive normal ECG QRS complexes (standard deviation of NN [normal RR], intervals [SDNN], and root mean square of successive differences [RMSSD]), as well as frequency domain measures of the variance of these intervals under different conditions of sympathetic and parasympathetic modulation (low frequency power [LF] and high frequency power [HF]), were determined.[33] Oximetry was measured using a pulse oximeter with a finger sensor. The oximeter was run continuously for 3 minutes to obtain each measurement and the average O_2 saturation and heart rate during this period was recorded. Microvascular endothelial function was measured via peripheral artery tonometry using the portable EndoPAT 2000 instrument (Itamar Medical Ltd., Cesari, Israel). Reactive hyperemia index (RHI) was determined based on a computer algorithm. Blood pressure was measured in the dominant arm with the subject seated, using an automated sphygmomanometer, taking the average of the last two of three readings 1 minute apart in keeping with clinical recommendations.[34] KoKo Legend spirometers (nSpire Health, Longmont, CO) were used to measure forced expiratory volume in 1 second, forced vital capacity, and forced expiratory flow at 25% to 75% of vital capacity. Single-breath on-line measures of fraction of exhaled nitric oxide (FeNO) were measured using a Niox Mino (Aerocrine AB, Solna, Sweden). Spirometry measures and FeNO were obtained by trained technicians according to American Thoracic Society criteria and European Respiratory Society Guidelines and each subject was assigned to the same instrument and technician on all visits. Subjects used mini-Wright peak flow meters to measure daily peak expiratory flow rates. Results of three trials were recorded daily before and after exercise. Urine was collected before and after exercise at the beginning and end of a 4-hour period during which the other health measure data were collected. Urinary endpoints were normalized using creatinine values, which were determined using a Roche Diagnostics CREA kit (Indianapolis, IN) and a Cobas Fara clinical chemistry analyzer. Enzyme-linked immunosorbent assay (ELISA) kits were used to determine concentrations of 8-isoprostane (Cayman Chemicans, Ann Arbor, MI) and 8-hydroxy-2′-deoxyguanosine (8-OHdG, Cosmo Bio, Carlsbad, CA) as per manufacturer's instructions. Malondialdehyde (MDA) was determined using an Agilent 1200 HPLC following the protocol described by Larstad et al.[35]

Outcome variables were log transformed if necessary to reduce skew. Linear mixed effect regression models were employed to analyze the association of the AQHI and individual pollutants with health measures, accounting for repeated measures among study subjects, treating time-invariant individual covariates, and time-variant environmental variables as fixed effects, and subjects as random effects. All models included age, sex, body mass index (BMI) (less than or equal to 25, greater than 25), smoking history (never, ever), and dichotomous variables for medication use (statins, other cardiovascular drugs). Spirometry models also included height and use of respiratory medication. First order autoregressive models were used to account for serial correlation. Effects of temporal trends and cycles were accounted for using a linear function of time and day of week variables. Base models employed air pollutants at lags of 0 to 2 days each with natural spline functions of temperature with three degrees of freedom at lags of 0 to 2 days (nine models). Associations were analyzed separately for 2013 and 2014 and heterogeneity between years was examined using Cochran's Q statistic.[36] If the P value of Q was greater than 0.05, fixed effects pooled estimates were calculated. Percent change in health measures associated with air pollution was calculated by dividing the absolute change (regression coefficient multiplied by increment in pollution concentration) by the mean value of the health measure for untransformed variables, and for log transformed variables as the exponential of the product of the regression coefficient and the increment in pollution concentration, minus one. Statistical analyses were conducted in SAS EG (64 bit) version 5.1 (SAS Institute, Cary, NC) and R version RX64 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptive Results

Participant characteristics are summarized in Table 1. Participants were generally similar in the two rounds of data collection. Most were between 55 and 65 years of age, although there was a larger proportion 65 and over and of women in 2014. Nearly all participants were Caucasian. Use of statins and other cardiovascular drugs were most prevalent. Less than 10% of participants reported using either respiratory medication or oral hypoglycemic agents. The vast majority of participants had greater than a high school education. The prevalence of each of allergies, diabetes, and cardiac and respiratory disease was 10% or less in both years.

Descriptive statistics for air pollution and weather are shown in Table 2. CO, NO_2, and SO_2 concentrations were very low compared with urban centers[1–27] and, therefore, were not included

TABLE 1. Participant Characteristics

Characteristic	2013 *n* (%) Total *n* = 36	2014 *n* (%) Total n = 41
Age		
Mean (SD)	63 (5)	65 (6)
55–59	11 (30.6%)	8 (19.5%)
60–64	16 (44.4%)	12 (29.3%)
65–69	6 (16.7%)	13 (31.7%)
70+	3 (8.3%)	9 (22.0%)
Sex		
Female	20 (55.6%)	27 (65.9%)
Ethnicity		
Caucasian	36 (100.0%)	39 (95.1%)
Smoking		
Ever	15 (41.7%)	13 (31.7%)
Current	0	0
Education		
High school or less	5 (13.9%)	7 (17.1%)
Post secondary	31 (86.1%)	34 (82.9%)
Body mass index		
Normal (18.5–24.9 kg/m^2)	13 (36.1%)	12 (29.3%)
Overweight (25–29.9 kg/m^2)	14 (38.9%)	16 (39.0%)
Obese ($\geq$30 kg/m^2)	9 (25.0%)	13 (31.7%)
Medication		
Statins	9 (25.0%)	11 (26.8%)
Other cardiovascular drugs*	9 (25.0%)	13 (31.7%)
Air conditioning		
Present	23 (63.9%)	26 (63.4%)
Dehumidfier		
Present	25 (69.4%)	25 (61.0%)

SD, standard deviation.
*Includes beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, diuretics, and other antihypertensive agents.

in analyses of associations with health measures. Ozone and temperature mean and standard deviation were somewhat higher in 2013 while $PM_{2.5}$ mean and standard deviation were higher in 2014. In 2013, no outdoor activity was canceled because of weather or air quality advisories, and in 2014, eight outdoor activity person-days were canceled due to thunderstorms or extreme heat. Descriptive statistics for physiological measures are shown in Table 3. Distributions of daily and weekly measures were comparable in 2013 and 2014.

Associations with Air Pollution

Associations of the AQHI with selected cardio-respiratory measures are shown in Figs. 1 and 2 by lag of air pollution and temperature, expressed as percent change per interquartile range increment in AQHI. Data for all measures other than heart rate were log transformed. Since percent change was calculated differently for log transformed and untransformed variables, they cannot be compared directly.[37] Results are shown for post-exercise measures, with the exception of endothelial function (RHI), for which associations were more consistent with pre-exercise measures (see Figures, Supplemental Digital Content 1 and 2, http://links.lww.com/JOM/A330, which show associations with post-exercise RHI and pre-exercise values of other measures). Associations with HRV measures were more readily apparent in 2013 compared with 2014, when they were mostly smaller or null (Fig. 1). Where significant associations were observed, they were generally not particularly sensitive to lag of temperature. Associations of the AQHI with decreased HRV in 2013 were strongest at lag 0 days, as were associations with increased heart rate and decreased endothelial function (RHI) in both 2013 and 2014. In contrast, in both 2013 and 2014 the AQHI was associated with increased FeNO at all lags 0 to 2 days (Fig. 2). Associations were also observed of several measures with $PM_{2.5}$ and ozone concentrations (not shown).

Median values of percent change in outcome measure across temperature lags, for the daily lag(s) of $PM_{2.5}$, ozone and AQHI exhibiting the strongest association with each measure and least sensitivity to temperature lag, are shown in Fig. 3. Pooled estimates combining 2013 and 2014 indicated that the AQHI was associated with a significant increase in heart rate (2.1%, 95% confidence interval [CI] 0.8%, 3.3% per interquartile range [IQR]), significant decreases in HRV measures (HF, −19.1%, 95% CI −29.1%, −7.7%; RMSSD, −9.5%, 95% CI −14.5%, −4.3%), as well as decreased RHI (−6.5%, 95% CI −10.1%, −2.7%). Significant positive associations with FeNO were observed in both 2013 and 2014, but there was significant heterogeneity in effect between years ($P = 0.02$). Significant associations were also observed of several measures with $PM_{2.5}$ and ozone. The AQHI, ozone and $PM_{2.5}$ exhibited consistent negative associations with daily PEFR and oxygen saturation, and positive associations with 8-hydroxy-2′-deoxyguanosine (8OHdG) while associations with other cardio-respiratory measures and oxidative

TABLE 2. Air Pollution and Weather Descriptive Statistics (Daily 3 hour Maximum)

Variable*	Year	*N*	Mean	Std. Dev.	Percentile 25	Percentile 75	Maximum
CO (ppm)	2013	73	0.3	0.1	0.2	0.3	1.0
	2014	85	0.4	0.4	0.3	0.4	2.0
NO_2 (ppb)	2013	73	3.2	1.1	2.3	3.9	5.5
	2014	87	3.1	1.5	2.3	3.8	7.9
O_3 (ppb)	2013	73	47.8	16.2	35.6	59.7	94.4
	2014	87	44.2	13.9	34.5	53.5	85.3
$PM_{2.5}$ ($\mu g/m^3$)	2013	73	12.3	8.4	6.0	18.1	45.7
	2014	89	15.9	10.5	8.5	21.2	58.1
SO_2 (ppb)	2013	73	1.3	1.4	0.3	1.8	7.2
	2014	86	1.2	2.3	0.1	1.1	17.1
Air quality health index†	2013	73	3.1	1.1	2.2	3.9	6.3
	2014	87	3.0	1.0	2.2	3.6	5.7
Temperature (°C)	2013	73	23.8	3.5	21.3	25.8	31.0
	2014	87	22.2	3.4	19.6	24.2	29.4

*CO, carbon monoxide, NO_2, nitrogen dioxide, O_3, ozone, $PM_{2.5}$, particulate matter of median aerodynamic diameter less than 2.5 μm, SO_2, sulfur dioxide.
†AQHI scale is 1–3, low health risk, 4–6, moderate health risk, 7–10, high health risk, >10, very high health risk.

TABLE 3. Physiological Measures Descriptive Statistics (Pre-Exercise)

Parameter*	Year	*N*	Mean	Std. Dev.	Percentile 25	Percentile 75
Daily						
O_2 saturation (%)	2013	2419	97.5	0.8	97.0	98.0
	2014	2389	97.6	0.9	97.3	98.0
Systolic bp (mm Hg)	2013	2420	117.1	13.1	108.3	125.3
	2014	2390	121.1	14.4	110.7	130.3
Diastolic bp (mm Hg)	2013	2418	72.0	8.0	67.0	77.3
	2014	2388	72.2	8.7	66.0	78.0
PEFR (L/min)	2013	2405	489.0	116.0	400.0	575.0
	2014	2386	463.7	109.2	380.0	530.0
Weekly						
Heart rate (beat per minute)	2013	343	61.3	9.0	55.0	67.0
	2014	336	61.3	9.2	56.3	66.8
SDNN (mS)	2013	343	50.2	18.1	39.0	60.0
	2014	339	51.1	16.0	40.0	61.0
RMSSD (mS)	2013	343	31.7	16.1	22.0	38.0
	2014	339	30.1	13.6	21.0	38.0
LF (mS^2)	2013	343	414.7	576.2	140.0	482.6
	2014	339	423.9	589.7	129.7	514.6
HF (mS^2)	2013	343	292.5	361.0	94.5	336.1
	2014	339	227.8	221.5	89.1	306.3
FeNO (ppb)	2013	343	18.7	8.2	12.7	22.5
	2014	333	24.5	12.3	16.7	28.7
RHI	2013	345	2.1	0.7	1.6	2.5
	2014	336	2.4	0.7	1.8	2.8
FEV_1 (L)	2013	306	2.85	0.59	2.44	3.25
	2014	313	2.49	0.5	2.15	2.75
FVC (L)	2013	306	3.80	0.79	3.26	4.44
	2014	313	3.33	0.7	2.8	3.78
MDA (nmol/mg Cr)	2013	342	2.0	0.7	1.5	2.4
	2014	340	2.6	0.9	2.0	2.9
8-isoprostane (pg/mg Cr)	2013	341	351.3	482.8	215.6	392.3
	2014	340	366.1	227.1	241.0	417.7
8-OHdG (ng/mg Cr)	2013	340	4.5	4.1	1.9	5.6
	2014	287	3.2	2.0	1.7	4.1

*8-OHdG, 8-hydroxy-2′-deoxyguanosine; bp, blood pressure; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HF, high frequency power; LF, low frequency power; MDA, malondialdehyde; PEFR, peak expiratory flow rate; RHI, reactive hyperemia index; RMSSD, root mean square of successive differences; SDNN, standard deviation of NN (normal RR) intervals.

stress markers were less consistent (see Figures, Supplemental Digital Content 3 and 4, http://links.lww.com/JOM/A330, which show associations with other cardio-respiratory measures, and urinary oxidative stress markers, respectively).

In sensitivity analyses, associations of the AQHI with HRV were generally reduced in magnitude and statistical significance when daily pre-exercise heart rate was included as a covariate. In some instances, associations of oxidative stress markers with the AQHI were somewhat larger in magnitude when non creatinine-corrected values were employed with creatinine as a covariate, but they remained non significant (not shown).

Changes Over Study Duration

Associations between cardio-respiratory measures and day of study were insensitive to lag of air pollution and temperature. Median values across lags of air pollution and temperature, expressed as percent of mean observed values of each outcome measure per 70 days (the study duration), are shown in Fig. 4. Significant improvements (opposite in direction to effects observed in association with air pollution) were observed over the course of the study for most measures. Pooled estimates of effects in 2013 and 2014 indicated a significant reduction in heart rate (−6.1%, 95% CI −8.4%, −3.8%), significant increases in HRV measures (HF, 31.3%, 95% CI 6.1%, 62.5%, RMSSD, 15.1%, 95% CI 4.8%, 26.3%), and RHI (11.9%, 95% CI 5.2%, 19.1%) over the course of the study. FeNO increased significantly over the study duration in both 2013 and 2014, but there was significant heterogeneity in effect between years ($P < 0.0001$). Significant positive associations were also observed between study duration and PEFR, systolic and diastolic blood pressure and oxygen saturation (see Figures, Supplemental Digital Content 5 and 6, http://links.lww.com/JOM/A330, which show associations with other cardio-respiratory measures, and urinary oxidative stress markers, respectively).

Subgroup Analyses

Few significant differences were observed between men and women in associations with HRV measures, FeNO, or RHI in 2013 or 2014 (see Tables, Supplemental Digital Content 7 and 8, http://links.lww.com/JOM/A330, which show differences in associations by sex in 2013 and 2014, respectively). In 2013, significant differences were observed in associations between the AQHI and HRV measures by statin use (see Table, Supplemental Digital Content 7, http://links.lww.com/JOM/A330, which shows differences in associations by statin use in 2013); associations were generally negative and significant among those not taking statins, and positive or null among statin users. Similarly, in 2013, significant positive associations were observed between study duration and HRV measures, FeNO and RHI in those not taking statins, while they

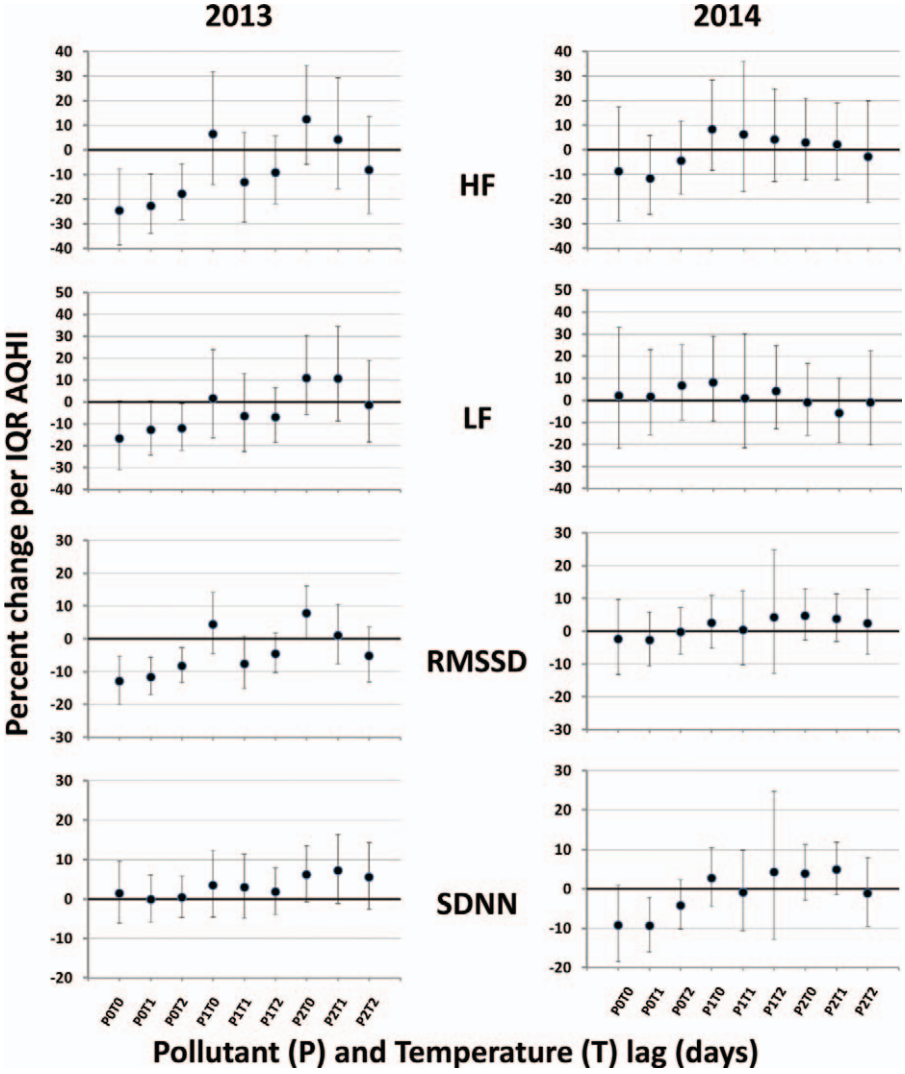

FIGURE 1. Percent change (95% CI) post-exercise high frequency (HF) and low frequency (LF) power, root mean square successive differences (RMSSD), standard deviation NN (SDNN) per IQR AQHI, by lag air pollution (P) and temperature (T). Analyses employed log transformed values. AQHI, air quality health index; CI, confidence interval.

were null in statin users, but the difference in effect was only significant for LF. Differences in effects by statin use were not consistently observed in 2014 (see Table, Supplemental Digital Content 8, http://links.lww.com/JOM/A330, which shows differences in associations by statin use in 2014).

DISCUSSION

We found significant associations between air pollution and subclinical adverse changes in cardio-respiratory physiological measures among older adults in a rural area characterized by moderate concentrations of regional pollutants—ozone and $PM_{2.5}$—and low concentrations of traffic and industrial air pollutants. Associations were more consistent across multiple outcomes in 2013 compared with 2014, and in 2013 there were significant differences in observed associations between statin users and non-users. The reduced associations with air pollution observed in 2014 may be attributable to overall reduced time spent outdoors in 2014 due to poorer weather. Although air pollution concentrations and temperature were similar, there was more than twice as much rain between June 1 and August 31of 2014 compared with 2013 (166 mm vs. 71 mm). Associations of air pollution with subclinical adverse effects exhibited coherence among several measures, strengthening the likelihood of a causal association.

Subclinical cardiovascular measures represent responses to air pollution exposure which do not result in overt events such as myocardial infarction, heart failure, stroke or death, but provide evidence of possible pathophysiological mechanisms which could underlie these observable events.[28] Reduced heart rate variability, for example, may indicate cardiovascular autonomic imbalance[28] and provide information on future mortality risk independent of that provided by traditional risk factors,[33] while impaired endothelial function may directly trigger cardiovascular events.[28] Similarly, increased FeNO reflects local eosinophilic pulmonary inflammation,[24] which may be associated with other pulmonary or extrapulmonary effects. Increased levels of systemic markers of inflammation or oxidative stress, or of vasoactive substances, could reflect pathways for diverse systemic adverse effects.[19]

Numerous previous panel studies have examined links between air pollution and cardio-respiratory measures among older adults (see Table, Supplemental Digital Content 9, http://links.lww.com/JOM/A330, which summarizes results from earlier studies). Our observations of a 2% increase in heart rate and 10% to 20% decrease in heart rate variability parameters in association with an interquartile range change in AQHI are consistent with the direction and magnitude of effect observed in elsewhere.[1,4–11] However, other studies reported no or positive associations,[2–3,12] and a recent review concluded that the totality of evidence did not support the

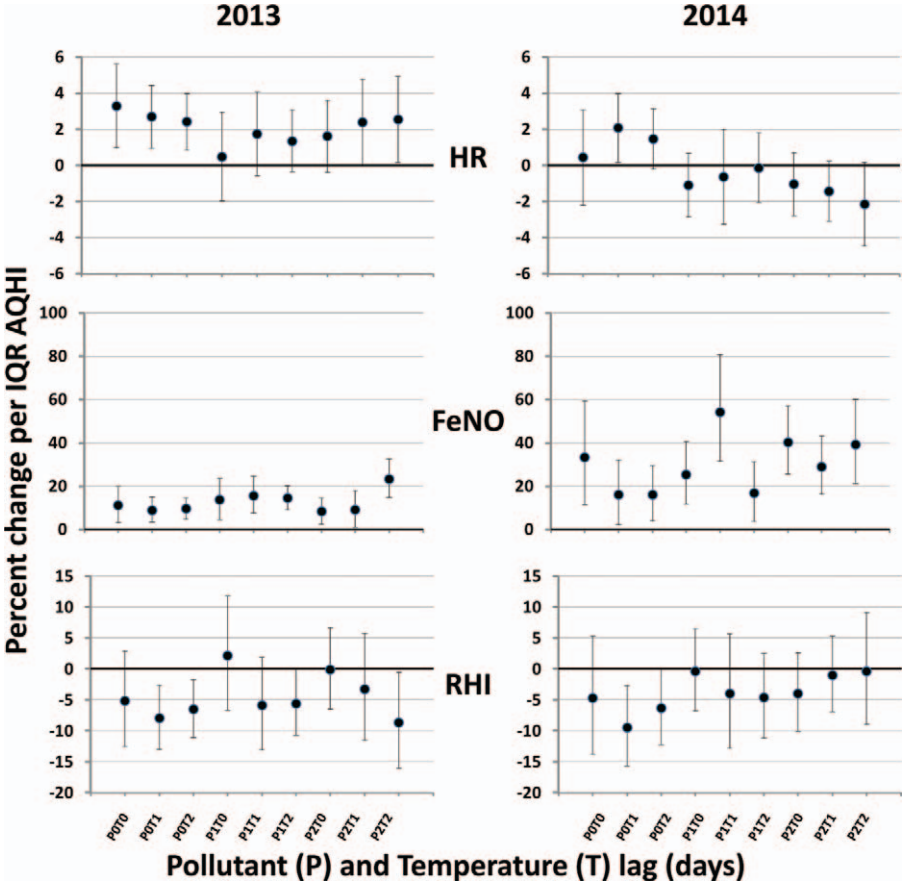

FIGURE 2. Percent change (95% CI) post-exercise heart rate (HR) and fraction exhaled nitric oxide (FeNO), and pre-exercise reactive hyperemia index (RHI) per IQR AQHI, by lag of air pollution (P) and temperature (T). Analyses employed untransformed values for HR, others were log transformed. AQHI, air quality health index; CI, confidence interval.

existence of an association between $PM_{2.5}$ and HRV.[37] Several other studies also found that associations with air pollution occurred at short lag times (hours to less than 1 day).[1,4–8,10,11] Our observation that associations of the AQHI with HRV were reduced in magnitude and statistical significance when daily pre-exercise heart rate was included as a covariate is not surprising in that heart rate (both pre- and post-exercise) exhibited a positive association with the AQHI. Heart rate has not been consistently

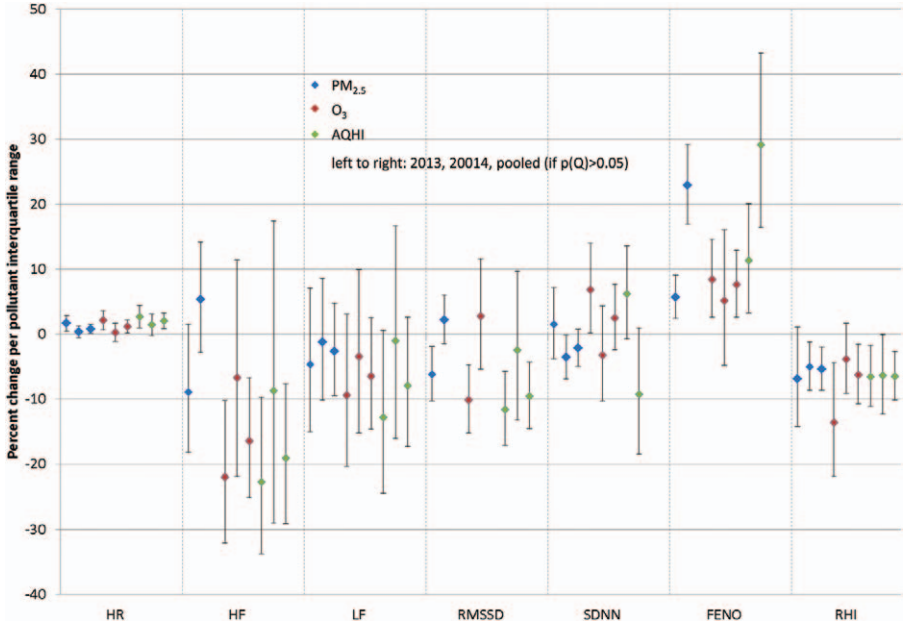

FIGURE 3. Percent change (95% CI) post-exercise heart rate (HR), heart rate variability (HF, LF, RMSSD, SDNN) and fraction exhaled nitric oxide (FeNO), and pre-exercise reactive hyperemia index (RHI) per IQR $PM_{2.5}$, O_3, AQHI. HR untransformed, others log transformed. AQHI, air quality health index; CI, confidence interval; HF, high frequency; LF, low frequency; RMSSD, root mean square successive differences; SDNN, standard deviation NN.

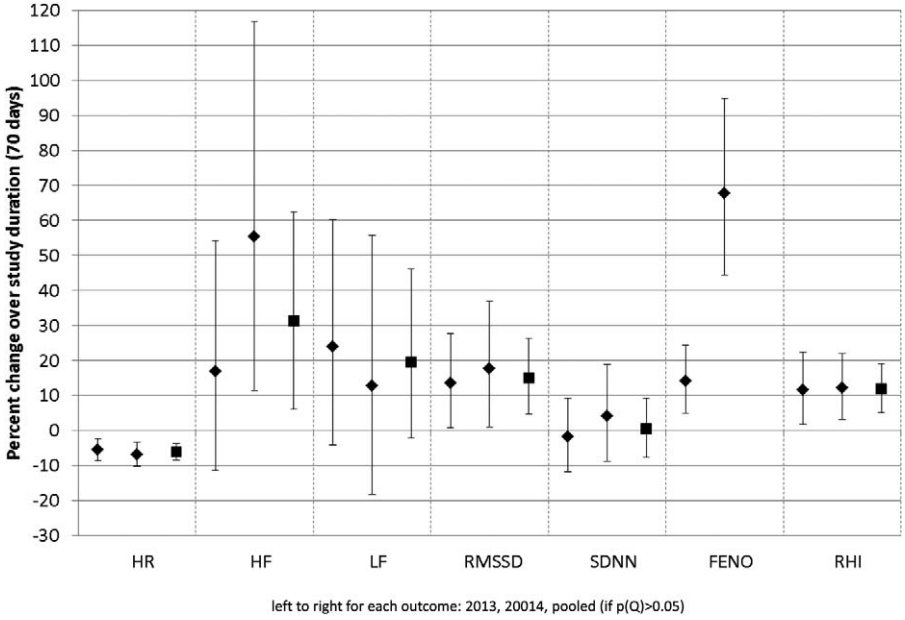

FIGURE 4. Percent change (95% CI) post-exercise heart rate (HR), heart rate variability (HF, LF, RMSSD, SDNN), fraction exhaled nitric oxide (FeNO), reactive hyperemia index (RHI) per 70 days. HR untransformed, others log transformed. AQHI, air quality health index; CI, confidence interval; HF, high frequency; LF, low frequency; RMSSD, root mean square successive differences; SDNN, standard deviation NN.

included as a covariate in HRV analyses in other studies. Similar to our findings, one study reported that reduced HRV in response to air pollution was only observed in those not taking statins, and more specifically in those with the glutathione s-transferase M1 null genotype not taking statins.[38] Increased FeNO in healthy adults has also been previously reported within 6 hours of exposure to coarse particles.[24] Studies of O_2 saturation have been inconsistent,[13–15,21] but of those that have detected significant associations with air pollution, they have been small in magnitude, similar to our findings, at lags of 0 or 1 day.[13,14] Previous studies have reported significant increases in MDA[26] and 8-OHdG[27] within days of air pollution exposure, similar to our results for 8-OHdG. Our findings from 2013 of an approximately 1 mm Hg increase in systolic and diastolic blood pressure per IQR increase in AQHI at lag 2 days are also consistent with the magnitude of effect observed in other studies.[16–22] Lag times observed in these studies have varied from 0 to 5 days.

As an incidental finding, we also observed significant improvements in several outcomes over the duration of the study (in the opposite direction to associations with air pollution). These effects were somewhat more consistent between the 2 study years than effects of air pollutants. While the absence of a control group prevents us from conclusively attributing these effects to the daily regimen of light outdoor activity, the health benefits of physical activity are well-established[39] and outdoor physical activity in particular may have additional mental health benefits compared with indoor activity.[40] Previous studies have demonstrated improvements in cardio-respiratory physiological measures following aerobic training in older adults, but generally after longer training periods of up to 6 to 12 months. Study designs have included cross-sectional studies, prospective observational studies, and randomized controlled trials. Similar to our findings, effects have included reduced resting heart rate,[41,42] increased HRV,[41–43] increased endothelial function,[44,45] and increased pulmonary flow and volume measures.[24,46] Increased FeNO, similar to our findings, has also been reported.[24,47] Small increases (less than 10 ppb or 20%) in FeNO would not be considered clinically important relative to criteria for individuals with chronic airway disease,[48] but could nonetheless signify a subclinical negative impact of exercise training. Our findings of small increases in blood pressure over the duration of the study differ from results of a recent meta-analysis, which reported pooled estimates of decreases in systolic and diastolic blood pressure,[49] although a small number of individual studies included in the meta-analysis also reported increases in blood pressure. Whether our findings could result from some other factor like calibration drift is not clear. Findings regarding markers of oxidative stress have been mixed. Consistent with our findings, reduced urine 8-OHdG[50,51] has been previously reported in relation to exercise programs.

Strengths and Limitations

A key strength of our study is the relatively long duration and large sample size compared with most previous panel studies of air pollution, combined with daily measurements and prescribed daily activity. Although some previous studies were of similar duration to ours, none involved daily prescribed activity, and only one examined whether there was a trend in cardio-respiratory parameters over the duration of the study.[47] To our knowledge, our study is also only the second of its kind conducted in a rural area.[47] Conducting the study over two summers also allowed us to evaluate the consistency of results over two time periods, and examination of several cardio-respiratory physiological measures permitted us to evaluate coherence among a variety of effects.

We lacked personal monitoring data, but we deployed a dedicated monitor close to the site where weekly health measures were conducted, which would tend to reduce exposure measurement error with respect to weekly health measures. While greater error might be present with respect to daily measures when subjects were further from the monitoring site, the community is small and there are no major local pollution sources, suggesting that concentrations of $PM_{2.5}$ and ozone would be expected to be relatively homogeneous over the study area. Pollutant concentrations measured at the study site were highly correlated with those at a government monitor 15 km away. We also lacked data on daily activity other than prescribed outdoor exercise undertaken as part of the study protocol. The repeated measures design has the advantage that subjects served as their own controls for the purpose of evaluating the impact of temporal changes in air pollution exposure. However, since we did not have a control group which did not engage in prescribed daily outdoor activity, we cannot conclusively attribute the incidental

finding of improvements in several measures over time to a cardio-respiratory training effect. In particular, improvement in PEFR could represent improved technique rather than improved fitness. Daily physical activity and health measures at home were unsupervised, thus we have no objective data on the actual duration and intensity of outdoor activity. However, health measure data exhibited plausible distributions consistent with previous studies and mean post-exercise heart rate was greater than mean pre-exercise heart rate. We conducted numerous hypothesis tests which increases the probability of false positive findings, however coherence among multiple measures strengthens the likelihood that our findings reflect true associations.

CONCLUSIONS

Our findings of associations between the AQHI and subclinical adverse cardio-respiratory effects provide support for the applicability of the AQHI as a predictor of health effects in rural areas, even though the AQHI is based on the association between air pollution and mortality in large urban centres. Associations of air pollution with adverse effects exhibited coherence among several measures, strengthening the likelihood of a causal association. Differences in response by statin use were observed consistently in 2013 but not 2014 and require replication in other studies. Our findings suggest that older adults living in rural areas may benefit from reducing outdoor activity when air pollution levels are particularly high in order to reduce acute adverse cardio-respiratory effects. However, additional research is needed to determine at what values of the AQHI or pollutant concentrations outdoor activity should be avoided, and whether short term risks could be averted while preserving longer term benefits of outdoor physical activity. Future research is also needed to examine possible alternative pollutant weightings for the AQHI based on observed associations.

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