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OUTDOOR OZONE AND BUILDING RELATED SYMPTOMS IN THE BASE STUDY

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Abstract

Reactions between ozone and indoor contaminants can influence human health and indoor air quality. The U.S. EPA Building Assessment Survey and Evaluation (BASE) study data were analyzed for associations between outdoor ozone concentrations and building related symptom (BRS) prevalence. Multiple logistic regression (MLR) models, adjusted for personal, workplace and environmental variables, revealed positive relationships ($p<0.05$) between ozone concentrations and upper respiratory (UR), dry eyes, neurological and headache BRS (odds ratios ranged from 1.03-1.04 per 10 $\mu g\ m^{-3}$ increase in outdoor ozone concentrations). Other BRS had marginally significant relationships with ozone ($p<0.10$). A linear dose-response in UR symptoms was observed with increasing outdoor ozone ($p=0.03$); most other symptoms showed similar but not statistically significant trends. Outdoor ozone correlated with indoor concentrations of several aldehydes, a pattern suggesting that indoor ozone chemistry was occurring. Coupled with the MLR ozone-BRS analysis, this correlation supports the hypothesis that ozone-initiated indoor reactions play an important role in the indoor air quality and building occupant health. Replication with increased statistical power and with longitudinal data is needed. If the observed associations are confirmed as causal, ventilation system ozone removal technologies could improve building occupant health when higher ambient ozone levels are present.

Keywords

ozone initiated chemistry, sick building syndrome, aldehydes, dose response, multiple logistic regression, national ambient air quality standard

Practical Implications

Chronic exposure indoors to reactive, irritating, and toxic compounds may lead to increased morbidity and mortality, a decrease in productivity and in the ability to learn. Ambient ozone generated outdoors is entrained into building ventilation systems where it reacts with materials and the air indoors. Terpenes and some other classes of organic compounds very common in buildings have been shown to react with ozone, producing sensory and toxic irritants as both gases and particles. The work presented in this paper provides the first epidemiological evidence of a link between ambient ozone levels and a range of upper and lower respiratory, mucosal and neurological symptoms observed in office buildings, commonly known as building related symptoms (BRS) or "sick building syndrome". After controlling for confounding, analysis of the data indicates that the prevalence of certain BRS appears to increase by as much as a factor of two when outdoor ozone levels increase from those found in low-ozone regions to those typical of high-ozone regions. Although the findings in this study need to be replicated with improved statistical designs, the implication of the finding is that reducing the amount of ozone entrained into building ventilation systems may substantially reduce the prevalence of BRS

Introduction

Building related symptoms (BRS), also known as sick building syndrome symptoms, are a set of health symptoms with unknown etiology that building occupants report when they are in a

building, but that lessen when they leave or are away from the building (Levin 1989). BRS include respiratory and mucosal effects as well as neurological symptoms such as headache and fatigue.

Although the causes of BRS are still unknown, low ventilation per person rates (<10 l/s/person) have consistently been associated with BRS (Seppänen et al. 1999). Seppänen et al. [1999] concluded in an extensive review of the literature that ventilation rates of less than 10 l/s per person were associated with relative risks of 1.1-6 for BRS in occupants. Erdmann and Apte (Erdmann and Apte 2004) found in a large random survey of U.S. office buildings that for every 100 ppm increase in indoor minus outdoor carbon dioxide concentrations (dCO_2) office workers experienced 8% to 23% increased odds of having certain mucous membrane or lower respiratory BRS. These findings support the hypothesis that the indoor air quality of a building plays an important role in BRS.

One probable reason for associations of low per-person ventilation rates with BRS is that they act as a proxy or surrogate for increased levels of indoor air pollutants, such as volatile organic compounds (VOCs) and odors generated by buildings, contents, or occupants. This is because provision of less outdoor air for the indoor environment leads to less dilution of air contaminants from indoor sources. Thus, lower ventilation rates imply potentially higher levels of indoor air pollutants, while high ventilation can increase the removal of these indoor contaminants (Weschler et al, 1987; Levin, 1991).

One factor that influences the indoor air quality of buildings is chemical interactions and reactions between oxidizing agents and organic molecules found indoors, such as chemicals used as cleaners (Weschler 2004). One such oxidizing agent is ozone, an indoor contaminant with well established links to morbidity and mortality (Lippmann 1989, Weschler et al. 2006). The dominant source of indoor ozone involved in these reactions is ambient outdoor ozone that penetrates indoors (Weschler 2000). Indoor ozone concentrations tend to lag behind outdoor ozone concentration and typically range from 10-50% of outdoor concentrations (Weschler 2006). The indoor/outdoor ozone is affected by multiple factors including ventilation rate, residence time, and limitations in availability of compounds that have fast reactions that reduce ozone concentrations. Removal of entrained outdoor ozone occurs because it reacts with compounds on surfaces, in the air, and in building materials or equipment (Weschler et al. 1992, Nazaroff et al. 2006). Importantly, even though indoor ozone concentrations are reduced, people spend the majority of their day indoors; therefore a substantial fraction of a person's exposure to ozone occurs indoors (Weschler 2006). Furthermore, health risks are increased not only by low-level chronic exposure to ozone, but also by exposure to the irritating byproducts of ozone reactions. Studies published in recent years have shown that the products of these reactions are often more irritating than their chemical precursors (Weschler and Shields 2000, Mølhave et al. 2005, Tamas et al. 2006).

Reactions of ozone with certain organic molecules occurring indoors at typical concentrations can produce short-lived products that are highly irritating and may also have chronic toxicity or carcinogenicity (Weschler 2000, Wolkoff et al. 2000, Wilkins et al. 2001, Destaillats et al. 2006, Nazaroff et al. 2006). Known products of indoor ozone reactions include formaldehyde, acetaldehyde and other organic acids (see Weschler 2006, Table 1 for thorough summary of

ozone reaction products) some of which are known to cause ill health in humans. Formaldehyde, for example, is classified as a carcinogen (Cogliano et al. 2005). Because of their irritancy, it is thought that many of these reaction byproducts have a large impact on the overall indoor air quality of a building (Weschler 2000, 2004).

Mølhave et al. (2005) investigated the interaction between indoor ozone and household dust. Subjects exposed to the dust (75 μg m^{-3} of total re-suspended office dust) and ozone (300 ppb = 590 μg m^{-3}) treatments in climate controlled chambers for 3 hours had significantly ($p<0.05$) reduced peak expiratory flow (a measure of respiratory function) when compared to subjects from the ozone only or dust only treatments. Subjects exposed to the dust-ozone treatment also reported a significant increase in the "feeling of dry eyes" ($p<0.03$), "feeling of sleepiness" ($p<0.02$) and "feeling of skin irritation" ($p<0.02$) when compared to subjects in the two other exposure groups. These negative health symptoms (dry eyes, sleepiness and skin irritation) are similar to the symptoms that occupants report when they experience BRS, suggesting that indoor ozone chemistry may play a role in BRS.

More recently Tamás et al. (2006), varied ozone and limonene concentrations in occupied test office spaces and found similar interactions as the Mølhave et al. study. One of the most interesting findings from Tamás et al.'s work was that 40 ppb of limonene with no ozone did not affect the perceived air quality of a room, but when ozone was added to the room with 40 ppb of limonene, such that ozone's residual concentration was 32 ppb (a typical urban indoor concentration), nearly half of the of participants became dissatisfied with the perceived indoor air quality. In addition, the combination of ozone and limonene resulted in substantially greater sensory pollution loads (measured in Olfs) than either limonene or ozone alone. These results suggest the interactions between ozone and limonene (and possibly other terpenes) can seriously impact the perceived indoor air quality and may impact the health of occupants as well.

While these lab studies suggest that a relationship between ozone and ill health symptoms may exist, there is a lack of studies that have found the same link outside of the laboratory. Few, if any, field experiments or analyses of field data have been conducted to determine if such an association is detectable. The analysis presented here attempts to identify ozone-BRS relationships using data obtained from office workers during the US EPA Building Assessment Survey and Evaluation (BASE) study of 100 US office buildings.

We hypothesized that given the knowledge of indoor ozone-driven reactions and the potential for physiological effects of the products from these reactions, increasing levels of outdoor ozone would lead to higher prevalence of BRS among occupants within a building. This was predicted to occur through higher transfer rates of ozone into the indoors increasing the quantity of irritating VOC oxidation products from ozone-VOC reactions indoors. It is known that the resulting reaction products are harmful compounds and that occupants will be exposed to them when they are present. It is expected that at sufficient levels of exposure to these contaminants the occupants would experience irritant and possibly other health symptoms and that the symptoms would diminish with the removal of exposures, consistent with the definition of BRS.

Methods

Data

The data used in this analysis were gathered during the US EPA BASE study that took place from 1994-1998. Each of the 100 randomly selected office buildings was studied for one week either during the winter or summer. The BASE study collected data on environmental factors (e.g. indoor and outdoor temperature, relative humidity, CO_2 concentrations, and selected VOCs), study space ventilation rates, building characteristic (e.g. heating, ventilation, and air conditioning [HVAC] system configuration and maintenance), workplace factors (e.g. cleaning schedules, cleanliness, occupant density) and personal factors (e.g. age, sex, medical conditions, smoking status, health symptoms). Personal data were collected via a confidential self-administered questionnaire distributed to the occupants. Further details of the building selection process and study methodologies have been discussed elsewhere in greater detail (Womble et al. 1993, Womble et al. 1996, EPA 2003).

VOC concentrations were measured indoors at three locations in each study space. Sampling was conducted on Wednesday of the study week and consisted of workday (approximately 08:00-17:00) time weighted averages. Three sampling methods were employed to measure VOCs: dinitrophenyl hydrazine (DNPH) was utilized for formaldehyde and acetaldehyde while SUMMA® canisters and multisorbent tubes were used for the remaining compounds (EPA 2003).

Neither indoor nor outdoor ozone concentration measurements were included in the original BASE study. The EPA acquired (blindly through a third party contractor) contemporaneous outdoor ozone concentration data from historical records of ambient air quality monitoring stations near the study buildings after the BASE study data collection was completed. No information is available on the indoor ozone concentrations of the BASE study buildings.

Variables

This analysis uses the weekly definition of BRS utilized by previous studies which analyzed the BASE data (Apte et al. 2000, Erdmann and Apte 2004). A health symptom was classified as building related if both of the following conditions were met: 1) the symptom occurred on at least 1 day per week during the four weeks prior to administration of the questionnaire and 2) the symptom got better when the occupant was away from his/her work environment. Both criteria were determined from occupant response on the self-administered questionnaire.

Four individual BRS were analyzed. Individual symptoms included: cough, dry eyes, dry/irritated skin, and headache. In addition, three aggregate BRS categories were constructed: lower respiratory (LR), upper respiratory (UR) and neurological (NEURO). Aggregate BRS categories were defined as the presence of at least one of the respective symptoms: LR (wheeze, shortness of breath or chest tightness), UR (nose/sinus congestion, sore throat or sneeze) and NEURO (fatigue or trouble concentrating).

Four continuous variables were created from the ozone data. Hourly ozone data from the day when the self-administered questionnaire was taken (typically Thursday) were used to construct

a 24-hour average concentration variable (AVOZ), an average workday (08:00-17:00) concentration variable (WDOZ), and an average late workday (15:00-18:00) concentration variable (LWDOZ). AVOZ, WDOZ and LWDOZ were scaled by a factor of 10 to make interpretation of results more intuitive. Thus AVOZ, WDOZ and LWDOZ have units of 10 $\mu g\ m^{-3}$. (See Appendix 1 for details of the ozone data). The fourth ozone variable, WEDOZ, consists of the workday (08:00-17:00) ozone concentrations on the day when VOC monitoring occurred.

Indoor VOC concentration data from three locations within each study space were averaged to obtain an average VOC concentration for each building. The choice of VOC data (canister or multisorbent) used in this analysis varied based on the individual compound and its sampling characteristics. The data selected for each compound were based on which sampling method had the fewest concentration measurements below the sampling method's respective lowest detection limit in order to use the best available information. Preference was given to sampling methods that were consistent across as many buildings as possible. This was an issue because the specific VOC analytes were changed in the study protocol several times during the course of the BASE study, so that many of the compounds were not measured in all buildings.

Statistical Methods

The statistical analyses reported in this paper were conducted using SAS 8.2 software for Windows PC (SAS 1989) using established biostatistical methods (Kleinbaum et al. 1982, Selvin 1995). The relationship between ambient ozone concentrations and BRS in the BASE study was analyzed using the SAS Logistic procedure. We calculated odds ratios (ORs), Wald Maximum Likelihood (WML) statistics, 95% confidence intervals and p-values. Crude (unadjusted, bivariate logistic regression) and adjusted (multivariate logistic regression) models were constructed for each of the four individual symptoms and the 3 aggregate symptom categories. The explanatory variables of interest were AVOZ, WDOZ and LWDOZ. Each explanatory variable was examined in a separate set of logistic regression models.

Adjusted logistic models were controlled for personal, environmental and workplace factors that were suspected to confound the BRS-ozone relationship. Covariates used in the adjusted models included occupant sex, environmental sensitivities, age and smoking status, thermal exposure, indoor minus outdoor carbon dioxide concentration (dCO_2) as an indicator of ventilation per occupant, indoor relative humidity (RH), TMB (a tracer of outdoor automobile pollution), building heating and cooling degree days[1] (HDD and CDD) and the season in which the building was studied. Details of the selection process and methods of calculation for each of these variables can be found in Apte et al. (Apte et al. 2000) and Erdmann and Apte (Erdmann and Apte 2004).

Each ambient ozone variable, in addition to inclusion in MLR models as single continuous variables, was also modeled in two alternate forms. A categorical variable for ozone, using

[1] Heating degree days and cooling degree days are calculated over a year by adding up the differences between each day's mean daily temperature and the temperature of 18°C (or 65°F), above or below which the building is assumed not to need any heating or cooling, respectively.

dummy variables, represented five levels of exposure, to assess the dose-response relationship between ozone and BRS. The five categories represented quintiles of the ozone data, using the lowest quintile (bottom 20%) as a reference level. Finally, interval-level variables, with values of 1-5 representing the quintile categories, were used in the MLR models to determine the significance of an assumed linear dose-response relationship. The WML statistic and associated p-value for this interval-level variable was used as a measure-of-fit of the dose-response relationship for the adjusted categorical associations between ozone measures and BRS (SAS 1989).

To determine the possibility of ozone-initiated indoor chemistry, VOC concentrations were correlated with WEDOZ (averaged 1-hour ambient ozone concentrations contemporaneous with the VOC sampling) and Pearson correlation coefficients (r-values) were calculated. Compounds were eliminated if $r<0.10$. This was done because with such a small r-value the magnitude of the relationship between ozone concentration and VOC concentration is negligible.

Results

Ozone Data

Ambient ozone data were available for all 100 buildings in the BASE study; however, one building was missing data for Wednesday. The distributions of the four continuous ozone variables are presented in Figure 1. The ranges for AVOZ, WDOZ, LWDOZ and WEDOZ were 4.9-132 $\mu g\ m^{-3}$, 4.9-169 $\mu g\ m^{-3}$, 4.9-210 $\mu g\ m^{-3}$ and 4.9-166 $\mu g\ m^{-3}$, respectively. The means for each variable were 50, 67, 71 $\mu g\ m^{-3}$ and 66 $\mu g\ m^{-3}$, respectively. Only one building had its workday average ambient ozone concentration (WDOZ) greater than 157 $\mu g\ m^{-3}$ (80 ppb, the 8-hour National Ambient Air Quality Standard, NAAQS).

Study Population

Building occupants returned over 4,200 questionnaires, which corresponded to a response rate of about 85%. The majority of respondents were female (66%), non-smokers (85%), over the age of 40 (55%) and had at least one doctor diagnosed or self-reported sensitivity to the environment (81%). Environmental and workplace parameters were described fully by Erdmann and Apte (2004).

Using data from the questionnaires and the BRS definition, the prevalence of the four individual BRS ranged from 4.7%-18.6%, while the prevalence for the three aggregate BRS categories ranges from 4.2%-21.0% (Table 1).

Ozone-BRS Logistic Regression Results

Results from the logistic regression analyses are presented in Tables 2, 3 and 4. Crude and adjusted odds ratios (ORs) along with their 95% confidence intervals and p-values from the AVOZ and WDOZ analysis are presented in Tables 2 and 3, respectively. Model results were very similar for these ozone variables. Of note is that in crude and adjusted models, for both ozone variables, the odds ratios were consistently above unity for all BRS excepting “Dry Skin.”

In the crude models, UR and NEURO had significant ($p<0.05$) positive relationships with outdoor ozone concentrations. After adjusting the models for personal, environmental and building characteristics, only UR remained significantly associated with outdoor ozone at the 95% confidence level and p-values for LR and dry eyes were 0.06 and 0.09, respectively.

The estimates from the LWDOZ analysis (Table 4) show more statistically significant elevations. In the crude models, significant ($p<0.05$) ORs for UR, cough, dry eyes, NEURO, and headache BRS ranged from 1.02-1.03 per 10 $\mu g\ m^{-3}$. In the adjusted models UR, dry eyes, NEURO and headache were significant at the 95% confidence level. LR was found to be marginally significant ($p=0.09$). Although the LWDOZ point estimate ORs are identical to or even lower than for AVOZ, the confidence intervals are narrower, making LWDOZ more significant. This observation is discussed below.

Dose-Response Analysis

Figure 2 shows estimates for associations of the categorical levels of ozone, and the p-values for trend in dose-response, for LWDOZ and BRS after adjustment for personal, workplace and environmental factors. LWDOZ had the strongest and most significant relationship to BRS, so its dose-response results are presented here. Visually LR, UR, dry eyes and headache seem to indicate increasing odds of illness as ozone concentration increase; however, one of the ozone level ORs for each symptom deviated from the expected pattern. The results of the interval-level ozone variable MLR that was used to test for significance of a linear trend indicate, however, that only UR had a significant ($p<0.05$) linear dose-response relationship with LWDOZ.

Covariates in Adjusted Models

For completeness it is necessary to include information on the statistical associations between the model covariates and the BRS outcome. Many of the covariates had significant ($p<0.05$) relationships with the BRS symptoms. The magnitude of the ORs and their significance were similar between the three sets of models. Using the LWDOZ models as an example, the statistically significant relationships between the covariate and the respective symptoms are summarized in Table 5. The behavior of covariates "Season", and "dCO_2" in the models is of interest and is discussed below.

VOC and Ozone Correlations

The WEDOZ-VOC correlation analysis contained a total of 40 compounds. The number of buildings in which specific VOCs were sampled ranged from 13 to 100 depending upon the compound because the VOC analysis protocols changed during the study. All but one building had ozone data for Wednesday; therefore the maximum sample size in the analysis was 99 buildings. Table 6 shows the Pearson Correlation results for the 20 VOCs with $r \geq 0.10$. Nonanal was most strongly associated with increasing outdoor ozone ($r = 0.60$; $p < 0.0001$). Other aldehydes (acetaldehyde, pentanal and hexanal), as well as 1-butanol, the texanol isomers, 2-butoxyethanol and chloromethane also were positively associated with increasing outdoor ozone ($p < 0.05$). In contrast, benzene, ethylbenzene and o-xylene were negatively associated (of these, only benzene had a p-value < 0.05).

Discussion

While these results do not demonstrate causality, they show that increased outdoor ozone concentrations are consistently associated with the reporting of certain BRS symptoms in office workers. In all three sets of ozone models the consistency of the ORs exceeding 1 (given the null hypothesis of no relationship) suggests a robust positive association between ozone and some BRS, and a study that is too small to clearly detect this association for several other symptoms.

The observation that a lack of statistical power exists is underscored when we look at LR and cough. Building-related LR and cough generally have much lower prevalence in office workers (here 4.2% and 5.1%, respectively) than those symptoms that had statistically significant relationships with ozone (e.g., UR, eyes, NEURO, headache, with prevalences here ranging from 15-21%). LR and cough, despite increased ORs of the same magnitude as the outcomes with low p-values, had P-values ranging from 0.06-0.12 and were not significant at $p<0.05$ in any of the adjusted models. Outcomes with only 5% prevalence require larger sample sizes to detect a significant difference at the 95% confidence level, and thus the study was underpowered to detect ORs of the size seen. To study these outcomes, a larger sample size of building occupants or a more sensitive outcome measure will be necessary in future studies.

Ozone Data

It should be noted that the distance from each BASE building to the corresponding ambient ozone monitoring station varied from less than 0.5 km to over 300 km. This was because many of the buildings studied in the winter season were nearest to ozone monitoring sites that did not record hourly ozone concentrations in the winter. In this case the next nearest hourly monitoring site that was collecting data were used. When the logistic regression models presented here were redone using only data from ozone monitoring stations that were less that 24 kilometers from the buildings (a natural cut point given the distribution of the distances from ozone monitoring site to their respective buildings) no major changes in the observed associations occurred. Therefore, in order to be more representative of the entire BASE data set and of the United States office building stock as a whole, the analyses using all of the data are presented here.

That only one building in these analyses experienced WDOZ concentrations greater than the NAAQS has major implications for the relevance of the findings in this study. First, the ambient ozone conditions are typical of those experienced in the U.S. Second, since the analyses are based on ozone concentrations that are low relative to the NAAQS, the observed risks are based on conservative conditions. Third, the results suggest that the NAAQS may not be low enough to protect against building related symptoms across much of the U.S.

Multiple Logistic Regression Results

When interpreting the ORs in these analyses, it is important to realize that they estimate the average increase in odds of BRS for every 10 $\mu g\ m^{-3}$ increase in outdoor ozone concentrations, assuming a linear relationship and that the ozone/BRS relationship is causal. The observed ORs translate into roughly a 3-4% increase in BRS risk for every 10 $\mu g\ m^{-3}$ increase in ambient ozone concentration. If one considers the large range of ozone concentrations present in this analysis

(AVOZ: 127 μg m^{-3}, WDOZ: 164 μg m^{-3} and LWDOZ: 205 μg m^{-3}) a 3-4% increase in the odds of having BRS per 10 μg m^{-3} increase in ozone becomes a very large increase in overall odds for those occupant in building with high outdoor ozone concentrations. Using the LWDOZ analysis as an example, with the occupants of buildings with the mean ozone concentration (71 μg m^{-3}) as the referent, those in buildings with the highest ozone concentration (210 μg m^{-3}) have an effective increase in odds of 68%, 49%, 49% and 43% for having UR, dry eyes, neurological, and headache BRS, respectively. If one now uses the occupants from the lowest ozone "exposure" buildings as the reference group, the odds of occupants in the highest ozone "exposure" buildings having BRS increases substantially by 114%, 80%, 80% and 69% for UR, dry eyes, neurological, and headache, respectively.

Continuing to use the LWDOZ models as examples and using the percent risk reduction (PRR) calculation, as done in Erdmann and Apte (Erdmann and Apte 2004) and Apte et al. (Apte et al. 2000), we can estimate the percentage of BRS that office workers suffer that is due to increased outdoor ozone concentrations. These PRR analyses assume that the findings in this study are repeatable with similar results in new research. The PRR calculations suggest that, if reductions were made in ambient ozone levels entrained into the building to the lowest level observed in the BASE study (4.9 μg m^{-3}), building sites one could expect to see a 48%, 35%, 35% and 33% reduction in UR, dry eyes, NEURO and headache BRS, respectively. These reductions assume that the relationship between ozone and BRS is causal and that all other factors are held constant while ozone reductions are made. This potential to cause large reductions in the BRS indicates another large benefit from reducing outdoor ozone concentrations. More practically, reducing the amount of outdoor ozone that enters into the indoor environment may be a viable alternative. The latter can be accomplished using various types of carbon based filter technologies or absorbent filter materials (Gundel et al. 2002, Shair 1981, Shields et al. 1999, and Kelly and Kinkaid, 1993).

It is interesting that the strongest and most significant relationships between ozone and BRS were in the model using late workday concentrations of outdoor ozone. Exposures to products of indoor chemistry are expected to peak shortly after ozone levels reach their peak and this typically occurs in the late afternoon. The LWDOZ data reflect the concentrations at this time period.

Dose-Response

The dose-response analysis for LWDOZ presented in Figure 2 showed somewhat noisy point estimates and confidence intervals, but this is expected due to the reduction of power caused by dividing the data into quintiles. However, even with this reduction in power, a dose-response trend appears to be present for several of the symptoms and a linear dose-response trend is significant for UR. The fact that only UR had a significant p-value should be taken in perspective as this value was obtained under the assumption that the dose-response relationship is in fact linear on the logarithmic scale of odds ratios. The lack of significant dose-response relationships for other symptoms and the non-linear dose-response patterns for some symptoms may indicate a more complex dose-response behavior for ozone and BRS, or may merely indicate the need for greater statistical power. Both considerations should be kept in mind, so that future studies or analyses do not assume that ozone and BRS have a linear relationship.

Covariates in Model

Results from the MLR models suggest that BRS prevalence is greater during the winter. This may be due to misclassification of seasonal illnesses (such as colds or influenza), or may be an indicator of another, undetermined environmental/seasonal risk factor for BRS. Consistent with the other BRS studies, females had increased risk of BRS when compared to males. It is unknown if this has to do with reporting bias, or biological differences, or differences in jobs or work environments. The most noteworthy personal risk factor for BRS in the models was the environmental sensitivity variable, indicating that occupants who had doctor diagnosed or self reported environmentally mediated illnesses, such as asthma, allergies or sensitivity to tobacco smoke, were at substantially increased risk of having BRS. The consistency of the ORs for HDD and CDD being less than 1 indicates that occupants of buildings with greater cooling and heating needs (i.e. climates with more extreme low and high temperatures) have levels of BRS. This is consistent with the literature indicating that mechanical ventilation and especially air conditioners are risk factors for BRS (Seppänen and Fisk 2002). The lack of consistency in the associations between thermal exposure and BRS (ORs for symptoms were both above and below unity and no relationships were statistically significant) may indicate that thermal exposure in the ranges found in the BASE study does not play a large role in determining the overall risk for occupant BRS, or that there is a non-linear relationship between these factors.

One of the most interesting findings that emerged during the examination of the covariates in the MLR models was the lack of significant relationships between dCO_2 and BRS symptoms (with the exception of UR). Previous studies (Apte et al. 2000, Erdmann and Apte 2004) have found statistically significant links between increasing levels of indoor minus outdoor CO_2 and combined mucous membrane, dry eyes, sore throat, nose/sinus, sneeze, and wheeze BRS. The BRS definitions in that study were very similar, and in some cases identical to those in the current analyses (Table 7). It was argued that increased dCO_2 was proportional to lower per-person ventilation rate, and in turn, to increasing levels of indoor air contaminants. It was inferred that the inverse association of ventilation with symptoms was because ventilation removed indoor air contaminants that were causing symptoms. Additional study is required to better understand the impact of ambient ozone entrainment into buildings on the relationship between dCO_2 and symptoms

Winter season, after controlling for ozone and the other covariates in the model, had odds ratios for BRS consistently greater than unity, indicating significant, 27% to 53% increased prevalences of cough, UR, dry eyes and headache . All non-significant symptoms also had ORs>1. When the ozone covariate was excluded from the multivariate models, the SEASON variable was only weakly associated with BRS (data not shown), with ORs that ranged from about 0.99 to 1.3 with no clear pattern related to symptom class. Only the UR symptoms were statistically significant (OR = 1.23, p = 0.02). Addition of the ozone variable appears to adjust for the seasonal variability of ozone-related effects such that an additional, unexplained winter season effect, not explained here, is now visible.

VOC-Ozone Correlations

The result of the WEDOZ-VOC correlation should be viewed as qualitative in nature. This is because there was such variation in the sample size between different VOCs, and because variation in the sources of VOC makes the detection of such a relationship between ozone and certain VOC difficult given the experimental methods employed in the BASE study (i.e. post-study collection of outdoor ozone data, no data on indoor ozone concentrations and no real-time VOC concentration data). In other words, one should primarily concentrate on the direction of the association (positive or negative) and the magnitude of association.

The VOC correlation analysis presents evidence that indeed, ozone chemistry is taking place and may be contributing to the observed BRS prevalence in the buildings. In the absence of ozone chemistry, one would expect the indoor concentration of VOCs in the study buildings to vary randomly, without correlation with the indoor or outdoor ozone concentrations. Of interest, formaldehyde acetaldehyde, pentanal, hexanal and nonanal, which are known products of indoor ozone chemistry, have fairly large, positive r-values, indicating that the relationship between ozone and these compounds track together in a positive direction. The association between ambient ozone and nonanal is particularly strong. Thus with increasing ozone concentrations, and therefore increased ozone reactions with unsaturated hydrocarbons, we would expect to see an increase in aldehyde production, which we do.

Three compounds, benzene, ethylbenzene and o-xylene, are all present in motor vehicle exhaust. In many cases outdoor-to-indoor transport is the major source of these compounds in indoor air. Motor vehicle exhaust also contains nitric oxide (NO), which reacts very quickly with ozone in the gas phase (Weschler and Shields, 1994). The observed negative correlations of benzene, ethylbenzene and o-xylene with ozone may reflect the co-occurrence of these compounds and NO in motor vehicle exhaust. Unfortunately, NO was not measured in the BASE study so this hypothesis cannot be verified by examining for a negative correlation between ozone and NO.

A prior analysis (Apte and Erdmann 2002) of the BASE data examined the relationships between specific VOC concentrations and BRS symptoms and found no consistent trends. In logistic regression analyses, no clear patterns of relationships or trends between individual VOC concentrations and BRS were found with the exception of d-limonene. In these prior analyses the ORs for d-limonene was statistically significant ($p<0.05$) for 4 out of the 6 symptoms and ranged from 0.91-0.97 per ppb, indicating that increasing levels of d-limonene were protective against BRS (or conversely, that decreasing level of d-limonene increased occupants risk of BRS). One cause of decreased levels of d-limonene is reactions of d-limonene with ozone. Thus increased d-limonene concentrations may appear protective because they indicate fewer ozone-d-limonene reactions, and therefore fewer harmful reaction products indoors. This hypothesis is consistent with finding by Tamas et al. (2006) which showed that d-limonene and ozone interactions affected odor more than either d-limonene or ozone alone.

Analysis and Statistical Limitations

While the results of the analyses presented here lend support to the hypothesis that ozone chemistry affects human health and BRS, the limitations of the cross-sectional study design limits any causal conclusions. However, prior information on biological and physical

mechanisms lends plausibility to the hypothesis of a causal link between ozone and BRS. From a biological perspective, studies have shown that the interaction and reaction of ozone with indoor pollutants increase negative odors indoors (Tamas et al. 2006) and can reduce study participants' respiratory function (Molhave et al. 2005). Physically, studies have shown that harmful reaction products are produced from ozone reactions with indoor pollutants (Wolkoff et al. 2000, Wilkins et al. 2001, Destaillats et al. 2006, Nazaroff et al. 2006). These two facts support the need for further studies to establish if there is a causal link between ozone and BRS.

In addition, the use of outdoor ozone data collected at varying distances from the study buildings limits the accuracy of results, as does the absence of indoor ozone data. One important element that should be incorporated into future studies is the collection of detailed real-time data on specific VOCs whose increase or decrease in concentrations can be used to trace ozone oxidative chemistry and whose indoor sources are known and well understood. This will enable researchers to track the interrelationship between ozone concentrations, VOC concentrations and the prevalence of BRS within a study space.

While questionnaire data on symptoms and other personal variables were collected at the individual level, environmental variables for each individual were based on study space averages. The VOC values assigned to each study participant are thus inexact, and by contributing measurement error, tend to lead to underestimates for any risk factors. More detailed studies which attempt to classify actual individual level exposure to environmental variables would be needed to remove this source of possible bias, but this would involve tremendous costs if using current exposure assessment methods. A related statistical limitation of this study comes from the study design itself. Study space averages or study space-level data for all environmental variables were applied to each occupant, but the analyses used the individual occupant as the unit of analysis. Thus the individual level observations included in the statistical models are not truly independent from each other, because the working environment was shared by all study occupants within each building. And occupants within each building may be more correlated with each other than with those in other buildings, in ways not accounted for in logistic regression models. In general, analyzing such data as if individuals were fully dependent will result in some overestimation of the true precision of estimates. Prior analyses of BASE data using generalized estimating equations to adjust for these potential correlations, however, have shown that the effects on precision are minimal (Mendell et al. 2006).

Emerging Areas of Interest

Continued study is needed to fully explore the role that ozone indoor chemistry plays in BRS. One emerging area is the interaction of ozone and ventilation air filters in the mechanical ventilation systems of buildings. Ozone that is present in the air must pass through an air filter in entering the HVAC system from outdoors and when being recirculated indoors. This provides a surface where chemical reactions can occur. A recent study using used air filters found reductions in downstream ozone concentrations (Beko et al. 2006), indicating that ozone was being destroyed on or in the filter itself. A new facet to this line of research explores what effect the type of filter medium has on BRS within a building (Buchanan and Apte 2006). An interaction between ozone and air filters may help to further explain the causes of BRS in the workplace.

Not only might reducing indoor ozone reduce the amount of BRS in a building, but new studies suggest that reduction of even low levels of chronic exposure to ozone may reduce overall mortality rates as well (Bell et al. 2006). Thus, indoor mitigation and reduction of ozone may serve a dual purpose: reduction of BRS and the reduction of direct ozone-mediated mortality. Although replication of this work is necessary, findings of this study strengthen the argument for controlling the entry of ozone into the indoor environment. Such measures would be most helpful, in locations where outdoor environments have elevated ozone concentrations, in preventing high levels of ozone from entering into buildings through HVAC systems. Such measures were discussed briefly in Weschler et al. (2006), and may include both enhanced filtration in mechanical ventilation systems and scheduling strategies for both mechanical and natural ventilation systems. Carbon filters have been shown continuously effective, for over three years (Weschler, 1994) or even longer (Weschler et al. 2006), at removing large fractions of ozone from incoming ventilation air when sufficient carbon was employed.

Overall Results

Overall, the analyses of ambient ozone associations with BRS in the BASE study data produced the following information.

- Only one of the 100 BASE buildings had daytime ambient ozone levels in excess of the US EPA NAAQS of 157 $\mu g\ m^{-3}$ during the study time period
- In both crude and adjusted models, the odds ratios for ozone were consistently above unity for all BRS excepting "Dry Skin"
- BRS were most strongly associated with ambient ozone averages that included the late workday time period.
- When comparing the BRS risk for occupants of buildings with the mean level of late workday ozone concentration (LWDOZ, 71 $\mu g\ m^{-3}$) to risk for those in buildings with the highest observed ozone concentration (210 $\mu g\ m^{-3}$) an increased odds of 68%, 49%, 49% and 43% for having UR, dry eyes, neurological, and headache BRS, respectively was found.
- Likewise, when comparing the BRS risk for occupants of buildings with the lowest observed late workday ozone concentration (LWDOZ) to those in buildings with the highest observed ozone concentration, the risk of having BRS increases substantially, to 114%, 80%, 80% and 69% for UR, dry eyes, neurological, and headache symptoms, respectively.
- By reducing ambient ozone levels entrained into buildings to the lowest level observed in the BASE study (4.9 $\mu g\ m^{-3}$), one might (if associations observed here were causal) expect to see a 45%, 35%, 35% and 33% reduction in upper respiratory, dry eyes, neurological and headache BRS, respectively.
- BRS risks appear in many cases to have a dose-response trend with increasing outdoor ozone levels. The upper respiratory symptom group was observed to have a linear and statistically significant trend of increasing symptom prevalence with increasing outdoor ozone levels.
- Formaldehyde, acetaldehyde, pentanal, hexanal and nonanal, known products of indoor ozone chemistry, showed fairly large positive correlations with ozone. The association between ambient ozone and nonanal was particularly strong. All these compounds are known sensory irritants and some are known carcinogens.

Conclusions

A clear relationship between ambient ozone concentrations and building-related health symptoms has been identified in this study. The hypothesis that the cause of these symptoms is ozone-initiated indoor chemistry is supported by the positive correlation between ozone and aldehydes. Caution must be taken not to place too much credence on this single study, and replication is needed to verify the findings. If additional studies support these findings, the implication is that reduction of ambient ozone entrained into building HVAC systems before it can react with indoor air and surfaces has the potential to significantly reduce building related symptoms.

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Tables

Table 1: Number of respondents to survey questions (n) and the prevalence of BRS symptoms in the 100 building BASE study.

BRS	n	Prevalence
LR	4318	4.2%
Cough	4260	5.1%
UR	4308	21.0%
Dry Eyes	4245	18.6%
Neurological	4313	19.2%
Dry Skin	4201	4.7%
Headache	4249	15.2%

Table 2: Crude and adjusted association per 10 μg m^{-3} between 24-hour ozone (AVOZ) and BRS including ORs, 95% Confidence Intervals and p-values.

BRS	Crude Models			Adjusted Models		
	OR	95% CI	p-value	OR	95% CI	p-value
LR	1.04	0.99-1.1	0.14	1.07	1.00-1.15	0.06
Cough	1.02	0.97-1.07	0.52	1.05	0.99-1.12	0.12
UR	**1.03**	**1.01-1.06**	**0.02**	**1.04**	**1.01-1.08**	**0.02**
Dry eyes	1.02	1.00-1.05	0.11	1.03	1.00-1.07	0.09
NEURO	**1.03**	**1.00-1.06**	**0.05**	1.03	0.99-1.07	0.16
Dry Skin	0.97	0.92-1.03	0.29	0.99	0.92-1.06	0.74
Headache	1.03	1.00-1.06	0.08	1.03	0.99-1.08	0.13

Table 3: Crude and adjusted association per 10 μg m^{-3} between workday ozone (WDOZ) and BRS including ORs, 95% Confidence Intervals and p-values.

BRS	Crude Models			Adjusted Models		
	OR	95% CI	p-value	OR	95% CI	p-value
LR	1.03	0.99-1.07	0.14	1.05	0.99-1.1	0.10
Cough	1.01	0.97-1.05	0.56	1.04	0.99-1.09	0.12
UR	**1.02**	**1.00-1.04**	**0.05**	**1.03**	**1.00-1.06**	**0.03**
Dry eyes	1.02	1.00-1.04	0.11	1.02	1.00-1.05	0.10
NEURO	**1.02**	**1.00-1.04**	**0.06**	1.02	0.99-1.05	0.19
Dry Skin	0.98	0.94-1.02	0.21	0.99	0.94-1.04	0.65
Headache	1.02	1.00-1.04	0.13	1.02	0.99-1.05	0.18

Table 4: Crude and adjusted association per 10 μg m^{-3} between late workday ozone (LWDOZ) and BRS including ORs, 95% Confidence Intervals and p-values.

BRS	Crude Models			Adjusted Models		
	OR	95% CI	p-value	OR	95% CI	p-value
LR	1.03	1.00-1.06	0.08	1.04	1.00-1.08	0.09
Cough	1.02	0.99-1.05	0.23	1.03	0.99-1.07	0.11
UR	**1.03**	**1.01-1.05**	**<0.001**	**1.04**	**1.02-1.06**	**0.001**
Dry eyes	**1.02**	**1.01-1.04**	**0.01**	**1.03**	**1.01-1.05**	**0.01**
NEURO	**1.03**	**1.01-1.05**	**0.002**	**1.03**	**1.01-1.05**	**0.02**
Dry Skin	0.99	0.95-1.02	0.37	0.99	0.95-1.04	0.79
Headache	**1.02**	**1.00-1.04**	**0.03**	**1.03**	**1.00-1.05**	**0.04**

Table 5. Associations between BRS symptoms and covariates in the LWDOZ MLR models.

Covariate	**Units**	**OR range ($p < 0.05$)**	**BRS variables with $p < 0.05$**	**OR >1 ($p > 0.05$).**
Season[1]	Winter relative to summer	**1.27-1.53**	cough, UR, dry eyes and headache	LR, NEURO, dry skin
Sex		**1.79-2.89**	All symptoms	
Age	40+ years relative to < 40	**1.19-1.42**	LR, cough and dry eyes	UR, NEURO, dry skin
dCO_2	Per 100 ppm	**1.08**	UR	LR, dry eyes, NEURO, dry skin
Smoking status	Current smoker relative to non-smoker	**1.27-1.87**	LR, UR, NEURO, and headache	cough, dry eyes, dry skin
Environmental sensitivities	Sensitve[2] relative to not sensitive	**1.59-4.83**	All symptoms	
CDD	°C-days	**0.98**	UR and dry eyes.	headache
HDD	°C-days	**0.97**	LR	headache
RH	RH < 20%			LR, UR, dry skin
TMB	ppb	**1.18**	Dry skin	LR, UR, cough, dry eyes, NEURO, and headache
Thermal exposure	Per 10 °C-h above 20 °C			cough, dry eyes, NEURO, dry skin

[1] See discussion in text

[2] Presence of at least one doctor diagnosed or self-reported environmental sensitivity

Table 6: Ozone and VOC correlation analysis results ($R \geq 0.10$), sorted by saturation, presence of a carbon-oxygen double bond and r-value.

Compound	r	n	Saturated	C=O	Sampling method
Formaldehyde	0.18+	99	N	Y	DNPH
Acetaldehyde	0.28*	85	N	Y	DNPH
Pentanal	0.40*	40	N	Y	Multisorbent
Hexanal	0.38*	40	N	Y	Multisorbent
Nonanal	0.60**	40	N	Y	Multisorbent
Ethanol	0.49+	13	Y	N	Canister
1-Butanol	0.38*	40	Y	N	Multisorbent
2-Ethylhexanol	0.25	40	Y	N	Multisorbent
Phenol	0.26	40	N	N	Multisorbent
2-Butoxyethanol	0.32*	40	Y	N	Multisorbent
Ethyl Acetate	0.12	69	N	Y	Multisorbent
Texanol 1&3	0.32*	40	N	Y	Multisorbent
TXIB	0.19	40	N	Y	Multisorbent
n-Undecane	0.11	86	Y	N	Canister
Benzene	-0.29*	69	N	N	Multisorbent
o-Xylene	-0.12	69	N	N	Multisorbent
Ethylbenzene	-0.19	69	N	N	Multisorbent
Naphthalene	0.13	69	N	N	Multisorbent
d-Limonene	0.11	99	N	N	Canister
Chloromethane	0.24*	86	Y	N	Canister

+: $p < 0.10$, *: $p < 0.05$, **: $p < 0.0001$

Table 7. Adjusted association between Indoor-Outdoor CO_2 (dCO_2 per 100 ppm) and BRS in the BASE data. Statistically significant associations ($p < 0.05$) printed in bold.

BRS	dCO_2 Ozone Excluded		dCO_2 Ozone Included	
	OR	95% CI	OR	95% CI
LR	**1.16**	**1.02-1.32**	1.11	0.97-1.27
Cough	1.03	0.91-1.17	0.99	0.87-1.14
UR	**1.13**	**1.06-1.21**	**1.08**	**1.01-1.16**
Dry eyes	**1.09**	**1.02-1.17**	1.06	0.98-1.14
NEURO	1.04	0.97-1.12	1.01	0.93-1.09
Dry Skin	1.06	0.94-1.21	1.07	0.93-1.23
Headache	1.03	0.95-1.11	1.00	0.92-1.08

Figures

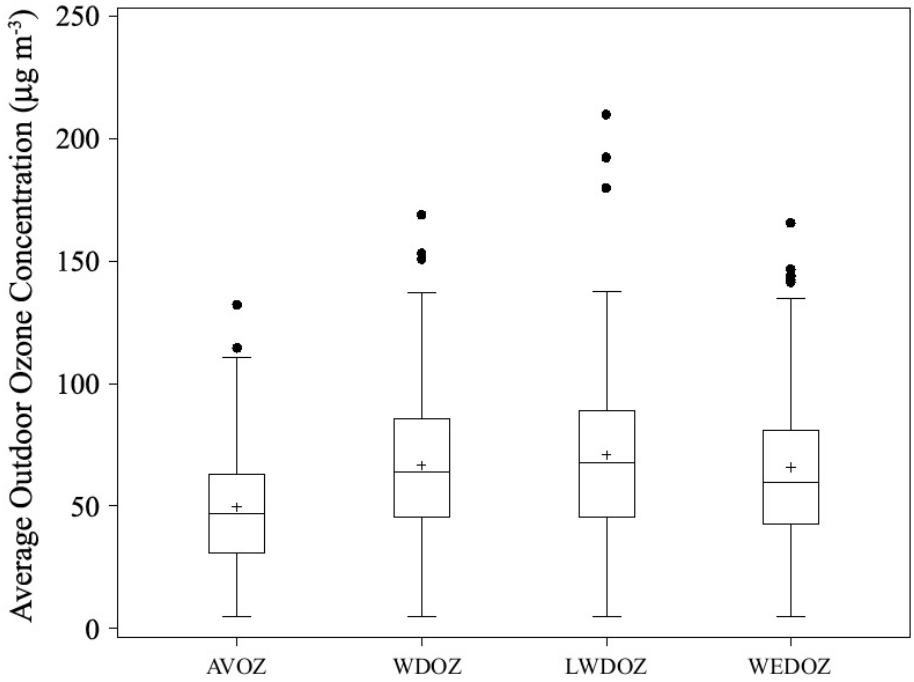

Figure 1: Distribution of the four continuous ozone variables. The large box represents the inter-quartile range (IQR), the "+" is the mean, while the horizontal line dividing the box is the median. The upper and lower whiskers represent the 1.5 times the IQR above the 75th percentile or below the 25th percentile, respectively and the solid dots are values above the upper whisker.

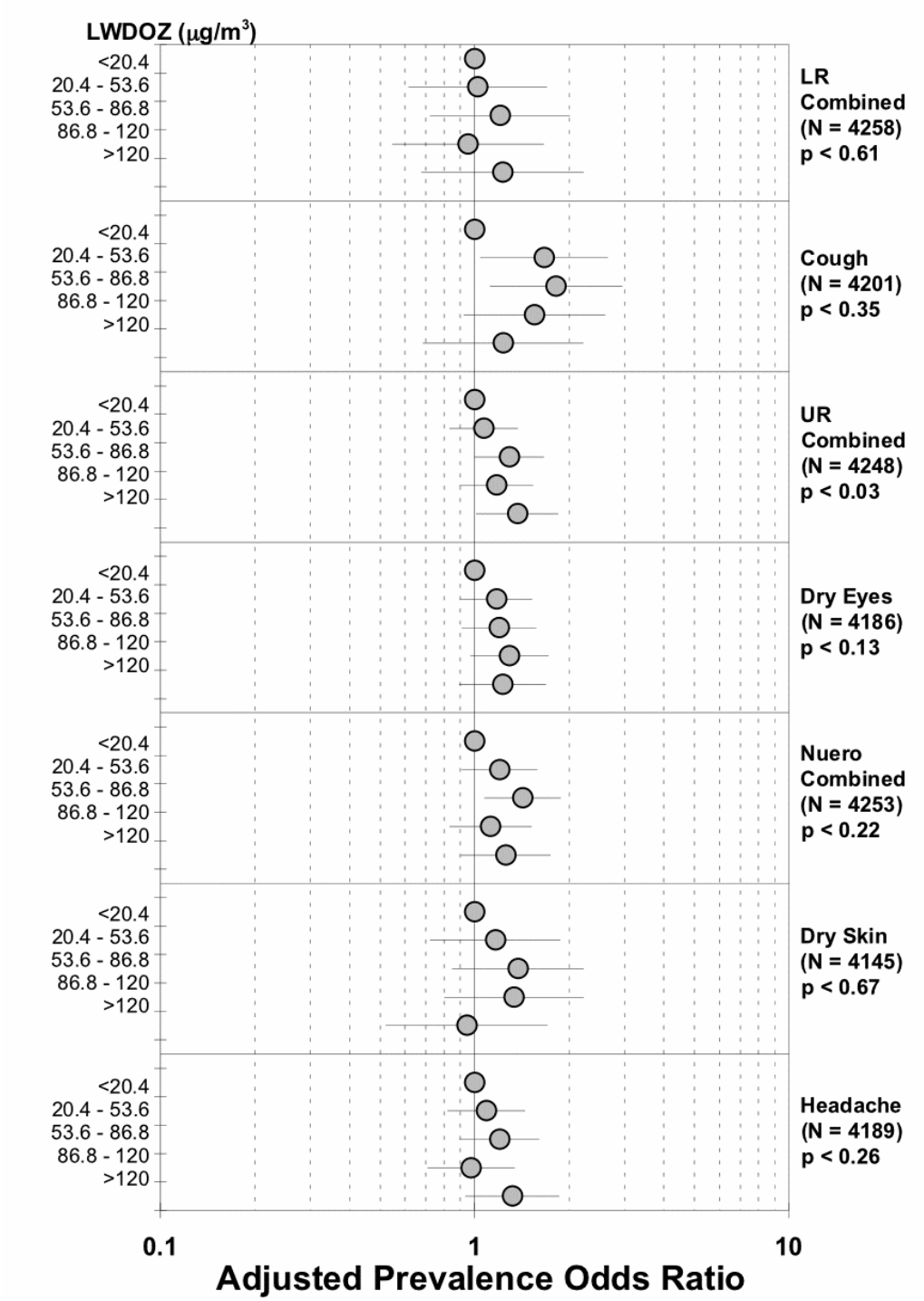

Figure 2: Dose-Response graph for late workday (15:00-18:00) outdoor ozone concentrations (LWDOZ). ORs and their 95% confidence interval are shown for each of the BRS symptoms at the given LWDOZ concentrations, relative to the lowest ozone exposure cohort (<20.4 μg m^{-3}). N is the sample size in the models. The p-values were obtained assuming a linear dose-response relationship between LWDOZ and BRS in a MLR model using a single 5-part categorical ozone variable that represented the five ozone ranges on the left of the figure.

Appendix

List of ozone data: Annual Mean, AVOZ, WDOZ and LWDOZ data in $\mu g\ m^{-3}$

Building	Annual	AVOZ	WDOZ	LWDOZ
ARFW01	49	59	64	61
ARFW02	49	36	41	59
ARFW03	49	81	88	93
AZHS02	59	58	90	86
AZHS04	59	78	105	108
AZHW10	47	58	79	74
AZHW11	47	53	80	50
AZHW12	47	45	74	67
CAES17	57	58	90	99
CAEW07	37	29	56	66
CAEW09	37	44	57	42
CAJS01	29	29	25	27
CAJS02	29	28	25	32
CAJS03	29	37	33	41
CAJS21	32	32	57	65
CAJS22	45	19	19	19
CAJS23	44	33	64	80
CAJW18	55	31	58	50
CAJW19	47	28	60	78
CAJW20	55	58	76	81
CAJW24	35	8	12	5
CAJW25	35	54	70	68
CAJW26	35	41	46	62
COAS02	31	49	66	57
COAS04	31	46	73	48
COAS06	31	31	49	26
FLDW07	51	41	63	76
FLDW08	51	38	57	59
FLDW10	51	36	39	44
FLGS01	62	64	85	79
FLGS04	62	56	64	70
FLGS11	54	22	32	20
FLGS12	54	35	46	30
GADS01	62	73	137	124
GADS02	62	65	114	138
GADS03	57	58	70	100
ILBS01	71	86	88	92
ILBS02	71	66	62	74
ILBS03	71	71	69	110
LAGW04	46	41	61	58
LAGW05	46	41	57	74
LAGW06	46	55	86	73
MABW05	43	11	16	13
MABW06	43	5	5	5
MABW08	43	22	25	41
MDDS01	57	27	25	27
MDDS03	57	91	137	135
MDDS04	57	68	114	120
MIBW01	32	23	24	21
MIBW03	32	7	10	7
MIBW04	32	20	21	20
MNBW01	45	45	67	86
MNBW02	45	54	70	77
MNBW04	45	56	67	81
MOCS01	51	61	77	84
MOCS05	66	85	115	108
NCDW02	54	14	28	17
NCDW03	54	15	23	26
NCDW06	54	46	47	41
NECW01	52	30	35	47
NECW02	52	20	28	24
NECW03	52	60	65	79
NMES01	47	111	124	120
NMES02	58	61	92	83
NMES03	58	52	69	79
NVAW01	46	56	46	51
NVAW02	48	36	53	63
NVAW03	46	38	66	80
NYBS01	49	78	67	83
NYBS02	49	105	151	130
NYBS04	49	55	74	79
NYBS05	55	64	110	116
NYBS06	55	48	67	93
NYBS07	55	132	169	193
ORIS02	35	32	56	56
ORIS03	35	31	56	66
ORIS04	35	33	50	65
PABS03	60	97	127	180
PABS04	60	115	153	210
SCDW01	48	42	54	52
SCDW02	48	9	12	21
SDBW01	60	65	68	70
SDBW02	60	61	59	62
SDBW04	48	13	19	16
TNDS05	66	69	100	96
TNDS06	66	31	51	51
TNDS07	66	75	120	120
TNFS08	59	70	130	124
TNFS09	59	41	66	65
TNFS10	59	46	74	67
TXFS01	50	67	83	87
TXFS02	50	83	112	111
TXFS07	49	58	87	118
TXFS08	49	62	98	120
TXFS09	49	90	117	130
TXFW05	42	19	16	18
TXFW06	54	58	61	58
WAIW01	35	59	58	68
WAIW03	27	31	33	31
WAIW04	27	32	45	48