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Excess prenatal loss and respiratory illnesses of infant macaques living outdoors and exposed to wildfire smoke

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Abstract

Global climate change has transformed predictions of fire seasons in the near future, and record-breaking wildfire events have had catastrophic consequences in recent years. In September 2020, multiple wildfires subjected Oregon to hazardous air quality for several days. In this retrospective cohort study, we aimed to examine prenatal loss, morbidity, and mortality of rhesus (*Macaca mulatta*) and Japanese macaques (*Macaca fuscata*) exposed to poor air quality from the nearby wildfires. Detailed medical records from 2014 to 2020 of 580 macaques housed outdoors at a research facility in Beaverton, Oregon were used to evaluate the association between these health outcomes and wildfire smoke exposure. Logistic regression models estimated excess prenatal loss, hospitalization rates, respiratory problems, and mortality during and following the wildfire event, and Kruskal-Wallis statistics were used to determine if infant growth was affected by wildfire smoke exposure. Risk of pregnancy loss (Relative Risk = 4.1; $p < 0.001$) and odds of diagnosis with a respiratory problem (Odds Ratio = 4.47; $p = 0.003$) were higher in exposed infant macaques compared to non-exposed infants. Infant growth was not affected by poor air quality exposure. Our findings suggest wildfire smoke exposure poses a risk to the health of infants and pregnant individuals and should be monitored more closely in the future.

Keywords

miscarriage; abortion; rhesus macaques; Japanese macaques; air quality

Introduction

Since the Industrial Revolution, greenhouse gas emissions have caused global mean surface temperatures to increase by over 1°C, and substantial changes in weather extremes are expected if the anthropogenic greenhouse gas emissions continue to raise global temperatures an additional 1°C before the end of the 21st century (Allen, 2018; Hoegh-Guldberg & J.Guiot, 2018). The increased daily temperature is expected to lengthen the wildfire season across the world and lead to more frequent wildfires per year, particularly in Canada, Brazil, China, Australia, Russia, and the western United States (Sun Q, 2019). If the global temperatures rise unchecked 4–9°C by 2100, the fire season of the Pacific Northwest

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Region of the United States is predicted to increase by nearly two months and the chances of large fires could increase as much as 8-fold in local regions such as the Clackamas River basin near Portland, Oregon (Davis et al., 2017; McEvoy et al., 2020; Thomson et al., 2011). These predictions are dire to address because this area already is suffering from the annual wildfire season and wildfire smoke with the current climate.

In early September 2020, a series of wildfires known as the Labor Day fires started that burned 340,353 hectares of forest in western Oregon and Washington over two weeks (Abatzoglou et al., 2021; Reilly et al., 2022). The resultant wildfire smoke generated record-breaking poor air quality that blanketed the Portland, Oregon metropolitan area. Pollutants released into the atmosphere from the nearby wildfires made the air hazardous to breathe (Navarro & Vaidyanathan, 2020). While public health agencies recommended people stay indoors and limit their exposure to the poor air quality as much as possible, nonhuman primates at the Oregon National Primate Research Center (ONPRC) were housed outdoors and fully exposed to the unhealthy or worse air for 9 days in a row. This event occurred in early September, at the very end of the rhesus (*Macaca mulatta*) and Japanese macaque (*Macaca fuscata*) birthing seasons (Anderson, 1979; Scucchi et al., 1983). Thus, many young newborn and late-gestation pregnant female macaques were exposed to the wildfire smoke.

Rhesus macaque cohorts exposed to wildfire smoke in the Northern California, USA wildfires in 2008 (Black et al., 2017) and 2018 (Brown et al., 2022; Capitanio et al., 2022; Willson et al., 2021) provided observational studies of the ill effects of wildfire smoke. Opportunistic investigators showed wildfire smoke correlated with immune dysregulation, compromised lung function (Black et al., 2017), early gestation miscarriages, preterm births, epigenetic changes, and adverse biobehavioral effects (Capitanio et al., 2022). Large epidemiologic studies in humans have also found incidences of wildfires were associated with low birth weight, preterm birth, and risk factors for overall mortality (Chen et al., 2021; Heft-Neal et al., 2022; Holstius et al., 2012).

Wildfires release a mix of carbon monoxide, hazardous air pollutants, and fine organic and inorganic particles smaller than 2.5 μm in diameter (PM2.5). PM2.5 pollution is the main component of wildfire smoke and the greatest threat to the health of organisms breathing air. PM2.5 are inhaled deeply into the lungs and are thought to lead to airway inflammation, oxidative stress, and respiratory or cardiovascular effects (EPA, 2019; Holstius et al., 2012; Schöllnberger et al., 2002). Wildfire air pollution is often assessed by measuring PM2.5 in ambient air (Black et al., 2017; Capitanio et al., 2022; Willson et al., 2021). The Environmental Protection Agency, Under the Clean Air Act, sets national ambient air quality standards for PM2.5, and over 4,000 monitoring stations, owned and operated mainly by state environmental agencies, measure concentrations of PM2.5 across the United States to provide accurate scientific data to ensure air quality meets the national ambient air quality standards.

While causal relationships between health outcomes and ambient air pollutants released from wildfire smoke are difficult to study, investigators have linked cardiovascular and pulmonary events to local poor air quality events usually using PM2.5 measurements (Liu

et al., 2015; Requia et al., 2021). Exposure to poor air quality can lead to worse health outcomes for groups particularly sensitive to air pollution, including infants, pregnant women, those with pre-existing health conditions, and persons older than 65 years of age (Liu et al., 2017). Excess human mortality and increased respiratory-related mortality associated with the 2020 Labor Day fires were studied (Liu et al., 2021). However, the COVID-19 pandemic overlapped and likely confounded the results (Liu et al., 2021). SARS-CoV-2 seroconversion was monitored extensively in rhesus and Japanese macaques housed in our study, and, to date, the animals remain free of COVID-19 disease. Additionally, the macaques are monitored closely to meet health and breeding benchmarks which provides a robust and contained population to find reliable data compared to human hospital records or wildlife population studies. For these reasons, these nonhuman primate cohorts could provide a clearer understanding of the effects of wildfire smoke than previous studies.

We investigated wildfire poor air quality exposure *in utero* and in early life to examine effects on nonhuman primate pregnancy loss, early infant growth, and early infant morbidity and mortality. We hypothesized that macaques exposed to the wildfire smoke event *in utero* or during early infancy would have higher miscarriage rates, infant mortality, and infant morbidity than in previous years. We also hypothesized that infants exposed to wildfire smoke events *in utero* or early infancy would have lower growth rates than less exposed infants in previous years. We compared cohorts born or exposed at similar times of the year as the Labor Day fires because rhesus and Japanese macaques are seasonal breeders, and infant survival may be affected by birth dates early or late in the year.

Methods

Subjects.

No living animals were used directly during the course of this study. Data were collected in an electronic medical records system that uses case classifiers, Systematic Nomenclature of Medicine (SNOMED) codes, and free text to capture routine husbandry practices and veterinary medical care. Data included conceptions, births, pregnancy losses, housing, and demographic and health condition information. All animals in the electronic health records were housed at the ONPRC and managed under the IACUC-approved protocol of the Oregon Health and Science University West Campus. This research adhered to the American Society of Primatologists (ASP) Principles for the Ethical Treatment of Non-Human Primates and adhered to the legal requirements of the United States, where the research was conducted. As part of the preventative veterinary medicine program at ONPRC, all animals were tested annually for SARS-CoV-2 with a serological antibody assay (CSA: SARS COV-2, Intuitive Biosciences©, Madison, WI). All animals tested negative throughout the study period and remain negative at the time of this publication. Therefore, SARS-CoV-2 was not a confounder in our study.

Housing was in accordance with standards established by the U.S. Federal Animal Welfare Act and the Guide for Care and Use of Laboratory Animals. All shelter structures associated with outdoor housing areas are open-air without air filtration. Animals are housed in groups in continuous full contact. Figures for outdoor housing are previously published (Prongay et al., 2013). Permanently installed sprinklers and misters provided water for vegetation and

a source of cooling during the wildfire smoke event. Standard colony practices involving records of indoor/outdoor transfers allowed complete identification and enumeration of individual monkeys who were outdoors on a day-by-day basis during the 9-day exposure period across all 7 years.

One to four times per year, on a rotating schedule, all animals were sedated with ketamine HCl (10 mg/kg IM; Ketathesia™, Henry Schein Animal Health®, Dublin, OH) for routine group management, including physical examinations, pregnancy evaluation, weighing, mammalian old tuberculin skin test, antihelminth administration (Ivomec®, ivermectin 1%, Merial, Lyon, France), and blood draws for serology and genetic testing. Pregnancy detection and trimester status was done by bimanual palpation with rectal probe by professional primate veterinarians. All pregnancies were confirmed, and a trimester status was assigned by palpation only (Mahoney, 1975).

Air quality.

Rhesus macaques and Japanese macaques housed outdoors were exposed to poor air quality September 10–18, 2020 from five major fires burning during this period covering 340,353 hectares (3,404 km^2) in Oregon (Abatzoglou et al., 2021; Reilly et al., 2022). The closest major fire, the Riverside fire, burned 55,868 hectares (559 km^2) and was approximately 68 km southeast from the ONPRC. (Federal Emergency Management Agency, 2020; Forest Grove, 2020)

PM2.5 were measured by the Oregon Department of Environmental Quality's (DEQ) PM2.5 monitoring site at the Beaverton Highland Park Monitoring Station (EPA #41-067-0111; Latitude 45.47019, longitude −122.8164), which is approximately 7.4 km from ONPRC. The site is within the Tualatin Valley, where the ONPRC is located, and is the most likely air quality monitoring site to represent the ambient air in which outdoor macaques were exposed. This site uses a Correlated Radiance Research M903 Nephelometer with a heated inlet to measure fine air particulates. Daily 24 hour average PM2.5 measurement raw data from this sensor were obtained from the EPA's Air Quality System database from years 2014 through 2020 (United States Environmental Protection Agency, 2020).

Other pollutants present in wildfire smoke were measured in a lesser capacity than PM2.5 by DEQ's Air Toxin monitoring system. In this program, stainless steel passivated Summa cannisters are used to collect whole air samples from across Oregon approximately every six days. The closest air toxin testing to the ONPRC were KairosPDX National Air Toxics Trends Station (EPA #41-051-2010; Latitude 45.5581, longitude −122.671) in Portland, Oregon (16.5 km from ONPRC) where samples are tested for Volatile Organic Compounds, and Hare Field air monitoring station (EPA #41-067-0004; Latitude 45.5285, longitude −122.972) in Hillsboro, Oregon (7.4 km from ONPRC) where carbonyl compounds are tested. Wildfire smoke constituents that are tested at these sites include acrolein, benzene, chromium, and formaldehyde. Only data collected during the exposure year and month were available in a limited amount and reported for informational use. Comparisons or associations of these other components of wildfire smoke with health effects in macaques at ONPRC could not be investigated in this study.

Pregnancy loss cohorts.

Days when PM2.5 exceeded the EPA's standard for PM2.5 24h average include September 10th, 2020, through September 18th, 2020; these dates were used as the timeframe for determining each exposure group (Figure 1). Cohorts from 2014–2019 were restricted to the same dates each year (September 10th – September 18th) as the wildfire smoke event to rule out seasonality as a confounding factor. Due to the difference in exposure to PM2.5 between animals living outdoors in 2020 and animals living outdoors during years 2014–2019, two exposure groups were formed. Fetuses of animals carried by outdoor housed female macaques *in utero* from September 10th, 2020, to September 18th, 2020, were included in the exposed group. Fetuses of animals that were pregnant and lived outdoors in the six previous years during the same dates each year (September 10th, 2014 – September 18th, 2014, through 2019) were included in the less exposed group. Data from any animals that were outdoors for less than the entire 9-day exposure time frame for each year (September 10th – September 18th of 2014 through 2020) were excluded from all analyses. In all, 2 observations were removed from the 2014 cohort, 10 from 2015, 7 from 2016, 10 from 2017, 7 from 2018, 6 from 2019 and 3 from 2020.

Pregnancies that were detected between 2014 and 2020 were captured during routine screenings. From the date of the pregnancy detection and the trimester of each pregnancy, a conception date was estimated. First-trimester pregnancies were estimated to be at 55 days gestational age, second-trimester pregnancies at 110 days, and third-trimester pregnancies at 165 days. When dams had multiple pregnancy records for the same pregnancy, these were reduced by only keeping the latest pregnancy record. Pregnancies that resulted in an offspring were connected to the birth record via parentage data. Births that occurred from dams without a recorded pregnancy were included as additional instances of conception. Pregnancies that were not connected to an offspring record were assumed to be pregnancy losses. A conception date was estimated for births as 165 days before the birth date (the average gestational age for macaques) or by gestational age for pregnancies (Hartman, 1928). Pregnancies and births were included in the study population if the estimated conception date was between the first day of the exposure period and 165 days past the last day of the exposure period.

Pregnancy loss outcomes.

Births were marked as pregnancy losses when categorized as one of the following; type of death was recorded as a miscarriage (<120 days gestation), stillbirth (>120 days gestation, never breathed), or a neonatal death that was born and died on the same day. Pregnancies that ended in prenatal loss, pregnancies that had no record of a live birth, or births with no pregnancy record where the offspring was born and died on the same day were defined as pregnancy losses; all other observations signified live births.

Pregnancy loss statistics.

The total number of conceptions, pregnancy losses, live births, and the proportion of pregnancies lost each year was calculated. A background rate of pregnancy loss in the less exposed group was calculated as the average percentage of pregnancies lost over the years when data was collected for the less exposed group (September 10th – September 18th, 2014,

through 2019). A relative risk (RR) was calculated for each less exposed cohort (each year from 2014–2019) compared to the exposed cohort (the year 2020) and for the less exposed group as a whole (years 2014–2019 combined) compared to the exposed group. The RR was calculated as the proportion of pregnancies lost in the exposed group divided by the proportion of pregnancies lost in the less exposed group and represents the likeliness of pregnancy loss in the exposed group compared to the likeliness of pregnancy loss in the less exposed group.

Adverse health outcomes cohorts.

Health outcomes of exposed versus less exposed animals included a comparison of mortality, respiratory disease, and hospitalization up to one-year post-exposure, and weight gain in the first year of life. Three exposure groups were defined to compare the difference in association between fetuses exposed *in utero*, exposed infants, and less exposed infants.

The *in utero* exposed group was defined as animals born between the first day (September 10th, 2020) and 165 days past the end of the exposure period (March 2nd, 2021), where the dam was outdoors during the exposure period where 24h average PM2.5 concentrations exceeded standards set by the EPA (September 10th, 2020 – September 18th, 2020) and the infant was born alive and survived at least one day. The exposed infant group includes animals born between June 9th, 2020, and September 9th, 2020 (three months old or less at the beginning of the exposure period), and the infant was outdoors during the exposure period. The less exposed infant group was also born between June 9th and September 9th but during years without exposure (2016 – 2019) and were all outdoors during the same period as the exposure group (September 10th – September 18th of each year) during years with considerably lower PM2.5 concentrations (Figure 1). In all exposure groups, data from animals that were not outdoors for the entire 9-day exposure period of September 10th – September 18th of 2016 through 2020 were excluded from all analyses. In all, 0 observations were deleted from the 2020 in utero exposed data, 5 from the 2020 infant exposed data, and a total of 81 from the 2016–2019 less exposed data (19 from 2016, 22 from 2017, 15 from 2018, and 25 from 2019). Infants 3 months or younger have been previously identified as a vulnerable age group of macaques to wildfire smoke (Black et al., 2017).

Only natural deaths that were defined as neonatal, spontaneous, or euthanasias due to health reasons were included for mortality events. Respiratory problems were defined as an animal that was diagnosed with respiratory disease by a veterinarian or died of a respiratory-related illness. All deceased animals underwent a necropsy performed by an American College of Veterinary Pathologists-boarded veterinary pathologist which provided respiratory causes of death. The respiratory outcome variable was collapsed into a binary outcome so that animals with multiple respiratory problems were only included once. Hospitalizations were defined by the primary condition when an animal was removed from their outdoor breeding group to a hospital location for an illness. Preventive medicine cases, traumas or injuries, and infants hospitalized for their dam’s illnesses were excluded from the hospitalization dataset. When animals were moved several times within a short period for the same medical condition, the records were de-duplicated. The outcome variable was binary, and animals with single or multiple hospitalizations were only included once. All health outcomes

(mortality, respiratory problems, and hospitalizations) were collected for animals in each exposure group from the first day of exposure to 365 days past the last day of exposure. The number of cases in each outcome by exposure group and the percentage of the exposure group affected was calculated.

Adverse health outcomes statistics.

Exploratory and descriptive analyses were performed to evaluate demographic characteristics of the three groups and explore the timing of health outcomes. Covariates collected for inclusion in regressions include the sex of the offspring (male or female), species (Rhesus macaque or Japanese macaque), if the dam was primiparous, dam age at the time of birth (categorized into quartiles), and the age of the offspring for analyses of weight. The frequency of these four demographic characteristics was determined in each exposure group. For categorical variables, the number of animals and the percent of that level in each exposure group were determined. A p-value was calculated by Pearson's chi-squared test as the difference between exposure groups. Among continuous variables, the mean and standard error was calculated within the variable for each exposure group and a p-value was calculated by analysis of variance as the difference between exposure groups.

Logistic regression models were utilized to evaluate the association between exposure group and each outcome. Offspring sex, species, dam parity, and dam age were included as covariates individually and as two-way interaction terms in logistic regressions for each outcome. Backward elimination using the reference p-value of 0.05 was used to determine the predictive variables. A total of 15 backward elimination steps were completed per outcome. Each model was checked for collinearity using variance inflation factor (VIF), which was less than 5. Lastly, body weights of animals in exposure groups were included for up to one year of age for each animal in only rhesus macaques. There were insufficient Japanese macaque weight records to use for analysis. In cases where animals were weighed multiple times within 30 days, only the oldest observation was kept. There was more than one weight sample for 260 of the 405 animals in the dataset. This dataset has within-participant data, which lacks independence, and a linear mixed effect model was chosen to evaluate the longitudinal relationship of exposure group on weight gain. The linear mixed effect model included covariates offspring sex, species, dam parity, dam age, and weight per days old as potential predictors. A Kruskal-Wallis rank sum test was utilized to determine if there was a difference between groups in the weight per days old as individual data points and not as within-participant observations.

Data cleaning, transformation, and statistics were performed using the R statistical program, version 4.1.2 (R Core Team, 2021). RR was calculated using the R package "epitools". The logistic regressions were fit using the "glm" function in R with the specification "family = binomial", and the linear mixed effect was calculated using the R package "nlme" (R Core Team, 2021).

Results

Daily PM2.5 Measurements.

Macaques in our wildfire smoke groups were exposed to elevated PM2.5 that exceeded the EPA's 24h National Ambient Air Quality Standard (35 μg/m^3; 100 AQI) for 9 days during the period of September 10–18, 2020, including three days in the EPA's AQI category Hazardous (>250 μg/m^3), four days in Very Unhealthy (150–250 μg/m^3), one day in Unhealthy category (55–150 μg/m^3), and one day in the Unhealthy for Sensitive groups category (35.5–55 μg/m^3; Figure 1). Daily 24h PM2.5 air reached high as 278 μg/m^3. The less exposed groups were animals in the years 2014 to 2019. Wildfire smoke and poor air quality occur every year in the less exposed group but to a much lesser severity (Figure 1). PM2.5 air concentrations were higher than the 24h standard 35 μg/m^3 for 2 days in year 2015, 7 days in year 2017, and 6 days in year 2018. 24h PM2.5 air concentrations in the less exposed group never were in Unhealthy, Very Unhealthy, or Hazardous categories, and the less exposed group was never exposed to 24h PM2.5 concentrations more than 65 μg/m^3.

Other wildfire components.

There were temporary increases in other air toxins found in wildfire smoke during the wildfire event period. Acrolein, acetaldehyde, benzene, hexavalent chromium, and formaldehyde were all elevated in air samples within 20 km of the ONPRC taken on September 12, 2020. As the wildfire smoke event ended, these air toxins levels returned to more typical concentrations in local samples taken September 24, 2020, and September 30, 2020. State-wide monitoring found Benzene, acetaldehyde, 1,3-Butadiene, acrolein, and manganese were at concentrations 40 times their annual average, and benzene, benzo[a]pyrene, and formaldehyde were found above acute risk-based concentration standards set by DEQ (DEQ, 2022; Fellows et al., 2021). Oregon DEQ reported that phthalates were measured at a level above background in state-wide monitoring during the wildfire event, but these levels were below the acute risk thresholds set by the state risk assessments.

Pregnancy losses.

Pregnancy loss was more likely in the group of pregnant females exposed to wildfire smoke. Overall, pregnancies conceived during the 2020 cohort were 4.1 times as likely to have been lost compared to pregnancies conceived between 2014 and 2019 (RR = 4.1; 95% CI = 3.2, 5.4, $p < 0.001$) (Table 1). In 2020, 52.4% of pregnancies were lost compared to an average of 12.7% from 2014–2019.

Infant morbidity & mortality.

Wildfire smoke exposure was investigated as a risk factor for infant mortality, respiratory problems, and hospitalizations. The demographics table (Table 2) shows no significant difference in the percent of male animals ($X2 = 0.86$, $df = 2$, $p = 0.652$) and mean dam age between exposure groups ($F(2, 577) = 0.10$, $p = 0.905$). The percent of primiparous first-time females trended slightly higher in our exposure group ($X2 = 2.36$, $df = 2$, $p = 0.308$). The percentage of animals that were rhesus macaques was borderline significantly

different (X2 = 6.10, df = 2, p = 0.047) between exposure groups. Rhesus macaques were the most common species in our less exposed and exposed groups. Notably, the *in utero* exposure group was entirely rhesus macaques, and no Japanese macaques were born after being exposed *in utero* to the wildfire events to include in our dataset.

We evaluated the relationship between the covariates (offspring sex, species, dam age, and dam parity), exposure group, and the health outcomes by logistic regression. There were seven respiratory problems diagnosed in the infant exposure group (9.3%, n=75) and eleven respiratory problems in the less exposed group (2.3%, n=489; Table 3). No problems were found in the *in utero* exposure group (n=16; Table 3). The respiratory problems diagnosed in the infant exposure group (n=75) included five (6.7%) pneumonia cases, one (1.3%) upper respiratory infection, and one (1.3%) pulmonary edema case. Problems in the less exposed group (n=489) included nine (1.8%) pneumonia cases, one (0.2%) pharyngitis case, and one (0.2%) epistaxis case. No problems were found in the *in utero* exposure group (n=16; Table 3). Infants exposed to wildfire smoke between 0 and 3 months old had significantly greater odds of diagnosis with a respiratory condition within a year post-exposure compared to infants not exposed to wildfire smoke (OR = 4.47; 95% CI 1.60, 11.76; p = 0.003; Table 4). There were no covariates that contributed to the model, and only exposure group remained in the model after backward elimination (Table S1). An odds ratio with the independent variable for exposure group and no other covariates is presented in Table 4. The *in utero* exposure group had an unremarkable OR, which rendered our comparisons unviable (OR <0.0001; 95% CI -inf, inf). This was likely due to the absence of Japanese macaques in the *in utero* group and the lack of events that occurred in the *in utero* group to compare with our less exposed group.

There were ten mortality events found in the infant exposure group (13.3%, n=75) and 40 in the less exposed group (8.2%, n=489). No mortality events occurred for our *in utero* exposure group (n=16; Table 3). The primary findings for mortality events found in the infant exposure group (n=75) included six (8.0%) cases of gastrointestinal issues, one (1.3%) pneumonia infection, one (1.3%) pulmonary edema case, one (1.3%) left ventricular hypertrophy case, and one (1.3%) cerebral edema case. Primary findings for a total of 40 mortality events in the less exposed group (n=489) included 33 (6.7%) gastrointestinal issues, two (0.4%) cholangiohepatitis cases, two (0.4%) pneumonia cases, one (0.2%) cerebral edema case, one (0.2%) wound case, and (0.2%) one encephalomyelitis case. No mortality events occurred for our *in utero* exposure group (n=16; Table 3). There was no significant difference in the odds of mortality in the year after a wildfire smoke event between the exposed and less exposed infant groups (OR = 1.78; 95% CI 0.80, 3.64; p = 0.129; Table 4). After backward elimination, only species was predictive of mortality in this model (Table S2). An odds ratio with the independent variable for exposure group adjusted for species is presented in Table 4. Again, the *in utero* exposure group had an unremarkable OR which rendered this group's comparisons unviable (OR <0.001; 95% CI -inf, inf; Table 4).

There were thirteen hospitalizations that occurred in the infant exposure group (17.3%, n=75) and 81 hospitalizations in the less exposed group (16.6%, n=489). No hospitalizations occurred for the *in utero* exposure group (n=16; Table 3). Animals in the exposed group

(n=75) were hospitalized for ten (13.3%) dehydration and diarrhea cases, and three (4.0%) pneumonia or upper respiratory infections. Hospitalizations for the less exposed group (n=489) included 76 (15.5%) diarrhea and dehydration cases and five (1.0%) pneumonia or upper respiratory infections. No hospitalizations occurred for our *in utero* exposure group (n=16; Table 3). There was no significant difference between exposed and less exposed groups in the odds of hospitalization in the year after a wildfire smoke event (OR = 1.09; 95% CI 0.55, 2.04; p = 0.799; Table 4). After backward elimination, only species was predictive of hospitalization in this model (Table S3). An odds ratio with the independent variable for exposure group adjusted for species is presented in Table 4. Like the infant mortality and respiratory models, the *in utero* exposure group had an unremarkable OR which rendered this group's comparisons unviable (OR <0.001; 95% CI -inf, inf; Table 4).

Growth faltering.

Due to limited data in Japanese macaques, this dataset was limited to only rhesus macaques. Exposure group did not predict weight changes or growth rate in animals under a year. The linear mixed effect model showed no difference in weight gain between exposure groups (exposed *in utero* group: $\beta = -0.0187$, $t(401) = -0.401$, $p = 0.689$; exposed infants group: $\beta = -0.002$, $t(401) = -0.093$, $p = 0.926$, less exposed infants group: reference). After backward elimination, weight per days old and infant sex were predictive of weight gain, estimates presented are comparing exposure groups after adjustment for weight per days old and infant sex. A Kruskal-Wallis rank sum test discovered no significant difference in weight by age between exposure groups ($H = 0.688$, $df = 2$, $p = 0.709$). Figure 2 shows little variability in weight change up to one year of post-exposure between exposure groups.

Discussion

The 2020 Labor Day fires culminated in heavy wildfire smoke and PM2.5 levels that exposed outdoor housed monkeys to eight days of unhealthy and hazardous ambient air. Our study showed pregnancy loss was significant in breeding macaque females, 4.1 times as risky than past birthing seasons with less exposure. We also were able to follow health outcomes after infant macaques were exposed *in utero* or at an early age. We looked at morbidity, mortality, and growth for their first year of life and found that early age infants exposed to wildfire smoke had 4.5 times the odds of developing a respiratory problem afterward than less exposed infants.

The study was observational and a retrospective look into the effects of poor air quality from wildfires. Wildfire severity worldwide is trending upwards, correlating with effects predicted to occur with global climate change (Sun Q, 2019). Unlike humans who seek access to air filters, masks, and indoor air space, the macaques in our studies had no protection and no refuge from the hazardous air quality, just as wild species may face. Standard research laboratory practices provided complete population counts and detailed records to study health outcomes. Thus, our results on captive macaques strongly indicate that hazardous poor air quality due to wildfire smoke may have negative effects on pregnancies and infant health, which could generalize to macaques or other species living in the wild.

Particulate matter in wildfire smoke deposits directly on the lungs and leads to local oxidative stress and inflammation that enters systemic circulation (Adetona et al., 2016; Williams et al., 2013). Wildfire smoke also contains polycyclic aromatic hydrocarbons (PAHs) that can create oxidative stress in the lungs as well. The damage from particulate matter, oxidative stress, and inflammation can cause more respiratory problems after the wildfire event. In other studies, tracking respiratory health outcomes after wildfire events has shown PM2.5 levels were associated with pneumonia in many species including humans, dolphins, and now macaques (Nhung et al., 2017; Venn-Watson et al., 2013).

Infant macaques may be more susceptible to particulates because they are in a vulnerable developmental stage and breathe more air relative to their body weight than adults, which may lead to more particles that penetrate deeply into their lungs compared to older conspecifics (Bennett et al., 2008). While in pregnancy, individuals can experience physiologic changes, including higher respiratory rates, that may make them more susceptible to exposure itself (Stone et al., 2019). Consistent with other evidence, this data also supports short-term, acute exposure can exert a powerful impact on health (Johnson & Garcia-Menendez, 2022). The drastic change in the rate of macaque pregnancy loss in the year 2020 compared to 2014–2019 demonstrated here is an extreme example of the potential causal link between wildfire smoke and detrimental health effects in pregnancy.

Our study is not the first to study wildfire smoke effects with pregnancy outcomes in macaques. Willson et al. 2021 found pregnancies were lost when macaques were exposed to wildfire smoke in Davis, California from the nearby Camp Fire in 2018. The wildfire smoke and concentrations of PM2.5 were considerably lower than our concentrations found during the Oregon Labor Day fires. The Camp Fire was 160 km away and exposed macaques to upwards of 185 $\mu g/m^3$ PM2.5 concentrations and 12 days of PM2.5 levels exceeding the EPA's 24h National Ambient Air Quality Standard (35 $\mu g/m^3$). The resultant pregnancy losses went up to 18% from a baseline 10%. Comparatively, the Riverside fire burned 67 km away, and ONPRC macaques were exposed to a maximum 24h average of 278 $\mu g/m^3$ PM2.5 concentration. The duration of poor air quality was three days longer in California than the nine days experienced at the ONPRC, but eight of the days were at PM2.5 levels greater than 185 $\mu g/m^3$ which was the maximum 24h mean level recorded in Willson's study. The large difference in air quality was also followed by a large difference in pregnancy losses; at ONPRC the pregnancy losses went up to 52.4% from a baseline of 12.7%.

In our analysis, the odds of respiratory problems were higher in exposed infants compared to less exposed infants. While animals exposed *in utero* had no observations of respiratory problems, animals exposed as infants were more likely to have a respiratory problem in the year following exposure compared to animals not exposed as infants. This same association was not present in mortality or hospitalizations. This result is consistent with other observational studies in humans, where respiratory sequelae are often the most measurable effects (Heaney et al., 2022; Liu et al., 2015; Reid et al., 2016).

Interestingly, animals exposed *in utero* did not experience any tested outcomes (mortality, respiratory problems, or hospitalizations) within the one year following exposure. Given the average incidence rates in the other two groups of respiratory illness (3.1%), hospitalizations

(16.2%), and mortality (8.6%), it would be expected to have at least one instance of any outcome within a group where n = 16. However, we hypothesize that this group may be an example of live-birth bias, wherein the exposure is related to a higher pregnancy loss rate among fetuses that would have been at higher risk for morbidity and mortality in infancy (Neophytou et al., 2021). In this case, when more pregnancies were lost in 2020, animals that were to be born more likely to experience respiratory illness, hospitalization, or early mortality were instead lost as fetuses and therefore not included in the analysis of health outcomes in infancy.

There was no detectable difference in weight gain post-exposure between exposed and less exposed animals. However, there were a limited number of observations in both exposed groups, with only 20 observations in the *in utero* exposure group while there were 93 in the exposed infants and 719 observations in the less exposed infants group. This discrepancy in sample size limited our approach to detecting a difference in weight change between exposure groups, especially in the linear mixed model that relies on serial observations for each individual. Other robust retrospective studies that followed pregnancy in exposed groups showed a decrease in birth weight (Holstius et al., 2012).

During the Labor Day fires, ambient fine particulate (PM 2.5) levels exceeded the 24-hour National Ambient Air Quality Standard (35 μg/m^3) of the United States Environmental Protection Agency, reaching 24 hour averages of PM2.5 as high as 278 μg/m^3. Statically significant associations were observed between pregnancy losses and respiratory disease in infants exposed to the poor air quality measured by PM2.5 levels. However, there are other components of wildfire smoke which may lead to adverse health events. Even the contribution plant species combusted in wildfires can make up different chemical compositions to PM2.5 concentrations that may have differences in lung toxicity which we are unable to account for in our study (Kim et al. 2018). Willson et al. 2021 reported elevated phthalates in the air during the wildfire smoke event of the 2018 Camp Fire in California. Phthalates are released into wildfire smoke when man-made objects burn that contain plastic, and phthalates have also been associated with prenatal losses (Kay et al., 2013). However, the concentrations of phthalates necessary to cause adverse health effects are shown to be 500 PPM (Kay et al., 2013; Saillenfait et al., 2008) which is over 3,000 times higher than phthalate concentrations recorded near macaques studied in the Willson et al. study. During the Oregon 2020 Labor Day fires, special procedures were not in place to measure air toxins like phthalates around the ONPRC macaques; however, a limited number of these samples were taken on September 12, 2020, during the Labor Day fires but not necessarily from areas near our macaques or near the wildfires. Phthalates were measured at a level above background, but these levels were far below concentrations of thought to cause prenatal losses (DEQ, 2022; Fellows et al., 2021; Kay et al., 2013). Testing also showed many other toxic components of wildfire smoke rose during the wildfire and declined afterwards. Benzene, acetaldehyde, 1,3-Butadiene, acrolein, and manganese were found at concentrations 40 times their annual average and benzene, benzo[a]pyrene, and formaldehyde were found above acute risk-based concentrations (DEQ, 2022; Fellows et al., 2021). Acetaldehydes, acrolein, benzene, hexavalent chromium, and formaldehyde were found to have spiked and declined after the wildfire smoke decreased. Some of these chemicals are considered carcinogens or ocular and respiratory irritants (Adetona et al.,

2016). There may be acute or long-term effects that may have contributed to pregnancy losses or post-event respiratory disease in infants. Continuous, localized air toxin monitoring and reporting around the ONPRC would enable a proper assessment of possible health effects of phthalates, respiratory irritants, and other air toxins in wildfire smoke.

Acrolein and benzene can both travel through HVAC filtration and expose primates housed indoors (Snyder et al., 1993). HVAC filters remove PM2.5, but they cannot filter these smaller aromatic chemicals or gases found in wildfire smoke. During the wildfire smoke event, activated carbon filters were placed in line with HVAC filters of buildings to remove not only PM2.5 but also VOCs and PAHs like acrolein and benzene. The animals housed indoors were protected from these respiratory irritants and carcinogens. The only protections available for outdoor housed macaques were management practices to keep the macaque troop activity as low as possible. Non-essential animal movements and catching were halted outdoors to avoid activities that would make monkeys breathe faster or more deeply. Rounding up outdoor group housed animals to move them indoors was not attempted as this was a risk that would lead to increased activity.

Limitations.

The *in utero* exposure group was limited in the number of animals (n = 16), and therefore results in this case were uninterpretable. This effect may have been demonstrated had the sample size been larger. We also acknowledge that individual pregnant NHPs may have experienced varying levels of wildfire smoke in the prior years in addition to the exposure year 2020 which could be measured as chronic cumulative exposure, but, due to the complexities of studying chronic cumulative exposure, we were not able to discern this. Dichotomization of the quantitative exposure data also involved exclusion of observations on NHPs who were outdoors less than the full 9 days in all years. This led to selection bias and loss of information. However, we support the dichotomization of our study cohorts into “exposed” and “less exposed” since this approach is consistent with other observational studies in the field (Willson et al., 2021).

In conclusion, our results suggest wildfire smoke exposure *in utero* and to infants can lead to health consequences for infant macaques. Our monkeys were exposed nearly continuously to unhealthy and hazardous air quality and likely represent exposure to wild populations that cannot escape to safer air to breathe. This observational study of this closely monitored macaque colony demonstrated the associations between excess prenatal loss and respiratory disease to exposure to wildfire smoke, which would have otherwise been difficult to discern in a large population of wild macaques. It is critically important that we use all available nonhuman primate models to comprehensively understand the consequences of wildfire smoke, and we act with these comparative studies to mitigate health effects for humans and in wild populations by working with stakeholders to minimize the damage of global climate change. Without changes to human carbon emissions, inevitably, events like those of the Labor Day fires will occur more frequently.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The data supporting our findings in this study are available upon request. The PM2.5 data used in this study are publicly available at https://aqs.epa.gov/aqsweb/documents/data_api.html. The individual-level health data used are available upon request to the corresponding author.

Conflict of interest: none declared.

Abbreviations

SNOMED	Systematic Nomenclature of Medicine
EPA	Environmental Protection Agency
ONPRC	Oregon National Primate Research Center
PM2.5	fine particulate matter
RR	relative risk
OR	odds ratio
CI	confidence interval
VIF	variance inflation factor
AQI	air quality index

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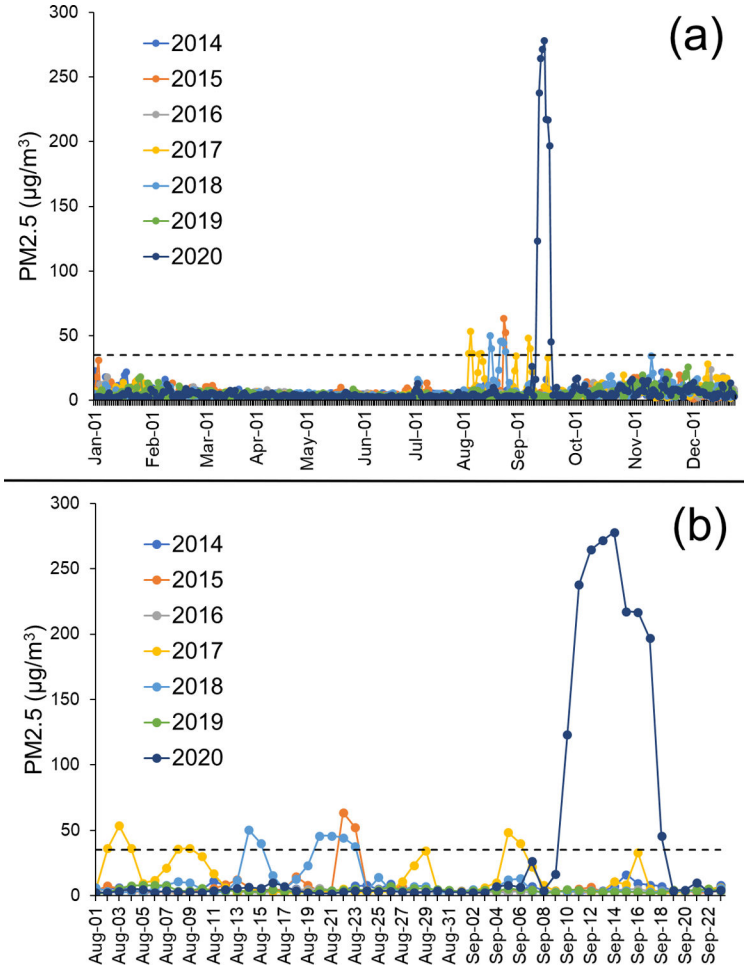

Figure 1:

Daily 24-hour average PM2.5 concentrations from 2014 to 2020 at Beaverton Highland Park air quality monitoring station near the ONPRC. The top plot (a) has daily 24-hour average PM2.5 concentrations for full calendar years, and the bottom plot (b) details daily 24-hour average PM2.5 concentrations between August 1st and September 24th. The air quality monitoring station is located approximately 7.4 km southeast of the ONPRC. A dashed black line marks the EPA NAAQS standard for 24-hour average PM2.5 concentrations which is 35 µg/m^3.

Abbreviations: PM2.5, fine particulate matter; EPA NAAQS, Environmental Protection Agency National Ambient Air Quality Standards; ONPRC, Oregon National Primate Research Center

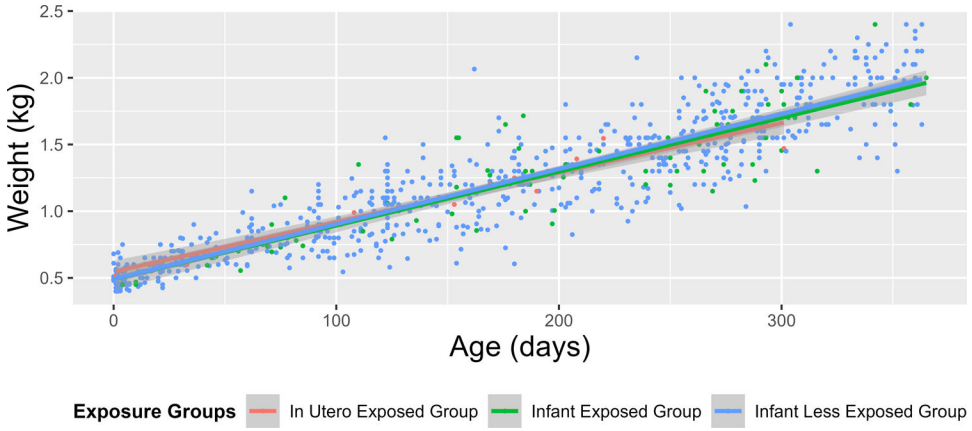

Figure 2.

Weight per days old in rhesus macaques from ONPRC up to one-year post-exposure, stratified by exposure group. Data collected years 2016–2021 from PRIMe.

Abbreviations: ONPRC, Oregon National Primate Research Center; PRIMe, Primate Records and Information Management

Table 1.

Counts of total conceptions, pregnancy losses, live births, proportion of pregnancies lost, and relative risk of pregnancy loss in rhesus and Japanese macaques from ONPRC by year, data collected years 2014–2020 from PRIMe

Year	Total Conceptions	Pregnancy Losses	Live Births	Proportion of Pregnancies Lost[†]	RR (95% CI)[‡]
2020	82	43	39	0.524	1.0 (Ref)
2019	103	8	95	0.078	**6.8 (3.4, 13.6)**
2018	177	23	154	0.130	**4.0 (2.6, 6.2)**
2017	245	29	216	0.118	**4.4 (3.0, 6.6)**
2016	211	33	178	0.156	**3.4 (2.3, 4.9)**
2015	153	18	135	0.118	**4.5 (2.8, 7.2)**
2014	120	17	103	0.142	**3.7 (2.3, 6.0)**

Abbreviations: ONPRC, Oregon National Primate Research Center; PRIMe, Primate Records and Information Management; RR, relative risk; CI, confidence interval; Ref, reference

[†]Proportion of pregnancies lost calculated as the number of pregnancy losses divided by number of total conceptions

[‡]Relative risk is calculated for every year compared to 2020, statistically significant results are bolded as determined by 95% confidence interval

[§]All years combined (2020 v. 2014–2019): RR = 4.1 (3.2, 5.4)

[¶]Proportion of pregnancies lost from 2014–2019 = 0.127

Table 2.

Baseline demographic characteristics of rhesus and Japanese macaques from ONPRC and their dams classified by exposure group, data collected years 2016–2021 from PRIMe

Selected Variables	Exposed In Utero (n=16) Count or Mean (% or SE)[†,‡]	Exposed Infants (n=75) Count or Mean (% or SE)[†,‡]	Less exposed Infants (n=489) Count or Mean (% or SE)[†,‡]	P Value[§]
Percent Male	8 (50.0)	32 (42.7)	236 (48.3)	0.652
Percent Rhesus	16 (100.0)	53 (70.7)	359 (73.4)	**0.047**
Percent first-time dams	5 (31.2)	29 (38.7)	146 (29.9)	0.308
Dam Age (Years)	7.62 (2.83)	7.92 (3.97)	8.03 (4.09)	0.905

Abbreviations: ONPRC, Oregon National Primate Research Center; PRIMe, Primate Records and Information Management; SE, Standard Error

[†]Categorical variables are represented by the number of animals that fit the demographic characteristic listed in selected variables and the percent of animals that fit the demographic characteristic listed, stratified by exposure group

[‡]Continuous variables are represented by a mean value and SE for each exposure group

[§]Statistically significant differences between exposure groups are bolded (as calculated by Pearson's chi-squared test for categorical variables and one-way ANOVA for continuous variables, alpha = 0.05)

Table 3.

Comparison of respiratory illness cases, hospitalizations, and mortalities in rhesus and Japanese macaques from ONPRC stratified among exposure groups, macaques are followed for one-year post-exposure, data collected years 2016–2021 from PRIMe

Condition	Exposed in utero group (n = 16)†	Exposed infants group (n = 75)†	Less exposed infants group (n = 489)†	Total (n = 580)†
Respiratory Illness	0	7 (9.33%)	11 (2.25%)	18 (3.10%)
Hospitalizations	0	13 (17.33%)	81 (16.56%)	94 (16.21%)
Mortalities	0	10 (13.33%)	40 (8.18%)	50 (8.62%)

Abbreviations: ONPRC, Oregon National Primate Research Center; PRIMe, Primate Records and Information Management

†Percent (%) of the exposure group that had a respiratory illness event, was hospitalized, or died

Table 4.

Odds ratio reconstructed from logistic regression models for mortality, respiratory problems, and hospitalizations in rhesus and Japanese macaques from ONPRC adjusted for exposure group and covariates, macaques are followed for one-year post-exposure, data collected years 2016–2021 from PRIMe

Outcome and Level	OR (95% CI)[†,‡]
Mortality	
In utero exposed group	NA[§]
Infant exposed group	1.78 (0.80, 3.64)
Less exposed infant group	1.0 (Ref)
Respiratory Problems	
In utero exposed group	NA[§]
Infant exposed group	**4.47 (1.60, 11.76)**
Less exposed infant group	1.0 (Ref)
Hospitalizations	
In utero exposed group	NA[§]
Infant exposed group	1.09 (0.55, 2.04)
Less exposed infant group	1.0 (Ref)

Abbreviations: ONPRC, Oregon National Primate Research Center; PRIMe, Primate Records and Information Management; OR, odds ratio; CI, confidence interval; Ref, reference; NA, not applicable

[†]Respiratory problems model is unadjusted for covariates; mortality outcome is adjusted for species, and hospitalizations outcome is adjusted for species

[‡]Statistically significant odds ratio results are bolded as determined by 95% confidence interval

[§]No observations of the studied outcomes were in the in utero exposed group, leading to an unremarkable OR