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Outdoor air pollution and mosaic loss of chromosome Y in older men from the Cardiovascular Health Study

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Abstract

Background—Mosaic loss of chromosome Y (mLOY) can occur in a fraction of cells as men age, which is potentially linked to increased mortality risk. Smoking is related to mLOY; however, the contribution of air pollution is unclear.

Objective—We investigated whether exposure to outdoor air pollution, age, and smoking were associated with mLOY.

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Competing financial interests

None of the other authors declares any actual or potential competing financial interests.

Methods—We analyzed baseline (1989–1993) blood samples from 933 men ≥65 years of age from the prospectiveCardiovascular Health Study. Particulate matter ≤10 μm (PM10), carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone data were obtained from the U.S. EPA Aerometric Information Retrieval System for the year prior to baseline. Inverse-distance weighted air monitor data were used to estimate each participants' monthly residential exposure. mLOY was detected with standard methods using signal intensity (median log-R ratio (mLRR)) of the male-specific chromosome Y regions from Illumina array data. Linear regression models were used to evaluate relations between mean exposure in the prior year, age, smoking and continuous mLRR.

Results—Increased PM10 was associated with mLOY, namely decreased mLRR (p-trend=0.03). Compared with the lowest tertile (≤28.5 μg/m^3), the middle (28.5–31.0 μg/m3; β=−0.0044, p=0.09) and highest (≥31 μg/m3; β=−0.0054, p=0.04) tertiles had decreased mLRR, adjusted for age, clinic, race/cohort, smoking status and pack-years. Additionally, increasing age (β=−0.00035, p=0.06) and smoking pack-years (β=−0.00011, p=1.4E-3) were associated with decreased mLRR, adjusted for each other and race/cohort. No significant associations were found for other pollutants.

Conclusions—PM10 may increase leukocyte mLOY, a marker of genomic instability. The sample size was modest and replication is warranted.

Keywords

Loss of Chromosome Y; Genetic Mosaicism; Genomic Instability; Air Pollution; PM10

1. Introduction

Chromosome Y (ChrY) is a defining genetic characteristic for maleness, and it includes genes that regulate crucial biological pathways related to fertility, maturation and basic cellular processes (Quintana-Murci and Fellous 2001). Across the lifecourse, altered dosage of these critical genes affects essential biological processes (Mank 2009). ChrY is gradually lost in a fraction of cells as men progressively age (Dumanski et al. 2015; Forsberg et al. 2014; Zhou et al. 2016), resulting in mosaic loss of chromosome Y (mLOY). Genetic mosaicisms occur when a population of cells within a person do not share the same genetic signatures (Carr 1963; Zhou et al. 2016). Somatic abnormalities of ChrY can originate at any post-zygotic stage of development and across the lifecourse (Freed et al. 2014). ChrY mosaicisms may be due to erroneous DNA replication and segregation, environmental exposures, or other contributing factors (Carr 1962; 1963; Dumanski et al. 2015; Freed et al. 2014). The occurrence rate of mosaicisms in ChrY is substantially greater than those of the X-chromosome (ChrX) and autosomes (Machiela et al. 2016). Approximately 7–18% of men over age 70 years have detectable mLOY in leukocytes (Forsberg et al. 2014; Zhou et al. 2016), compared with approximately 0.25% for ChrX in women (Machiela et al. 2016). The resulting disruption of gene expression and function from mLOY may have biological consequences for men. Recent studies found that older men with higher frequency of leukocyte mLOY have elevated risks of Alzheimer's disease and possibly some cancers (Forsberg et al. 2014; Machiela et al. 2017; Noveski et al. 2016; Zhou et al. 2016). Additionally, a previous study reported that mLOY in leukocytes was potentially associated with elevated risks of all-cause and non-hematologic cancer mortality (Forsberg et al. 2014);

median survival times among men with detectable mLOY were 5.5 years shorter on average compared with those without mLOY (Dumanski et al. 2015). However, these findings were not substantiated in a substantially larger independent study (Zhou et al. 2016).

Cigarette smoking is associated with mLOY (Dumanski et al. 2015; Zhou et al. 2016). A large pooled study found that current smokers had increased occurrence of leukocyte mLOY compared to never and former smokers in the TwinGene, Uppsala Longitudinal Study of Adult Men (ULSAM), and Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohorts (Dumanski et al. 2015). These findings were corroborated in a subsequent investigation in the prospective cohorts, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO), and Cancer Prevention Study-II (CPS-II) (Zhou et al. 2016).

Since exposure to cigarette smoke could promote mLOY in leukocytes, we hypothesized that outdoor exposure to air pollutants may be similarly detrimental to the genome. Air pollutants including particulate matter (PM) <10 μm (PM10), ozone (O3), nitrogen dioxide (NO2), and sulfur dioxide (SO2) are significant public health burdens that have been shown to promote inflammation, oxidative stress, and genomic aberrations (Bekki et al. 2016; Ceretti et al. 2014; Duan et al. 2016; Gao et al. 2016; Gualtieri et al. 2011; Vattanasit et al. 2014; Yan et al. 2015). Furthermore, outdoor air pollution in the form of PM10 has been found to infiltrate homes and contribute to indoor levels (Xu et al. 2014). Outdoor PM shares common toxic components with cigarette smoke and is associated with similar health outcomes (Gilmour et al. 2006); in particular, increased risks of lung cancer and non-accidental mortality (Dockery et al. 1993; Hystad et al. 2013; Loomis et al. 2013; Villeneuve et al. 2015). The relationships between exposure to air pollutants and mLOY have yet to be investigated. Therefore, we evaluated cross-sectional associations between average outdoor air pollutant concentrations (i.e. PM10, O3, NO2, SO2, and carbon monoxide (CO)) at the place of residence in the year prior to leukocyte DNA collection and the frequency of mLOY in men aged 65 years and older from the United States. In particular, we focused attention on PM10 because of accumulating evidence of associations with cardiovascular outcomes (Shanley et al. 2016), as well as lung cancer risk (Raaschou-Nielsen et al. 2013) and mortality (Dockery et al. 1993). Additionally, we evaluated the associations between age, smoking, and mLOY to assess the consistency of our findings with those from previous studies (Dumanski et al. 2015; Forsberg et al. 2014; Haitjema et al. 2017; Machiela et al. 2017; Noveski et al. 2016; Zhou et al. 2016).

2. Methods

2.1 Study Population

The Cardiovascular Health Study (CHS) is a longitudinal, prospective cohort study of men and women aged ≥65 years, with the primary aim of investigating the development and progression of cardiovascular disease (CVD) (Eckel et al. 2012; Fried et al. 1991). A total of 5201 participants were recruited in 1989–1990 (Cohort 1) from four U.S. counties (i.e. Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA) via age- and sex-stratified random sampling from Medicare eligibility lists. Eligibility criteria included being able to self-respond and give informed consent; not be institutionalized; not

be wheelchair-bound; not be receiving treatment for cancer; and not likely to move away in the next three years. An additional 687 African-Americans were recruited in 1992–1993 (Cohort 2), bringing the total study population to 5888 participants. Demographic, anthropometric, lifestyle, and medical information were collected from participants during baseline and annual clinical examinations. Additionally, whole blood was collected from the participants at baseline (1989–1993).

2.2 Outdoor Air Pollution Exposure Estimation

The CHS Environmental Factors Ancillary Study (EFAS) was initiated in 1999 and included evaluation of the influence of long-term air pollution exposures on cardiovascular and pulmonary physical measures and outcomes. Reliable air monitoring data were available for three of the four CHS counties during the period of interest (1988-2000); therefore, EFAS was restricted to CHS participants in Forsyth County North Carolina, Sacramento County California, and Allegheny County Pennsylvania. Air pollution data for PM10, PM2.5, NO2, SO2, CO, and O3were obtained from the Environmental Protection Agency's Aerometric Information Retrieval System (EPA AIRS) and the California Air Resources Board (CARB). These data are subjected to quality checks by their respective data stewards, while limited additional quality checks were conducted by EFAS. All available data for PM2.5 were retrieved; however, the National Ambient Air Quality Standard (NAAQS) (e.g., regulatory limit) for PM2.5 was established by the EPA in 1997, and measurements before and around this time were too sparse to produce an exposure estimation comparable for other pollutants during our study period. Given the deficits in spatial and temporal coverage of the PM2.5 data, monthly exposure could not be estimated for the entire study period. Therefore, PM2.5 was excluded from the analyses. Sacramento County had O3 data year-round; however, during the non-ozone season (November–March), Pittsburgh had limited O3 data and Forsyth County had no O3 data. Therefore, analyses for O3 were restricted to months with data.

For each CHS participant in EFAS counties, a residential history (baseline through the last point of follow-up) was constructed from CHS records and each address was geocoded. An indicator for the quality of match data for each set of geocodes was provided as part of the geocoding service. A code of 1 indicated the best match, with the quality and accuracy degrading as the code number increased up to 4. Observations with codes of 3 and 4 were removed from our analyses.

Subject-specific monthly average daily ambient pollutant exposure for PM10, NO2, SO2, CO, and O3 were estimated using a previously published validated method (Eckel et al. 2016; Eckel et al. 2012; Rivera-Gonzalez et al. 2015; Wong et al. 2004). Briefly, inverse-distance weighting (IDW) was used to spatially interpolate air pollution levels for each study month at each subject's residence(s) using pollutant measurements from up to three air monitors. A maximum interpolation radius of 50 km was used. This method weights more heavily the measurements made at monitors closer to the point of interest (e.g., a residence). A quality code of 1-to-3 (or 9 if no monitoring stations with valid data are located within the maximum interpolation radius of the residence location) was provided with each interpolated value. For the current analyses, we only used monthly estimates with the

highest (i.e., 1) or second highest (i.e., 2) spatial interpolation quality code. A code of 1 means spatial interpolations were based on IDW of data from the three closest stations located within 5 km of the point of interest (residence location); this method is used whenever one or more stations located within 5 km of the residence have valid data. A code of 2 means spatial interpolations were based on IDW of data from the three closest stations, with the closest station located between 5 km and 25 km of the residence; this method is used when there are no stations within 5 km, and there are one or more stations located within 25 km of the residence. Notably, in EFAS (which included over 3900 CHS participants), for the 5293 residences included in the spatial interpolation analysis, over 90% of the monthly data are of quality 1 or 2 for PM10 and NO2. For the current analyses, we analyzed subject-specific exposure estimates (mean of the monthly 24-hour averages) in the 12 months prior to baseline.

2.3 Genotyping Signal Intensity Data

In 2007–2008, genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using Illumina (San Diego, CA) 370CNV Duo BeadChip genotyping arrays and the raw fluorescent intensity signals were extracted. The data for each multiplexed array is self-normalized using the information contained in that specific array. The normalization algorithm adjusts for nominal intensity variations observed in the two-color channels, background differences between the channels, and possible crosstalk between the dyes.

2.4 Inclusion/Exclusion Criteria

Among the 5888 CHS participants, DNA was extracted from blood samples of 3980 participants who consented to genetic testing and were free of CVD at baseline. We excluded 1908 participants from the GWAS genotyping due to the presence of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke, transient ischemic attack, or lack of available DNA, at baseline which left 2072 participants.

Among the 5888 participants, only 2478 men (2135 White and 343 African-American) were considered for our study. We excluded 3393 women and 17 men of other population ancestry. From the 2478 men, only 1926 White and African-Americans who participated in CHS EFAS from the three counties were further considered in our study.

Among men who participated in CHS EFAS, had reliable air monitoring data, was genotyped and met genetic quality control criteria (genotyping quality score <0.255 for variance of adjacent probe signal intensity), an effective study sample of 933 men remained in the analyses

2.5 Mosaic loss of Chromosome Y

Y-chromosome mosaicism for each participant was represented by the standardized signal intensity values (median log-R ratio (mLRR)) based on raw genotyping array data that were extracted from a previously conducted GWAS (dbGaP Study Accession: phs000287.v5.p1). The mLRR is a continuous metric and was derived from the fluorescent signal intensity of

481 probes that covered a male-specific region (MSR) of the Y-chromosome (ChrY: 7,502,455 – 21,979,204) (NCBI Build 36.1), bearing no homology to the X-chromosome. The mLRR is the total signal intensity of probes in this MSR, relative to the signal intensity from a canonical set of normal controls. The mLRR is proportional to the copy number of Y-chromosomes in a population of cells. In leukocytes, a mLRR estimate close to zero reflects a normal Y-chromosome copy number state, a positive mLRR estimate reflects mosaic gains in Y-chromosome copy number, and a negative mLRR estimate reflects mLOY in a proportion of cells. The mLRR was categorized as a continuous variable for all associational analyses. Additionally, the mLRR was categorized as dichotomous (detectable and undefined mLOY) for descriptive statistics based on a threshold (mLRR < −0.15 and mean LRR/standard deviation (SD) ≤ −0.25) derived using previously described methods (Zhou et al. 2016). GWAS output files was analyzed using Nexus-Copy-Number-6.1 (BioDiscovery). All copy number variant calls were made by the software and manually inspected.

2.6 Analyses

We analyzed cross-sectional baseline data (1989–1993) for 933 older men (777 White, 156 African-American) ≥65 years of age. The distribution and normality of continuous variables were assessed using histograms and Shapiro-Wilks tests, respectively. Between categories, differences in continuous variables were assessed using Kruskal-Wallis tests, and using Chi-square or Fisher's Exact tests for categorical variables. Spearman correlations were used to assess monotonic relations between continuous air pollutant levels and continuous demographic and lifestyle characteristics.

Linear regression models were used to evaluate relations between mean exposure in the year before blood draw and continuous mLRR at baseline. Potential confounders and covariates were chosen based on previous studies (Dumanski et al. 2015; Forsberg et al. 2014; Haitjema et al. 2017; Machiela et al. 2017; Noveski et al. 2016; Zhou et al. 2016) and statistical considerations. The models were adjusted for age at baseline blood draw (years), body mass index (BMI, kg/m^2), clinic location (Winston-Salem (Forsyth County), NC, Sacramento, CA, Pittsburgh, PA), race/cohort (White Cohort 1, African-American Cohort 1, African-American Cohort 2), smoking status (never, former, current at baseline) and pack-years. We also evaluated lifetime occupation, physical activity, HDL and LDL cholesterol levels, alcohol use (drinks/week), education (less than high school, high school/GED, some vocational/college, graduate school), history of respiratory diseases (chronic obstructive pulmonary disease, asthma, bronchitis, emphysema), and history of any cancer diagnosis as covariates. However, these variables were not significantly associated with the outcome, did not change the findings, and thus were not included in the final models. Additional analyses were conducted by stratifying on potential effect modifiers including race, clinic, smoking status, and history of any cancer diagnosis. Separate models were used for each air pollutant (i.e. PM10, CO, NO2, O3, SO2,) as the main exposure. The air pollutants were categorized as tertiles to assess non-linear associations (PM10: <28.48, ≥28.48 to <36.08, ≥36.08 $\mu g/m^3$; CO: <0.98, ≥0.98 to <1.28, ≥1.28 ppb; NO2: <17.25, ≥17.25 to <25.95, ≥25.95 ppb; O3: <19.60, ≥19.60 to <27.95, ≥27.95 ppb; SO2: <9.87, ≥9.87 to <16.12, ≥16.12 ppb), in separate analyses. Linear trend tests were also conducted by fitting the tertiles as an ordinal variable in the models.

To assess the consistency of our mLOY data with those from previous studies (Dumanski et al. 2015; Forsberg et al. 2014; Haitjema et al. 2017; Machiela et al. 2017; Noveski et al. 2016; Zhou et al. 2016), we also analyzed the associations between mLOY and age, smoking status, and smoking pack-years in separate linear regression models. These were established factors related to mLOY. We conducted these analyses both unadjusted, and reciprocally-adjusted for each variable in addition to race/cohort. P-values <0.05 were considered statistically significant. Air pollutants that had statistically significant results in the age-adjusted and multivariable-adjusted analyses, in addition to having similar directions of association across the stratified analyses were considered noteworthy. Statistical analyses were conducted using SAS v9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Baseline study population characteristics

At baseline, the average age was 72.6 ± 5.5 years and the average BMI was 26.4 ± 3.5 kg/m^2 (Table 1). Over half of the participants (55.8%) were former smokers, while 12.1% were current smokers. The participants smoked an average of 24.6 ± 28.6 pack-years and consumed an average of 5 ± 12 alcoholic drinks per week throughout their lifetime. A high proportion of the participants went to college or vocational school (36.4%); however, African-Americans had a considerable proportion who only had a high school education or lower. White men were predominantly employed in professional, technical, managerial, or administrative occupations (55.7%); while African-Americans were mostly employed as skilled trade workers (50.6%). Most of the participants did not have a history of diabetes (68.7%), cancer (85.7%), or respiratory diseases (81.2%).

Air pollutant concentrations differed across CHS clinic locations and have been previously described in detail (Eckel et al. 2012). In our study sample of participants who fulfilled the inclusion and quality control criteria, the average annual concentration of PM10 was highest for those residing in Sacramento, CA (38.0 ± 15.2 μg/m^3), followed by Pittsburgh, PA (34.8 ± 7.8 μg/m^3), and Winston-Salem, NC (30.5 ± 4.4 μg/m^3) (p<0.0001). These annual average PM10 levels were below the NAAQS regulatory limit of 50 μg/m^3 at the time of data collection (EPA 2008). PM10 was not significantly correlated with other covariates that have been previously linked to mLOY, including age (rho=−0.04, p=0.18) and smoking pack-years (rho=−0.01, p=0.80).

The average mLRR of the male-specific ChrY region was −0.0319 ± 0.0300 (Table 1). When the mLRR was dichotomized, 7.1% of men in this study sample had detectable mLOY. Further, the frequency of detectable mLOY was 7.6% in the lowest tertile of PM10, 5.8% in the middle tertile, and 7.7% in the highest tertile. Similar lack of variation in detectable mLOY was observed across tertiles of the other pollutants.

3.2 Associations between smoking, age, and leukocyte mLOY

Increased pack-years of smoking was found to be significantly associated with decreased mLRR (β=−0.00010, 95% CI: −0.00017 to −0.00003, p=3.5E-3), reflecting an increase in mLOY frequency in a population (Table 2). The smoking pack-year association remained

significant after adjusting for age and race/cohort (β=−0.00011, 95% CI: −0.00018 to −0.00004, p=1.4E-3). Further, compared with never smokers, former and current smokers had non-significantly decreased mLRR. Among this study population of men aged ≥65 years, increasing age was non-significantly associated with decreased mLRR (β=−0.0003, 95% CI: −0.0007 to 0.0001, p=0.09). When further adjusting for smoking pack-years and race/cohort, age remained non-significantly associated with decreased mLRR (β=−0.0003, 95% CI: −0.0007 to 1.25E-05, p=0.06).

3.3 Associations between annual average outdoor air pollutant concentrations and leukocyte mLOY

PM10 was inversely associated with mLRR in the age-adjusted and multivariable-adjusted analyses (Table 3). When adjusted for covariates, increased PM10 was significantly associated with decreased mLRR (p-trend for tertiles=0.03). Compared with the lowest tertile (≤28.5 μg/m^3), the middle (28.5–31 μg/m^3; β=−0.0044, 95% CI: −0.0094 to 0.0007, p=0.09) and highest (≥31 μg/m^3; β=−0.0054, 95% CI: −0.0104 to −0.0003, p=0.04) tertiles were associated with decreased mLRR, with the highest tertile being significantly different. Further, the direction of the associations was similar compared to the overall analyses when restricting to those without a history of any cancer diagnosis (Supplementary Table 1), current non-smokers (Table 4) and never smokers (data not shown), and when stratified by race (Supplementary Table 1) and clinic locations (Supplementary Table 1). No significant associations were found for O3, CO, NO2, and SO2 in the main analyses.

4. Discussion

We investigated the relationship between outdoor exposure to air pollutants and mLOY. We found that increased exposure to PM10 was associated with higher frequency of mLOY in older men from the United States, even at pollutant levels below the NAAQS annual average regulatory limit of 50 μg/m^3 at the time of data collection. The direction of the findings for PM10 was generally consistent across smoking status, race, and clinic locations. We did not find significant associations with O3, CO, NO2, and SO2. Consistent with other studies, we found that increased pack-years of smoking was related to higher frequency of mLOY. Furthermore, we observed a possible association between increasing age and mLOY, but a larger study is needed to substantiate this finding. We found that approximately 7% of this population of older men had detectable mLOY, which was in concordance with previous studies (Dumanski et al. 2015; Forsberg et al. 2014; Zhou et al. 2016). To our knowledge, this was the first study to investigate the relationship between outdoor air pollution exposure and ChrY mosaicism.

We assessed the influence of potential effect modifiers and confounders on our findings. First, we evaluated whether the associations between PM10 and mLOY were modified by self-reported race (reflective of occupational, socioeconomic, genetic, or environmental factors), clinic location, and history of any cancer. When the analyses were stratified by self-reported race, clinic location, or history of any cancer we found that the direction and magnitudes of associations were consistent with the overall analyses. We also assessed whether current smoking may potentially bias the relationship between PM10 and mLOY.

When the analyses were restricted to never smokers and current non-smokers at baseline, we found that the results were consistent with the overall analyses.

We found that increased pack-years of smoking was significantly associated with mLOY, after accounting for age and race/cohort. In the TwinGene cohort, Dumanski et al. (2015) also found that smokers with detectable mLOY had significantly greater pack-years of smoking compared with smokers without detectable mLOY (Dumanski et al. 2015). Further, we found marginally non-significant associations between former and current smoking status and greater frequency of mLOY. In TwinGene and ULSAM cohorts, the investigators found that current smokers had significantly decreased continuous mLRR compared with former and never smokers, reflecting greater frequency of mLOY (Dumanski et al. 2015). Zhou et al. (2016) also found that detectable mLOY was significantly associated with current smoking; however, the relationship weakened with increasing years after cessation (Zhou et al. 2016). Given that PM10 and cigarette smoke share common components, it is reasonable that their relations with mLOY may be similar, although additional studies of PM10 are needed to assess this relationship (Gilmour et al. 2006). A prime example of a genotoxic component common to both PM10 and cigarette smoke is polycyclic aromatic hydrocarbons (PAHs). A prominent species of PAHs known as benzo[a]pyrene was classified as a Group 1 carcinogen by the International Agency for Research on Cancer (1983, 1986). Upon enzymatic conversion by cytochrome P-450, metabolites of PAHs can chemically alter DNA by forming adducts with guanine, which can result in the disruption of normal DNA structure and function (Moorthy et al. 2015).

We observed a non-significant association between increasing age and greater frequency of mLOY. The association with age remained non-significant after accounting for smoking pack-years and race. Similarly, Dumanski et al. (2015) found non-significant associations between age and mLOY in the ULSAM and PIVUS cohorts, but a significant association in TwinGene (Dumanski et al. 2015). The strongest evidence for a relationship with age was from the Zhou et al. (2016) study, which found increased frequency of detectable mLOY in those over 80 years of age compared to those under 60 years of age (Zhou et al. 2016). Our marginal findings for age may be attributed decreased statistical power, and because our study population was restricted to an elderly population who were ≥65 years of age with narrow variation. Similarly, the age range in ULSAM and PIVUS was narrower than TwinGene, which may explain why age was not significantly associated with mLOY in that study (Dumanski et al. 2015).

There were limitations and assumptions that need to be considered when interpreting the findings. First, this was a cross-sectional study, which only captured the relationships at a single time point. This study design precluded assessment of time trends of mLOY in leukocytes. However, the air pollution measurements did temporally precede the ChrY mosaicism measurements, strengthening our inferences. We only had air pollution and residential data in the year prior to blood draw. If the induction time of air pollution exposure was longer than one year, we assumed that the participants were residentially stable prior to baseline, that relative levels of air pollution exposure were preserved, and that air monitoring data in the year preceding blood draw were correlated with the time period when mLOY was induced. Second, we used IDW to spatially interpolate air pollution

concentrations from stationary air monitors to individual participant residences. IDW is a well-established and validated exposure assessment method in epidemiologic studies of outdoor air pollution. Other common methods include dispersion models, land use regression, and increasingly, hybrid approaches that combined models with available satellite, measurements, and other ancillary data (Hoek 2017; Jerrett et al. 2005; Ozkaynak et al. 2013). There is no consensus regarding a single method appropriate for estimating population exposure to outdoor air pollution; each approach has limitations depending on the spatial and temporal variability of the pollutant of interest, availability of measurement data, the averaging period (e.g., short- vs. long-term) and study design (Bravo et al. 2012; Dionisio et al. 2016; Hoek 2017; Nethery et al. 2008)). The disadvantage of interpolation methods like IDW is a relatively limited ability to capture fine-scale spatial variability in air pollution exposures such as those from intra-urban local sources; the longer-term (monthly) averaging period in our data may have mitigated this concern (Dionisio et al. 2016). Although we acknowledge the potential for exposure misclassification, we expect it would be non-differential (random) which would increase the variance and make it more difficult to detect associations. However, we observed a robust association for PM10, which was likely a conservative estimate of the true association. Second, the sample size was modest overall and for subgroup analyses, which limited our ability to detect subtle associations. However, significant and consistent results were still found for PM10. Third, the ChrY signal intensities were measured using an early-generation Illumina genotyping platform that only had 481 probes covering the male-specific region of ChrY. In comparison, previous studies using the Illumina 2.5M and HumanOmniExpress-chips had approximately 2560 and 1690 probes that covered male-specific ChrY regions, respectively (Dumanski et al. 2015). However, our background rates of detectable mLOY (~7%), in addition to our findings for the relations between mLOY, age, and smoking were in concordance with those from previous studies (Dumanski et al. 2015; Zhou et al. 2016).

5. Conclusion

Our findings suggest that even at levels below NAAQS regulatory limits at the time of study, increased outdoor PM10 exposure may contribute to leukocyte mLOY, reflecting genomic instability, in older men from the United States. No significant associations were found for O3, CO, NO2, and SO2. Our findings suggest that mLOY may in part mediate the link between PM10 and its related adverse health outcomes. However, given the limitations of the study, caution is recommended when interpreting the results. Replication in larger longitudinal cohort studies is warranted to substantiate these findings. Future prospective studies would benefit from improved air exposure assessment with continuous personal or residential monitors, in addition to repeated blood draws to capture secular trends in leukocyte mLOY.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ChrY	Chromosome Y
mLOY	mosaic loss of Chromosome Y
mLRR	median log R ratio
ChrX	Chromosome X
CHS	Cardiovascular Health Study
EFAS	CHS Environmental Factors Ancillary Study
CVD	cardiovascular disease
PM10	particulate matter <10 μm
O3	ozone
NO2	nitrogen dioxide
SO2	sulfur dioxide
CO	carbon monoxide
MSR	male-specific region

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Highlights

- Investigated whether exposure to outdoor air pollution was associated with loss of Chromosome Y in leukocytes, which reflects overall genomic instability
- Analyzed baseline blood samples from 933 U.S. men 65 years of age from the prospective Cardiovascular Health Study
- Particulate matter 10 μm (PM10), carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone data were obtained from the U.S. EPA Aerometric Information Retrieval System and used to derive subject-specific outdoor residential exposure estimates
- Increased exposure to PM10 from outdoor air pollution may contribute to loss of Chromosome Y in leukocytes

Table 1

Baseline study population characteristics of the Cardiovascular Health Study

			Cohort 1 (1989–1990)				Cohort 2 (1992–1993)			
	Total n=933		White n=777		African- American n=31		African- American n=125		p-value	
Demographic, Lifestyle, and Anthropometric Characteristics										
Age, years, mean, SD	72.6	(5.5)	72.6	(5.4)	73.0	(5.6)	72.5	(5.7)	0.87	
Body mass index (BMI), kg/m^2, mean, SD	26.4	(3.5)	26.2	(3.5)	27.6	(2.8)	26.8	(4.1)	0.01	*
Smoking Status, n, %										
Never	298	(31.9)	258	(33.2)	8	(25.8)	32	(25.6)	5.0E-4	*
Former	521	(55.8)	441	(56.8)	17	(54.8)	63	(50.4)		
Current	113	(12.1)	78	(10.0)	6	(19.4)	29	(23.2)		
Smoking pack-years, mean, SD	24.6	(28.6)	24.7	(28.8)	22.0	(20.1)	24.7	(29.2)	0.93	
Alcohol intake, drinks per week, mean, SD	5	(12)	5	(9)	5	(9)	6	(23)	0.04	*
Physical activity, kcal, mean SD	2036	(2081)	2197	(2166)	1576	(1420)	1146	(1305)	1.5E-8	*
Education, n, %										
Less than High										
School	145	(15.5)	101	(13.0)	11	(35.5)	33	(26.4)	2.6E-4	*
High School / GED	301	(32.3)	249	(32.0)	8	(25.8)	44	(35.2)		
Vocational / College	340	(36.4)	300	(38.6)	7	(22.6)	33	(26.4)		
Graduate School	147	(15.8)	127	(16.3)	5	(16.1)	15	(12.0)		
Life Occupation, n, % Professional, technical, managerial, administrative	478	(51.2)	433	(55.7)	7	(22.6)	38	(30.4)	4.8E-12	*
Sales/clerical	102	(10.9)	94	(12.1)	0	(0.0)	8	(6.4)		
Skilled trade worker	249	(26.7)	170	(21.9	17	(54.8)	62	(49.6)		
Operator/laborer	16	(1.7)	15	(1.9)	0	(0.0)	1	(0.8)		
Farming	1	(0.1)	1	(0.1)	0	(0.0)	0	(0)		
Other	87	(9.3)	64	(8.2)	7	(22.6)	16	(12.8)		
Clinic, n, %										
Winston-Salem, NC	293	(31.4)	247	(31.8)	9	(29.0)	37	(29.6)	0.02	*
Sacramento, CA	327	(35.0)	285	(36.7)	5	(16.1)	37	(29.6)		

	Cohort 1 (1989–1990)						Cohort 2 (1992–1993)			
	Total n=933		**White n=777**		**African- American n=31**		**African- American n=125**		**p-value**	
Pittsburgh, PA	313	(33.5)	245	(31.5)	17	(54.8)	51	(40.8)		
Medical History and Characteristics										
Ever diagnosed with any cancer, n, %										
No	800	(85.7)	663	(85.3)	29	(93.5)	108	(86.4)	0.43	
Yes	133	(14.3)	114	(14.7)	2	(6.5)	17	(13.6)		
History of respiratory disease (COPD, asthma, bronchitis, emphysema), n, %										
No	758	(81.2)	628	(80.8)	26	(83.9)	104	(83.2)	0.76	
Yes	175	(18.8)	149	(19.2)	5	(16.1)	21	(16.8)		
HDL Cholesterol, mg/dL, mean, SD	48.8	(12.7)	48	(12)	55	(14)	52	(14)	4.0E-4	*
LDL Cholesterol, mg/dL, mean, SD	115.5	(95.4)	115	(95)	123	(37)	117	(106)	0.34	
Diabetes Status, n, %										
Normal	641	(68.7)	540	(69.5)	17	(54.8)	84	(67.2)	2.0E-5	*
Impaired Fasting										
Glucose	146	(15.6)	124	(16.0)	6	(19.4)	16	(12.8)		
New Diabetes	89	(9.5)	61	(7.9)	4	(12.9)	24	(19.2)		
Existing Diabetes	55	(5.9)	51	(6.6)	4	(12.9)	0	(0)		
Leukocyte Chromosome Y Mosaicism										
Continuous ChrY mosaicism, ChrY: 7,502,455 – 21,979,204 fluorescent intensity (median log-R ratio; mLRR), mean, SD	−0.0319	(0.0300)	−0.0339	(0.0308)	−0.0317	(0.0296)	−0.0190	(0.0213)	8.1E-8	*
Detectable mosaic loss of ChrY (mLOY), n, %										
No	867	(92.9)	716	(92.1)	30	(96.8)	121	(96.8)	0.12	
Yes	66	(7.1)	61	(7.9)	1	(3.2)	4	(3.2)		
Annual subject-specific outdoor residential air pollution concentration before blood draw										
PM_{10}, µg/m3, mean, SD	34.3	(10.4)	35.7	(10.2)	32.8	(5.4)	27.4	(5.8)	9.9E-24	*
CO, ppb, mean, SD	1.2	(0.5)	1.3	(0.6)	1.2	(0.4)	0.9	(0.2)	1.2E-15	*
NO_2, ppb, mean, SD	21.2	(6.3)	21.0	(6.3)	23.6	(6.8)	21.4	(4.7)	0.06	
O_3, ppb, mean, SD	24.6	(8.3)	24.8	(7.7)	22.9	(7.8)	23.3	(10.4)	0.02	*

	Cohort 1 (1989–1990)				Cohort 2 (1992–1993)		
	Total n=933		**White n=777**	**African- American n=31**	**African- American n=125**		**p-value**
SO_2, ppb, mean, SD	13.2	(6.7)	13.5 (6.9)	16.7 (8.2)	12.4	(5.3)	0.07

* p-values<0.05 were considered statistically significant. Discrepancy in counts due to missing data. Between categories, differences in continuous variables were assessed using Kruskal-Wallis tests, and using Chi-square and Fisher's Exact tests for categorical variables.

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Table 2

Unadjusted associations between demographic, anthropometric, and medical characteristics and mosaic loss of chromosome Y

	β	95% CI Lo	95% CI Up	p-value	
Demographic, Lifestyle, and Anthropometric Characteristics					
Age, years	−0.0003	−0.0007	0.0001	0.09	
Body mass index (BMI), kg/m^2	0.0001	−0.0004	0.0007	0.63	
Smoking Status					
Never	Ref				
Former	−0.0039	−0.0082	0.0003	0.07	
Current	−0.0059	−0.0124	0.0006	0.07	
Smoking pack-years	−0.00010	−0.00017	−0.00003	3.50E-03	*
Alcohol intake, drinks per week	−0.00008	−0.00025	0.00009	0.34	
Education					
Less than High School	0.0007	−0.0052	0.0067	0.81	
High School / GED	Ref				
Vocational / College	−0.0031	−0.0078	0.0016	0.20	
Graduate School	−0.0031	−0.0090	0.0028	0.31	
Life Occupation					
Professional, technical, managerial, administrative	Ref				
Sales/clerical	0.0022	−0.0043	0.0086	0.51	
Skilled trader worker	0.0027	−0.0019	0.0073	0.25	
Operator/laborer	−0.0019	−0.0169	0.0132	0.81	
Farming	0.0166	−0.0425	0.0757	0.58	
Other	0.0004	−0.0065	0.0072	0.92	
Clinic					
Winston-Salem (Forsyth County), NC	Ref				
Sacramento, CA	−0.0012	−0.0059	0.0035	0.62	
Pittsburgh, PA	0.0026	−0.0022	0.0074	0.29	
Medical History and Characteristics					
Ever diagnosed with any cancer					

	β	95% CI Lo	95% CI Up	p-value
No	Ref			
Yes	−0.0028	−0.0083	0.0028	0.33
History of respiratory disease (COPD, asthma, bronchitis, emphysema)				
No	Ref			
Yes	−0.0015	−0.0064	0.0035	0.55
LDL Cholesterol, mg/dL	−0.00001	−0.00003	0.00001	0.40
HDL Cholesterol, mg/dL	−0.00003	−0.00019	0.00012	0.67
Diabetes Status				
Normal	Ref			
Impaired Fasting Glucose	0.0033	−0.0022	0.0086	0.24
New Diabetes	0.0035	−0.0032	0.0101	0.30
Existing Diabetes	−0.0002	−0.0085	0.0081	0.96

* p-values <0.05 were considered statistically significant. Separate unadjusted linear regression models were used for each variable. The outcome was the fluorescent signal intensity (median log-R ratio (mLRR)) of a male-specific region of ChrY: 7502455–21979204 measured using Illumina 370CNV-Duo genotyping arrays. Decreased mLRR reflects greater mosaic loss of chromosome Y (mLOY) in a population of leukocytes.

Table 3

Cross-sectional associations between annual average outdoor residential air pollution concentrations and leukocyte mosaic loss of chromosome Y

	Age-adjusted					Multivariable-adjusted				
Air pollutant	**β**	**95% CI Lo**	**95% CI Up**	**p-value**		**β** [Ψ]	**95% CI Lo**	**95% CI Up**	**p-value**	
Coarse Particulate Matter (PM_{10})										
tertile 2 vs. 1	−0.0059	−0.0105	−0.0013	0.01	*	−0.0044	−0.0094	0.0007	0.09	
tertile 3 vs. 1	−0.0070	−0.0116	−0.0023	3.50E−03	*	−0.0054	−0.0104	−0.0003	0.04	*
Ordinal p-trend				2.80E-03	*				0.03	*
Carbon monoxide (CO)										
tertile 2 vs. 1	0.0001	−0.0047	0.0048	0.98		0.0003	−0.0050	0.0056	0.91	
tertile 3 vs. 1	−0.0007	−0.0055	0.0041	0.77		0.0023	−0.0029	0.0076	0.39	
Ordinal p-trend				0.77					0.37	
Nitrogen dioxide (NO_2)										
tertile 2 vs. 1	−0.0011	−0.0058	0.0037	0.66		−0.0027	−0.0081	0.0027	0.32	
tertile 3 vs. 1	0.0014	−0.0033	0.0062	0.56		−0.0012	−0.0082	0.0059	0.75	
Ordinal p-trend				0.56					0.72	
Ozone (O_3)										
tertile 2 vs. 1	−0.0036	−0.0083	0.0011	0.14		−0.0029	−0.0076	0.0019	0.23	
tertile 3 vs. 1	0.0004	−0.0044	0.0051	0.88		0.0064	0.0003	0.0126	0.04	
Ordinal p-trend				0.94					0.20	
Sulfur dioxide (SO_2)										
tertile 2 vs. 1	−0.0006	−0.0053	0.0040	0.79		0.0018	−0.0039	0.0075	0.54	
tertile 3 vs. 1	0.0020	−0.0027	0.0066	0.41		0.0010	−0.0126	0.0146	0.88	
Ordinal p-trend				0.44					0.62	

[*] p-values<0.05 were considered statistically significant. The outcome was the fluorescent signal intensity (median log R ratio (mLRR)) of a male-specific region of ChrY: 7502455–21979204 measured using Illumina 370CNV-Duo genotyping arrays. Decreased mLRR reflects greater mosaic loss of chromosome Y (mLOY) in a population of leukocytes.

[Ψ] Single pollutant linear regression models were adjusted for clinic, race/cohort, age, BMI, smoking status and pack-years. The effective sample size was 933 men for the age-adjusted analyses and 897 for the multivariable-adjusted analyses due to missing smoking pack-year data. Tertiles (PM_{10}: <28.48, 28.48 to <36.08, 36.08 μg/m3; CO: <0.98, 0.98 to <1.28, 1.28 ppb; NO_2: <17.25, 17.25 to <25.95, 25.95 ppb; O_3: <19.60, 19.60 to <27.95, 27.95 ppb; SO_2: <9.87, 9.87 to <16.12, 16.12 ppb).

Table 4

Cross-sectional associations between annual average outdoor residential air pollution concentrations and leukocyte mosaic loss of chromosome Y in current non-smokers

	Age-adjusted					Multivariable-adjusted				
Air pollutant	**β**	**95% CI Lo**	**95% CI Up**	**p-value**		**β** [Ψ]	**95% CI Lo**	**95% CI Up**	**p-value**	
Coarse Particulate Matter (PM_{10})										
tertile 2 vs. 1	−0.0054	−0.0102	−0.0006	0.03	*	−0.0035	−0.0088	0.0017	0.19	
tertile 3 vs. 1	−0.0064	−0.0112	−0.0017	0.01	*	−0.0051	−0.0102	−9.72E-06	0.05	*
Ordinal p-trend				0.01	*				0.04	*
Carbon monoxide (CO)										
tertile 2 vs. 1	0.0005	−0.0045	0.0055	0.84		0.0004	−0.0051	0.0059	0.89	
tertile 3 vs. 1	−0.0005	−0.0054	0.0044	0.84		0.0020	−0.0034	0.0074	0.47	
Ordinal p-trend				0.83					0.46	
Nitrogen dioxide (NO_2)										
tertile 2 vs. 1	−0.0006	−0.0055	0.0043	0.81		−0.0022	−0.0078	0.0034	0.44	
tertile 3 vs. 1	0.0017	−0.0032	0.0066	0.50		−0.0003	−0.0075	0.0070	0.95	
Ordinal p-trend				0.49					0.90	
Ozone (O_3)										
tertile 2 vs. 1	−0.0039	−0.0087	0.0010	0.12		−0.0032	−0.0081	0.0016	0.19	
tertile 3 vs. 1	−0.0001	−0.0050	0.0048	0.97		0.0062	−0.0001	0.0125	0.05	
Ordinal p-trend				0.89					0.25	
Sulfur dioxide (SO_2)										
tertile 2 vs. 1	0.0010	−0.0038	0.0058	0.68		0.0033	−0.0025	0.0091	0.26	
tertile 3 vs. 1	0.0025	−0.0023	0.0073	0.31		0.0043	−0.0106	0.0192	0.57	
Ordinal p-trend				0.32					0.28	

[*] p-values<0.05 were considered statistically significant. The outcome was the fluorescent signal intensity (median log R ratio (mLRR)) of a male-specific region of ChrY: 7502455–21979204 measured using Illumina 370CNV-Duo genotyping arrays. Decreased mLRR reflects greater mosaic loss of chromosome Y (mLOY) in a population of leukocytes.

[Ψ] Single pollutant linear regression models were adjusted for clinic, race/cohort, age, BMI, and smoking pack-years. The effective sample size was 820 men for the age-adjusted analyses and 790 for the multivariable-adjusted analyses due to missing smoking pack-year data. Tertiles (PM_{10}: <28.48, 28.48 to <36.08, 36.08 μg/m^3; CO: <0.98, 0.98 to <1.28, 1.28 ppb; NO_2: <17.25, 17.25 to <25.95, 25.95 ppb; O_3: <19.60, 19.60 to <27.95, 27.95 ppb; SO_2: <9.87, 9.87 to <16.12, 16.12 ppb).