ARTICLE IN PRESS

Environment International xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Methylome-wide association study provides evidence of particulate matter air pollution-associated DNA methylation

Rahul Gondalia[a,*], Antoine Baldassari[a], Katelyn M. Holliday[a,b], Anne E. Justice[a,c], Raúl Méndez-Giráldez[a], James D. Stewart[a], Duanping Liao[d], Jeff D. Yanosky[d], Kasey J.M. Brennan[e], Stephanie M. Engel[a], Kristina M. Jordahl[f], Elizabeth Kennedy[g], Cavin K. Ward-Caviness[h], Kathrin Wolf[i], Melanie Waldenberger[j], Josef Cyrys[i,k], Annette Peters[i], Parveen Bhatti[f], Steve Horvath[l,m], Themistocles L. Assimes[n], James S. Pankow[o], Ellen W. Demerath[o], Weihua Guan[p], Myriam Fornage[q], Jan Bressler[r], Kari E. North[a,s], Karen N. Conneely[t], Yun Li[u,v,w], Lifang Hou[x,y], Andrea A. Baccarelli[e], Eric A. Whitsel[a,z]

[a] Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
[b] Department of Community and Family Medicine, Duke University School of Medicine, Durham, NC, USA
[c] Geisinger Health System, Danville, PA, USA
[d] Division of Epidemiology, Department of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, PA, USA
[e] Laboratory of Environmental Epigenetics, Departments of Environmental Health Sciences and Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA
[f] Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, USA
[g] Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[h] Environmental Public Health Division, National Health and Environmental Effects Research Laboratory, 104 Mason Farm Rd, Chapel Hill, NC, USA
[i] Institute of Epidemiology, Helmholtz Zentrum München, Ingolstaedter Landstrasse 1, Neuherberg, Germany
[j] Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Ingolstaedter Landstrasse 1, Neuherberg, Germany
[k] Environmental Science Center, University of Augsburg, Augsburg, Germany
[l] Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
[m] Biostatistics, School of Public Health, University of California Los Angeles, Los Angeles, CA, USA
[n] Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
[o] Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA
[p] Division of Biostatistics, University of Minnesota, Minneapolis, MN, USA
[q] Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA
[r] Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA
[s] Carolina Center for Genome Sciences, University of North Carolina, Chapel Hill, NC, USA
[t] Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA
[u] Department of Genetics, University of North Carolina, Chapel Hill, NC, USA
[v] Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA
[w] Department of Computer Science, University of North Carolina, Chapel Hill, NC, USA
[x] Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University Chicago, Evanston, IL, USA
[y] Center for Population Epigenetics, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University Chicago, Evanston, IL, USA
[z] Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

Abbreviations: AA, African American; AV, annual visit; ARIC, Atherosclerosis Risk in Communities; AS311, Ancillary Study 311; AQS, United States Environmental Protection Agency Air Quality System; BAA23, Broad Agency Award 23; CI, confidence interval; CpG, Cytosine-phosphate-Guanine; CT, Clinical Trial; DNAm, deoxyribonucleic acid methylation; CVD, cardiovascular disease; EA, European American; eFORGE, Functional element Overlap analysis of Regions; EMPC, Epigenetic Mechanisms of PM-Mediated CVD Risk; FDR, false discovery rate; GTP, Grady Trauma Project; GWAS, genome-wide association study; HLA, Hispanic/Latino American; KORA, Cooperative Health Research in the Region Augsburg study; LLS, Long Life Study; LMM, linear mixed models; MESA, Multi-Ethnic Study of Atherosclerosis; MICE, multiple imputation by chained equations; MWAS, methylome-wide association study; NAAQS, National Ambient Air Quality Standards; OS, Observational Study; PE, prediction error; PM_{10}, PM $<$ 10 µm in diameter; $PM_{2.5}$, PM $<$ 2.5 µm in diameter; $PM_{2.5\text{–}10}$, PM $>$ 2.5 and $<$ 10 µm in diameter; QQ, quantile-quantine; RMSS, root mean square standardized; SD, standard deviation; SE, standard error; SPE, standardized prediction error; WHI, Women's Health Initiative

* Corresponding author at: 123 W. Franklin St., Chapel Hill, NC 27516, USA.
E-mail address: rahgonda@unc.edu (R. Gondalia).

https://doi.org/10.1016/j.envint.2019.03.071
Received 4 December 2018; Received in revised form 28 March 2019; Accepted 29 March 2019
0160-4120/ © 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

Please cite this article as: Rahul Gondalia, et al., Environment International, https://doi.org/10.1016/j.envint.2019.03.071

A R T I C L E I N F O

Handling Editor: Hanna Boogaard

Keywords:
Particulate matter
DNA methylation
Epigenetics
Air pollution
Epigenome-wide association study

A B S T R A C T

Background: DNA methylation (DNAm) may contribute to processes that underlie associations between air pollution and poor health. Therefore, our objective was to evaluate associations between DNAm and ambient concentrations of particulate matter (PM) ≤2.5, ≤10, and 2.5–10 µm in diameter ($PM_{2.5}$; PM_{10}; $PM_{2.5–10}$).
Methods: We conducted a methylome-wide association study among twelve cohort- and race/ethnicity-stratified subpopulations from the Women's Health Initiative and the Atherosclerosis Risk in Communities study (n = 8397; mean age: 61.5 years; 83% female; 45% African American; 9% Hispanic/Latino American). We averaged geocoded address-specific estimates of daily and monthly mean PM concentrations over 2, 7, 28, and 365 days and 1 and 12 months before exams at which we measured leukocyte DNAm in whole blood. We estimated subpopulation-specific, DNAm-PM associations at approximately 485,000 Cytosine-phosphate-Guanine (CpG) sites in multi-level, linear, mixed-effects models. We combined subpopulation- and site-specific estimates in fixed-effects, inverse variance-weighted meta-analyses, then for associations that exceeded methylome-wide significance and were not heterogeneous across subpopulations ($P < 1.0 \times 10^{-7}$; $P_{Cochran's\ Q} > 0.10$), we characterized associations using publicly accessible genomic databases and attempted replication in the Cooperative Health Research in the Region of Augsburg (KORA) study.
Results: Analyses identified significant DNAm-PM associations at three CpG sites. Twenty-eight-day mean PM_{10} was positively associated with DNAm at cg19004594 (chromosome 20; *MATN4*; $P = 3.33 \times 10^{-8}$). One-month mean PM_{10} and $PM_{2.5–10}$ were positively associated with DNAm at cg24102420 (chromosome 10; *ARPP21*; $P = 5.84 \times 10^{-8}$) and inversely associated with DNAm at cg12124767 (chromosome 7; *CFTR*; $P = 9.86 \times 10^{-8}$). The PM-sensitive CpG sites mapped to neurological, pulmonary, endocrine, and cardiovascular disease-related genes, but DNAm at those sites was not associated with gene expression in blood cells and did not replicate in KORA.
Conclusions: Ambient PM concentrations were associated with DNAm at genomic regions potentially related to poor health among racially, ethnically and environmentally diverse populations of U.S. women and men. Further investigation is warranted to uncover mechanisms through which PM-induced epigenomic changes may cause disease.

1. Introduction

Ambient particulate matter (PM) air pollution is a modifiable exposure that has been consistently associated with morbidity and mortality (Cohen et al., 2017; Di et al., 2017; Miller et al., 2007) attributed to cardiovascular disease (Brook et al., 2004, 2010), respiratory disease (Dominici et al., 2006; Gan et al., 2013; Laumbach and Kipen, 2012), and lung cancer (Pope et al., 2002; Raaschou-Nielsen et al., 2013). Despite the ubiquity of air pollution exposure and the continued population burden of PM (Cohen et al., 2017), the causal mechanisms underlying PM associations with poor health have not been adequately investigated.

One such mechanism could involve methylation of deoxyribonucleic acids (DNAm), conventionally measured at Cytosine-phosphate-Guanine (CpG) sites. DNAm is a heritable, but dynamic epigenetic modification that can influence gene expression without altering the DNA sequence (Clouaire and Stancheva, 2008; Neidhart, 2016) and may be central to mediation of PM-associated disease risk (Baccarelli et al., 2010; Bollati and Baccarelli, 2010; Zhong et al., 2016). Indeed, PM exposure has been implicated in whole blood DNAm near candidate genes involved in inflammation, oxidative stress, coagulation and vasoconstriction (Bellavia et al., 2013; Chen et al., 2015, 2016; Tarantini et al., 2009, 2013), abnormalities of which have established associations with cardiovascular and respiratory disease. A few studies have agnostically evaluated DNAm associations with PM on a methylome-wide scale (de F.C. Lichtenfels et al., 2018; Panni et al., 2016; Plusquin et al., 2017), but none have done so in large, sociodemographically and environmentally diverse, well-characterized populations of adult women and men.

The present study therefore examined methylome-wide associations between DNAm and ambient concentrations of PM ≤ 2.5, ≤10, and 2.5–10 µm in diameter ($PM_{2.5}$, PM_{10}, and $PM_{2.5–10}$) within the Women's Health Initiative (WHI) and the Atherosclerosis Risk in Communities study (ARIC) cohorts, and their replication in subpopulations of the Cooperative Health Research in the Region Augsburg (KORA) study.

2. Methods

2.1. Study design and populations

The study included 8397 consenting participants from subpopulations within the WHI and ARIC cohorts who had available peripheral blood leukocyte DNA.

The WHI is a multicenter prospective study of risk factors for cardiovascular disease (CVD), cancer, osteoporotic fractures, and other causes of morbidity and mortality among postmenopausal women (Anderson et al., 2003; NIH, 1998). Between 1993 and 1998, women aged 50–79 years from forty WHI clinical centers throughout the United States (US) were enrolled in the Clinical Trials (CT) (n = 68,132) or Observational Study (OS) (n = 93,676). All WHI participants completed a screening visit (SV). CT participants also completed an annual visit (AV) at one, three, six, and nine years after randomization (AV1, AV3, AV6, AV9), and OS participants three years after enrollment (AV3). An additional visit of CT and OS participant subsets occurred between 2011 and 2012 (ranging from 14 to 19 years after enrollment) as part of the WHI Long Life Study (LLS) (Anderson and LaCroix, n.d.).

For the current study, WHI participants were drawn from three ancillary studies: *Epigenetic Mechanisms of PM-Mediated CVD Risk* (WHI-EMPC) (Whitsel, n.d.), *Broad Agency Announcement 23* (WHI-BAA23) (Assimes et al., n.d.) and *Ancillary Study 311* (WHI-AS311) (Jordahl et al., 2018). WHI-EMPC is a study of epigenetic mechanisms underlying associations between ambient PM air pollution and CVD within the WHI CT. From this population, DNAm was measured in 2200 randomly selected participants (stage 1: SV, AV3, or AV6), remeasured in 200 participants at a second visit (stage 2: AV3 or AV6), and remeasured again in 43 participants at a third visit among those who participated in the WHI Long Life Study (stage 3: LLS), yielding 2443 total observations. WHI-BAA23, also known as *Integrative Genomics and Risk of CHD and Related Phenotypes in the Women's Health Initiative*, is a case-control study of coronary heart disease within the WHI CT (n = 1546) and OS (n = 442). By design, WHI-BAA23 oversampled African Americans and Hispanic/Latino Americans and required all participants to have undergone genome-wide genotyping and profiling of seven cardiovascular disease biomarkers. DNAm was measured in

blood collected at the SV, before the incidence of coronary heart disease. WHI-AS311 is a matched case-control study of bladder cancer among women within the WHI CT (n = 405) and OS (n = 455). Bladder cancer cases were matched to controls based on enrollment year, age at enrollment, follow-up time, and DNAm extraction method. DNAm was measured in blood collected at the SV, before the incidence of bladder cancer.

ARIC is a community-based prospective study of atherosclerosis and its clinical outcomes in four US communities: Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi (ARIC Investigators, 1989). Enrollment in 1987–1989 (Visit 1) was followed by five subsequent visits (Visits 2–6) between 1990 and 2017. The present study included all 2796 African Americans from Forsyth County or Jackson (ARIC-AA) with DNA and 1139 European Americans from Forsyth County or Minneapolis (ARIC-EA) with cerebral magnetic resonance imaging data (Mosley et al., 2005), all at Visits 2 (1990–1992) or 3 (1993–1995).

Replication involved up to 2176 participants from two studies of the population-based KORA cohort: F3 (n = 464) and F4 (n = 1712). KORA F3 (2004–2005) and F4 (2006–2008) are follow-up studies of the KORA S3 and S4 cohort participants, including German nationals aged 25–74 years from Augsburg, Germany (Holle et al., 2005; Wichmann et al., 2005).

2.2. Particulate matter exposure estimation

The study focuses on three ambient particulate matter (PM) air pollutants, including two ($PM_{2.5}$ and PM_{10}) that are regulated under the Clean Air Act by the US Environmental Protection Agency (EPA) according to its National Ambient Air Quality Standards (NAAQS) (EPA, 2017).

PM exposures were estimated at all geocoded WHI and ARIC participant addresses (Whitsel et al., 2004, 2006) in the contiguous US since the baseline examinations using two exposure modeling approaches, both based on US EPA Air Quality System (AQS) monitoring data for PM_{10} (since 1987) and $PM_{2.5}$ (since 1999). In the WHI, the median distance from geocoded participant addresses to PM_{10} and $PM_{2.5}$ EPA monitors was 7.8 and 7.6 km. In ARIC, it was 4.8 and 7.2 km. Geocoded address-specific daily mean PM_{10} concentrations (μg/m^3) were spatially estimated using national-scale, log-normal ordinary kriging. Exposure measurement error using kriging methods may yield misclassification and increase variance or bias associations (Alexeeff et al., 2014; Lee et al., 2012), therefore validity of the estimation was assessed, using standard cross-validation statistics: average prediction error (PE), standardized prediction error (SPE), root mean square standardized (RMSS), and standard error (SE). Observed values of PE and SPE near zero, RMSS near one, and RMS near SE have provided evidence of model validity (Liao et al., 2006, 2007).

Also, geocoded address-specific monthly mean concentrations (μg/m^3) were spatiotemporally estimated using generalized additive mixed models and geographic information system-based predictors. Because EPA AQS monitoring data for $PM_{2.5}$ were not widely available until 1999, spatiotemporal estimation also involved the log-transformed ratio of $PM_{2.5}$ to predicted PM_{10} between 1987 and 1999. A five- or ten-fold, out-of-sample cross-validation of the estimates in which the squared Pearson correlation between excluded monthly observations and model predictions (R^2 = 0.68–0.77) indicated that estimation models performed well (Yanosky et al., 2014).

Daily mean concentrations of PM_{10} were averaged over the 2-, 7-, 28-, and 365-day periods ending on (including) the examination day. Monthly mean concentrations of $PM_{2.5}$ and PM_{10} were averaged over the 12-month period ending on (including) the calendar month of examination. Finally, coarse PM ($PM_{2.5-10}$) concentrations for each averaging duration were calculated as differences between PM_{10} and $PM_{2.5}$ concentrations.

2.3. DNA methylation

Peripheral blood leukocytes were isolated from visit-specific, fasting blood drawn from study participants. DNA was extracted from the peripheral blood leukocytes and then DNAm was measured on a methylome-wide scale at 485,577 CpG sites using the Illumina 450K Infinium Methylation BeadChip (Illumina Inc.; San Diego, CA, USA). Methylation was quantitatively represented by beta, the proportion of methylated cytosines over the sum of methylated and unmethylated cytosines across the same loci. The data from all studies were quality controlled (Table S1), Beta Mixture Quantile (BMIQ)-normalized to adjust for probe bias (Teschendorff et al., 2013), and in WHI-EMPC, ComBat-adjusted for stage and plate using empirical Bayes methods (Johnson et al., 2007). Otherwise, technical covariates (assay plate, chip, and row) were available to control for batch effects; and leukocyte proportions (CD8+ T cell, CD4+ T cell, B cell, natural killer cell, monocyte, and granulocyte) to account for leukocyte composition (Houseman et al., 2012). Among ARIC-AA participants, missing lymphocyte, monocyte, neutrophil, eosinophil, and basophil proportions were imputed based on measured proportions. Analyses excluded CpG sites at which DNAm distributions were multi-modal (Andrews et al., 2016) in at least one study.

2.4. Multiple imputation

To avoid potential for selection bias in complete-data analysis when data are missing at random (Hernan et al., 2004), multivariate imputation by chained equations (MICE) (Azur et al., 2011; Stuart et al., 2009) as implemented in SAS 9.3 (Cary, NC) was used to impute infrequently missing $PM_{2.5}$, PM_{10}, and $PM_{2.5-10}$ concentrations (missing range: 3.3%, 3.5%) and other covariates (missing range: 0%, 10.4%), excluding methylome-wide DNAm. Binary and categorical data were imputed using the logistic and discriminant functions whereas interval-scale data were imputed using predictive means matching with a k-nearest neighbor (k = 5) approach.

2.5. Statistical analysis

All analyses were stratified by cohort and race/ethnicity (African-, European-, and Hispanic/Latino-American) and adjusted for age (years) at blood draw, education (high school education or lower, more than high school), smoking status (current, former, never), alcohol use (current, former, never), physical activity (metabolic equivalent of task [MET-hours/week]), body mass index (BMI, kg/m^2), neighborhood socioeconomic status (Roux et al., 2001), mean temperature (°C), mean dew point (°C), mean barometric pressure (kPa), season, and methylation-related variables, which included ten principal components (PCs) for genetic ancestry (when available), leukocyte proportions, and technical covariates. Analyses additionally controlled for cohort-specific covariates, including binary sex (male, female) in ARIC; randomly assigned treatment group (CT subpopulations of WHI-AS311, WHI-BAA23, WHI-EMPC); case-control status (WHI-AS311, WHI-BAA23); and control matching criteria (WHI-AS311).

In each subpopulation, covariate-adjusted, multi-level, linear, mixed-effects models (LMMs) were used to estimate DNAm-PM associations. In WHI-EMPC, three-level, longitudinal models had a random intercept for examination at the participant level, a random intercept and slope for PM at the WHI center level, and a random intercept for chip, as given by

$$DNAm_{ijk} = \beta_0 + \beta_1 PM_{ijk} + \beta_2 Z_{ijk} + b_{0k}^C + b_{1k}^C PM_{ijk} + b_{0jk}^P + b_{0ijk}^E + \varepsilon_{ijk}^E. \quad (1)$$

In WHI-BAA23 CT & OS, and WHI-AS311 CT & OS, two-level cross-sectional models had a random intercept and slope for PM at the WHI center level and a random intercept for plate and chip, as given by

$$DNAm_{ik} = \beta_0 + \beta_1 PM_{ik} + \beta_2 Z_{ik} + b^C_{0k} + b^C_{1k} PM_{ik} + b^E_{0ik} + \varepsilon^E_{ik}. \quad (2)$$

In ARIC-AA and ARIC-EA, one-level cross-sectional models had a random intercept for plate and chip, as given by

$$DNAm_i = \beta_0 + \beta_1 PM_i + \beta_2 Z_i + b^E_{0i} + \varepsilon^E_i. \quad (3)$$

Above, *i*, *j* and *k* denote the ith examination of the jth participant in the kth center; *DNAm* is the CpG site-specific beta value; β_0 is the intercept; *PM* is the 2-, 7-, 28-, 365-day, or 1- or 12-month mean of $PM_{2.5}$, PM_{10}, or $PM_{2.5–10}$; and *Z* is a vector of covariates. The terms $(b_0{}^C, b_1{}^C) \sim N(O, G)$ are a random intercept and a random slope for *PM* at the center level, $(b_0{}^P) \sim N(O, G)$ is a random intercept for examination at the participant level, $(b_0{}^E) \sim N(O, G)$ are random intercepts for technical covariates, and $\varepsilon^E \sim (O, \sigma^2)$ is the random error at the examination level. Measures of association (β_1) and their 95% confidence intervals ($\beta_1 \pm 1.96 \times$ *standard error*) were reported as an absolute percentage change in DNAm per 10 μg/m^3 increase in PM.

Given the focus on fixed effects, LMMs were fit with maximum likelihood using the MixedModels package (Bates, 2017) in Julia v0.6 (Bezanson et al., 2017). Stratum-specific results were combined using fixed-effects, inverse-variance weighted meta-analysis. Homogeneity of associations was assessed using Cochran's Q test statistic (Cochran, 1954). A $P_{Cochran's\ Q} < 0.10$ and Bonferroni-corrected threshold of $P < 1 \times 10^{-7}$ (i.e. assuming 500,000 independent CpG tests) were used to identify significant CpG associations. The threshold of suggestive significance was $P < 1 \times 10^{-5}$.

Examination of stratified and meta-analyzed results included reviewing quantile-quantile (QQ) plots of the observed -$\log_{10}$-transformed *P* values for each CpG site against the expected values from a theoretical χ^2 distribution and estimating the associated genomic inflation factor (λ), where λ is defined as the ratio of the observed to expected median $-\log_{10}P$ values (Devlin et al., 2001).

2.6. Technical validation

In a random subset of 200 WHI-EMPC participants, bisulfite pyrosequencing was used to validate the Illumina 450K measures of DNAm at ten PM_{10}- or $PM_{2.5}$-sensitive CpG sites ($P < 1 \times 10^{-5}$). CpG sites with poor next generation sequencing data or situated in CpG-rich, repetitive element, or low sequence complexity regions of the genome were not candidates for pyrosequencing. Site-specific comparisons of DNAm measures were based on mean Illumina 450K minus bisulfite pyrosequencing differences (Δ), Pearson correlation coefficients (r), and Deming regression estimates of their intercepts (α) and slopes (β) (Cornbleet and Gochman, 1979). When the two measures are nearly identical, Δ, r, α, and β approach values of 0, 1, 0, and 1, respectively.

2.7. Functional annotation

Published genotype-phenotype associations for variants annotated to or within 100 kilobases of genes containing statistically significant PM-sensitive CpG sites were identified in the National Human Genome Research Institute (NHGRI) Genome-Wide Association Study (GWAS) Catalog (Welter et al., 2014). Tissue-specific gene expression was assessed using the Genotype-Tissue Expression (GTEx) database (Lonsdale et al., 2013) and associations between DNAm and gene expression in human blood cells were obtained from a study of approximately 400,000 CpG sites and > 13,000 transcripts in the *Multi-Ethnic Study of Atherosclerosis* (MESA) and *Grady Trauma Project* (GTP) cohorts (Kennedy et al., 2018). PM-sensitive CpG sites ($P < 1 \times 10^{-5}$) were functionally characterized using experimentally derived Functional element Overlap analysis of ReGions from EWAS (eFORGE) v2.0 (Breeze et al., 2016) with data from the Encyclopedia of DNA elements (ENCODE) (Consortium, 2012), Roadmap Epigenomics Project (Bernstein et al., 2010), and BLUEPRINT (Stunnenberg et al., 2016). Overlap of CpG site-specific PM sensitivity, histone modification, and DNase I hypersensitivity were evaluated in eFORGE with a false discovery rate (FDR) threshold of 0.05.

2.8. Replication

Significant CpG sites that were not heterogeneous across subpopulations ($P < 1.0 \times 10^{-7}$; $P_{Cochran's\ Q} > 0.10$) underwent replication and meta-analyses in KORA F3 and F4. Pollutant- and averaging duration-specific replication thresholds were Bonferroni-corrected by dividing the conventional alpha level (0.05) by the number of CpG sites carried into replication.

Table 1
Characteristics of the study participants, by subpopulation.

Subpopulation			Race/ethnicity	n	% female	Age, yrs	Maximum CpGs	PM (μg/m^3), 1 mo $\bar{x}$ (SD)		
						$\bar{x}$ (SD)		PM_{10}	$PM_{2.5}$	$PM_{2.5–10}$
ARIC			AA	2664	63%	56.6 (5.9)	463,431	20.5 (4.6)	13.2 (3.1)	7.3 (2.1)
			EA	1100	58%	59.9 (5.4)	462,543	23.2 (5.3)	15.4 (4.3)	7.8 (3.5)
WHI	AS311	CT	EA	351	100%	64.7 (7.1)	461,136	19.8 (6.6)	11.9 (3.82)	7.9 (4.6)
		OS	EA	395	100%	66.2 (6.9)	461,136	19.9 (5.7)	12.0 (3.9)	7.9 (4.1)
	BAA23	CT	AA	371	100%	61.8 (6.3)	461,014	22.6 (6.2)	14.3 (4.2)	8.3 (3.8)
			EA	926	100%	67.8 (6.2)	461,014	19.7 (5.7)	11.7 (3.7)	8.0 (4.4)
			HLA	220	100%	60.7 (6.4)	461,014	21.4 (8.1)	10.3 (4.1)	11.1 (5.7)
		OS	AA	259	100%	62.8 (6.8)	461,014	22.3 (5.9)	14.0 (4.0)	8.3 (4.2)
			HLA	174	100%	62.8 (7.3)	461,014	23.0 (8.1)	11.0 (4.2)	11.9 (6.4)
	EMPC[a]		AA	553	100%	62.7 (6.9)	463,916	22.2 (6.2)	15.2 (5.1)	7.0 (4.7)
			EA	1072	100%	64.6 (7.1)	463,916	19.4 (6.0)	13.0 (5.0)	6.4 (5.2)
			HLA	312	100%	61.5 (6.1)	463,916	21.9 (7.1)	12.8 (6.3)	9.1 (5.3)
All			AA (45.8%) HLA (8.4%) EA (45.8%)	8397	83%	61.3 (7.4)	463,916	20.9 (5.8)	13.2 (4.3)	7.7 (4.0)

Abbreviations: AA, African American; ARIC, Atherosclerosis Risk in Communities; AS311, Ancillary Study 311; BAA23, Broad Agency Award 23; CpG, Cytosine-phosphate-Guanine; CT, Clinical Trial; EA, European American; EMPC, Epigenetic Mechanisms of PM-Mediated CVD Risk; HLA, Hispanic/Latino American; mo, month; OS, Observational Study; PM_{10}, PM < 10 μm in diameter; $PM_{2.5}$, PM < 2.5 μm in diameter; $PM_{2.5–10}$, PM > 2.5 and < 10 μm in diameter; SD, standard deviation; WHI, Women's Health Initiative; $\bar{x}$, mean.

[a] At the 1st visit. Methylation data also were available among 185 & 43 WHI-EMPC participants @ the 2nd & 3rd visits.

3. Results

The study consisted of twelve ARIC and WHI subpopulations, collectively representing 8397 participants, of whom 45.8% were African American, 8.4% were Hispanic/Latino American, and 83.0% were female (Table 1). Participants were on average 61.3 years of age and contributed methylation data at ≥461,014 CpG sites. One-month mean concentrations of PM_{10}, $PM_{2.5}$, and $PM_{2.5–10}$ were 20.9, 13.2, and 7.7 μg/m^3; varied by subpopulation and race/ethnicity (Tables 1 and S2); and did not exceed NAAQS in place at the time of data collection. Between-pollutant Pearson correlation coefficients depended on size fraction and averaging duration (Table 2). Overall, the median (range) was 0.35 (−0.14, 0.79) and among 2-, 7-, 28, and 365-day mean PM_{10} concentrations, it was 0.64 (0.43, 0.79). Correlations between PM_{10} and $PM_{2.5}$ concentrations were 0.73 and 0.64 when they were averaged over 1 and 12 months.

QQ plots (Fig. 1) based on the trans-ethnic, fixed-effects, inverse variance-weighted meta-analyses provided little evidence of inflation across pollutants and averaging durations: median (range) $\lambda = 1.01$, (0.89–1.07). Manhattan plots (Fig. 2) show three significant ($P < 1 \times 10^{-7}$) and 55 suggestively significant ($1 \times 10^{-5} < P < 1 \times 10^{-7}$) PM-sensitive CpG sites (Tables 3 and S3). The three significant CpG sites (cg19004594; cg24102420; cg12124767) were neither within ten base pairs of single nucleotide polymorphisms (minor allele frequency > 1%) nor previously identified as cross-reactive probes (Chen et al., 2013).

On chromosome 20 within an exonic CpG island of *MATN4*, a 10 μg/m^3 increase in 28-day mean PM_{10} was associated with a 0.3% (95% confidence interval [CI]: 0.2, 0.4) higher DNAm at cg19004594 ($P = 3.33 \times 10^{-8}$; Fig. 3A). On chromosome 3 intronic to *ARPP21*, a 10 μg/m^3 increase in 1-month mean PM_{10} was associated with a 0.5% (95% CI: 0.3, 0.7) lower DNAm at cg24102420 ($P = 5.84 \times 10^{-8}$; Fig. 3B). Cg24102420 is approximately 200 base pairs upstream from the transcriptional start site for microRNA 128-2 (*miR128-2*). On chromosome 7 intronic to *CFTR*, a 10 μg/m^3 increase in 1-month mean $PM_{2.5–10}$ was associated with a 0.5% (95% CI: 0.3, 0.7) lower DNAm at cg12124767 ($P = 9.86 \times 10^{-8}$; Fig. 3C). Furthermore, PM associations with cg19004594, cg24102420, and cg12124767 were similar across race/ethnic strata (Fig. S1). Complete annotations for all PM-sensitive CpG sites ($P < 1 \times 10^{-7}$) are available in Excel Table S1.

3.1. Technical validation

Overall, bisulfite pyrosequencing and Illumina 450K-based DNAm measures were similar (Table S4). The medians (interdecile ranges) of Δ, r, α and β were: 0.01 (−0.06, 0.07), 0.73 (0.20, 0.83), 0.04 (−0.27, 0.24), and 0.98 (0.09, 1.62). Corresponding estimates (95% CIs) for cg24102420 were −0.04 (−0.04, −0.03), 0.79 (0.73, 0.83), −0.16 (−0.38, 0.07) and 1.13 (0.88, 1.39). Cg19004594 and cg12124767 were not pyrosequenced.

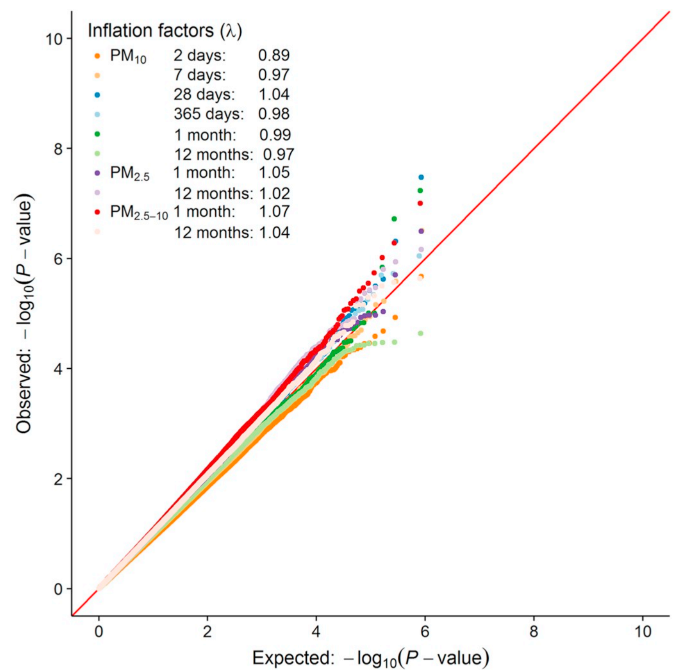

Fig. 1. Quantile-quantile (QQ) plot of observed vs. expected -$\log_{10}$ *P*-value of each CpG site from trans-ethnic, fixed-effects meta-analyses of 2-, 7-, 28-, and 365-day PM_{10} and 1- and 12-month PM_{10} and $PM_{2.5}$. The red diagonal line references the methylome-wide significance threshold ($P < 1.0 \times 10^{-7}$). Lambda (λ) is the inflation factor. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Functional annotation

MATN4 is highly expressed in the pancreas, reproductive tract, and skin (Fig. S2), but variants of this gene have not been significantly associated ($P < 5 \times 10^{-8}$) with any phenotypes in prior GWAS. *ARPP21* is primarily expressed in the brain (Fig. S3), is significantly associated with neuroticism and severe H1N1 influenza, and suggestively associated ($5 \times 10^{-8} < P < 5 \times 10^{-6}$) with entorhinal cortical thickness and childhood-onset asthma in prior GWAS. *CFTR* is expressed in various tissues, including the pancreas, colon, minor salivary gland,

Table 2
Particulate matter concentration (μg/m^3) means and Pearson correlations in the total population (n = 8397).

		PM_{10}	PM_{10}	PM_{10}	PM_{10}	PM_{10}	PM_{10}	$PM_{2.5}$	$PM_{2.5}$	$PM_{2.5–10}$	$PM_{2.5–10}$
		2 d	7 d	28 d	365 d	1 mo	12 mo	1 mo	12 mo	1 mo	12 mo
	$\bar{x}$ (SD)	31.9 (12.1)	31.1 (9.2)	30.9 (7.1)	31.2 (5.1)	20.9 (5.8)	20.9 (4.0)	13.2 (4.3)	13.2 (3.0)	7.7 (4.0)	7.8 (3.1)
PM_{10}	2 d	1.00									
PM_{10}	7 d	0.74	1.00								
PM_{10}	28 d	0.58	0.79	1.00							
PM_{10}	365 d	0.43	0.56	0.70	1.00						
PM_{10}	1 mo	0.39	0.48	0.54	0.27	1.00					
PM_{10}	12 mo	0.15	0.18	0.24	0.35	0.62	1.00				
$PM_{2.5}$	1 mo	0.29	0.36	0.41	0.17	0.73	0.39	1.00			
$PM_{2.5}$	12 mo	0.11	0.12	0.15	0.23	0.40	0.64	0.66	1.00		
$PM_{2.5–10}$	1 mo	0.25	0.31	0.35	0.21	0.67	0.48	−0.02	−0.13	1.00	
$PM_{2.5–10}$	12 mo	0.08	0.12	0.17	0.23	0.41	0.67	−0.14	−0.14	0.74	1.00

Abbreviations: d, day; mo, month; PM, particulate matter; PM_{10}, PM < 10 μm in diameter; $PM_{2.5}$, PM < 2.5 μm in diameter; $PM_{2.5–10}$, PM > 2.5 and < 10 μm in diameter; SD, standard deviation; $\bar{x}$, mean.

ARTICLE IN PRESS

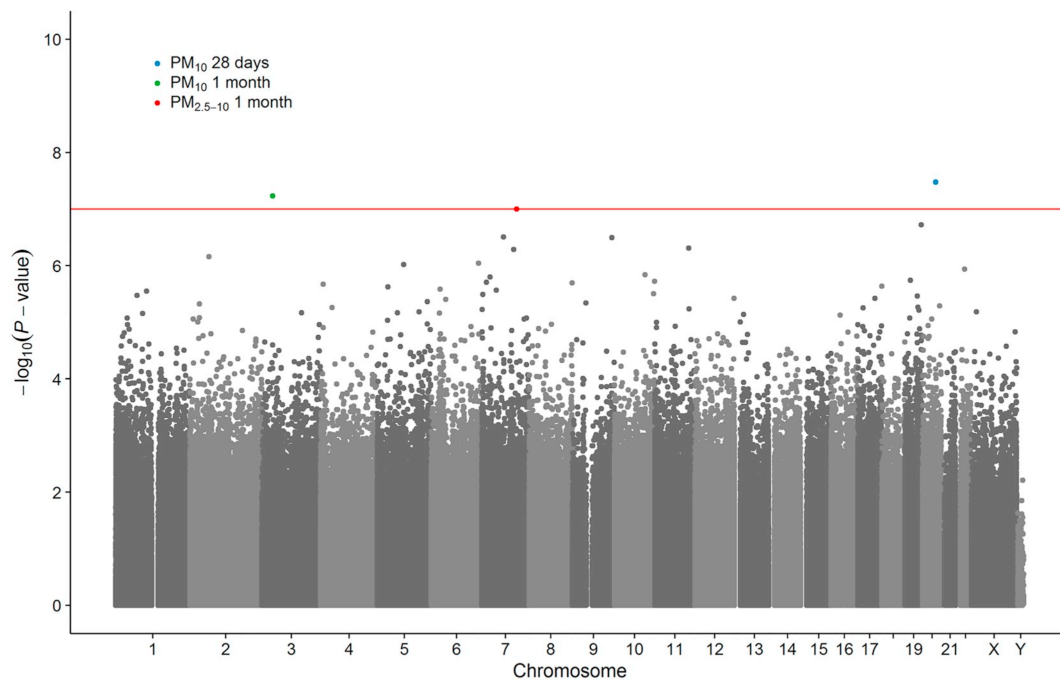

Fig. 2. Manhattan plot of $-\log_{10}$ *P*-value vs. chromosomal position of each CpG site from trans-ethnic, fixed-effects meta-analyses of 2-, 7-, 28-, and 365-day PM_{10} and 1- and 12-month PM_{10} and $PM_{2.5}$. The red line references the methylome-wide significance threshold ($P < 1.0 \times 10^{-7}$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Findings from trans-ethnic, fixed-effects meta-analyses ($P < 1 \times 10^{-7}$, $P_{Cochran's\ Q} > 0.10$).

Chr	Position[a]	CpG	Exposure	%Δ (95% CI)[b]	*P*	n_{obs}	Gene
20	43,926,884	cg19004594	PM_{10}, 28 d	0.3 (0.2, 0.4)	3.33×10^{-8}	8622	*MATN4*
3	35,785,890	cg24102420	PM_{10}, 1 mo	−0.5 (−0.7, −0.3)	5.84×10^{-8}	8575	*ARPP21/miR128-2*
7	117,299,297	cg12124767	$PM_{2.5–10}$, 1 mo	−0.5 (−0.7, −0.3)	9.96×10^{-8}	8577	*CFTR*

Abbreviations: Δ, change; Chr, chromosome; CI, confidence interval; CpG, Cytosine-phosphate-Guanine; d, days; mo, month; PM_{10}, PM < 10 µm in diameter; $PM_{2.5}$, PM < 2.5 µm in diameter; $PM_{2.5–10}$, PM > 2.5 and < 10 µm in diameter.

[a] Build 37.

[b] Absolute percentage point per 10 µg/m³ increase in PM_{10}.

digestive tract, and lung (Fig. S4). *CFTR* polymorphisms are associated with cystic fibrosis (CF), Barrett's esophagus/esophageal carcinoma, and coronary artery disease.

Differential methylation at cg19004594, cg24102420, or cg12124767 was not associated with gene expression in blood cells at any of the > 13,000 transcripts evaluated ($P > 10^{-5}$) in the MESA/GTP cohorts. Although genomic regions around PM-sensitive CpG sites were associated with tri-methylation of histone 3 at lysine 9 (H3K9me3) in natural killer cells, derived mesenchymal stem cells, the fetal adrenal gland, fetal lung fibroblasts, and foreskin fibroblasts (FDR < 0.05; Fig. 4), they were not associated with mono- or tri-methylation of histone 3 at lysine 4, 27, or 36 (H3K4me1, H3K4me3,

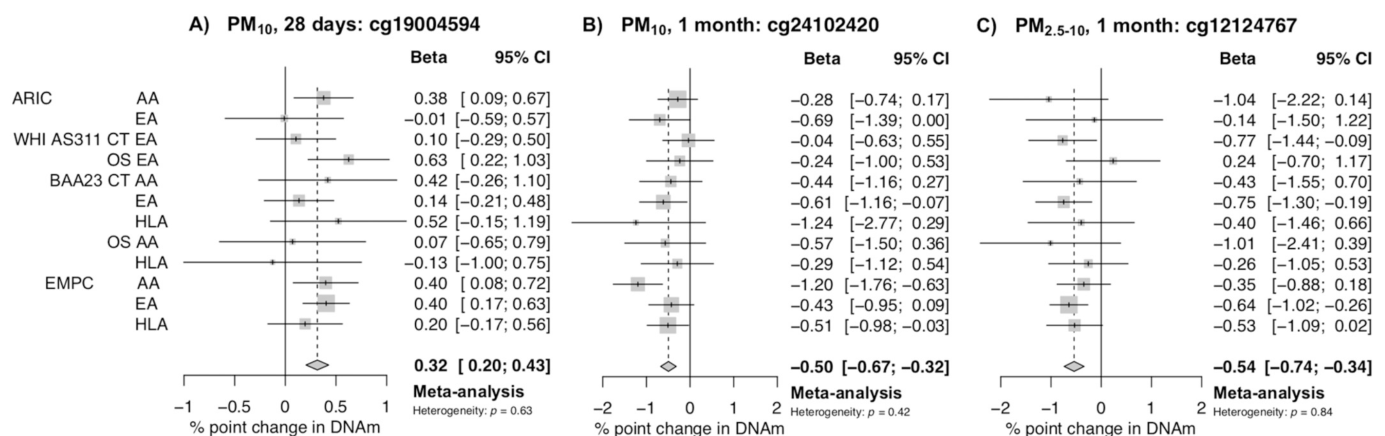

Fig. 3. Forest plots of PM-CpG associations (95% confidence intervals) for A) cg19004594, B) cg2410240, and C) cg12124767 with a 10 µg/m³ increase in PM by subpopulation and overall after fixed-effects meta-analysis.

Fig. 4. Enrichment of PM-sensitive CpG sites in regions overlapping H3K9me3 using Roadmap data.

H3K27me3, or H3K36me3) or DNase I hypersensitivity in any tissues catalogued by eFORGE.

3.3. Replication

The three statistically significant, non-heterogeneous PM-sensitive CpG sites (cg19004594; cg24102420; cg12124767) did not replicate in KORA F3/F4 (Table S5).

4. Discussion

This methylome-wide association study (MWAS) discovered three CpG sites at which higher levels of monthly mean ambient particulate matter air pollution concentrations were associated with DNAm. The DNAm-PM associations at all three CpG sites were homogeneous across the twelve subpopulations and each site was annotated to a neurological, pulmonary, endocrine, or cardiovascular disease-related gene (*MATN4*, *ARPP21* or *CFTR*). Although a recent MWAS also implicated cigarette smoking in DNA methylation at *ARPP21* and *CFTR* (Joehanes et al., 2016)—two genes that may underlie epigenetically mediated responses to inhalable environmental exposures—the CpG sites discovered herein are in different regions of *ARPP21* and *CFTR*, suggesting varied responses to particulate exposures, and none of them were associated with gene expression of blood cells in MESA/GTP.

Methylation of cg19004594 (exon of *MATN4*) was positively associated with 28-day mean PM_{10} concentrations. *MATN4* encodes Matrilin 4, a von Willebrand factor A domain-containing protein, which contributes to cardiac remodeling (Barallobre-Barreiro et al., 2012) and inhibits the proliferation of hematopoietic stem cells at rest. Additionally, environmental stressors trigger expression of the *CXCL12*-encoded chemokine (SDF1) (Liberda et al., 2010) and activation of its G protein-coupled receptor (CXCR4), leading to inhibition of Matrilin 4 and subsequent expansion of hematopoietic stem cell pools (Uckelmann et al., 2016). SDF1-activated CXCR4 also inhibits beta-adrenergically activated calcium influx through myocardial L-type calcium ion channels (Pyo et al., 2006), a process that may affect PM_{10}-associated ventricular action potential and electrocardiographic QT interval duration (Gondalia et al., 2017). Methylation of *MATN4* may therefore underlie commonly observed hematological and electrocardiographic of effects of PM_{10}.

Methylation at cg24102420 (intron of *ARPP21*) was positively associated with 1-month mean PM_{10} concentrations. *ARPP21* encodes a neuronal cAMP-regulated phosphoprotein, a regulator of calmodulin signaling (RCS) that is highly enriched in medium spiny neurons within the basal ganglia, cerebral cortex, and other regions of the brain (Rakhilin et al., 2004), with dual evidence of expression in cardiac tissues (Kahr et al., 2011; Kirchhof et al., 2011; Mathar et al., 2013). Variants of *ARPP21* have been associated with entorhinal cortical thickness (Furney et al., 2010). Calmodulin signaling (O'Day et al., 2015), entorhinal cortical thickness (Velayudhan et al., 2013), and PM air pollution (Cacciottolo et al., 2017) are all associated with Alzheimer's disease progression, suggesting a potential epigenetic mechanism of PM_{10}-related neuropathology.

Indeed, *ARPP21* and *miR128-2*, a microRNA within *ARPP21*, are both regulators of dendritic growth (Rehfeld et al., 2018). In a study of rats, exposure to ammonium sulfate, a major component of $PM_{2.5}$, was associated with diminished dendritic complexity in hippocampal neurons (Cheng et al., 2017). Additionally, *miR128* expression in peripheral blood of steel plant workers increased with increases in PM exposure, as was confirmed by an in vitro study of PM-treated pulmonary tissue (Bollati et al., 2015). Additional roles of *miR128* include the inhibition of *ABCA1* and *ABCG1*, adenosine triphosphate-binding cassette (ABC) transporter genes also involved in homeostasis of cholesterol (Adlakha et al., 2013), an established risk factor for stroke, myocardial infarction, and other common forms of cardiovascular disease.

Methylation at cg12124767 (intron of *CFTR*) was inversely

associated with 1-month mean $PM_{2.5–10}$ concentrations. *CFTR* encodes a transmembrane conductance regulator; specifically, an ABC transporter of chloride and thiocyanate ions. The *CFTR*-encoded ABC transporter controls fluid secretion and absorption in epithelial tissues (Saint-Criq and Gray, 2017). Its most common mutation impairs folding and trafficking of the encoded protein in pulmonary and pancreatic epithelia, causing CF and CF-related diabetes (Brennan et al., 2004). However, cigarette smoke and chronic inflammation also reduce *CFTR* chloride channel function (Rasmussen et al., 2014), a hypothesized molecular pathway underlying the development of chronic obstructive pulmonary disease (Rab et al., 2013). Furthermore, CFTR chloride channel currents in the myocardium shorten action potential and QT interval duration (Duan, 2013). Their activation by cAMP protein kinase A (PKA), protein kinase C (PKC), or extracellular adenosine triphosphate (ATP) through purinergic receptors (al-Awqati, 1995; Duan, 2013) can be arrhythmogenic (Cacciapuoti et al., 1991; Engler and Yellon, 1996; Leonard et al., 2017; Najeed et al., 2002; Yamazaki and Hume, 1997). Hypomethylation of *CFTR* at this site therefore highlights another epigenetic mechanism that may underlie PM_{10}-related pulmonary and electrocardiographic manifestations of disease.

While the putative mechanisms described above are biologically plausible, analyses on which they are based are limited by their reliance on DNAm derived from leukocytes. Although other (e.g. heart, lung, nervous) tissues may be more appropriate for studying the role of DNAm on human disease, their collection is highly invasive (McCullough et al., 2017; Zhong et al., 2016); as such, leukocytes extracted from peripheral blood are widely used surrogate tissues (Zhong et al., 2016) with demonstrated consistency of DNAm patterns across relevant tissues types (Byun et al., 2009; Fan and Zhang, 2009; Ma et al., 2014). Still, DNAm at cg19004594, cg24102420, cg12124767 was not associated with gene expression of blood cells in GTP/MESA (Kennedy et al., 2018). Unlike DNAm patterns though, gene expression is highly variable by tissue type (Aguet et al., 2017), and *MATN4*, *ARPP21* and *CFTR* are primarily expressed in other tissues.

The inability to replicate associations in KORA F3 and F4 participants is noteworthy. Although independent from the discovery populations, KORA represents a population of white, European men and women living in Augsburg, Germany, one distinct from that of the environmentally diverse, multi-racial/ethnic U.S. populations in the discovery. In addition, PM composition in ARIC and WHI (1990–2012) may differ from that in Augsburg during KORA F3 and F4 (2004–2006). Furthermore, PM concentrations in KORA were measured at community monitors, while those in WHI and ARIC were spatially or spatiotemporally estimated at participant geocoded addresses from monitoring networks in the 48 contiguous US states.

DNAm associations with $PM_{2.5}$ – potentially the driver for PM-associated disease (Brook et al., 2010) – were not detected in this study. Inability to do so may be due to lower power to detect $PM_{2.5}$ versus PM_{10} associations with DNAm given lower-variance $PM_{2.5}$ exposure estimates, lack of short-duration $PM_{2.5}$ data before 1999 when EPA AQS started monitoring it, and/or induction of $PM_{2.5}$ health effects that are not epigenetically mediated.

The analyses also were limited by predominantly cross-sectional data, high multiple testing burden, small effect sizes, and residual need for functional characterization. However, repeated measures of PM and DNAm over time were leveraged in WHI-EMPC to increase statistical power. Among-pollutant correlations also were moderate in this context, so the multiple comparisons made were not strictly independent. Similarly, the Bonferroni-corrected threshold used herein ($P < 1 \times 10^{-7}$) is conservative because of methylome-wide correlations among CpG sites (Saffari et al., 2018; Tsai et al., 2012), decreasing the likelihood of false positives. Moreover, observed effect sizes were consistent with those seen in other epigenetic studies of particulate matter exposure (de F.C. Lichtenfels et al., 2018; Panni et al., 2016; Plusquin et al., 2017) and smoking (Joehanes et al., 2016). Further investigation is nonetheless needed to determine the clinical impact of CpG-specific changes in methylation although functional validation of epigenetic associations was outside the scope of presently funded work. Still, this is a well-powered study of geographically diverse, multi-racial/ethnic populations of women and men with methylome-wide DNAm and geocoded address-specific PM data, that leveraged multivariate imputation to minimize selection-related biases otherwise known to affect epidemiologic associations in complete data analyses.

5. Conclusions

Findings from this large, racially/ethnically and environmentally diverse methylome-wide association study of women and men in EPA regions 1–10 suggest that ambient particulate matter air pollution affects DNAm at regions of the genome potentially related to neurological, pulmonary, endocrine, and cardiovascular disease. Although the discovered associations are biologically plausible, functional characterization in relevant tissues or animal models remains necessary to validate associations and elucidate putative epigenetic mechanisms of PM-associated disease.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.03.071.

Acknowledgements

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I and HHSN268201700005I). The authors thank the staff and participants of the ARIC study for their important contributions. Funding was also supported by 5RC2HL102419 and R01NS087541. Data from the ARIC study are available on request at https://www2.cscc.unc.edu/aric/distribution-agreements.

1The WHI program is funded by the NHLBI, U.S. Department of Health and Human Services, through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. WHI-AS311 was supported by American Cancer Society award 125299-RSG-13-100-01-CCE. All contributors to WHI science are listed at https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf. Data from the WHI are available on request at https://www.whi.org/researchers/SitePages/Write%20a%20Paper.aspx.

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC-Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ.

This work was supported by NIEHS grant R01-ES020836 (LH, AB, EAW), NHLBI contract HHSN268201100046C (KC), NIEHS grant R01-ES017794 (EAW), NHLBI National Research Service Award T32-HL007055 (RG), NIEHS National Research Service Award T32-ES007018 (KH), and NCI grant R25-CA094880 (KJ).

Conflicts of interest

No authors have declared a potential conflicts of interest.

References

Adlakha, Y.K., Khanna, S., Singh, R., Singh, V.P., Agrawal, A., Saini, N., 2013. Pro-apoptotic miRNA-128-2 modulates ABCA1, ABCG1 and RXRα expression and cholesterol homeostasis. Cell Death Dis. 4, e780.

Aguet, F.; Brown, A.A.; Castel, S.E.; Davis, J.R.; He, Y.; Jo, B.; Mohammadi, P.; Park, Y.;

ARTICLE IN PRESS

Parsana, P.; Segrè, A.V.; Strober, B.J.; Zappala, Z.; Cummings, B.B.; Gelfand, E.T.; Hadley, K.; Huang, K.H.; Lek, M.; Li, X.; Nedzel, J.L.; Nguyen, D.Y.; Noble, M.S.; Sullivan, T.J.; Tukiainen, T.; MacArthur, D.G.; Getz, G.; Addington, A.; Guan, P.; Koester, S.; Little, A.R.; Lockhart, N.C.; Moore, H.M.; Rao, A.; Struewing, J.P.; Volpi, S.; Brigham, L.E.; Hasz, R.; Hunter, M.; Johns, C.; Johnson, M.; Kopen, G.; Leinweber, W.F.; Lonsdale, J.T.; McDonald, A.; Mestichelli, B.; Myer, K.; Roe, B.; Salvatore, M.; Shad, S.; Thomas, J.A.; Walters, G.; Washington, M.; Wheeler, J.; Bridge, J.; Foster, B. A.; Gillard, B.M.; Karasik, E.; Kumar, R.; Miklos, M.; Moser, M.T.; Jewell, S.D.; Montroy, R.G.; Rohrer, D.C.; Valley, D.; Mash, D.C.; Davis, D.A.; Sobin, L.; Barcus, M. E.; Branton, P.A.; Abell, N.S.; Balliu, B.; Delaneau, O.; Frésard, L.; Gamazon, E.R.; Garrido-Martín, D.; Gewirtz, A.D.H.; Gliner, G.; Gloudemans, M.J.; Han, B.; He, A.Z.; Hormozdiari, F.; Li, X.; Liu, B.; Kang, E.Y.; McDowell, I.C.; Ongen, H.; Palowitch, J.J.; Peterson, C.B.; Quon, G.; Ripke, S.; Saha, A.; Shabalin, A.A.; Shimko, T.C.; Sul, J.H.; Teran, N.A.; Tsang, E.K.; Zhang, H.; Zhou, Y.-H.; Bustamante, C.D.; Cox, N.J.; Guigó, R.; Kellis, M.; McCarthy, M.I.; Conrad, D.F.; Eskin, E.; Li, G.; Nobel, A.B.; Sabatti, C.; Stranger, B.E.; Wen, X.; Wright, F.A.; Ardlie, K.G.; Dermitzakis, E.T.; Lappalainen, T.; Aguet, F.; Ardlie, K.G.; Cummings, B.B.; Gelfand, E.T.; Getz, G.; Hadley, K.; Handsaker, R.E.; Huang, K.H.; Kashin, S.; Karczewski, K.J.; Lek, M.; Li, X.; MacArthur, D.G.; Nedzel, J.L.; Nguyen, D.T.; Noble, M.S.; Segrè, A.V.; Trowbridge, C.A.; Tukiainen, T.; Abell, N.S.; Balliu, B.; Barshir, R.; Basha, O.; Battle, A.; Bogu, G.K.; Brown, A.; Brown, C.D.; Castel, S.E.; Chen, L.S.; Chiang, C.; Conrad, D.F.; Cox, N.J.; Damani, F.N.; Davis, J.R.; Delaneau, O.; Dermitzakis, E.T.; Engelhardt, B.E.; Eskin, E.; Ferreira, P.G.; Frésard, L.; Gamazon, E.R.; Garrido-Martín, D.; Gewirtz, A.D.H.; Gliner, G.; Gloudemans, M.J.; Guigo, R.; Hall, I.M.; Han, B.; He, Y.; Hormozdiari, F.; Howald, C.; Kyung Im, H.; Jo, B.; Yong Kang, E.; Kim, Y.; Kim-Hellmuth, S.; Lappalainen, T.; Li, G.; Li, X.; Liu, B.; Mangul, S.; McCarthy, M.I.; McDowell, I.C.; Mohammadi, P.; Monlong, J.; Montgomery, S.B.; Muñoz-Aguirre, M.; Ndungu, A.W.; Nicolae, D.L.; Nobel, A.B.; Oliva, M.; Ongen, H.; Palowitch, J.J.; Panousis, N.; Papasaikas, P.; Park, Y.; Parsana, P.; Payne, A.J.; Peterson, C.B.; Quan, J.; Reverter, F. ; Sabatti, C.; Saha, A.; Sammeth, M.; Scott, A.J.; Shabalin, A.A.; Sodaei, R.; Stephens, M.; Stranger, B.E.; Strober, B.J.; Sul, J.H.; Tsang, E.K.; Urbut, S.; van de Bunt, M.; Wang, G.; Wen, X.; Wright, F.A.; Xi, H.S.; Yeger-Lotem, E.; Zappala, Z.; Zaugg, J.B.; Zhou, Y.-H.; Akey, J.M.; Bates, D.; Chan, J.; Chen, L.S.; Claussnitzer, M.; Demanelis, K.; Diegel, M.; Doherty, J.A.; Feinberg, A.P.; Fernando, M.S.; Halow, J.; Hansen, K.D.; Haugen, E.; Hickey, P.F.; Hou, L.; Jasmine, F.; Jian, R.; Jiang, L.; Johnson, A.; Kaul, R. ; Kellis, M.; Kibriya, M.G.; Lee, K.; Billy Li, J.; Li, Q.; Li, X.; Lin, J.; Lin, S.; Linder, S.; Linke, C.; Liu, Y.; Maurano, M.T.; Molinie, B.; Montgomery, S.B.; Nelson, J.; Neri, F.J.; Oliva, M.; Park, Y.; Pierce, B.L.; Rinaldi, N.J.; Rizzardi, L.F.; Sandstrom, R.; Skol, A.; Smith, K.S.; Snyder, M.P.; Stamatoyannopoulos, J.; Stranger, B.E.; Tang, H.; Tsang, E. K.; Wang, L.; Wang, M.; Van Wittenberghe, N.; Wu, F.; Zhang, R.; Nierras, C.R.; Branton, P.A.; Carithers, L.J.; Guan, P.; Moore, H.M.; Rao, A.; Vaught, J.B.; Gould, S. E.; Lockart, N.C.; Martin, C.; Struewing, J.P.; Volpi, S.; Addington, A.M.; Koester, S.E.; Little, A.R.; Brigham, L.E.; Hasz, R.; Hunter, M.; Johns, C.; Johnson, M.; Kopen, G.; Leinweber, W.F.; Lonsdale, J.T.; McDonald, A.; Mestichelli, B.; Myer, K.; Roe, B.; Salvatore, M.; Shad, S.; Thomas, J.A.; Walters, G.; Washington, M.; Wheeler, J.; Bridge, J.; Foster, B.A.; Gillard, B.M.; Karasik, E.; Kumar, R.; Miklos, M.; Moser, M.T.; Jewell, S.D.; Montroy, R.G.; Rohrer, D.C.; Valley, D.R.; Davis, D.A.; Mash, D.C.; Undale, A.H.; Smith, A.M.; Tabor, D.E.; Roche, N.V.; McLean, J.A.; Vatanian, N.; Robinson, K.L.; Sobin, L.; Barcus, M.E.; Valentino, K.M.; Qi, L.; Hunter, S.; Hariharan, P.; Singh, S.; Um, K.S.; Matose, T.; Tomaszewski, M.M.; Barker, L.K.; Mosavel, M.; Siminoff, L.A.; Traino, H.M.; Flicek, P.; Juettemann, T.; Ruffier, M.; Sheppard, D.; Taylor, K.; Trevanion, S.J.; Zerbino, D.R.; Craft, B.; Goldman, M.; Haeussler, M.; Kent, W.J.; Lee, C.M.; Paten, B.; Rosenbloom, K.R.; Vivian, J.; Zhu, J. Genetic effects on gene expression across human tissues. Nature 2017;550:204.

al-Awqati, Q., 1995. Regulation of ion channels by ABC transporters that secrete ATP. Science 269, 805–806.

Alexeeff, S.E., Schwartz, J., Kloog, I., Chudnovsky, A., Koutrakis, P., Coull, B.A., 2014. Consequences of kriging and land use regression for PM2.5 predictions in epidemiologic analyses: insights into spatial variability using high-resolution satellite data. Journal of Exposure Science and Environmental Epidemiology 25, 138.

Anderson, G.L.; LaCroix, A., W64 - Long Life Study (Long Life Study).

Anderson, G.L., Manson, J., Wallace, R., Lund, B., Hall, D., Davis, S., Shumaker, S., Wang, C.-Y., Stein, E., Prentice, R.L., 2003. Implementation of the Women's Health Initiative study design. Ann. Epidemiol. 13, S5–S17.

Andrews, S.V., Ladd-Acosta, C., Feinberg, A.P., Hansen, K.D., Fallin, M.D., 2016. "Gap hunting" to characterize clustered probe signals in Illumina methylation array data. Epigenetics Chromatin 9 (56).

ARIC, 1989. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am. J. Epidemiol. 129, 687–702.

Assimes, T.; Tsao, P.; Absher, D.; Horvath, S., BA23 - Integrative Genomics and Risk of CHD and Related Phenotypes in the Women's Health Initiative.

Azur, M.J., Stuart, E.A., Frangakis, C., Leaf, P.J., 2011. Multiple imputation by chained equations: what is it and how does it work? Int. J. Methods Psychiatr. Res. 20, 40–49.

Baccarelli, A., Rienstra, M., Benjamin, E.J., 2010. Cardiovascular epigenetics. Circ. Cardiovasc. Genet. 3, 567.

Barallobre-Barreiro, J., Didangelos, A., Schoendube, F.A., Drozdov, I., Yin, X., Fernández-Caggiano, M., Willeit, P., Puntmann, V.O., Aldama-López, G., Shah, A.M., Doménech, N., Mayr, M., 2012. Proteomics analysis of cardiac extracellular matrix remodeling in a porcine model of ischemia/reperfusion injury. Circulation 125, 789–802.

Bates, D., 2017. Mixed-Effects Models in Julia. GitHub.

Bellavia, A., Urch, B., Speck, M., Brook, R.D., Scott, J.A., Albetti, B., Behbod, B., North, M., Valeri, L., Bertazzi, P.A., Silverman, F., Gold, D., Baccarelli, A, A., 2013. DNA hypomethylation, ambient particulate matter, and increased blood pressure: findings from controlled human exposure experiments. J. Am. Heart Assoc. 2.

Bernstein, B.E., Stamatoyannopoulos, J.A., Costello, J.F., Ren, B., Milosavljevic, A., Meissner, A., Kellis, M., Marra, M.A., Beaudet, A.L., Ecker, J.R., Farnham, P.J., Hirst, M., Lander, E.S., Mikkelsen, T.S., Thomson, J.A., 2010. The NIH roadmap epigenomics mapping consortium. Nat. Biotechnol. 28, 1045–1048.

Bezanson, J., Edelman, A., Karpinski, S., Shah, V.B., 2017. Julia: A fresh approach to numerical computing. SIAM Rev. 59, 65–98.

Bollati, V., Baccarelli, A., 2010. Environmental epigenetics. Heredity 105, 105–112.

Bollati, V., Angelici, L., Rizzo, G., Pergoli, L., Rota, F., Hoxha, M., Nordio, F., Bonzini, M., Tarantini, L., Cantone, L., Pesatori, A.C., Apostoli, P., Baccarelli, A.A., Bertazzi, P.A., 2015. Microvesicle-associated microRNA expression is altered upon particulate matter exposure in healthy workers and in A549 cells. J. Appl. Toxicol. 35, 59–67.

Breeze, Charles E., Paul, Dirk S., van Dongen, J., Butcher, Lee M., Ambrose, John C., Barrett, James E., Lowe, R., Rakyan, Vardhman K., Iotchkova, V., Frontini, M., Downes, K., Ouwehand, Willem H., Laperle, J., Jacques, P.-É., Bourque, G., Bergmann, Anke K., Siebert, R., Vellenga, E., Saeed, S., Matarese, F., Martens, Joost H.A., Stunnenberg, Hendrik G., Teschendorff, Andrew E., Herrero, J., Birney, E., Dunham, I., Beck, S., 2016. eFORGE: a tool for identifying cell type-specific signal in epigenomic data. Cell Rep. 17, 2137–2150.

Brennan, A.L., Geddes, D.M., Gyi, K.M., Baker, E.H., 2004. Clinical importance of cystic fibrosis-related diabetes. J. Cyst. Fibros. 3, 209–222.

Brook, R.D., Franklin, B., Cascio, W., Hong, Y., Howard, G., Lipsett, M., Luepker, R., Mittleman, M., Samet, J., Smith, S.C., Tager, I., 2004. Air pollution and cardiovascular disease. Circulation 109, 2655.

Brook, R.D., Rajagopalan, S., Pope, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C., Whitsel, L., Kaufman, J.D., 2010. Particulate matter air pollution and cardiovascular disease. Circulation 121, 2331.

Byun, H.-M., Siegmund, K.D., Pan, F., Weisenberger, D.J., Kanel, G., Laird, P.W., Yang, A.S., 2009. Epigenetic profiling of somatic tissues from human autopsy specimens identifies tissue- and individual-specific DNA methylation patterns. Hum. Mol. Genet. 18, 4808–4817.

Cacciapuoti, F., Spiezia, R., Bianchi, U., Lama, D., D'Avino, M., Varricchio, M., 1991. Effectiveness of glibenclamide on myocardial ischemic ventricular arrhythmias in non-insulin-dependent diabetes mellitus. Am. J. Cardiol. 67, 843–847.

Cacciottolo, M., Wang, X., Driscoll, I., Woodward, N., Saffari, A., Reyes, J., Serre, M.L., Vizuete, W., Sioutas, C., Morgan, T.E., Gatz, M., Chui, H.C., Shumaker, S.A., Resnick, S.M., Espeland, M.A., Finch, C.E., Chen, J.C., 2017. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. Transl. Psychiatry 7, e1022.

Chen, Y.A., Lemire, M., Choufani, S., Butcher, D.T., Grafodatskaya, D., Zanke, B.W., Gallinger, S., Hudson, T.J., Weksberg, R., 2013. Discovery of cross-reactive probes and polymorphic CpGs in the Illumina Infinium HumanMethylation450 microarray. Epigenetics 8.

Chen, R., Qiao, L., Li, H., Zhao, Y., Zhang, Y., Xu, W., Wang, C., Wang, H., Zhao, Z., Xu, X., Hu, H., Kan, H., 2015. Fine particulate matter constituents, nitric oxide synthase DNA methylation and exhaled nitric oxide. Environmental Science & Technology 49, 11859–11865.

Chen, R., Meng, X., Zhao, A., Wang, C., Yang, C., Li, H., Cai, J., Zhao, Z., Kan, H., 2016. DNA hypomethylation and its mediation in the effects of fine particulate air pollution on cardiovascular biomarkers: a randomized crossover trial. Environ. Int. 94, 614–619.

Cheng, L., Lau, W.K.W., Fung, T.K.H., Lau, B.W.M., Chau, B.K.H., Liang, Y., Wang, Z., So, K.F., Wang, T., Chan, C.C.H., Lee, T.M.C., 2017. PM2.5 exposure suppresses dendritic maturation in subgranular zone in aged rats. Neurotox. Res. 32, 50–57.

Clouaire, T., Stancheva, I., 2008. Methyl-CpG binding proteins: specialized transcriptional repressors or structural components of chromatin? Cell. Mol. Life Sci. 65, 1509–1522.

Cochran, W.G., 1954. The combination of estimates from different experiments. Biometrics 10, 101–129.

Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., Estep, K., Balakrishnan, K., Brunekreef, B., Dandona, L., Dandona, R., Feigin, V., Freedman, G., Hubbell, B., Jobling, A., Kan, H., Knibbs, L., Liu, Y., Martin, R., Morawska, L., Pope III, C.A., Shin, H., Straif, K., Shaddick, G., Thomas, M., van Dingenen, R., van Donkelaar, A., Vos, T., Murray, C.J.L., Forouzanfar, M.H., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389, 1907–1918.

Consortium, E.P., 2012. An integrated encyclopedia of DNA elements in the human genome. Nature 489, 57–74.

Cornbleet, P.J., Gochman, N., 1979. Incorrect least-squares regression coefficients in method-comparison analysis. Clin. Chem. 25, 432–438.

de F.C. Lichtenfels, A.J., van der Plaat, D.A., de Jong, K., van Diemen, C.C., Postma, D.S., Nedeljkovic, I., van Duijn, C.M., Amin, N., la Bastide-van Gemert, S., de Vries, M., Ward-Caviness, C.K., Wolf, K., Waldenberger, M., Peters, A., Stolk, R.P., Brunekreef, B., Boezen, H.M., Vonk, J.M., 2018. Long-term air pollution exposure, genome-wide DNA methylation and lung function in the LifeLines cohort study. Environ. Health Perspect. 027004, 126.

Devlin, B., Roeder, K., Wasserman, L., 2001. Genomic control, a new approach to genetic-based association studies. Theor. Popul. Biol. 60, 155–166.

Di, Q., Wang, Y., Zanobetti, A., Wang, Y., Koutrakis, P., Choirat, C., Dominici, F., Schwartz, J.D., 2017. Air pollution and mortality in the Medicare population. N. Engl. J. Med. 376, 2513–2522.

Dominici, F., Peng, R.D., Bell, M.L., Pham, L., McDermott, A., Zeger, S.L., 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 295.

Duan, D.D., 2013. Phenomics of cardiac chloride channels. Comprehensive Physiology.

Engler, R.L., Yellon, D.M., 1996. Sulfonylurea KATP blockade in type II diabetes and preconditioning in cardiovascular disease. Time for Reconsideration 94, 2297–2301.

EPA, 2017. What Are the Air Quality Standards for PM? U.S. Environmental Protection Agency.

Fan, S., Zhang, X., 2009. CpG island methylation pattern in different human tissues and its correlation with gene expression. Biochem. Biophys. Res. Commun. 383, 421–425.
Furney, S.J., Simmons, A., Breen, G., Pedroso, I., Lunnon, K., Proitsi, P., Hodges, A., Powell, J., Wahlund, L.O., Kloszewska, I., Mecocci, P., Soininen, H., Tsolaki, M., Vellas, B., Spenger, C., Lathrop, M., Shen, L., Kim, S., Saykin, A.J., Weiner, M.W., Lovestone, S., 2010. Genome-wide association with MRI atrophy measures as a quantitative trait locus for Alzheimer's disease. Mol. Psychiatry 16, 1130.
Gan, W.Q., FitzGerald, J.M., Carlsten, C., Sadatsafavi, M., Brauer, M., 2013. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am. J. Respir. Crit. Care Med. 187, 721–727.
Gondalia, R., Avery, C.L., Napier, M.D., Mendez-Giraldez, R., Stewart, J.D., Sitlani, C.M., Li, Y., Wilhelmsen, K.C., Duan, Q., Roach, J., North, K.E., Reiner, A.P., Zhang, Z.M., Tinker, L.F., Yanosky, J.D., Liao, D., Whitsel, E.A., 2017. Genome-wide association study of susceptibility to particulate matter-associated QT prolongation. Environ. Health Perspect. 125, 067002.
Hernan, M.A., Hernandez-Diaz, S., Robins, J.M., 2004. A structural approach to selection bias. Epidemiology 15, 615–625.
Holle, R., Happich, M., Löwel, H., Wichmann, H.-E., Group, n.f.t.M.K.S, 2005. KORA-a research platform for population based health research. Das Gesundheitswesen 67, 19–25.
Houseman, E.A., Accomando, W.P., Koestler, D.C., Christensen, B.C., Marsit, C.J., Nelson, H.H., Wiencke, J.K., Kelsey, K.T., 2012. DNA methylation arrays as surrogate measures of cell mixture distribution. BMC Bioinformatics 13, 1.
Joehanes, R.; Just, A.C.; Marioni, R.E.; Pilling, L.C.; Reynolds, L.M.; Mandaviya, P.R.; Guan, W.; Xu, T.; Elks, C.E.; Aslibekyan, S.; Moreno-Macias, H.; Smith, J.A.; Brody, J. A.; Dhingra, R.; Yousefi, P.; Pankow, J.S.; Kunze, S.; Shah, S.; McRae, A.F.; Lohman, K.; Sha, J.; Absher, D.M.; Ferrucci, L.; Zhao, W.; Demerath, E.W.; Bressler, J.; Grove, M.L.; Huan, T.; Liu, C.; Mendelson, M.M.; Yao, C.; Kiel, D.P.; Peters, A.; Wang-Sattler, R.; Visscher, P.M.; Wray, N.R.; Starr, J.M.; Ding, J.; Rodriguez, C.J.; Wareham, N.J.; Irvin, M.R.; Zhi, D.; Barrdahl, M.; Vineis, P.; Ambatipudi, S.; Uitterlinden, A.G.; Hofman, A.; Schwartz, J.; Colicino, E.; Hou, L.; Vokonas, P.S.; Hernandez, D.G.; Singleton, A.B.; Bandinelli, S.; Turner, S.T.; Ware, E.B.; Smith, A.K.; Klengel, T.; Binder, E.B.; Psaty, B.M.; Taylor, K.D.; Gharib, S.A.; Swenson, B.R.; Liang, L.; DeMeo, D.L.; Connor, G.T.; Herceg, Z.; Ressler, K.J.; Conneely, K.N.; Sotoodehnia, N.; Kardia, S.L.R.; Melzer, D.; Baccarelli, A.A.; van Meurs, J.B.J.; Romieu, I.; Arnett, D.K.; Ong, K. K.; Liu, Y.; Waldenberger, M.; Deary, I.J.; Fornage, M.; Levy, D.; London, S.J. Epigenetic signatures of cigarette smoking. Circ. Cardiovasc. Genet. 2016;
Johnson, W.E., Li, C., Rabinovic, A., 2007. Adjusting batch effects in microarray expression data using empirical Bayes methods. Biostatistics 8, 118–127.
Jordahl, K.M., Randolph, T.W., Song, X., Sather, C.L., Tinker, L.F., Phipps, A.I., Kelsey, K.T., White, E., Bhatti, P., 2018. Genome-wide DNA methylation in prediagnostic blood and bladder cancer risk in the Women's Health Initiative. Cancer Epidemiol. Biomark. Prev. 27, 689.
Kahr, P.C., Piccini, I., Fabritz, L., Greber, B., Schöler, H., Scheld, H.H., Hoffmeier, A., Brown, N.A., Kirchhof, P., 2011. Systematic analysis of gene expression differences between left and right atria in different mouse strains and in human atrial tissue. PLoS One 6, e26389.
Kennedy, E.M., Goehring, G.N., Nichols, M.H., Robins, C., Mehta, D., Klengel, T., Eskin, E., Smith, A.K., Conneely, K.N., 2018. An integrated-omics analysis of the epigenetic landscape of gene expression in human blood cells. BMC Genomics 19, 476.
Kirchhof, P., Kahr, P.C., Kaese, S., Piccini, I., Vokshi, I., Scheld, H.-H., Rotering, H., Fortmueller, L., Laakmann, S., Verheule, S., Schotten, U., Fabritz, L., Brown, N.A., 2011. PITX2c is expressed in the adult left atrium, and reducing Pitx2c expression promotes atrial fibrillation inducibility and complex changes in gene expression. Circ. Cardiovasc. Genet. 4, 123–133.
Laumbach, R.J., Kipen, H.M., 2012. Respiratory health effects of air pollution: update on biomass smoke and traffic pollution. J. Allergy Clin. Immunol. 129, 3–11.
Lee, S.-J., Serre Marc, L., van Donkelaar, A., Martin Randall, V., Burnett Richard, T., Jerrett, M., 2012. Comparison of geostatistical interpolation and remote sensing techniques for estimating long-term exposure to ambient PM2.5 concentrations across the continental United States. Environ. Health Perspect. 120, 1727–1732.
Leonard, C.E., Hennessy, S., Han, X., Siscovick, D.S., Flory, J.H., Deo, R., 2017. Pro- and antiarrhythmic actions of sulfonylureas: mechanistic and clinical evidence. Trends in Endocrinology & Metabolism 28, 561–586.
Liao, D., Peuquet, D.J., Duan, Y., Whitsel, E.A., Dou, J., Smith, R.L., Lin, H.-M., Chen, J.-C., Heiss, G., 2006. GIS approaches for the estimation of residential-level ambient PM concentrations. Environ. Health Perspect. 1374–1380.
Liao, D., Peuquet, D.J., Lin, H.-M., Duan, Y., Whitsel, E.A., Smith, R.L., Heiss, G., 2007. National kriging exposure estimation: Liao et al. respond. Environ. Health Perspect. 115, A338–A339.
Liberda, E.N., Cuevas, A.K., Gillespie, P.A., Grunig, G., Qu, Q., Chen, L.C., 2010. Exposure to inhaled nickel nanoparticles causes a reduction in number and function of bone marrow endothelial progenitor cells. Inhal. Toxicol. 22, 95–99.
Lonsdale, J., Thomas, J., Salvatore, M., Phillips, R., Lo, E., Shad, S., Hasz, R., Walters, G., Garcia, F., Young, N., Foster, B., Moser, M., Karasik, E., Gillard, B., Ramsey, K., Sullivan, S., Bridge, J., Magazine, H., Syron, J., Fleming, J., Siminoff, L., Traino, H., Mosavel, M., Barker, L., Jewell, S., Rohrer, D., Maxim, D., Filkins, D., Harbach, P., Cortadillo, E., Berghuis, B., Turner, L., Hudson, E., Feenstra, K., Sobin, L., Robb, J., Branton, P., Korzeniewski, G., Shive, C., Tabor, D., Qi, L., Groch, K., Nampally, S., Buia, S., Zimmerman, A., Smith, A., Burges, R., Robinson, K., Valentino, K., Bradbury, D., Cosentino, M., Diaz-Mayoral, N., Kennedy, M., Engel, T., Williams, P., Erickson, K., Ardlie, K., Winckler, W., Getz, G., DeLuca, D., MacArthur, D., Kellis, M., Thomson, A., Young, T., Gelfand, E., Donovan, M., Meng, Y., Grant, G., Mash, D., Marcus, Y., Basile, M., Liu, J., Zhu, J., Tu, Z., Cox, N.J., Nicolae, D.L., Gamazon, E.R., Im, H.K., Konkashbaev, A., Pritchard, J., Stevens, M., Flutre, T., Wen, X., Dermitzakis, E.T., Lappalainen, T., Guigo, R., Monlong, J., Sammeth, M., Koller, D., Battle, A., Mostafavi, S., McCarthy, M., Rivas, M., Maller, J., Rusyn, I., Nobel, A., Wright, F., Shabalin, A., Feolo, M., Sharopova, N., Sturcke, A., Paschal, J., Anderson, J.M., Wilder, E.L., Derr, L.K., Green, E.D., Struewing, J.P., Temple, G., Volpi, S., Boyer, J.T., Thomson, E.J., Guyer, M.S., Ng, C., Abdallah, A., Colantuoni, D., Insel, T.R., Koester, S.E., Little, A.R., Bender, P.K., Lehner, T., Yao, Y., Compton, C.C., Vaught, J.B., Sawyer, S., Lockhart, N.C., Demchok, J., Moore, H.F., 2013. The genotype-tissue expression (GTEx) project. Nat. Genet. 45, 580.
Ma, B., Wilker, E.H., Willis-Owen, S.A.G., Byun, H.-M., Wong, K.C.C., Motta, V., Baccarelli, A.A., Schwartz, J., Cookson, W.O.C.M., Khabbaz, K., Mittleman, M.A., Moffatt, M.F., Liang, L., 2014. Predicting DNA methylation level across human tissues. Nucleic Acids Res. 42, 3515–3528.
Mathar, I., Kecskes, M., Van Der Mieren, G., Jacobs, G., Uhl, S., Camacho Londoño, J.E., Flockerzi, V., Voets, T., Freichel, M., Nilius, B., Herijgers, P., Vennekens, R., 2013. Increased ß-adrenergic inotropy in ventricular myocardium from Trpm4$^{-/-}$ mice. Circ. Res. 114, 283–294.
McCullough, S.D., Dhingra, R., Fortin, M.C., Diaz-Sanchez, D., 2017. Air pollution and the epigenome: a model relationship for the exploration of toxicoepigenetics. Current Opinion in Toxicology 6, 18–25.
Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L., Kaufman, J.D., 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N. Engl. J. Med. 356, 447–458.
Mosley, T.H., Knopman, D.S., Catellier, D.J., Bryan, N., Hutchinson, R.G., Grothues, C.A., Folsom, A.R., Cooper, L.S., Burke, G.L., Liao, D., Szklo, M., 2005. Cerebral MRI findings and cognitive functioning. Neurology 64, 2056.
Najeed, S.A., Khan, I.A., Molnar, J., Somberg, J.C., 2002. Differential effect of glyburide glibenclamide and metformin on qt dispersion: a potential adenosine triphosphate sensitive k+ channel effect. Am. J. Cardiol. 90, 1103–1106.
Neidhart, M., 2016. DNA Methylation and Complex Human Disease EdˆEds. Elsevier, Amsterdam.
NIH, 1998. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control. Clin. Trials 19, 61–109.
O'Day, D.H., Eshak, K., Myre, M.A., 2015. Calmodulin binding proteins and Alzheimer's disease. J. Alzheimers Dis. 46, 553–569.
Panni, T., Mehta, A.J., Schwartz, J.D., Baccarelli, A.A., Just, A.C., Wolf, K.A., 2016. Genome-wide analysis of DNA methylation and fine particulate matter air pollution in three study populations: KORA F3, KORA F4, and the normative aging study. Environ. Health Perspect. 124, 983–990.
Plusquin, M., Guida, F., Polidoro, S., Vermeulen, R., Raaschou-Nielsen, O., Campanella, G., Hoek, G., Kyrtopoulos, S.A., Georgiadis, P., Naccarati, A., Sacerdote, C., Krogh, V., Bas Bueno-de-Mesquita, H., Monique Verschuren, W.M., Sayols-Baixeras, S., Panni, T., Peters, A., Hebels, D.G.A.J., Kleinjans, J., Vineis, P., Chadeau-Hyam, M., 2017. DNA methylation and exposure to ambient air pollution in two prospective cohorts. Environ. Int. 108, 127–136.
Pope III, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., Thurston, G.D., 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. Jama 287, 1132–1141.
Pyo, R.T., Sui, J., Dhume, A., Palomeque, J., Blaxall, B.C., Diaz, G., Tunstead, J., Logothetis, D.E., Hajjar, R.J., Schecter, A.D., 2006. CXCR4 modulates contractility in adult cardiac myocytes. J. Mol. Cell. Cardiol. 41, 834–844.
Raaschou-Nielsen, O., Andersen, Z.J., Beelen, R., Samoli, E., Stafoggia, M., Weinmayr, G., Hoffmann, B., Fischer, P., Nieuwenhuijsen, M.J., Brunekreef, B., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Sommar, J., Forsberg, B., Modig, L., Oudin, A., Oftedal, B., Schwarze, P.E., Nafstad, P., De Faire, U., Pedersen, N.L., Östenson, C.-G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Sørensen, M., Tjønneland, A., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Key, T.J., de Hoogh, K., Concin, H., Nagel, G., Vilier, A., Grioni, S., Krogh, V., Tsai, M.-Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Trichopoulou, A., Bamia, C., Vineis, P., Hoek, G., 2013. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). The Lancet Oncology 14, 813–822.
Rab, A., Rowe, S.M., Raju, S.V., Bebok, Z., Matalon, S., Collawn, J.F., 2013. Cigarette smoke and CFTR: implications in the pathogenesis of COPD. Am. J. Phys. Lung Cell. Mol. Phys. 305, L530–L541.
Rakhilin, S.V., Olson, P.A., Nishi, A., Starkova, N.N., Fienberg, A.A., Nairn, A.C., Surmeier, D.J., Greengard, P.A., 2004. Network of control mediated by regulator of calcium/calmodulin-dependent signaling. Science 306, 698–701.
Rasmussen, J.E., Sheridan, J.T., Polk, W., Davies, C.M., Tarran, R., 2014. Cigarette smoke-induced Ca2+ release leads to cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction. J. Biol. Chem. 289, 7671–7681.
Rehfeld, F., Maticzka, D., Grosser, S., Knauff, P., Eravci, M., Vida, I., Backofen, R., Wulczyn, F.G., 2018. The RNA-binding protein ARPP21 controls dendritic branching by functionally opposing the miRNA it hosts. Nat. Commun. 9, 1235.
Roux, A.V.D., Merkin, S.S., Arnett, D., Chambless, L., Massing, M., Nieto, F.J., Sorlie, P., Szklo, M., Tyroler, H.A., Watson, R.L., 2001. Neighborhood of residence and incidence of coronary heart disease. N. Engl. J. Med. 345, 99–106.
Saffari, A., Silver, M.J., Zavattari, P., Moi, L., Columbano, A., Meaburn, E.L., Dudbridge, F., 2018. Estimation of a significance threshold for epigenome-wide association studies. Genet. Epidemiol. 42, 20–33.
Saint-Criq, V., Gray, M.A., 2017. Role of CFTR in epithelial physiology. Cell. Mol. Life Sci. 74, 93–115.
Stuart, E.A., Azur, M., Frangakis, C., Leaf, P., 2009. Multiple imputation with large data sets: a case study of the Children's Mental Health Initiative. Am. J. Epidemiol. 169, 1133–1139.
Stunnenberg, H.G., Abrignani, S., Adams, D., de Almeida, M., Altucci, L., Amin, V., Amit,

I., Antonarakis, S.E., Aparicio, S., Arima, T., Arrigoni, L., Arts, R., Asnafi, V., Esteller, M., Bae, J.-B., Bassler, K., Beck, S., Berkman, B., Bernstein, B.E., Bilenky, M., Bird, A., Bock, C., Boehm, B., Bourque, G., Breeze, C.E., Brors, B., Bujold, D., Burren, O., Bussemakers, M.J., Butterworth, A., Campo, E., Carrillo-de-Santa-Pau, E., Chadwick, L., Chan, K.M., Chen, W., Cheung, T.H., Chiapperino, L., Choi, N.H., Chung, H.-R., Clarke, L., Connors, J.M., Cronet, P., Danesh, J., Dermitzakis, M., Drewes, G., Durek, P., Dyke, S., Dylag, T., Eaves, C.J., Ebert, P., Eils, R., Eils, J., Ennis, C.A., Enver, T., Feingold, E.A., Felder, B., Ferguson-Smith, A., Fitzgibbon, J., Flicek, P., Foo, R.S.Y., Fraser, P., Frontini, M., Furlong, E., Gakkhar, S., Gasparoni, N., Gasparoni, G., Geschwind, D.H., Glažar, P., Graf, T., Grosveld, F., Guan, X.-Y., Guigo, R., Gut, I.G., Hamann, A., Han, B.-G., Harris, R.A., Heath, S., Helin, K., Hengstler, J.G., Heravi-Moussavi, A., Herrup, K., Hill, S., Hilton, J.A., Hitz, B.C., Horsthemke, B., Hu, M., Hwang, J.-Y., Ip, N.Y., Ito, T., Javierre, B.-M., Jenko, S., Jenuwein, T., Joly, Y., Jones, S.J.M., Kanai, Y., Kang, H.G., Karsan, A., Kiemer, A.K., Kim, S.C., Kim, B.-J., Kim, H.-H., Kimura, H., Kinkley, S., Klironomos, F., Koh, I.-U., Kostadima, M., Kressler, C., Kreuzhuber, R., Kundaje, A., Küppers, R., Larabell, C., Lasko, P., Lathrop, M., Lee, D.H.S., Lee, S., Lehrach, H., Leitão, E., Lengauer, T., Lernmark, Å., Leslie, R.D., Leung, G.K.K., Leung, D., Loeffler, M., Ma, Y., Mai, A., Manke, T., Marcotte, E.R., Marra, M.A., Martens, J.H.A., Martin-Subero, J.I., Maschke, K., Merten, C., Milosavljevic, A., Minucci, S., Mitsuyama, T., Moore, R.A., Müller, F., Mungall, A.J., Netea, M.G., Nordström, K., Norstedt, I., Okae, H., Onuchic, V., Ouellette, F., Ouwehand, W., Pagani, M., Pancaldi, V., Pap, T., Pastinen, T., Patel, R., Paul, D.S., Pazin, M.J., Pelicci, P.G., Phillips, A.G., Polansky, J., Porse, B., Pospisilik, J.A., Prabhakar, S., Procaccini, D.C., Radbruch, A., Rajewsky, N., Rakyan, V., Reik, W., Ren, B., Richardson, D., Richter, A., Rico, D., Roberts, D.J., Rosenstiel, P., Rothstein, M., Salhab, A., Sasaki, H., Satterlee, J.S., Sauer, S., Schacht, C., Schmidt, F., Schmitz, G., Schreiber, S., Schröder, C., Schübeler, D., Schultze, J.L., Schulyer, R.P., Schulz, M., Seifert, M., Shirahige, K., Siebert, R., Sierocinski, T., Siminoff, L., Sinha, A., Soranzo, N., Spicuglia, S., Spivakov, M., Steidl, C., Strattan, J.S., Stratton, M., Südbeck, P., Sun, H., Suzuki, N., Suzuki, Y., Tanay, A., Torrents, D., Tyson, F.L., Ulas, T., Ullrich, S., Ushijima, T., Valencia, A., Vellenga, E., Vingron, M., Wallace, C., Wallner, S., Walter, J., Wang, H., Weber, S., Weiler, N., Weller, A., Weng, A., Wilder, S., Wiseman, S.M., Wu, A.R., Wu, Z., Xiong, J., Yamashita, Y., Yang, X., Yap, D.Y., Yip, K.Y., Yip, S., Yoo, J.-I., Zerbino, D., Zipprich, G., Hirst, M., 2016. The international human epigenome consortium: a blueprint for scientific collaboration and discovery. Cell 167, 1145–1149.

Tarantini, L., Bonzini, M., Apostoli, P., Pegoraro, V., Bollati, V., Marinelli, B., Cantone, L., Rizzo, G., Hou, L., Schwartz, J., Bertazzi, P.A., Baccarelli, A., 2009. Effects of particulate matter on genomic DNA methylation content and iNOS promoter methylation. Environ. Health Perspect. 117, 217–222.

Tarantini, L., Bonzini, M., Tripodi, A., Angelici, L., Nordio, F., Cantone, L., Apostoli, P., Bertazzi, P.A., Baccarelli, A.A., 2013. Blood hypomethylation of inflammatory genes mediates the effects of metal-rich airborne pollutants on blood coagulation. Occup. Environ. Med. 70.

Teschendorff, A.E., Marabita, F., Lechner, M., Bartlett, T., Tegner, J., Gomez-Cabrero, D., Beck, S., 2013. A beta-mixture quantile normalization method for correcting probe design bias in Illumina Infinium 450 k DNA methylation data. Bioinformatics 29, 189–196.

Tsai, P.-C., Spector, T.D., Bell, J.T., 2012. Using epigenome-wide association scans of DNA methylation in age-related complex human traits. Epigenomics 4, 511–526.

Uckelmann, H., Blaszkiewicz, S., Nicolae, C., Haas, S., Schnell, A., Wurzer, S., Wagener, R., Aszodi, A., Essers, M.A.G., 2016. Extracellular matrix protein Matrilin-4 regulates stress-induced HSC proliferation via CXCR4. J. Exp. Med. 213, 1961–1971.

Velayudhan, L., Proitsi, P., Westman, E., Muehlboeck, J.S., Mecocci, P., Vellas, B., Tsolaki, M., Kloszewska, I., Soininen, H., Spenger, C., Hodges, A., Powell, J., Lovestone, S., Simmons, A., 2013. Entorhinal cortex thickness predicts cognitive decline in Alzheimer's disease. Journal of Alzheimer's disease: JAD 33, 755–766.

Welter, D., MacArthur, J., Morales, J., Burdett, T., Hall, P., Junkins, H., Klemm, A., Flicek, P., Manolio, T., Hindorff, L., Parkinson, H., 2014. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res. 42, D1001–D1006.

Whitsel, E.A., AS315 - Epigenetic Mechanisms of PM-mediated CVD Risk.

Whitsel, E.A., Rose, K.M., Wood, J.L., Henley, A.C., Liao, D., Heiss, G., 2004. Accuracy and repeatability of commercial geocoding. Am. J. Epidemiol. 160, 1023–1029.

Whitsel, E.A., Quibrera, P.M., Smith, R.L., Catellier, D.J., Liao, D., Henley, A.C., Heiss, G., 2006. Accuracy of commercial geocoding: assessment and implications. Epidemiologic Perspectives & Innovations: EP + I 3, 8.

Wichmann, H., Gieger, C., Illig, T., Group, M.K.S., 2005. KORA-gen—resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)) 67, S26.

Yamazaki, J., Hume, J.R., 1997. Inhibitory effects of glibenclamide on cystic fibrosis transmembrane regulator, swelling-activated, and Ca2+-activated Cl− channels in mammalian cardiac myocytes. Circ. Res. 81, 101–109.

Yanosky, J.D., Paciorek, C.J., Laden, F., Hart, J.E., Puett, R.C., Liao, D., Suh, H.H., 2014. Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. Environmental Health: A Global Access Science Source 13 (63).

Zhong, J., Agha, G., Baccarelli, A.A., 2016. The role of DNA methylation in cardiovascular risk and disease. Methodological Aspects, Study Design, and Data Analysis for Epidemiological Studies 118, 119–131.