Association between ambient air pollution and cardiac morpho-functional phenotypes: Insights from the UK Biobank population imaging study

Running title: Association between air pollution and cardiac structure

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Abstract

Background

Exposure to ambient air pollution is strongly associated with increased cardiovascular morbidity and mortality. Little is known about the influence of air pollutants on cardiac structure and function. We aim to investigate the relationship between chronic past exposure to traffic-related pollutants and the cardiac chamber volume, ejection fraction and left ventricular remodelling patterns after accounting for potential confounders.

Methods

Exposure to ambient air pollutants including particulate matter and nitrogen dioxide was estimated from the Land Use Regression models for years between 2005 and 2010. Cardiac parameters were measured from cardiovascular magnetic resonance imaging studies of 3,920 individuals free from pre-existing cardiovascular disease in the UK Biobank population study. The median (interquartile range [IQR]) duration between the year of exposure estimate and the imaging visit was 5.2 (0.6) years. We fitted multivariable linear regression models to investigate the relationship between cardiac parameters and traffic-related pollutants after adjusting for various confounders.

Results

The studied cohort was 62±7 years old and 46% were men. In fully-adjusted models, fine particulate matter ($PM_{2.5}$) concentration was significantly associated with larger left ventricular end-diastolic volume and end-systolic volume (effect size = 0.82%, 95% confidence interval [CI] = 0.09 to 1.55%, p = 0.027 and effect size = 1.28%, 95% CI = 0.15 to 2.43%, p = 0.027,

respectively, per IQR increment in $PM_{2.5}$) and right ventricular end-diastolic volume (effect size = 0.85%, 95% CI = 0.12 to 1.58%, p = 0.023, per IQR increment in $PM_{2.5}$). Likewise, higher nitrogen dioxide (NO_2) concentration was associated with larger biventricular volume. Distance from the major roads was the only metric associated with lower left ventricular mass (effect size = -0.74%, 95% CI = -1.3% to -0.18%, p = 0.01, per IQR increment). Neither left and right atrial phenotypes nor left ventricular geometric remodelling patterns were influenced by the ambient pollutants.

Conclusions

In a large asymptomatic population with no prevalent cardiovascular disease, higher past exposure to $PM_{2.5}$ and NO_2 was associated with cardiac ventricular dilatation, a marker of adverse remodelling which often precedes heart failure development.

Keywords: air pollution; $PM_{2.5}$; NO_2; cardiovascular phenotypes; cardiovascular magnetic resonance imaging

Clinical Perspective

What is New?

- Although ambient air pollutants are known to be associated with increased cardiovascular morbidity and mortality, limited information is available on the link between air pollutants and cardiac structure and function.
- In this cross-sectional analysis of a large population free from pre-existing cardiovascular disease, higher past exposure to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) were associated with larger cardiac biventricular volumes, which is a well-recognised pathophysiological adaptation, heralding heart failure development.
- Proximity to major roads, a surrogate for chronic air pollution exposure, was additionally associated with higher left ventricular mass which is known to portend adverse outcomes.

What Are the Clinical Implications?

- The association between ambient air pollution and adverse cardiac phenotypic changes in individuals without prevalent cardiovascular disease suggests that air pollution should be recognised as a major modifiable risk factor which needs to be targeted via public health measures.
- These cardiac morphological alterations are apparent despite relatively low exposure levels meeting the current air quality standards, making a strong case to double efforts to control emission of the noxious pollutants.

Introduction

Deleterious effect of air pollutants on cardiovascular health is well established. Several studies have demonstrated strong associations between exposure to air pollution and increased risks of coronary artery disease, heart failure, stroke, cardiovascular mortality and all-cause mortality [1]. Traffic-related environmental pollution consists of a complex mixture of gaseous and particulate components, alongside auxiliary elements such as noise and psychological stress. Amongst all air pollutants, particulate matter (PM) pollution – specifically fine particulates with an aerodynamic diameter less than 2.5μm ($PM_{2.5}$) – has repeatedly been associated with cardiovascular morbidity and mortality. Inhalation of $PM_{2.5}$ can initiate and sustain physiological and biochemical changes through elevation of pulmonary and systemic inflammatory and oxidative stress, autonomic imbalance, endothelial dysfunction, hypertension, atherosclerosis, and thrombosis, which are all key substrates for adverse cardiac remodelling leading to detrimental outcomes [2].

Cardiac morpho-functional parameters are prognostically important biomarkers in health and disease. Left ventricular (LV) mass, for example, is a well-recognised predictor of cardiovascular morbidity and mortality even in individuals without established cardiovascular disease (CVD) [3]. LV geometric patterns and the morpho-functional indices of other cardiac chambers also carry prognostic information in the setting of CVD [4–11]. Although the associations between ambient air pollutants and increased incidence of myocardial infarction and heart failure have been established [12,13], there is a paucity of information in the current literature about the influence of air pollution on cardiac structure and function. Determining

the impact of individual air pollutant on cardiac phenotypes is challenging for several reasons due to socioeconomic confounders, relatively small effect sizes and the variability of exposure and outcome measurement techniques.

The UK Biobank is a large-scale prospective cohort study of half a million people, aged between 40-69 years. In addition to a rich repository of information on demographics, risk factors and environmental exposure data, a sub-group of UK Biobank participants undergo deep phenotyping with cardiovascular magnetic resonance (CMR), which is the reference imaging modality for quantification of the cardiac structural phenotypes [14]. In this study, we aim to explore the association between chronic past exposure to traffic-related ambient air pollution and the cardiac imaging parameters after accounting for various potential confounders in the UK Biobank cohort. We hypothesised that annual average air pollutants and other traffic-related factors quantified approximately 5 years prior to cardiac imaging have a detectable adverse association with cardiac imaging phenotypes in individuals free from known cardiovascular disease.

Methods

Data access

The data, analytic methods, and study materials will be returned to the UK Biobank. The UK Biobank will make these data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any person. All researchers will be subject to the same application process and approval criteria as specified by the UK Biobank. Please see the UK Biobank's website for the detailed access procedure (http://www.ukbiobank.ac.uk/register-apply/).

Study population

The UK Biobank is a large population-based prospective cohort study which has collected a wealth of information on health and lifestyle data, physical measurements, biological samples, and cardiac phenotypes derived from CMR. This ambitious project aims to provide resources to disentangle the genetic and environmental determinants of complex diseases affecting middle and old age. The study protocol has been described in detail previously [15]. In brief, approximately 9.2 million UK residents aged between 40-69 years, who were registered with the UK National Health Service and living up to twenty-five miles from one of the 22 study assessment centres, were invited to join the study. Amongst those who responded the invite, more than 500,000 people were enrolled in 2006 to 2010. The sample size of 500,000 was calculated *a priori* for reliable detection of the effects of different exposures on a wide variety of conditions in nested case-control studies. Although the UK Biobank cohort is not designed to be representative of the UK general population (due to 'healthy volunteer' selection bias), it is well-suited to study exposure-disease relationships due to its large size and heterogeneity of exposure measures [16]. The baseline summary characteristics of the cohort can be viewed in the data showcase on UK Biobank's website (www.ukbiobank.ac.uk). The CMR imaging sub-study was commenced in 2014 and this study included the first 5,065 consecutive participants who returned for imaging enhancement in 2014-2015. The study complies with the Declaration of Helsinki and was approved by our institutional review body. All participants provided informed written consent. The UK Biobank's scientific protocol and operational procedures were approved by the Northwest Research Ethics Committee in the UK.

Ambient air pollution, noise and traffic exposure

The annual average concentration of $PM_{2.5}$, PM_{10} (PM with an aerodynamic diameter of less than 10 μm), PM_{coarse} (PM with an aerodynamic diameter between 2.5 to 10 μm), $PM_{2.5}$ absorbance (a measurement of the blackness of $PM_{2.5}$ filter – a proxy for elemental or black carbon), nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were calculated centrally by the UK Biobank using a Land Use Regression (LUR) model developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project [17,18]. LUR models calculate the spatial variation of annual average air pollutant concentration at participants' home addresses given at the baseline visit, using the predictor variables obtained from Geographic Information System (GIS) such as traffic, land use, and topography. Since NO_2 and PM_{10} annual concentration data were available for several years (2005, 2006, 2007 and 2010 for NO_2 and 2007 and 2010 for PM_{10}), we averaged the values to get the mean estimate. All other particulate matter and nitrogen pollutants had the exposure data for a single year (2010). The median leave-one-out cross-validated variance explained by the model was 71% for $PM_{2.5}$, 77% for PM_{10}, 68% for PM_{coarse}, 89% for $PM_{2.5}$ absorbance, 82% for NO_2 and 78% for NO_x.

Average exposure to noise for year 2009 was estimated from a model based on common noise assessment methods in Europe (CNOSSOS-EU) [19]. This technique allows large-scale noise mapping for epidemiological studies using data on traffic flow, speed and composition, land cover, building heights, road network, air temperature, and wind direction. Noise pollution was represented by 24-hour (daily) sound pressure level (A-weighted sound level in decibels) averaged over a year as suggested by World Health Organization [20].

Traffic intensity on the nearest major road was defined as the total number of motor vehicles per 24 hours, averaged over the course of one year. The traffic count and road network data were provided by the UK Department for Transport and the Ordnance Survey Meridian 2 (OSM2) road network (scale 1:50000, 1 metre accuracy) in year 2009. Proximity to traffic was characterised by the distance from home address to the nearest major road.

CMR parameters

The detailed CMR protocol and analysis methods have been described previously [21]. In brief, all CMR studies were acquired with a wide bore 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) and analyses were performed using cvi[42] post-processing software (Version 5.1.1, Circle Cardiovascular Imaging Inc., Calgary, Canada). LV mass and volumes; right ventricular (RV) volumes; left atrial (LA) and right atrial (RA) volumes were manually measured from balanced steady-state free precession (bSSFP) cine short and long axis images. The following cardiac phenotypes were included: LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction (LVEF), LV mass (LVM), RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV ejection fraction (RVEF), LA maximal volume, LA ejection fraction (LAEF), RA maximal volume, RA ejection fraction (RAEF), and LV geometric remodelling patterns. The LV geometric remodelling patterns were classified according to LV mass indexed to body surface area and LV mass to end-diastolic volume ratio (LVMVR, CMR-equivalent of relative wall thickness) as previously described [22]. Normal cut-off values for LV mass and LVMVR were obtained from the 95% prediction intervals of sex-specific reference ranges [21]. Four distinct LV geometric remodelling patterns were defined: (i) Normal (normal indexed LV mass and LVMVR), (ii) Concentric

remodelling (normal indexed LV mass and increased LVMVR), (iii) Eccentric hypertrophy (increased indexed LV mass and normal LVMVR), and (iv) Concentric hypertrophy (increased indexed LV mass and increased LVMVR).

Statistical analyses

Since air pollution estimates were modelled using participants' home address given at the baseline visit, we restricted the data analysis to those who remained at the same address between the baseline and imaging visits. We also excluded individuals with any known cardiovascular disease based on the self-reported questionnaires and hospital episode data in order to mitigate the potential impact of established cardiac conditions on the imaging parameters. All continuous variables were assessed for normality using histograms and quantile-quantile plots. Natural logarithmic transformation was performed on non-Gaussian dependent variables where possible. Descriptive statistics for continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) while categorical variables were presented as number (percentage).

We imputed missing data by multiple imputation by chained equations (MICE) approach to create 50 complete datasets [23]. We used predictive mean matching for continuous variables, logistic regression for binary variables, and polytomous regression for categorical variables. All covariates and interaction terms were included in the imputation models. The maximum iteration was set at 50 and convergence was confirmed by visual examination of trace plots.

We constructed separate multiple linear regression models to examine the associations between each air pollutant and continuous cardiac CMR variables. For categorical LV geometric remodelling patterns, we used multinomial logistic regression to model the effect of pollution. In all statistical models, we adjusted for: (i) demographics – age at imaging visit,

sex, and ethnicity; (ii) anthropometrics – height, and body mass index (BMI); (iii) socioeconomic factors – average household income, employment status, Townsend deprivation index, and educational attainment; (iv) cardiac risk factors – systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), smoking status, regular alcohol use, hypertension, diabetes mellitus, and respiratory disease; (v) medications – anti-hypertensive medication, lipid-lowering medication, and insulin; (vi) physical activity – seven-day average acceleration from accelerometer. All covariates were chosen *a priori* for their established or presumed influence on the cardiovascular structure and function. The measurement protocols and covariate definitions were provided in the "Definitions of covariates" section in Supplemental Methods. The beta-coefficients (effect estimates) of log-transformed variables were anti-logged and expressed as percentage change. The mean estimates and standard errors of the beta-coefficients for the imputed datasets were combined with Rubin's rules (see Supplemental Methods) [24]. Since we have scaled all pollutants by their respective IQR before entering into the regression models, their effect estimates represent the change in dependent CMR variable per IQR increment in pollutant.

We conducted the following secondary analyses: (i) an analysis of effect modification by age, sex, and smoking status by introducing cross-product terms, (ii) an analysis excluding hypertension, diabetes, SBP, DBP, and HR due to their potential mediating effects on the relationship between air pollution and cardiac phenotypes, (iii) an analysis of the confounding effects of noise and proximity to traffic on the significant associations between air pollutants and cardiac measurements, and (iv) an analysis of cases with clinically unrecognized myocardial infarction (MI) based on the evaluation of CMR images. Cases with possible MI were first selected by identifying thin left ventricular myocardial segments (end-diastolic wall thickness < 5.5 mm for the basal and mid segments) and possible regional

hypokinesis (systolic wall thickening – end-systolic wall thickness minus end-diastolic wall thickness – of < 2mm) as recommended by Baer et al. [25,26]. These cases were then manually evaluated by three analysts with significant experience in reporting clinical CMR studies (MK, NA – both EACVI CMR level 3-certified cardiologists – and KF with four years' experience in reporting clinical CMR studies).

Sensitivity analyses were conducted by: (i) restricting the sample to participants with complete data, (ii) indexing continuous CMR-derived phenotypes by height$^{2.7}$, and (iii) restricted cubic spline (RCS) transformation of exposure variables to investigate non-linear relationships. The optimal number of knots for RCS-transformed variables was determined by the Akaike information criterion. Non-linearity was assessed with the analysis-of-variance F statistics and visualized with line plots. The regression model assumptions were checked with residuals plots. A *p*-value of < 0.05 was considered significant. Multiple imputation, multinomial regression and restricted cubic spline transformation were performed using 'mice', 'nnet' and 'rms' packages, respectively [27–29]. We used R (version 3.4.3) for all statistical analyses [30].

Results

Baseline demographics

A total of 5,065 individuals were considered for this study. Of these, we excluded 738 individuals who had moved home between the baseline and imaging visit. A further 407 individuals were excluded due to pre-existing CVD – highest prevalent CVD was coronary artery disease (n [%] = 198 [4.6%]), resulting in 3,920 individuals included in the final

analysis (Figure 1). The baseline characteristics of the final cohort are presented in Table 1. The mean age of the cohort was 61.7 years and 45.6% were men. The median (IQR) annual average concentration of the two main pollutants, $PM_{2.5}$ and NO_2, were 9.9 (1.32) $\mu g/m^3$ and 28.2 (11.4) $\mu g/m^3$, respectively. The median (IQR) duration between the year of exposure estimate and the imaging visit was 5.2 (0.6) years. There was no clinically significant difference in characteristics between the whole cohort and complete cases without missing data (Supplemental Table 1).

Relationship between particulate matter pollutants and cardiac phenotypes

The associations between particulate matter pollutants and cardiac phenotypes are presented in Table 2 and Figure 2. After adjustment for all covariates, $PM_{2.5}$ concentration was significantly associated with larger biventricular volume (effect size for LV EDV = 0.82%, 95% confidence interval [CI]: 0.09 to1.55%, p = 0.027; effect size for LV ESV = 1.28%, 95% CI: 0.15 to 2.43%, p = 0.027; effect size for RV EDV = 0.85%, 95% CI: 0.12 to 1.58%, p = 0.023, per IQR increment in $PM_{2.5}$ concentration). Likewise, PM10 had identical association patterns with slightly smaller magnitude of effect sizes per IQR increment. Neither $PM_{2.5}$ nor PM_{10} was associated with other cardiac parameters and LV geometric remodelling patterns. PM_{coarse} and $PM_{2.5}$ absorbance did not have any association with the cardiac phenotypes.

Relationship between oxides of nitrogen and cardiac phenotypes

Table 3 presents the relationships between nitrogen pollutants and cardiac parameters after adjustment for all covariates. Higher NO_2 concentration was significantly correlated with

larger LV EDV and RV EDV (effect size for LV EDV = 0.91%, 95% CI: 0.12 to 1.7%, p = 0.025; effective size for RV EDV = 0.85%, 95% CI: 0.06 to 1.65%, p = 0.035, per IQR increment in NO_2 concentration) (Figure 2). However, NO_x had no significant association with CMR-derived measurements.

Relationship between noise, road traffic factors and cardiac phenotypes

The associations between noise, distance to the nearest major road and traffic intensity and CMR-derived phenotypes are detailed in Table 4. Being exposed to higher ambient sound level was associated with larger LV ESV (effect size = 0.69%, 95% CI: 0.03 to 1.35%, p = 0.041, per IQR increment in 24-hour sound level averaged over a year). Interestingly, in addition to the significant association with biventricular volume, living further away from major roads was also associated with lower LV mass (effect size = -0.74%, 95% CI: -1.3 to -0.18%, p = 0.01, per IQR increment in distance to major roads). There was no significant relationship between traffic intensity and any of the cardiac morpho-functional phenotypes.

Effect modification and mediator analyses

We investigated if age, sex, and smoking status modify the significant relationships between each pollutant and cardiac phenotypes. Smoking status was the only important effect modifier, where being a current smoker significantly enhanced the positive association between PM_{10} concentration and RVEDV (effect size difference = +3.3% for current smoker compared to non-smoker, 95% CI: 0.06 to 6.7%, p = 0.046). The regression models which were not adjusted for hypertension, diabetes, SBP, DBP and HR produced results with

similar magnitude in effect size when compared with the fully-adjusted models (Supplemental Tables 2-4).

The wall motion assessment to determine unrecognized MI cases revealed 600 cases with possible regional wall motion abnormalities (RWMA) based on cut-off values of LV end-diastolic wall thickness < 5.5mm and LV systolic wall thickening of < 2mm. After manual evaluation, we discovered 43 CMR studies with truly hypokinetic LV segments (10 studies with global hypokinesis and 33 studies with regional hypokinesis). The distribution of hypokinetic segments in the 33 cases with RWMA are displayed in Supplemental Figure 1. We observed that mid to apical inferior and lateral segments were most commonly affected. Due to the limited number of cases with probable unrecognised MI based on cine CMR data (<1% of the entire cohort), we were not able to assess the relationship between air pollution and unrecognised or unreported MI.

We found that the associations between $PM_{2.5}$ and NO_2 concentrations and LV volume were not independent of noise or distance to major roads and vice-versa (i.e., the relationships between noise/distance to major roads and LV volume were also confounded by $PM_{2.5}$ and NO_2). The associations between $PM_{2.5}$ and NO_2 and RV volume were independent of noise but not from distance to major roads.

Sensitivity analyses

Sensitivity analyses including only participants with complete data gave no materially different results. Equivalently, fitting the models with continuous CMR parameters indexed to height$^{2.7}$ produced similar findings. There was no consistent evidence to support non-linear

relationships between air pollutants and cardiac measurements (Supplemental Figure 2). The fitted model diagnostic plots showed no evidence of heteroscedasticity or deviation from normality of residuals.

Discussion

In a cross-sectional investigation of 3,920 individuals free from known cardiovascular disease, this study identified the following important findings: (i) higher concentration to $PM_{2.5}$ and NO_2 were associated with biventricular enlargement; (ii) the lack of association between PM_{coarse} and cardiac phenotypes suggests that the association between PM and cardiac chamber size was predominantly driven by the finer particles; (iii) other environmental stressors such as noise pollution and proximity to major roads were also correlated with LV dilatation; (iv) amongst all traffic-related factors, only proximity to major roads was predictive of higher LV mass; (v) no perceptible difference in traditional LV geometric remodelling pattern in relation to differing air pollutant concentration was found.

Accumulating evidence based on meta-analyses indicates an increased risk of heart failure hospitalisation associated with higher $PM_{2.5}$ and NO_2 exposure (1.28% increase in risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 1.7% increase in risk per 10 parts per billion increase in NO_2) [13,31]. However, the connection between air pollution and cardiac remodelling, which is likely to precede the development of heart failure by months to year, had not received an in-depth investigation. Previous studies in this arena typically examined a limited number of pollutants or cardiac phenotypes [32–34], animal models [35,36] or had relatively small sample sizes [37,38]. Our study is the largest single epidemiological study to date that investigated the association between chronic exposure to several traffic-related pollutants and cardiac structural variations

using highly precise and reproducible CMR measurements, which further enhanced the statistical power.

This is the first study to report the association between $PM_{2.5}$ and NO_2 concentration and LV dilatation – an ominous sign which often heralds cardiac decompensation – in a population free from pre-exiting cardiovascular disease.

Association between ambient pollutants and cardiac parameter – summary of evidence

The findings from this study should be interpreted in the context of the currently available evidence in animal and human studies. In a controlled-exposure study with mice, prolonged exposure to concentrated $PM_{2.5}$ (mean exposure chamber concentration of 85.3 $\mu g/m^3$) led to increased LV dimensions, decreased fractional shortening and reduction in contractile reserve to dobutamine [36]. Similarly, in-utero and early life exposure to concentrated $PM_{2.5}$ in mice appeared to increase LV cavity size and impair LV function with histological evidence of cardiac collagen deposition [39,40]. A human study which assessed the cross-sectional association between residential air pollution and cardiac measurements derived from echocardiogram (ECHO) in 671 White Europeans found a reduction in LV longitudinal strain and strain rate with higher levels of $PM_{2.5}$, PM_{10}, NO_2 and black carbon [38]. Similar to our study, no association was found between the ambient pollutants and the LA volume, LV mass or LV EF. However, in contrast to our study, they found no correlation between LV dimension and the ambient pollutants, which could be explained by the well-recognised limitation of two-dimensional (2D) ECHO in measurement of LV dimensions and the study being significantly underpowered. The Study on the Influence of Air Pollution on Lung (SALIA) cohort with 264 elderly women (mean age of 74.4 years) reported some signals of association between larger indexed LA volume and higher $PM_{2.5}$, NO_2 and NO_x exposure [41].

The lack of association between LA size and pollution concentration in our study could be due to much lower level of exposure (mean $PM_{2.5}$ of 9.86 $\mu g/m^3$ in our cohort vs 17.4 $\mu g/m^3$ in SALIA cohort) and younger age of the participants.

Another ECHO-based study by Weaver et al. in 4,866 African-American individuals (Jackson Heart Study (JHS)) did not find any association between the distance to major roads and LV EF and LA diameter index, in parallel to our results [42]. Intriguingly, they reported a small increase in pulmonary artery systolic pressure (PASP) in those living 300-999m from major roads (compared to those who lived ≥ 1000m) – a finding which may explain the mechanism of RV dilatation in relation to the distance to major roads observed in our study. A follow-up study in the same JHS cohort found a 1.2mm larger LV end-systolic diameter in participants residing < 150m from a major road in comparison to those living ≥ 1000m), although no association was detected between indexed LV mass and proximity to major roads [43].

Perhaps, the most comparable study to-date was conducted in the Multi-ethnic Study of Atherosclerosis (MESA) cohort (sample size of 3,827; age 45-84 years), which also underwent CMR imaging [32]. Interestingly, they only investigated the impact of $PM_{2.5}$ and proximity to traffic on LV EF and LV mass. In their fully-adjusted models, living within 50m of a major road was associated with higher indexed LV mass while $PM_{2.5}$ did not influence LV mass or LV EF – these results are consistent with our findings. Another MESA study by Leary and colleagues which explored the relationship between NO_2 and NO_x exposure and RV phenotypes observed a small increase RV mass and RV EDV per IQR increase in NO_2 [33]; the latter finding was replicated in our study, however, RV mass was not available in our cohort for comparison.

All available epidemiologic evidence to-date including our findings suggests that ambient particulate and nitrogen pollutants predominantly affect the ventricular chamber size and possibly, the long-axis function, while exerting a minimal influence on other cardiac indices such as LV radial function or LA size. Residential proximity to major roadways is regarded as a surrogate for long-term exposure to traffic-related pollutants and has been known to be associated with adverse cardiovascular and pulmonary outcomes [44]. Unlike the ambient pollutants, it is associated with higher LV mass, a well-recognised cardiovascular prognosticator, which could be due to the contributions from unmeasured noxious elements (such as sympathetic stimulation from stress and annoyance) and residual confounding from latent socioeconomic factors. Given the known links between coronary artery disease and air pollution, the effect estimates of the associations between air pollutants and cardiac parameters in our study are likely to be conservative due to *a priori* exclusion of individuals with pre-existing CVD.

Biological mechanisms mediating cardiac remodelling

Air pollution exposure is known to be associated with elevation of oxidative stress, immune-mediated systemic inflammation and hypercoagulation which can induce atherosclerosis, myocardial ischaemic damage and associated cardiac remodelling [45–48]. Indeed, ventricular enlargement in association with $PM_{2.5}$ and NO_2 in our cohort free from known cardiovascular disease could be due to adverse remodelling secondary to unrecognized or silent MI. In our study, the prevalence of probable MI based on cine CMR data was low (<1% of the entire cohort). Although the true prevalence of silent MI is likely to be higher, we were unable to ascertain subtle subendocardial infarction in the absence of late gadolinium contrast

enhancement images. The population prevalence of unrecognized MI was previously reported to be 16.7% in an Icelandic cohort [49], although the latter imaged a much older population (mean age of 76.7 years vs 61.7 years in our study) and had benefited from augmented sensitivity and specificity afforded by the aforementioned contrast agent. Another potential contributing mechanism is through vasoconstriction and systemic hypertension due to a combination of endothelial dysfunction and autonomic imbalance. However, in our study, systolic and diastolic components of blood pressure and presence of hypertension do not appear to mediate the association between air pollution and cardiac parameters, suggesting that oxidative stress is likely to be predominantly responsible for cardiac phenotypic alterations which often precede clinical heart failure.

Strength and Limitations

Our study is the first to report the deleterious influence of a wide range of ambient pollutants on prognostically important cardiac chamber size in humans free from any pre-existing cardiovascular disease. The strengths of this study include a large sample size, highly accurate and reproducible measurements by CMR imaging and uniform data collection protocols which increase the precision of effect estimates. Our study has a number of limitations. First, we used estimated outdoor pollution at participants' home address which does not take into account (i) individual activity pattern such as time spent at home or in traffic, (ii) degree of pollutant infiltration into buildings, and (iii) indoor air pollution and workplace exposure. Second, biomarkers of oxidative damage such as malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), 4-oxo-2-nonenal (4-ONE), and acrolein, were not measured in our cohort which prevented us from validating our findings mechanistically. Third, multiple testing correction was not performed for the regression models. However, the

inflation of type-I error may be somewhat diminished, although not completely removed, by correlation within exposure and outcome variables – approximately 70% of ambient air pollutants (exposure) and directly-measured CMR variables (outcome) were at least moderately inter-correlated (Pearson correlation coefficient [r] > 0.5) and ~ 30% of both exposure and outcome variables were significantly correlated (Pearson r > 0.7). Finally, the intrinsic weaknesses of the cross-sectional study design mean that the findings should be interpreted with caution while corroborating longitudinal data is pending.

Clinical implications

The current European standard of acceptable annual $PM_{2.5}$ concentration is less than 25 $\mu g/m^3$ while the World Health Organisation (WHO) air quality guidelines stipulate a more stringent long-term target of 10 $\mu g/m^3$ [50,51]. Although the relatively low average concentration level in our study population not only achieves the WHO target but surpasses the current European standard by a significant margin, we observed a detectable cardiac remodelling effect which usually heralds detrimental outcomes. Although the effect sizes found in our analyses are relatively small, they are comparable to the impact of other cardiovascular risk factors on cardiac phenotypes (for example, a previous study in the same cohort reported a 2% larger LV ESV per SD [18.1 mmHg] increase in SBP vs a 1.28% larger LV ESV per IQR [1.32 $\mu g/m^3$] increase in $PM_{2.5}$ concentration in this study) [52].

Conclusions

In this large UK-wide middle-aged population, we found a significant association between higher annual average $PM_{2.5}$ and NO_2 concentration and larger biventricular volume, which is

a hallmark of adverse cardiac remodelling. These cardiac structural alterations in the absence of known cardiovascular disease alludes to a silent pathophysiological adaptation which should be monitored and targeted for treatment. Our findings add to the growing evidence of the damaging effects of ambient pollution even in the setting of relatively low exposure levels. Efforts to reduce air pollutant emission should be prioritised accordingly in public health initiatives and legislative measures.

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Disclosures

SEP provides consultancy to Circle Cardiovascular Imaging Inc, Calgary, Canada. Other authors have no conflicts of interest to declare.

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Figure titles and legends

Figure 1. Case selection flowchart

Figure 2. Association between annual average concentrations of $PM_{2.5}$ and NO_2 and cardiac parameters

The figure shows the marginal means (with 95% confidence interval) of cardiac parameters at different levels of $PM_{2.5}$ and NO_2 concentrations. Marginal means were estimated from the linear regression models adjusted for all covariates. Intervals of pollutant concentrations (x-axis) were chosen to closely represent the range of pollutant concentration observed in the cohort.

Higher levels of $PM_{2.5}$ and NO_2 were associated with larger LVEDV and RVEDV. No significant association was observed between air pollutants and other cardiac parameters.

LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; EDV, end-diastolic volume; EF, ejection fraction

Table 1. Participant characteristics

		Entire cohort (N=3,920)
Demographics		
Age, years		61.7 (7.4)
Male sex		1787 (45.6)
Caucasian ethnicity		3805 (97.1)
Height, cm		169.5 (9.4)
Weight, kg		75.1 (15.1)
BMI, kg/m^2		26.6 (4.3)
Average household income		
	< £18,000	480 (13.6)
	£18,000 to £30,999	1036 (29.3)
	£31,000 to £51,999	1054 (29.9)
	£52,000 to £100,000	750 (21.2)
	> £100,000	210 (5.9)
Townsend deprivation index		-2.00 (2.65)
Degree-level or professional education		2495 (63.6)
Employment status		
	Skilled job	3097 (79.1)
	Unskilled job	693 (17.7)
	Unemployed	121 (3.1)
	Retired	4 (0.1)

Clinical characteristics		
Systolic blood pressure, mmHg		137 (18)
Diastolic blood pressure, mmHg		79 (10)
Heart rate, bpm		71 (12)
Hypertension		1108 (28.3)
Dyslipidaemia		866 (22.1)
Diabetes mellitus		175 (4.5)
Antihypertensive medication		786 (20.1)
Lipid-lowering medication		718 (18.3)
Insulin		25 (0.6)
Smoking status		
	Never	2398 (61.3)
	Previous	1342 (34.3)
	Current	171 (4.4)
Regular alcohol use (≥ 3 times per week)		1757 (44.8)
Seven-day average acceleration, milli-gravity		28.19 (9.17)
Cardiac phenotypes		
LV EDV, ml		142.3 (33.0)
LV ESV, ml		58.1 (18.3)
LV SV, ml		84.2 (19.3)
LV EF, %		59.5 (6.2)
LV mass, g		88.4 (24.0)
LV remodelling patterns		

	Normal	3504 (92.2)
	Concentric remodelling	140 (3.7)
	Eccentric hypertrophy	123 (3.2)
	Concentric hypertrophy	33 (0.9)
RV EDV, ml		151.2 (37.1)
RV ESV, ml		66.7 (22.3)
RV SV, ml		84.5 (19.4)
RV EF, %		56.5 (6.5)
LA maximal volume, ml		66.7 (20.2)
LA minimal volume, ml		27.6 (12.1)
LA SV, ml		39.1 (11.2)
LA EF, %		59.5 (8.3)
RA maximal volume, ml		78.4 (25.4)
RA minimal volume, ml		45.2 (18.1)
RA SV, ml		33.2 (12.5)
RA EF, %		42.7 (10.3)
Ambient pollutants		
$PM_{2.5}$*, $\mu g/m^3$		9.9 (1.32)
PM_{10}*, $\mu g/m^3$		18.8 (2.11)
PM_{coarse}*, $\mu g/m^3$		6.1 (0.72)
$PM_{2.5}$ absorbance (elemental carbon)*, per meter		1.13 (0.29)
NO_2*, $\mu g/m^3$		28.2 (11.4)
NO_x*, $\mu g/m^3$		41.5 (17.1)
24-hour sound level averaged over 1 year*, dB		54.9 (3.6)

Distance to the nearest major road*, m	356 (555)
Traffic intensity on the nearest major road per day averaged over 1 year*, vehicles/day	15896 (10947)
Duration between exposure estimate and imaging visit*, years	5.2 (0.6)

Numbers are mean (SD) or number (%), unless otherwise stated.
BMI, body mass index; LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; MVR, mass to end-diastolic volume ratio.
*Indicates data presented as median (interquartile range)

Table 2. Associations between annual average particulate matter concentration and cardiac phenotypes

Phenotype	$PM_{2.5}$ (per IQR [1.32 μg/m^3] change)		PM_{10} (per IQR [2.11 μg/m^3] change)		PM_{coarse} (per IQR [0.72 μg/m^3] change)		$PM_{2.5}$ absorbance (per IQR [0.29 m^{-1}] change)	
	Effect size [95% CI]	P-value	Effect size [95% CI]	P-value	Effect size [95% CI]	P-value	Effect size [95% CI]	P-value
LV EDV*	0.82 [0.09 - 1.55]	**0.027**	0.81 [0.12 - 1.5]	**0.021**	0.37 [-0.03 - 0.76]	0.069	0.34 [-0.26 - 0.94]	0.272
LV ESV*	1.28 [0.15 - 2.43]	**0.027**	1.07 [0 - 2.15]	**0.049**	0.47 [-0.14 - 1.09]	0.133	0.28 [-0.64 - 1.21]	0.557
LV EF	-0.16 [-0.45 - 0.13]	0.269	-0.09 [-0.36 - 0.18]	0.507	-0.05 [-0.2 - 0.1]	0.527	0.01 [-0.22 - 0.24]	0.948
LV mass*	0.4 [-0.39 - 1.2]	0.321	0.4 [-0.35 - 1.16]	0.292	0.22 [-0.21 - 0.66]	0.316	0.06 [-0.59 - 0.71]	0.865
RV EDV*	0.85 [0.12 - 1.58]	**0.023**	0.77 [0.08 - 1.46]	**0.028**	0.27 [-0.12 - 0.67]	0.176	0.36 [-0.24 - 0.96]	0.245
RV ESV*	1.11 [-0.01 - 2.25]	0.051	0.66 [-0.39 - 1.73]	0.218	0.39 [-0.22 - 1]	0.209	0.42 [-0.49 - 1.35]	0.364
RV EF	-0.08 [-0.36 - 0.21]	0.598	0.07 [-0.19 - 0.34]	0.6	-0.05 [-0.2 - 0.1]	0.503	-0.03 [-0.26 - 0.2]	0.783
LA maximal volume*	0.55 [-0.75 - 1.86]	0.409	0.46 [-0.74 - 1.68]	0.457	0.23 [-0.46 - 0.92]	0.516	0.7 [-0.35 - 1.76]	0.191
LA EF	-0.06 [-0.47 - 0.35]	0.778	-0.13 [-0.5 - 0.25]	0.504	-0.04 [-0.26 - 0.17]	0.686	-0.07 [-0.4 - 0.26]	0.672
RA maximal volume*	-0.23 [-1.5 - 1.05]	0.719	-0.85 [-2.01 - 0.33]	0.159	-0.55 [-1.22 - 0.13]	0.114	-0.61 [-1.63 - 0.41]	0.24
RA EF	-0.1 [-0.57 - 0.37]	0.678	-0.1 [-0.55 - 0.34]	0.65	-0.01 [-0.27 - 0.24]	0.911	0.23 [-0.16 - 0.62]	0.247
LV geometric patterns								
Concentric remodelling†	1.03 [0.15 - 7.25]	0.976	1.04 [0.15 - 7.33]	0.97	1.01 [0.14 - 7.11]	0.995	1.06 [0.15 - 7.45]	0.957

Eccentric hypertrophy†	1.11 [0.67 - 1.85]	0.682	0.98 [0.61 - 1.58]	0.938	0.84 [0.6 - 1.18]	0.314	0.95 [0.62 - 1.45]	0.811
Concentric hypertrophy†	1.02 [0.41 - 2.51]	0.974	1.11 [0.45 - 2.73]	0.826	1.13 [0.46 - 2.79]	0.785	1.05 [0.43 - 2.59]	0.914

All estimates were fully-adjusted for age, sex, ethnicity, height, body mass index, socioeconomic factors, cardiac risk factors, medications and physical activity.

*log-transformed dependent variables – their effect estimates represent percentage change per IQR increase in exposure variable.

†The effect estimates for these variables represent the odds ratio, where reference is normal LV geometry.

IQR, interquartile range; CI, confidence interval; LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction

Table 3. Associations between annual average nitrogen dioxide and nitrogen oxides concentration and cardiac phenotypes

Phenotype	NO_2 (per IQR [11.4 μg/m^3] change)		NO_x (per SD [17.1 μg/m^3] change)	
	Effect size [95% CI]	P-value	Effect size [95% CI]	P-value
LV EDV*	0.91 [0.12 - 1.7]	**0.025**	0.63 [-0.05 - 1.33]	0.071
LV ESV*	0.88 [-0.35 - 2.12]	0.161	1 [-0.07 - 2.09]	0.066
LV EF	0.01 [-0.3 - 0.32]	0.965	-0.13 [-0.4 - 0.14]	0.334
LV mass*	-0.35 [-1.2 - 0.51]	0.424	0.13 [-0.62 - 0.89]	0.73
RV EDV*	0.85 [0.06 - 1.65]	**0.035**	0.58 [-0.11 - 1.26]	0.099
RV ESV*	0.64 [-0.58 - 1.87]	0.306	0.83 [-0.22 - 1.89]	0.123
RV EF	0.13 [-0.18 - 0.43]	0.421	-0.08 [-0.35 - 0.18]	0.535
LA maximal volume*	0.74 [-0.65 - 2.15]	0.299	0.48 [-0.74 - 1.71]	0.442
LA EF	-0.33 [-0.78 - 0.11]	0.145	-0.2 [-0.59 - 0.19]	0.309
RA maximal volume*	-0.66 [-2.02 - 0.72]	0.347	-0.42 [-1.61 - 0.77]	0.486
RA EF	-0.14 [-0.65 - 0.37]	0.594	-0.14 [-0.59 - 0.3]	0.532
LV geometric patterns				
Concentric remodelling†	0.93 [0.13 - 6.61]	0.946	0.93 [0.13 - 6.6]	0.945
Eccentric hypertrophy†	1.05 [0.61 - 1.8]	0.855	1.03 [0.65 - 1.64]	0.891
Concentric hypertrophy†	0.86 [0.35 - 2.11]	0.735	0.93 [0.38 - 2.3]	0.876

All estimates were fully-adjusted for age, sex, ethnicity, height, body mass index, socioeconomic factors, cardiac risk factors, medications and physical activity.

*log-transformed dependent variables – their effect estimates represent percentage change per IQR increase in exposure variable.

†The effect estimates for these variables represent the odds ratio, where reference is normal LV geometry.

IQR, interquartile range; CI, confidence interval; LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction

Table 4. Associations between annual average 24-hour sound level, distance to nearest major road and annual average traffic intensity on the nearest major road over 24 hour and cardiac phenotypes

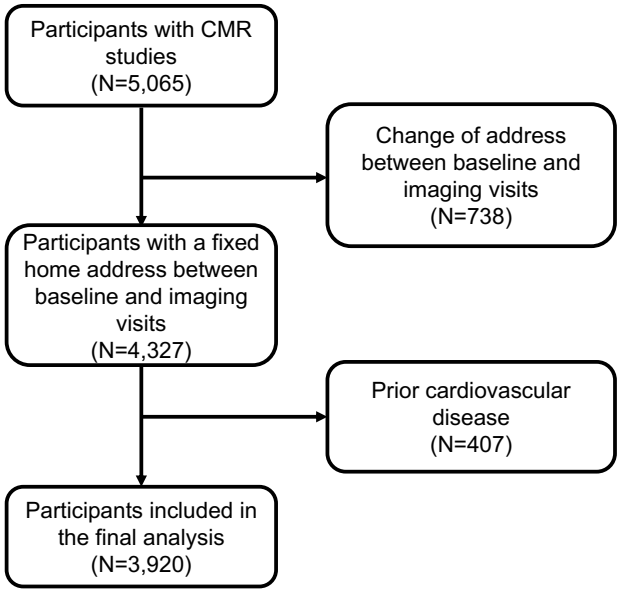
Phenotype	Average 24-hour sound level (per IQR [3.6 dB] change)		Distance to the nearest major road (per IQR [555 m] change)		Average traffic intensity (per IQR [10947 vehicles/24h] change)	
	Effect size [95% CI]	P-value	Effect size [95% CI]	P-value	Effect size [95% CI]	P-value
LV EDV*	0.36 [-0.07 - 0.78]	0.1	-0.45 [-0.95 - 0.06]	0.082	0.16 [-0.08 - 0.41]	0.195
LV ESV*	0.69 [0.03 - 1.35]	**0.041**	-0.99 [-1.77 - -0.2]	**0.014**	0.02 [-0.36 - 0.41]	0.906
LV EF	-0.12 [-0.29 - 0.04]	0.141	0.2 [0 - 0.4]	0.05	0.05 [-0.05 - 0.15]	0.302
LV mass*	0.36 [-0.1 - 0.82]	0.126	-0.74 [-1.3 - -0.18]	**0.01**	0.11 [-0.16 - 0.38]	0.415
RV EDV*	0.05 [-0.37 - 0.48]	0.808	-0.65 [-1.16 - -0.15]	**0.011**	0.17 [-0.08 - 0.42]	0.19
RV ESV*	0.28 [-0.37 - 0.94]	0.402	-1.02 [-1.8 - -0.25]	**0.01**	0.12 [-0.26 - 0.5]	0.541
RV EF	-0.09 [-0.26 - 0.07]	0.259	0.15 [-0.05 - 0.35]	0.134	0.02 [-0.08 - 0.11]	0.705
LA maximal volume*	0.21 [-0.55 - 0.98]	0.583	-0.32 [-1.22 - 0.58]	0.48	0.01 [-0.42 - 0.45]	0.954
LA EF	-0.06 [-0.31 - 0.18]	0.602	0.11 [-0.18 - 0.4]	0.46	-0.01 [-0.15 - 0.13]	0.865
RA maximal volume*	-0.12 [-0.85 - 0.63]	0.759	-0.36 [-1.24 - 0.53]	0.429	-0.29 [-0.72 - 0.14]	0.189
RA EF	-0.05 [-0.32 - 0.23]	0.749	-0.05 [-0.39 - 0.28]	0.751	0.05 [-0.11 - 0.21]	0.548
LV geometric patterns						
Concentric remodelling†	1.02 [0.14 - 7.17]	0.986	0.99 [0.14 - 6.99]	0.992	1.01 [0.14 - 7.13]	0.992
Eccentric hypertrophy†	0.93 [0.68 - 1.27]	0.659	0.91 [0.62 - 1.35]	0.654	0.83 [0.61 - 1.12]	0.216
Concentric hypertrophy†	1.01 [0.41 - 2.49]	0.985	1.06 [0.43 - 2.61]	0.904	1.1 [0.44 - 2.71]	0.841

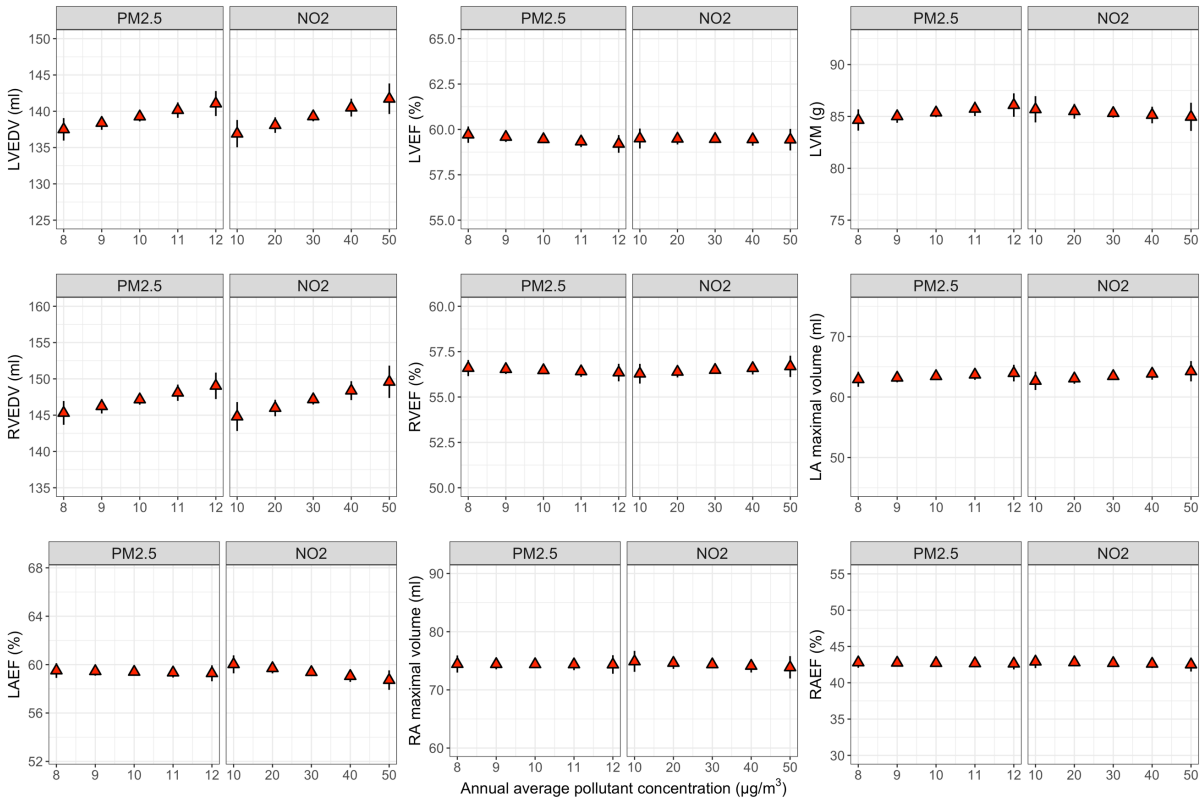
All estimates were fully-adjusted for age, sex, ethnicity, height, body mass index, socioeconomic factors, cardiac risk factors, medications and physical activity.

*log-transformed dependent variables – their effect estimates represent percentage change per IQR increase in exposure variable.

†The effect estimates for these variables represent the odds ratio, where reference is normal LV geometry.

IQR, interquartile range; CI, confidence interval; LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction


Participants with CMR studies (N=5,065)
Change of address between baseline and imaging visits (N=738)
Participants with a fixed home address between baseline and imaging visits (N=4,327)
Prior cardiovascular disease (N=407)
Participants included in the final analysis (N=3,920)


PM2.5
NO2
LVEDV (ml)
LVEF (%)
LVM (g)
RVEDV (ml)
RVEF (%)
LA maximal volume (ml)
LAEF (%)
RA maximal volume (ml)
RAEF (%)
Annual average pollutant concentration (μg/m3)