Long-term exposure to road traffic noise, ambient air pollution and cardiovascular risk factors in the HUNT and Lifelines cohorts

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ABSTRACT

Aims: Blood biochemistry may provide information on associations between road traffic noise, air pollution and cardiovascular disease risk. We evaluated this in two large European cohorts (HUNT3, Lifelines).

Methods and Results: Road traffic noise exposure was modelled for 2009 using a simplified version of the Common Noise Assessment Methods in Europe (CNOSSOS-EU). Annual ambient air pollution (PM_{10}, NO_2) at residence was estimated for 2007 using a Land Use Regression model. The statistical platform DataSHIELD was used to pool data from 144,082 participants aged ≥ 20 years to enable individual-level analysis. Generalized linear models were fitted to assess cross-sectional associations between pollutants and high-sensitivity C-reactive protein (hsCRP), blood lipids and for (Lifelines only) fasting blood glucose, for samples taken during recruitment in 2006-2013.

Pooling both cohorts, an interquartile range (IQR) higher day-time noise (5.1dB(A)) was associated with 1.1%(95%CI: 0.02%-2.2%) higher hsCRP, 0.7%(95%CI:0.3%-1.1%) higher triglycerides and 0.5%(95%CI:0.3%-0.7%) higher high-density lipoprotein(HDL); only the association with HDL was robust to adjustment for air pollution. An IQR higher PM_{10} (2.0μg/m^3) or NO_2 (7.4μg/m^3) was associated with higher triglycerides (1.9%, 95%CI:1.5%-2.4% and 2.2%, 95%CI:1.6%-2.7%), independent of adjustment for noise. Additionally for NO_2, a significant association with hsCRP (1.9%, 95%CI: 0.5%-3.3%) was seen. In Lifelines, an IQR higher noise (4.2dB(A)) and PM_{10} (2.4μg/m^3) was associated with 0.2%(95%CI: 0.1%-0.3%) and 0.6%(95%CI:0.4%-0.7%) higher fasting glucose respectively, with both remaining robust to adjustment for air/noise pollution.

Conclusion: Long-term exposures to road traffic noise and ambient air pollution were associated with blood biochemistry, providing a possible link between road traffic noise/air pollution and cardio-metabolic disease risk.

Keywords: traffic noise, air pollution, systemic inflammation, blood lipids, blood glucose

Translational Perspective

Road traffic noise and air pollution are the two most common environmental stressors and both have been associated with cardiovascular disease in a growing number of studies. Evidence for the long-term effects of both pollutants on traditional cardiovascular risk factors is limited. Our results based on two large European population-based cohorts suggest that both road traffic noise and ambient air pollution may increase systemic inflammation, blood glucose levels and risk for potential lipid disturbance. Our findings highlight the importance to consider environmental causes in the prevention and pathogenesis of cardiovascular disease and the collective efforts needed to mitigate noise and air pollution.

Introduction

Increasing numbers of studies have suggested that long-term exposure to road traffic noise[1] and ambient air pollution[2] have been linked to cardiovascular disease (CVD) morbidity and mortality via different but not mutually exclusive hypothesised mechanistic pathways[3].

As proposed by Babisch[4], traffic noise as an environmental stressor exerts adverse health effects via both direct (e.g. sleep disturbance) and indirect (e.g. annoyance) pathways. Based on the stress reaction model, both pathways lead to a physiologic acute response, for example, elevated levels of stress hormones, through activations of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medulla axis[3]. In the long-term, stress hormone such as cortisol is overly produced to restore homeostasis partly by increasing the supply of energy in the forms of glucose and fatty acids[5,6]. Catecholamines are an important stress hormone to boost this supply by breaking down triacylglycerol[5]. In addition, overproduction of cortisol is also believed to inhibit insulin secretion as well as to impair insulin sensitivity in both the liver and adipose tissue[6]. For air pollution, oxidative stress is the principal hypothesised mechanism to explain the adverse health effects, with other pathways including impaired endothelial function, systemic inflammation, activation of autonomous nervous system (ANS) and direct transfer of particles from lung to blood circulation also contributing[2].

It is biologically plausible to hypothesise that via these aforementioned mechanistic pathways both long-term noise and air pollution exposures may lead to adverse changes in CVD risk factors including systemic inflammation, blood lipids and glucose[2-4], thus mediating the links between these exposures and manifest CVD. However, epidemiological evidence linking these exposures, especially noise, with CVD risk factors is rather limited[3,7]. Noise could also be a potential confounder in any associations between air pollution and CVD risk factors, which merits further investigation[7].

We evaluated cross-sectional associations between long-term road traffic noise, ambient air pollution and high sensitivity C-reactive protein (hsCRP), blood lipids and glucose levels in two large European

cohorts. Harmonised exposure and health data were analysed at the individual-level via *DataSHIELD*(8), a novel statistical platform that allows pooling of data via distributed data analysis.

Methods

Study populations

Two cohorts, HUNT3(9) and Lifelines(10), were included in this study as part of the BioSHaRE (Biobank Standardisation and Harmonisation for Research Excellence in the European Union-BioSHaRE-EU) project.

The HUNT (Helseundersøkelsen i Nord-Trøndelag) study is a population-based health survey conducted in the county of Nord-Trøndelag in central Norway, targeting all residents aged≥20 years(9). We used data from the third survey (HUNT3) undertaken in 2006-2008, during which 50,805 residents participated and provided data, all of whom were included in our study.

Lifelines is a prospective multi-generational population-based cohort study to examine the health and health-related behaviours of people living in northern Netherlands(10). Compared to those of the HUNT study, study areas of Lifelines are more densely populated(11). During baseline recruitment (2006-2013), a random selection of residents aged 25-50 years and their family members registered in general practices were invited to participate. Quality-checked data from 93,277 participants were available for analysis by the time our study was conducted.

Ethical approvals for this study were obtained from the Regional Committee for Medical and Health Research Ethics in Norway for HUNT and from the Medical Ethical Committee of the University Medical Center Groningen for Lifelines.

Biochemistry data

Details of the collection, transport, storage and analysis of the blood samples in each cohort have been published(9,10). In brief, for both cohorts, blood samples were collected and transported on the same day, and were stored at -80°C for future analysis. Non-fasting blood samples were collected in HUNT3 whilst fasting blood samples were collected in Lifelines. Samples were analysed in a central laboratory for each cohort, following respective quality control measures.

Serum concentrations of hsCRP (mg/L), total cholesterol (mmol/L), triglycerides (mmol/L), and high-density lipoprotein (HDL) cholesterol (mmol/L) were measured in both cohorts. Additionally for Lifelines, fasting blood glucose (mmol/L) and glycated haemoglobin (HbA1c) concentrations (mmol/mol) were also measured.

Exposure assessment

A simplified version of the CNOSSOS-EU (Common noise assessment methods in European Union) noise modelling framework(12) was developed and run for each cohort. Noise sound pressure level was estimated on all roads within 500 meters of home address at recruitment. Noise propagation due to refraction and diffraction, absorption from buildings, distance and angle of view were considered in the model. Road network geography, calculated hourly vehicle flows using a daily average traffic profile, building heights, land cover and meteorological data were obtained for the respective study areas. To account for participants living on minor roads that were not captured in the national level traffic datasets, a fixed low-level baseline traffic flow (600 vehicles per day) was assigned. Traffic data were for the year 2009 and land cover data were for the year 2006. Annual mean A-weighted sound pressure level in decibels (dB(A)) for day-time noise (average sound level from 07:00 to 19:00) and night-time noise (average sound level from 23:00 to 07:00) and weighted 24-hour noise (Lden) were modelled at recruitment address of participants in both cohorts.

An European harmonised Land Use Regression (LUR) model at a resolution of 100x100m was used to assign annual air pollution estimates, PM_{10} (Particulate Matter with aerodynamic diameter≤10μm) and NO_2 (nitrogen dioxide), for year 2007 at participant's recruitment address(13). The model used information from over 1,500 monitoring sites across western Europe, satellite-based ground-level air pollution data and land use variables obtained from a Geographic Information System (GIS)(13).

Covariates

Age, sex, smoking status, smoking pack-years, education, paid employment, alcohol consumption and 'ever-had' hypertension and diabetes were obtained from questionnaires at recruitment. Height (cm) and weight (kg) were measured after removal of heavy clothes and shoes and body mass index (BMI, kg/m^2) was computed. Time at residence of recruitment in years was calculated for each participant. Season of blood draw was based on the calendar month the participant attended for clinical

measurements. All these covariates were retrospectively harmonised across the two cohorts, following a validated protocol(14).

Statistical analyses

Statistical analyses for hsCRP and blood lipids were performed using *DataSHIELD* v4.1.2(8). In brief, the *DataSHIELD* approach involves setting up secure servers hosting harmonised data in geographically dispersed research sites (e.g. Groningen for Lifelines and London for HUNT3) and allowing a central computer to conduct remote federated analyses of individual-level data without physically pooling this data. *DataSHIELD* offers an effective solution to overcome the complex ethico-legal issues associated with a physical sharing of the data. Analyses on fasting blood glucose and HbA1c were conducted in Lifelines only also using *DataSHIELD* in 'single-site' mode which provides, in effect, a privacy-protected analysis in an R statistical environment.

All outcomes were modelled as a log-transformed value to improve linearity and results were expressed as percent change per inter-quartile range (IQR) higher exposure.

Spearman correlations between metrics of road traffic noise and ambient air pollution were calculated for each cohort. Associations between the noise, PM_{10}, NO_2 and each biochemical parameter were analysed using multivariate linear regression. Both noise and air pollution metrics were analysed on a continuous scale, assuming a linear effect. Additionally noise was categorised as <55, 55-60, $\geq$60 dB(A) for daytime and <45, 45-50, $\geq$50 dB(A) for night-time noise respectively.

The covariates were chosen *a priori* based on current knowledge. The sequence of models was as follows: adjusted for study (in pooled analyses on hsCRP and blood lipids), age (continuous) and sex (**Model1**), further adjusted for season of blood draw, smoking status and pack-years, education, employment and alcohol consumption (**Model2**). Based on Model2, ambient air pollution (or road traffic noise) were additionally added to the noise (or air pollution) model (**mutually adjusted model**).

Sensitivity analyses were conducted based on Model2: a) further adjusting for BMI; b) further adjusting for ever-had hypertension and diabetes; c) restricting analyses to those living at current address$\geq$10 years; d) as with a previous study(15), excluding those with an hsCRP over 10 mg/ L from the analysis as levels above this may indicate a current infection.

We also conducted study-specific analyses for hsCRP and blood lipids and then pooled estimates via meta-analysis using R 'metafor' packages v3.2.2.

Results

Overall there were 144,082 participants, mean age (SD) was 47.6 (13.7) years, and 56% (n=82,574) were women (Table1).

Across the two cohorts, median Lday was 51.6 dB(A), with an IQR of 5.1 dB(A); median PM_{10} and NO_2 were 18.8 and 17.2 µg/m^3, with an IQR of 2.0 and 7.4 µg/m^3 respectively (Supplement-1). Spearman correlations between PM_{10} and Lday was 0.04 (HUNT3) and 0.38 (Lifelines); similar correlations were seen for NO_2. Daytime and night-time noise or 24-hour noise were almost perfectly correlated (r=0.99). We therefore report only results for daytime noise here.

In the pooled analyses of both HUNT3 and Lifelines, an IQR increase in daytime noise, PM_{10} and NO_2 was significantly associated with higher levels of hsCRP (Table 2) in the fully adjusted model (Model2), but significance only remained for NO_2 (1.7%, 95% confidence interval (CI): 0.2%-3.2%) in the model further adjusted for noise (mutually adjusted model).

An IQR increase in daytime noise, PM_{10} and NO_2 was significantly associated with 0.7% (95%CI:0.3%-1.1%), 1.9% (95%CI:1.5%-2.4%) and 2.2% (95%CI:1.6%-2.7%) higher levels of triglycerides respectively (Table 3). However, when Model 2 was mutually adjusted for both noise and air pollution, significance remained for both air pollutants, but not noise. We found no associations between any of the exposures and total cholesterol (Supplement-2), but significant positive associations between noise or NO_2 and HDL cholesterol were observed(Table 3).

In the analyses of fasting glucose in Lifelines only(Table 4), an IQR increase in daytime noise, PM_{10} and NO_2 was significantly associated with 0.2% (95%CI:0.1%-0.3%), 0.6% (95%CI:0.4%-0.7%) and 0.6% (95%CI:0.4%-0.8%) higher levels of fasting glucose respectively. These significant associations remained in the mutually adjusted models. Corresponding associations were not seen for HbA1c (Supplement-2).

Sensitivity analyses only resulted in minor changes to the main findings described for each biochemistry parameter, except that the significant positive associations between air pollution and

HDL cholesterol were no longer seen after further adjustment for BMI (supplement-3). Treating noise as a categorical variable in Model2 showed that for hsCRP, triglycerides and fasting glucose, significant associations were only observed among those with a day-time noise level ≥60 vs. <50 dB(A) (supplement-4).

Study-specific meta-analyses for hsCRP and blood lipids yielded similar results to the pooled analyses on *DataSHIELD* (Supplement-5).

Discussion

In this large population-based study, we found that higher long-term road traffic noise was significantly associated with higher levels of hsCRP, triglycerides, HDL cholesterol and fasting glucose, with the latter two associations remaining after further adjustment for air pollution. Higher PM_{10} or NO_2 exposure was significantly associated with higher levels of triglycerides and fasting glucose, independent of road traffic noise. Both air pollutants were also significantly associated with higher hsCRP levels, but the significance for PM_{10} was lost after adjustment for traffic noise.

Road traffic noise effects

There have been very few studies investigating the effects of road traffic noise on cardiovascular risk factors to date. Chronic noise exposure may trigger the same responses (e.g. oxidative stress, systemic inflammation) as air pollutants[6] and it has been suggested that the link between long-term psychological stress and CVD may operate via a chronic low-grade systemic inflammation[16]. We are not aware of any other studies exploring the association between road traffic noise and hsCRP. We observed a small increase in hsCRP levels in relation to noise exposure when assessed as a continuous variable. Analysing noise as a categorical variable suggested that there may exist a threshold of 60 dB(A), above which a significant positive association on hsCRP was seen in our study. However, significance was lost after adjustment for air pollution.

The over-production of stress hormones (e.g. catecholamines) following long-term noise exposure is believed to increase the supply of fatty acids and glucose by breaking down triacylglycerol[5]. In support of this hypothesised mechanism, we found significant positive associations between road traffic noise exposure and triglycerides. Only one population-based study was conducted previously

and reported no association with total cholesterol(17). In our study, we found no associations with total cholesterol either, but a positive significant association was unexpectedly found with HDL cholesterol. There is no biological plausible explanation for this association and it is possible that this is a chance finding due to multiple testing. Findings across a small number of occupational studies were not consistent with regards to which lipids were adversely affected by noise exposures(18). The role of traffic noise in the perturbations in lipid levels is rarely investigated(3) and our findings should be interpreted with caution until further studies have confirmed this result.

Our study provides novel evidence that increasing road traffic noise is associated with increasing fasting blood glucose levels, independent of air pollution effects. Only one study in the early 1990s reported a positive trend (p-value<0.05) between higher day-time noise level and increased glucose level in men(19). Another study in Stockholm found no associations between aircraft noise exposure and impaired fasting glucose(20). In a Danish prospective cohort, a 10dB higher road traffic noise at diagnosis was associated with a 8% (95%CI: 2%-14%) higher risk of incident diabetes, after adjustment for air pollution(21).

Air pollution effects

An inflammatory response to ambient air pollution has been perceived as one of the key mechanisms that may explain air pollution effects on CVD(2). Our findings on elevated hsCRP for both air pollutants generally support this concept. An analysis of 22,561 adults from six European cohorts observed a significant association between elevated hsCRP levels and living close to traffic but not for modelled air pollutants(15). A longitudinal analysis with repeated measurements of hsCRP in Germany found that each IQR (2.4µg/m^3) higher $PM_{2.5}$ was associated with 5.4% (95%CI: 0.6%-10.5%) higher hsCRP, independent of short-term air pollution(22). Two other studies in England(23) and Sweden(24) reported no associations with hsCRP.

Inflammation-induced adverse lipid metabolism and lipid oxidation may be among the possible mechanisms underlying the associations between air pollution and perturbations in lipid levels(25). A study of nearly 40,000 adults aged 50-64 years in Copenhagen reported that both $PM_{2.5}$ and NO_2 were significantly associated with elevated non-fasting total cholesterol(17). Data on other lipid measures were not available. Similarly, a nationwide USA study of 11,623 participants (median age: 41 years)

reported significant positive associations between annual PM_{10} exposure and both triglycerides and total cholesterol levels(25). Association with HDL cholesterol was positive but non-significant. Partly in line with this, we found both higher PM_{10} and NO_2 were significantly associated not only with elevated triglycerides but also HDL cholesterol levels, although for the latter the association was non-significant after further adjustment for BMI.

Air pollution may also affect glucose homeostasis via pathways including increased adipose tissue inflammation and oxidative stress as well as impaired insulin responses in the liver and adipose tissue(3). Our findings of significant associations with fasting glucose for long-term PM_{10} and NO_2 exposures were partly consistent with previous studies of various designs(26-29). However, we did not observe an association with HbA1c. Annual average of PM_{10} and NO_2 was significantly associated with increased fasting glucose and HbA1c among elderly participants in Taiwan(26) while in Germany higher regional PM_{10} levels were significantly associated with higher HbA1c levels among patients with diabetes(28). A study of 363 elderly German women reported that long-term exposure to NO_2 may contribute to impaired glucose metabolism, although significance was lost after correction for multiple testing(27). Recently, a nationwide cross-sectional study of 11,847 adults in China observed that satellite-based modelled annual $PM_{2.5}$ at residence was significantly associated with both increased fasting glucose and HbA1c(29).

Strengths and limitations

Strengths include our ability to simultaneously examine the effects of noise and air pollution exposure on cardiovascular risk factors in this large sample. In addition, data across the two cohorts were harmonised and then individual-level analyses and data pooling were carried out via *DataSHIELD*, making this one of the largest such studies to date. The novel use of *DataSHIELD* was validated through meta-analysis of the two cohorts involved, with *DataSHIELD* giving similar effect estimates but (as expected) smaller confidence intervals as individual participant data were analysed together.

Limitations include the cross-sectional nature of the study, longitudinal studies are needed to strengthen these findings. Modelled noise and air pollution estimates at home address will inevitably have some misclassification (e.g. time spent away from home). However, this was likely non-differential with regard to biochemistry measurements. Correlations between PM_{10} and NO_2 were high

which precluded a co-pollutant analysis. Some simplified inputs were used in our noise model to enable a harmonised approach across the two cohorts investigated(30); this may have resulted in non-differential misclassification of noise exposure that would be expected to bias results toward the null. The European harmonised LUR model for air pollution was likely less accurate for the HUNT cohort for two reasons. First, no Norwegian monitoring air pollution data were used in the model building and therefore the performance of this LUR model cannot be formally measured in Norway. However, the use of this LUR model for the HUNT cohort was reasonably justified based on the model's moderate to good performance in other Scandinavian countries. Second, the road networks used in the air pollution/noise models building for the Netherlands had a more complete representation of both major and minor roads whilst for Norway the road networks only had major roads included. Therefore, the relatively low correlation between noise and air pollution seen for the HUNT cohort may be driven in part by the less detailed data inputs. While road traffic is a major source of both noise and air pollutants, these variables are not always closely correlated(31). Noise and air pollution estimates at recruitment address were modelled to a single year 2009 and 2007 respectively, which may differ by several years from when recruitment took place in both cohorts (2006-2013). We made a reasonable assumption that the spatial contrast in levels of both exposures will have been relatively stable over these years. Estimates may have residual confounding, as information about environmental tobacco smoke, diet, exercise and area-level socioeconomic status were not harmonised and therefore were not included in our models. Finally, we used nominal *P*-values, so given the number of tests it is possible that some observed associations may be chance findings; replication in other studies is therefore recommended.

In our study, the observed effects of road traffic noise and air pollution on CVD risk factors are small and potentially within the precision of a laboratory measurement for an individual. The clinical impact of an increase in risk of that magnitude on any individual would be very small if not negligible, despite statistical significance. However, the importance of these population-based results is that they suggest that the entire distribution of these risk factors may be shifted towards a less favourable profile at population level, i.e. 'at-risk' populations may be increased. Our results contribute to the evidence base to identify potential mechanisms and quantify impacts of both road noise and air

pollution exposures on cardiovascular disease at population level. Future work will explore potential for effect modification and whether effects are confined to a subset of the population.

In conclusion, we found significant associations of long-term exposure to road traffic noise and ambient air pollution with CVD biochemical parameters, providing a possible link between noise or air pollution exposure and cardiovascular disease.

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Table 1 Characteristics of study populations in both cohorts

	Pooled data	HUNT3	Lifelines
Total N	144,082	50,805	93,277
Age, years, mean±SD	47.6±13.7	52.7±16.7	44.9±12.3
Sex, women, (%)	56	55	59
BMI, kg/m^2, mean±SD	26.5±4.4	27.2±4.4	26.1±4.3
BMI categories, (%)			
<25 kg/m^2	41	33	45
25-30 kg/m^2	41	44	39
≥30 kg/m^2	18	23	16
Smoking status, (%)			
Never-smoker	44	43	45
Ex-smoker	32	32	32
Current-smoker	24	25	23
Current working status, (%)			
Not in paid employment	25	36	19
In paid employment	75	64	81
Education level, (%)			
primary education or less	11	31	2
Secondary education	62	47	68
Post-secondary school or above	28	22	30
Ever-had diabetes	3	4	2
Ever-had hypertension	24	22	25
Alcohol consumption, gram per week, mean±SD	31.6±88.8	28.0±40.0	56.9±71.5

hsCRP, mg/L, median±IQR	1.2±2.1	1.2±2.1	1.2±2.2
Total cholesterol, mmol/L, mean±SD	5.2±1.0	5.5±1.1	5.0±1.0
HDL cholesterol, mmol/L, mean±SD	1.4±0.4	1.4±0.3	1.5±0.4
Triglycerides, mmol/L, mean±SD	1.3±0.9	1.6±1.0	1.1±0.8
Fasting glucose, mmol/L, mean±SD	-	-	5.0±0.8
HbA1c, mmol/mol, mean±SD	-	-	37.5±4.8

Table 2 Cross-sectional associations between per IQR higher exposure and hsCRP: pooled analyses

from HUNT3 and Lifelines

			%changes (95%CI) in hsCRP			
Exposure	IQR	N	Model1	N	Model2	Model2*
Daytime noise	5.1dB(A)	90,689	**0.4 (0.1-0.8)**	55,930	**1.1 (0.02-2.2)**	1.0 (-0.1-2.2)[a]
						0.9 (-0.3-2.0)[b]
PM_{10}	2.0μg/m^3	87,622	**1.3 (0.2-2.4)**	51,238	**1.4 (0.1-2.7)**	0.9 (-0.4-2.3)
NO_2	7.4μg/m^3	87,957	1.0 (-0.1-2.2)	51,459	**1.9 (0.5-3.3)**	**1.7 (0.2-3.2)**

Model 1: adjusted for cohort, age, sex;

Model 2: further adjusted for season of blood draw, smoking status and pack-years, education, employment and

alcohol consumption.

Model 2*: further adjusted for air pollution (a for PM_{10}, b for NO_2), or daytime noise, based on Model 2.

BOLD indicates where significance level <0.05.

Table 3 Cross-sectional associations between per IQR higher exposure and triglycerides and HDL cholesterol: pooled analyses from HUNT3 and Lifelines

			%changes (95%CI) in triglycerides			
Exposure	IQR	N	Model1	N	Model2	Model2*
Daytime noise	5.1dB(A)	119,464	**0.7 (0.4-1.0)**	81,799	**0.7 (0.3-1.1)**	0.2 (-0.2-0.7)[a]
						0.3 (-0.2-0.7)[b]
PM_{10}	2.0µg/m^3	111,547	**1.4 (1.0-1.8)**	72,794	**1.9 (1.5-2.4)**	**1.9 (1.4-2.4)**
NO_2	7.4µg/m^3	111,893	**1.6 (1.1-2.0)**	73,026	**2.2 (1.6-2.7)**	**2.1 (1.6-2.7)**

			%changes (95%CI) in HDL cholesterol			
Exposure	IQR	N	Model1	N	Model2	Model2*
Daytime noise	5.1dB(A)	118,866	**0.3 (0.2-0.5)**	81,590	**0.5 (0.3-0.7)**	**0.4 (0.1-0.6)[a]**
						0.3 (0.04-0.5)[b]
PM_{10}	2.0µg/m^3	110,834	**0.1 (0.04-0.2)**	72,551	0.2 (-0.1-0.4)	0.04 (-0.2-0.3)
NO_2	7.4µg/m^3	111,178	**0.4 (0.2-0.7)**	72,783	**0.5 (0.3-0.8)**	**0.4 (0.1-0.7)**

Model 1: adjusted for cohort, age, sex

Model 2: further adjusted for season of blood draw, smoking status and pack-years, education, employment and alcohol consumption.

Model 2*: further adjusted for air pollution (a for PM_{10}, b for NO_2), or daytime noise, based on Model 2.

BOLD indicates where significance level <0.05.

Table 4 Cross-sectional associations between per IQR higher exposure and fasting glucose: analyses of Lifelines cohort

			%changes (95%CI) in fasting glucose			
Exposure	IQR	N	Model1	N	Model2	Model2*
Daytime noise	4.2dB(A)	72,401	**0.2 (0.1-0.3)**	62,765	**0.2 (0.1-0.3)**	**0.2 (0.06-0.3)[a]**
						0.1 (0.03-0.3)[b]
PM_{10}	2.4μg/m^3	59,898	**0.5 (0.4-0.7)**	52,234	**0.6 (0.4-0.7)**	**0.5 (0.3-0.6)**
NO_2	8.8μg/m^3	60,182	**0.5 (0.4-0.7)**	52,543	**0.6 (0.4-0.8)**	**0.5 (0.3-0.7)**

Model 1: adjusted for age, sex

Model 2: further adjusted for season of blood draw, smoking status and pack-years, education, employment and alcohol consumption.

Model 2*: further adjusted for air pollution (a for PM_{10}, b for NO_2), or daytime noise, based on Model 2.

BOLD indicates where significance level <0.05.
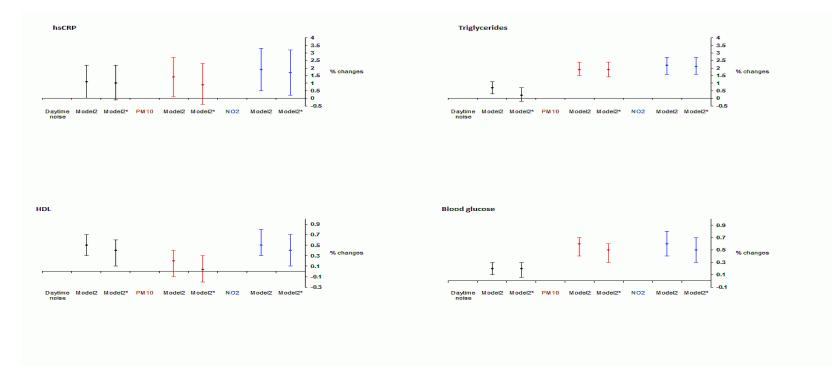
Figure legends

Figure 1. Cross-sectional associations between per IQR* higher exposure and percent changes in each CVD biochemical parameter

Model 2: adjusted for cohort (pooled analysis only), age, sex, season of blood draw, smoking status and pack-years, education, employment and alcohol consumption. Model 2*: further adjusted for PM_{10} or daytime noise. *IQR: Inter-quartile range, which is 5.1 dB(A) for daytime noise, 2.0 µg/m^3 for PM_{10}, 7.4µg/m^3 for NO_2 for analyses on hsCRP and lipids; 4.2 dB(A) for daytime noise, 2.4 µg/m^3 for PM_{10}, 8.8 µg/m^3 for NO_2 for analyses on blood glucose.

Online supplements

Long-term exposure to road traffic noise, ambient air pollution and cardiovascular risk factors in the HUNT and Lifelines cohort

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Supplement-1

Table S1.1: Distributions of exposures in this study by cohort and in the pooled data

NO$_2$, μg/m^3	N	5%	10%	25%	50%	75%	90%	95%	Mean(SD)	IQR
HUNT3	50,628	8.2	8.8	10.1	11.9	15.4	18.6	19.5	13.0 (3.9)	5.3
Lifelines	62,212	13.6	14.1	16.6	20.6	25.4	28.9	31.1	21.2 (5.7)	8.8
Pooled	112,840	11.5	12.1	14.1	17.2	21.5	24.9	26.6	18.0 (5.1)	7.4
PM$_{10}$,μg/m^3	N	5%	10%	25%	50%	75%	90%	95%	Mean(SD)	IQR
HUNT3	50,567	9.7	10	10.4	11.2	12	12.6	12.9	11.3 (1.1)	1.6
Lifelines	61,927	21	21.4	22.3	23.6	24.7	25.7	26.5	23.6 (1.7)	2.4
Pooled	112,494	16.6	17.0	17.7	18.8	19.7	20.6	21.2	18.8 (1.5)	2.0
Daytime noise(Lday)	N	5%	10%	25%	50%	75%	90%	95%	Mean(SD)	IQR
HUNT3	45,644	39.1	39.5	43.6	47.4	50.3	52.9	54.6	47.0 (4.9)	6.7
Lifelines	74,744	51.3	51.7	52.4	53.9	56.6	60.4	63.9	55.2 (4.0)	4.2
Pooled	120,388	47.0	47.3	49.3	51.6	54.4	57.7	60.6	52.3 (4.3)	5.1
Nighttime noise(lnight)	N	5%	10%	25%	50%	75%	90%	95%	Mean(SD)	IQR
HUNT3	45,644	35.1	35.2	37.5	40.2	42.5	44.8	46.4	40.3 (3.7)	5.0
Lifelines	74,744	42.5	42.8	43.6	45.1	47.8	51.6	55.1	46.4 (4.0)	4.2
Pooled	120,388	39.8	40.1	41.5	43.4	45.9	49.2	52.0	44.2 (3.9)	4.4

NO$_2$ and PM$_{10}$ were estimated based on the pan-European LUR model for year 2007 while noise estimates (Lday and Lnight) were for year 2

Table S1.2: Spearman correlations between air pollutants and road traffic noise (Lday and Lnight)

HUNT3 (N=45,581)	NO_2	PM_{10}	LDAY
NO_2	-		
PM_{10}	0.80	-	
Lday	-0.05	0.04	-
Lnight	-0.04	0.06	0.99
Lifelines (N=62,653)	NO_2	PM_{10}	LDAY
NO_2	-		
PM_{10}	0.78	-	
Lday	0.43	0.38	-
Lnight	0.46	0.40	0.99

Lday: day-time noise level at 07:00-19:00; Lnight: night-time noise level at 23:00-07:00.

Table S2.1 Cross-sectional analyses between daytime noise, air pollution and cholesterol: pooled analyses of HUNT3 and Lifelines

			%changes (95%CI) in total cholesterol			
Exposure	IQR	N	Model1	N	Model2	Model2*
Daytime noise	5.1dB(A)	118,868	-0.1 (-0.2 to 0.02)	81,590	-0.1 (-0.2 to 0.1)	0.03 (-0.1 to 0.2)[a]
						0.01 (-0.2 to 0.2)[b]
PM$_{10}$	2.0µg/m^3	110,836	-0.5 (-0.6 to -0.3)	72,551	-0.1 (-0.3 to 0.05)	-0.1 (-0.3 to 0.06)
NO$_2$	7.4µg/m^3	111,180	-0.4 (-0.6 to -0.2)	72,783	-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.2)

Model 1: adjusted for cohort, age, sex;
Model 2: further adjusted for season of blood draw, smoking status and pack-years, education, employment and alcohol consumption.
Model 2*: further adjusted for air pollution (a for PM$_{10}$, b for NO$_2$), or daytime noise, based on Model 2.
BOLD indicates where significance level <0.05.

Table S2.2 Cross-sectional analyses between daytime noise, air pollution and HbA1c: analyses of Lifelines

			%changes (95%CI) in HbA1c			
Exposure	IQR	N	Model1	N	Model2	Model2*
Daytime noise	4.2dB(A)	56,026	-0.1 (-0.1 to 0.04)	50,194	-0.1(-0.1 to 0.05)	-0.1 (-0.1 to 0.08)[a]
						0.01 (-0.1 to 0.1)[b]
PM$_{10}$	2.4µg/m^3	47,628	-0.1 (-0.1 to 0.1)	43,481	-0.1(-0.2 to 0.1)	-0.1 (-0.2 to 0.1)
NO$_2$	8.8µg/m^3	47,686	-0.1(-0.3 to 0.04)	43,537	-0.1 (-0.3 to 0.05)	-0.1(-0.3 to 0.06)

Model 1: adjusted for age, sex;
Model 2: further adjusted for season of blood draw, smoking status and pack-years, education, employment and alcohol consumption.
Model 2*: further adjusted for air pollution (a for PM$_{10}$, b for NO$_2$), or daytime noise, based on Model 2.
BOLD indicates where significance level <0.05.

Table S3.1 Sensitivity analyses based on Model2

Daytime Noise		%changes (95%CI)			
	M2	M2+BMI	M2+long-term health	long residency only	hsCRP<10 mg/L only
HsCRP	**1.1(0.02 to 2.2)**	**1.8 (0.8 to 2.8)**	**1.3 (0.2 to 2.4)**	1.0 (-0.5 to 2.4)	0.9 (-0.1 to 1.8)
Total cholesterol	-0.1 (-0.2 to 0.1)	0 (-0.2 to 0.2)	0.03 (-0.1 to 0.2)	0.1(-0.2 to 0.3)	
Triglycerides	**0.7 (0.3 to**	**1.0 (0.6 to**	**0.7 (0.3 to 1.2)**	0.4 (-0.1 to 1.0)	

	1.1)	1.4)			
HDL cholesterol	0.5 (0.3 to 0.7)	0.3 (0.1 to 0.5)	0.4(0.2 to 0.6)	0.2 (-0.1 to 0.5)	
Fasting glucose	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.4)	0.2(0.1 to 0.4)	0.3 (0.2 to 0.5)	
HbA1c	-0.1(-0.1 to 0.05)	0% (-0.1 to 0.1)	-0.1(-0.1 to 0.1)	-0.1 (-0.2 to 0.1)	

PM_{10}		%changes (95%CI)			
	M2	M2+BMI	M2+long-term health	long residency only	hsCRP<10 mg/L only
HsCRP	1.4 (0.1 to 2.7)	2.6 (1.3 to 3.8)	1.9 (0.5 to 3.3)	2.0 (0.2 to 3.9)	1.0 (-0.1 to 2.2)
Total cholesterol	-0.1 (-0.3 to 0.05)	-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.1)	0.04 (-0.2 to 0.3)	
Triglycerides	1.9 (1.5 to 2.4)	2.4 (1.9 to 2.8)	1.9 (1.4 to 2.4)	2.7 (2.0 to 3.4)	
HDL cholesterol	0.2 (-0.1 to 0.4)	-0.1 (-0.3 to 0.1)	0.1 (-0.1 to 0.4)	-0.5 (-0.8 to -0.1)	
Fasting glucose	0.6 (0.4 to 0.7)	0.6 (0.5 to 0.7)	0.5 (0.3 to 0.6)	0.7 (0.5 to 1.0)	
HbA1c	-0.1(-0.2 to 0.1)	0.01 (-0.1 to 0.1)	-0.1 (-0.2 to 0.1)	0 (-0.2 to 0.2)	

NO_2		%changes (95%CI)			
	M2	M2+BMI	M2+long-term health	long residency only	hsCRP<10 mg/L only
HsCRP	1.9 (0.5 to 3.3)	3.9 (2.6 to 5.3)	2.2 (0.7 to 3.7)	2.3 (0.3 to 4.3)	1.8 (0.5 to 3.1)
Total cholesterol	-0.1 (-0.3 to 0.1)	-0.1 (-0.2 to 0.2)	-0.1 (-0.2 to 0.2)	0.3 (0 to 0.6)	
Triglycerides	2.2 (1.6 to 2.7)	2.9 (2.4 to 3.4)	2.0 (1.5 to 2.6)	2.9 (2.1 to 3.7)	
HDL cholesterol	0.5 (0.3 to 0.8)	0.1 (-0.1 to 0.4)	0.5 (0.3 to 0.8)	-0.1 (-0.4 to 0.3)	
Fasting glucose	0.6 (0.4 to 0.8)	0.7 (0.6 to 0.9)	0.5 (0.3 to 0.6)	0.8 (0.6 to 1.1)	
HbA1c	-0.1 (-0.3 to 0.05)	0 (-0.2 to 0.1)	-0.1 (-0.3 to 0.02)	-0.1 (-0.4 to 0.1)	

Model 2: further adjusted for season of blood draw, smoking status and pack-years, education, employment and alcohol consumption. Lday: daytime noise; Long-term health: ever-had hypertension and diabetes IQR for daytime noise, PM_{10} , NO_2 was 5.1 dB(A) ,2.0 and 7.4 μg/m^3 for analyses of hsCRP and lipids; IQR for daytime noise, PM_{10} , NO_2 was 4.2 dB(A), 2.4 and 8.8 μg/m^3 for analyses of fasting glucose.

Supplement-4

Table S4.1 Categorical noise estimates (% changes, 95%CI) in the main analyses Model 2

hsCRP, mg/L		Model2	Model2+NO_2	Model2+PM_{10}
Lday, dB(A)	N			
<55	40,577	1	1	1
55-60	10,972	0.1 (-2.2 to 2.5)	-0.7 (-3.3 to 2.0)	-0.4 (-3.0 to 2.3)

Lday, dB(A)	N			
>=60	4,381	**4.2** **(0.6 to 7.8)**	2.6 (-1.3 to 6.7)	3.4 (-0.5 to 7.5)

Total cholesterol, mmol/L

Lday, dB(A)	N			
<55	56,437	1	1	1
55-60	17,976	0.004 (-0.3 to 0.3)	0.1 (-0.3 to 0.5)	0.1 (-0. 2 to 0.5)
>=60	7,177	-0.2 (-0.7 to 0.3)	-0. 1 (-0.6 to 0.5)	-0.1 (-0.5 to 0.5)

HDL cholesterol, mmol/L

Lday, dB(A)	N			
<55	56,437	1	1	1
55-60	17,976	**0.8** **(0.4 to 1.3)**	**0.5** **(0.1 to 1.0)**	**0.7** **(0.2 to 1.2)**
>=60	7,177	**1.2** **(0.6 to 1.8)**	**0.9** **(0.2 to 1.6)**	**1.2** **(0.5 to 1.9)**

Triglycerides, mmol/L

Lday, dB(A)	N			
<55	56,630	1	1	1
55-60	17,990	0.04 (-0.8 to 0.9)	-0.4 (-1.3 to 0.6)	-0.2 (-1.2 to 0.7)
>=60	7,179	**1.9** **(0.6 to 3.1)**	0.3 (-1.1 to 1.7)	0.6 (-0.8 to 1.9)

Fasting glucose, mmol/L

Lday, dB(A)	N			
<55	38,984	1	1	1
55-60	16,903	0.1 (-0.1 to 0.3)	0.04 (-0.2 to 0.3)	0.1 (-0.2 to 0.3)
>=60	6,878	**0.6** **(0.3 to 0.9)**	0.4 (0.01 to 0.7)	**0.4** **(0. 1 to 0.8)**

HbA1c, mmol/mol

Lday, dB(A)	N			

<55	31,464	1	1	1
55-60	13,741	-0.1 (-0.2 to 0.2)	0.05 (-0.2 to 0.3)	0.01 (-0.2 to 0.2)
>=60	5,709	-0.1 (-0.4 to 0.2)	0.1 (-0.2 to 0.5)	0.05 (-0.3 to 0.4)

Bold indicates where significant level<0.05 ; Model 2 adjusted for cohort (pooled analyses only), age, sex, education, employment status, smoking status, smoking pack-years, alcohol consumption.; Lday: daytime noiseIQR for daytime noise and PM_{10} was 5.1 dB(A) and 2.0 µg/m^3 for analyses of hsCRP and triglycerides; IQR for daytime noise and PM_{10} was 4.2 dB(A) and 2.4 µg/m^3 for analyses of fasting glucose.

Supplement-5 cohort-specific results (%changes per IQR, 95%CI) and meta-analysis for HsCRP and blood lipids: results based on Model2.

Daytime noise

	HUNT3	Lifelines	Pooled (meta-analysis)	Pooled (*DataSHIELD*)
hsCRP	1.8 (-0.5 to 4.0)	0.4 (-0.7 to 1.6)	0.7 (-0.3 to 1.7)	**1.1 (0.02 to 2.2)**
Total cholesterol	-0.1 (-0.5 to 0.3)	0.03 (-0.1 to 0.2)	0 (-0.1 to 0.2)	-0.1 (-0.2 to 0.1)
Triglycerides	0.1 (-1.0 to 1.1)	0.8 (0.4 to 1.2)	**0.7 (0.3 to 1.1)**	**0.7 (0.3 to 1.1)**
HDL cholesterol	0 (-0.5 to 0.4)	0.5 (0.3 to 0.7)	**0.5 (0.3 to 0.7)**	**0.5 (0.3 to 0.7)**

PM_{10}

	HUNT3	Lifelines	Pooled	
hsCRP	2.7 (0.2 to 5.3)	0.4 (-1.4 to 2.1)	1.1 (-0.3 to 2.5)	**1.4 (0.1 to 2.7)**
Total cholesterol	-0.1 (-0.5 to 0.3)	0.1 (-0.1 to 0.3)	0.1(-0.1 to 0.3)	-0.1 (-0.3 to0.05)
Triglycerides	0.9 (-0.2 to 2.1)	2.7 (2.1 to 3.3)	**2.3 (1.8 to 2.8)**	**1.9 (1.5 to 2.4)**
HDL cholesterol	0.3 (-0.2 to 0.9)	0.2 (-0.1 to 0.5)	0.2 (0 to 0.5)	0.2 (-0.1 to 0.4)

NO_2

	HUNT3	Lifelines	Pooled	
hsCRP	1.4 (-1.0 to 3.8)	1.4 (-0.5 to 3.2)	1.4 (-0.1 to 2.8)	**1.9 (0.5 to 3.3)**
Total cholesterol	-0.1 (-0.5 to 0.3)	0.2 (0.01 to 0.5)	0.2 (0 to 0.4)	-0.1 (-0.3 to 0.1)
Triglycerides	0.3 (-0.7 to 1.4)	3.1 (2.5 to 3.8)	**2.4 (1.8 to 2.9)**	**2.2 (1.6 to 2.7)**
HDL cholesterol	0.5 (0 to 1.0)	0.6 (0.3 to 0.9)	**0.6 (0.3 to 0.8)**	**0.5 (0.3 to 0.8)**