



Road traffic noise, air pollution and incident cardiovascular disease: A joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts

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ABSTRACT

Background: This study aimed to investigate the effects of long-term exposure to road traffic noise and air pollution on incident cardiovascular disease (CVD) in three large cohorts: HUNT, EPIC-Oxford and UK Biobank.

Methods: In pooled complete-case sample of the three cohorts from Norway and the United Kingdom (N = 355,732), 21,081 incident all CVD cases including 5259 ischemic heart disease (IHD) and 2871 cerebrovascular cases were ascertained between baseline (1993–2010) and end of follow-up (2008–2013) through medical record linkage. Annual mean 24-hour weighted road traffic noise (Lden) and air pollution (particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$ [PM10], $\leq 2.5 \mu\text{m}$ [PM2.5] and nitrogen dioxide [NO2]) exposure at baseline address was modelled using a simplified version of the Common Noise Assessment Methods in Europe (CNOSSOS-EU) and European-wide Land Use Regression models. Individual-level covariate data were harmonised and physically pooled across the three cohorts. Analysis was via Cox proportional hazard model with mutual adjustments for both noise and air pollution and potential confounders.

Results: No significant associations were found between annual mean Lden and incident CVD, IHD or cerebrovascular disease in the overall population except that the association with incident IHD was significant among current-smokers. In the fully adjusted models including adjustment for Lden, an interquartile range (IQR) higher PM10 (4.1 $\mu\text{g}/\text{m}^3$) or PM2.5 (1.4 $\mu\text{g}/\text{m}^3$) was associated with a 5.8% (95%CI: 2.5%–9.3%) and 3.7% (95%CI: 0.2%–7.4%) higher risk for all incident CVD respectively. No significant associations were found between NO2 and any of the CVD outcomes.

Conclusions: We found suggestive evidence of a possible association between road traffic noise and incident IHD, consistent with current literature. Long-term particulate air pollution exposure, even at concentrations below current European air quality standards, was significantly associated with incident CVD.

1. Introduction

Traffic noise and air pollution are the leading environmental risk factors for health in Europe. A study using World Health Organisation (WHO) 2009 exposure response functions (WHO, 2009) estimated that noise from road, rail and air traffic in western European countries was associated with 400–1500 disability-adjusted life years (DALYs) per one

million Europeans, the second highest ranking after particulate air pollution (Hanninen et al., 2014).

As an environmental stressor, traffic noise is hypothesized to exert adverse health effects via both direct (e.g. sleep disturbance) and indirect (e.g. annoyance) pathways (Babisch, 2014). In acute response to noise, via activations of the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medulla axis, stress hormones such as

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adrenalin and cortisol are released (Munzel et al., 2017; Recio et al., 2016). In the long term, these adaptive physiological responses may result in adverse pathophysiological changes including to blood pressure, lipids and glucose, which ultimately may contribute to manifest cardiovascular disease (CVD) (Cai et al., 2017).

Beyond findings on annoyance and sleep disruption, the evidence base for cardiovascular effects of long-term traffic noise exposure, particularly those of road transport sources, has been substantially strengthened in the past decade. Of note, most evidence to date has linked noise exposure to hypertension (van Kempen and Babisch, 2012) and ischemic heart disease (IHD) (Babisch, 2014; Vienneau et al., 2015), although for the latter more evidence is needed to strengthen our understanding of the dose-response relationship and to identify susceptible subgroups. Evidence on associations with other CVD outcomes such as stroke (Halonen et al., 2015; Sorensen et al., 2011), atherosclerosis (Kalsch et al., 2014), atrial fibrillation (Monrad et al., 2016), heart failure (Heritier et al., 2017; Sorensen et al., 2017) and arterial stiffness (Foraster et al., 2017) is emerging but more studies are needed given the paucity of available data.

There is also a growing number of studies reporting associations between long-term air pollution exposures and cardiovascular morbidity and mortality (Newby et al., 2015), for which the main hypothesized underlying mechanism is via oxidative stress (Kelly and Fussell, 2017). Additionally, the combined contribution of road traffic noise and air pollution to CVD outcomes merits more investigation (Stansfeld, 2015) since both exposures share a common source and some similar mechanistic pathways leading to CVD (Babisch, 2014; Brook et al., 2010).

In this study, analysing harmonised noise, air pollution and health data from three large cohort studies, we aimed to separately investigate the associations between long-term residential road traffic noise, ambient air pollution and incident CVD, IHD and stroke, taking into account effects of potential confounders and co-adjustment of both road traffic noise and air pollution in the main model. We also examined possible effect modification of these associations for a range of a priori selected variables in this very large study sample.

2. Methods

2.1. Study populations

Three population-based cohorts, HUNT (Helseundersøkelsen i Nord-Trøndelag) (Krokstad et al., 2013), EPIC-Oxford (European Prospective Investigation into Cancer and Nutrition) (Davey et al., 2003) and UK Biobank (Sudlow et al., 2015), were included in this study as part of the BioSHaRE-EU (Biobank Standardisation and Harmonisation for Research Excellence) project.

The HUNT study is a population-based health survey conducted in the whole county of Nord-Trøndelag in central Norway, targeting all residents aged ≥ 20 years. We used data from the second survey (HUNT2) undertaken in 1995–1997, during which 65,232 residents participated and provided data (Krokstad et al., 2013). EPIC-Oxford is a component of the EPIC study (Riboli and Kaaks, 1997). During 1993–1999, 57,446 participants aged ≥ 20 years living throughout the United Kingdom (UK) were recruited through general practices or via postal methods and completed baseline assessments (Davey et al., 2003). UK Biobank, established during 2006–2010, recruited 502,649 participants aged 40–69 years across the UK (Sudlow et al., 2015). Informed consent and ethical approvals were obtained from all three cohorts.

2.2. Incident CVD outcomes

In each cohort, the same censoring date was set for both non-fatal and fatal incident CVD outcomes (Table 1). Since baseline recruitment, follow-up of first CVD event was based on linkages to both hospital

admission records and mortality registries using the unique National Health Service (NHS) number in the UK and Personal Identification Number (PIN) in Norway. Registry of hospital admission started in England on 1st April 1997 and therefore participants from England who were recruited into EPIC-Oxford prior to this date did not have hospital admission records between recruitment and 1st April 1997. These participants ($n = 7314$) were therefore excluded from analyses.

International Classification of Diseases (ICD) codes revisions 9 and 10 were used in the registries in both UK and Norway. The outcomes examined in this study were all CVD (ICD-9:390–459; ICD-10: I00–I99), IHD (ICD-9: 410–414; ICD-10: I20–I25) and cerebrovascular disease (ICD-9: 430–438; ICD-10: I60–I69). Incident cases were ascertained if one of the above codes appeared in the linked medical records between baseline recruitment and death, emigration or end of follow-up, whichever came first (event/censoring). Acute coronary events (ICD-9:410,411; ICD-10:I20.0, I21, I23, I24), ischemic stroke (ICD-9:433,434; ICD-10:I63), and hemorrhagic stroke (ICD-9: 431; ICD-10: I60, I61, I62) were also ascertained.

Participants who reported prevalent CVD, including hypertension, heart attack, angina and stroke at baseline questionnaire, were excluded from analyses. Further, by screening medical records, participants who had CVD diagnosed prior to baseline recruitment were also excluded (Table 1).

2.3. Exposure assessment

A simplified version (Morley et al., 2015) of the CNOSSOS-EU (Common noise assessment methods in European Union) noise modelling framework (Kephalopoulos et al., 2014) was developed and run for each cohort.

Noise sound pressure level was estimated on all roads within 500 m 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 (2001–2010) 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 flow (600 vehicles per day) was assigned (Gulliver et al., 2015). Traffic data were for the year 2009 and land cover data for the year 2006. Annual mean A-weighted sound pressure level in decibels (dB(A)) for daytime noise (averaged sound level from 07:00 to 19:00), night-time noise (averaged sound level from 23:00 to 07:00) and weighted 24-hour average noise (L_{den}) were modelled at baseline home address of participants in all three cohorts.

For all three cohorts, annual mean particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}) and nitrogen dioxide (NO_2) air pollution estimates at baseline home addresses for the year 2007 were assigned from a harmonised European Land Use Regression (LUR) model at a resolution of $100 \times 100 \text{ m}$ (Vienneau et al., 2013). The harmonised European LUR model was developed using monitored air pollution data from over 1500 monitoring sites across Western Europe, satellite-based ground-level concentrations of $\text{PM}_{2.5}$ (particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$) and NO_2 on a 10-km grid, land-use and traffic variables obtained from GIS (Geographic Information System).

Additional annual estimated $\text{PM}_{2.5}$ concentrations for year 2010 were available for EPIC-Oxford and UK Biobank, using the LUR models developed by the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Eeftens et al., 2012).

A detailed summary of variables used in exposure modelling was described in Supplementary Table S1.

2.4. Statistical analyses

We used Cox proportional hazards models, stratified by sex, with

Table 1
Baseline characteristics for pooled and cohort-specific populations.

	Pooled	HUNT2	EPIC-Oxford	UK Biobank	
Study region		Nord-Trøndelag, Norway	United Kingdom	United Kingdom	
Recruitment years		1995–1997	1993–1999	2006–2010	
Started date of medical registry		01/01/1995	01/04/1997(England) 01/01/1981(Scotland)	01/04/1997(England) 01/01/1981(Scotland)	
Censored date for follow-up		30/12/2013	31/12/2008	31/03/2010	
N at recruitment	625,327	65,232	57,446	502,649	
N with medical record linkages	612,911	63,087	37,790	468,341	
N with pre-existing CVD ^a cases before recruitment	182,183	12,037	4720	165,426	
N available for incident CVD analysis	387,035	51,050	33,070	302,915	
N available for complete-case analysis (% of originally recruited)	355,732(57%)	43,267(66%)	23,909(42%)	288,556(57%)	
Age (years), mean (SD)	52.9 (10.6)	45.7 (15.3)	40.2 (12.1)	55.1 (8.1)	p-value#
Females, %	58	53	77	57	< 0.001
Higher Education, %	57	22	55	63	< 0.001
Ever-smoker, %	44	56	37	43	< 0.001
Employed, %	66	73	75	64	< 0.001
Diabetes, %	2	1.4	0.8	2.2	< 0.001
Body mass index (kg/m ²), mean (SD)	26.3 (4.3)	25.9 (3.8)	23.3 (3.5)	26.6 (4.4)	< 0.001
Weekly alcohol consumption in grams, median (IQR)	110 (167)	12 (36)	44.5 (77)	129 (166)	< 0.001
Total person-years follow-up	1,246,044	608,804	258,549	378,691	< 0.001
Incident CVD cases	21,081	15,123	2576	3382	< 0.001
Incident IHD cases	3515	2764	307	444	< 0.001
Incident acute coronary events	1486	1200	126	160	< 0.001
Incident cerebrovascular cases	1845	1559	169	117	< 0.001
Incident ischemic stroke	923	820	47	46	< 0.001
Incident hemorrhagic stroke	307	198	80	29	< 0.001

^a Pre-existing CVD (cardiovascular disease) cases include self-reported heart attack, stroke, hypertension, and angina in recruitment as well as diagnosis of CVD in the registries prior to recruitment. BMI: body mass index; IQR: inter-quartile range; SD: standard deviation; IHD: ischemic heart disease; # chi-square test for statistically significant difference between the proportions of each categorical variable by cohort and one-way analysis of variance method to test statistically significant difference in means of each continuous variables by cohort.

age as the underlying time-scale (Thiebaut and Benichou, 2004), which allows comparison of individuals of the same age, to explore the associations between L_{den} , PM_{10} , $PM_{2.5}$ or NO_2 on a continuous scale and each of the incident CVD outcomes. The linearity assumption was evaluated in the fully adjusted model using categorical exposure in quintiles. Harmonised individual-level data from each cohort were physically pooled and then analysed using Stata (College Station, Texas, USA, v12.1).

Only participants with complete information on all the variables in the fully adjusted model were included in the analysis. Spearman correlations between metrics of noise and air pollution were calculated for each cohort and in the pooled data. Adjusted models were defined a priori, based on previous studies (Cesaroni et al., 2014; Munzel et al., 2014; Newby et al., 2015), as follows: Model1: adjusted for cohort; Model2 (**fully adjusted model**): further adjusted for education level (low, medium, high), employment (yes or no) and smoking status (never-, ex- and current-). All these covariates were retrospectively harmonised across all three cohorts, following a validated protocol (Fortier et al., 2011). Based on the fully adjusted model, ambient air pollution or road traffic noise was added to mutually adjusted models.

Continuous variables including smoking pack-years, body mass index (BMI), weekly consumption of alcohol in grams and a binary variable of ever-had diabetes, all of which were obtained from baseline questionnaires, were each added to the fully adjusted model in sensitivity analyses. We also conducted cohort-specific analyses (fully adjusted model) and pooled cohort-specific estimates via meta-analysis methods.

Subgroup analyses were conducted for key covariates selected a priori by sex, age (< 60 and ≥ 60 years), BMI (< 25, 25–30, ≥ 30 kg/m²), smoking status, education level and ever-had diabetes based on the fully adjusted model. Effect modifications were investigated by adding to the fully adjusted model an interaction term between noise or air pollution exposure and each of these variables. A second interaction term between the cohort indicator variable and the respective subgroup variable was also added, accounting for potential confounding due to differences in the effects of subgroup variables on incident

cardiovascular outcomes across the three cohorts. We also compared the health effect estimates between two groups: those exposed to both road traffic noise and air pollution at levels lower than current guidelines (55 dB(A) for L_{den} and 20 µg/m³ for annual PM_{10}) as set by Europe (European Environment Agency, 2014) and WHO respectively, versus those exposed to both pollutants at levels which exceed the guidelines.

Results are presented as hazard ratio (HR) and 95% confidence interval (CI) per an interquartile range (IQR) higher noise/air pollution exposure.

2.5. Meta-analysis on L_{den} and incident IHD

To help interpret our findings, we further updated meta-analytical evidence of road traffic noise effects on incident IHD by adding the most recent evidence from a large study (Bodin et al., 2016) and those of the present study to that compiled by Vienneau et al. (2015). Both fixed-effect and random-effect meta-analyses were conducted using the Stata “metan” package (Harris et al., 2008), with between-study heterogeneity assessed by the I^2 statistics (Higgins and Thompson, 2002).

3. Results

Pooling data from the three cohorts and after excluding those with pre-existing CVD ($n = 182,183$), those for whom record linkage was not possible ($n = 12,416$) and those for whom information on the main adjusted variables was missing ($n = 31,303$), a total of 355,732 participants were included in the complete-case analyses (Table 1). The mean age of the pooled population was 53 years and 58% were females. During follow-up (mean years of follow-up: 14.1, 10.8 and 1.3 for HUNT2, EPIC-Oxford and UK Biobank respectively), 21,081 incident CVD cases were recorded, with 3515 cases of incident IHD and 1845 cases of incident cerebrovascular disease.

In the pooled data, L_{den} ranged from 42.2 to 87.0 dB(A), with a median (IQR) of 54.6 (3.9) dB(A) (Table 2). The median (IQR) for PM_{10} , $PM_{2.5}$ and NO_2 was 21.3 (4.1), 9.9 (1.4) and 27.0 (12.8) µg/m³ respectively. Spearman correlations between L_{den} and air pollution were

Table 2Distribution of road traffic noise metrics (dB(A)) and air pollution ($\mu\text{g}/\text{m}^3$) in each cohort and in the pooled data (N = 355,732).

	Min	5%	25%	50%	75%	95%	Max	Mean (SD)	IQR
L_{den}									
HUNT2	42.2	42.6	46.0	49.4	52.0	56.2	69.9	49.2 (4.3)	6.0
EPIC-Oxford	51.5	51.7	53.7	55.2	57.3	66.9	84.8	56.3 (4.3)	3.6
UK Biobank	51.5	51.7	53.5	54.9	57.0	66.5	87.0	56.1 (4.2)	3.5
Pooled data	42.2	48.4	52.8	54.6	56.7	65.8	87.0	55.2 (4.8)	3.9
NO₂									
HUNT2	6.6	8.1	10.0	11.7	15.0	19.2	42.0	12.6(3.6)	5.0
EPIC-Oxford	7.0	14.0	20.9	27.0	34.0	55.0	120.7	29.1(12.1)	13.1
UK Biobank	7.0	16.5	23.2	28.4	34.1	50.1	138.4	29.9(10.3)	10.9
Pooled data	6.6	11.0	20.3	27.0	33.1	49.3	138.4	27.8(11.3)	12.8
PM₁₀									
HUNT2	7.8	9.7	10.4	11.1	11.9	12.8	18.1	11.1(1.0)	1.5
EPIC-Oxford	11.5	17.0	20.3	22.1	24.2	27.8	36.4	22.3(3.2)	3.9
UK Biobank	11.8	17.6	20.0	21.7	23.5	27.1	37.2	21.9(2.8)	3.5
Pooled data	7.8	10.8	19.1	21.3	23.3	26.9	37.2	20.6(4.4)	4.1
PM_{2.5}^a									
EPIC-Oxford	8.2	8.2	9.1	9.9	10.6	11.8	18.4	9.9(1.1)	1.5
UK Biobank	8.2	8.3	9.3	9.9	10.6	11.9	21.3	10.0(1.1)	1.3
Pooled data	8.2	8.2	9.2	9.9	10.6	11.9	21.3	10.0(1.1)	1.4

^a Data available for EPIC-Oxford and UK Biobank only (total N = 289,128; N for EPIC-Oxford was 23,905, for UK Biobank was 265,223).

generally low (with PM₁₀ or NO₂ was $r = 0.10$, with PM_{2.5} was $r = 0.23$), whilst between L_{den} and daytime or night-time noise were close to unity ($r = 0.99$) and correlation between PM₁₀ and NO₂ was $r = 0.76$. Analysis on daytime or night-time noise was neglected due to the high correlation with L_{den}. Correlations by cohorts were described in Supplementary Table S2.

3.1. Results on road traffic noise

In the fully adjusted model, no significant associations were observed between L_{den} and any of the incident CVD outcomes in the pooled analysis (Table 3). In the categorical analyses, most associations were non-significant except for the 2nd quintile of L_{den} (52.3–54.0 dB (A)), the association with all incident CVD was statistically significant (HR: 1.045, 95%CI: 1.002–1.090) (Fig. 1). Further adjusting for air pollution, smoking pack-year, BMI or diabetes status did not materially change the main findings for any outcome (Supplementary Table S3).

In the subgroup analyses for L_{den}-incident IHD, significant positive associations were observed for individuals with a BMI $\geq 30 \text{ kg}/\text{m}^2$ (HR: 1.080, 95%CI: 1.008–1.157) and current-smokers (HR: 1.066, 95%CI: 1.014–1.121) per IQR higher of 3.9 dB(A) (Supplementary Table S4), with a significant interaction term with L_{den} detected for smoking status only ($P_{\text{interaction}} = 0.031$).

In the updated meta-analysis, a borderline significant association between per 10 dB(A) higher L_{den} and incident IHD (HR: 1.03, 95%CI: 1.00–1.07, $p\text{-value} = 0.060$) was observed, with no heterogeneity being detected across studies ($I^2 = 9.7\%$, $P_{\text{heterogeneity}} = 0.353$) (Fig. 2).

3.2. Results on air pollution

A statistically significant association between long-term PM₁₀

exposure and all incident CVD (HR: 1.058, 95%CI: 1.025–1.093, per IQR of 4.1 $\mu\text{g}/\text{m}^3$ higher) was observed, persisted after further adjustment for L_{den} (Table 4). For PM_{2.5}, the association with all incident CVD became statistically significant after adding L_{den} into the fully adjusted model (HR: 1.037, 95%CI: 1.002–1.074, per IQR of 1.4 $\mu\text{g}/\text{m}^3$ higher). No significant associations were observed between PM₁₀ or NO₂ on a continuous scale and incident IHD or cerebrovascular disease. Sensitivity analyses did not substantially change the main findings (Supplementary Table S5).

In the categorical analyses (Fig. 3), compared to the 1st quintile, the 2nd to 5th quintiles of PM₁₀ were all significantly associated with incident IHD and incident CVD in an approximate bell-shaped relationship, with the risk starting to increase as low as 18 $\mu\text{g}/\text{m}^3$. Significant associations were also observed for the 2nd quintile of PM_{2.5} (9.1–9.7 $\mu\text{g}/\text{m}^3$) with incident cerebrovascular disease (HR: 1.496, 95%CI: 1.061–2.109) and incident CVD (HR: 1.083, 95%CI: 1.002–1.171). Associations with categorical NO₂ exposure were mostly non-significant. In the subgroup analyses, most interaction terms between air pollution and each of the variables were not statistically significant (Supplementary Table S6).

Compared to those participants who were exposed at residence to a L_{den} level $< 55 \text{ dB(A)}$ and a PM₁₀ level $< 20 \mu\text{g}/\text{m}^3$, higher hazard ratios were seen among participants whose exposure levels exceed these values for incident acute coronary events (HR: 1.93, 95%CI: 1.21–3.08), IHD (HR: 1.72, 95%CI: 1.32–2.25) and all CVD (HR: 1.22, 95%CI: 1.12–1.33). No significant difference in risk was seen for cerebrovascular events.

3.3. Cohort-specific results

In the cohort-specific analyses between air pollution and each of the

Table 3

Association (hazard ratio, 95%CI) between Lden (per IQR of 3.9 dB(A) higher) and each incident CVD outcome: pooled analyses of 355,732 participants from three cohorts.

	Crude	Fully adjusted	Fully adjusted + PM ₁₀	Fully adjusted + NO ₂
All CVD	1.001 (0.988–1.013)	0.998 (0.985–1.010)	0.996 (0.984–1.008)	0.997 (0.985–1.010)
Ischemic heart disease	1.018 (0.998–1.049)	1.012 (0.982–1.042)	1.011 (0.981–1.041)	1.012 (0.982–1.042)
Acute coronary events	1.039 (0.993–1.087)	1.032 (0.986–1.080)	1.032 (0.987–1.080)	1.032 (0.987–1.080)
Cerebrovascular disease	0.979 (0.940–1.020)	0.976 (0.937–1.017)	0.975 (0.936–1.016)	0.976 (0.937–1.017)
Ischemic stroke	0.999 (0.943–1.057)	0.996 (0.941–1.055)	0.995 (0.940–1.054)	0.996 (0.941–1.055)
Hemorrhagic stroke	0.938 (0.845–1.041)	0.934 (0.841–1.036)	0.933 (0.841–1.036)	0.934 (0.841–1.037)

Crude model: only adjusted for cohort; Fully adjusted model: further adjusted for employment, education level, smoking status. IQR: inter-quartile range. CVD: cardiovascular disease.

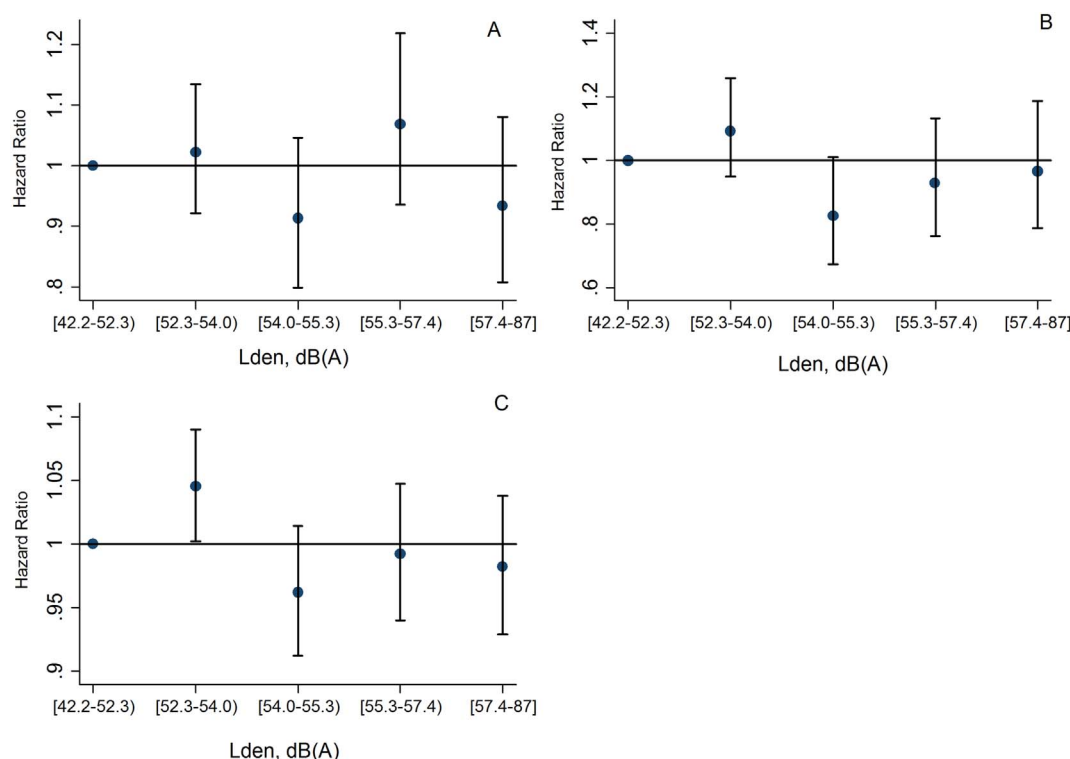


Fig. 1. Associations (hazard ratio, 95%CI) between Lden in quintiles and each incident CVD outcome in the fully adjusted model*: A) incident IHD, B) incident cerebrovascular disease, C) incident all CVD.

Fully adjusted model: cohort, employment, education level, smoking status, stratified by sex.

CVD outcomes, we observed large heterogeneity across the three cohorts (Table 5). Of note, in UK Biobank, positive associations between PM₁₀ or NO₂ and each of the three CVD outcomes were all statistically significant, whilst associations with incident all CVD or incident IHD were negative but statistically significant in HUNT2. Meta-analysed cohort-specific results for L_{den} yielded similar HRs as those presented in Table 3 and no heterogeneity was observed across the cohorts (Supplementary Table S7).

4. Discussion

Overall, we did not observe significant associations between road traffic noise and incident cardiovascular disease in over 350,000 individuals followed for over 1.2 million person-years. However, for incident IHD, the positive association was statistically significant among current-smokers. Significant positive associations between long-term PM₁₀ or PM_{2.5} exposure and all incident CVD were observed after adjustment for noise.

4.1. Road traffic noise

As with ours, most previous studies of road traffic noise on incident IHD generally reported a non-significant association (Babisch et al., 1994; Babisch et al., 1999; Babisch et al., 2005; Beelen et al., 2009; Bodin et al., 2016; Carey et al., 2016; Selander et al., 2009). To date, only two prospective cohort studies have reported a statistically significant association with either incident acute myocardial infarction (MI; ICD-10: I20) (RR: 1.12, 95%CI: 1.02 to 1.22, per 10 dB(A) L_{den}) (Sorensen et al., 2012) in Denmark or IHD mortality (HR:1.023, 95%CI: 1.012 to 1.034, per 10 dB(A) L_{den}) (Heritier et al., 2017) in Switzerland. Besides that for both studies the investigated outcomes were different from ours, other possible explanations for the contrast findings may include that 1) the Danish study has accounted for a full residential history during the 10-year follow-up in the assessment of noise

exposures, which may result in less exposure misclassifications; 2) Apart from using a sophisticated noise model, the nationwide Swiss study was also powered by a large sample size with over 4.4 million participants and 60,000 IHD mortality cases.

Unlike findings from the Danish study (Sorensen et al., 2012), we did not observe a clear dose-response relationship between road traffic noise and any of the CVD outcomes. In fact, in a recent review by Vienneau et al. (2015), shape of a dose-response relationship was less clear for road traffic noise, compared to aircraft noise, across the reviewed studies. Nevertheless, to help interpretation of our findings in relation to other studies and also to quantitatively assess the dose-response relationship between road traffic noise and incident IHD, we updated the meta-analytical evidence from Vienneau et al. (2015). Previously, based on eight road traffic noise studies, Vienneau et al. reported a pooled effect of 1.04 (95%CI: 1.00–1.10) per 10 dB(A) L_{den} on IHD incidence. Adding findings of the present study and those of the negative study from Bodin et al. (2016), we found a similar effect estimate but with a slightly narrower confidence interval (HR: 1.03, 95%CI: 1.00–1.07), due to the addition of our large study which accounted for 20% of weight. Two very large ecological studies have also been recently published. A small-area study of 8.6 million Londoners found daytime noise was significantly associated with IHD mortality, but not with hospital admissions, comparing areas with an annual mean noise level of 55–60 vs. < 55 dB(A) (Halonen et al., 2015). Another study in Germany reported a statistically significant association between 24-h road noise level and incident MI (2.8% per 10 dB increase, 95%CI: 1.2–4.5) using data from health insurance databases (Seidler et al., 2016). Both studies were only adjusted for age, sex and area-level variables, hence are not directly comparable to those of individual-level cohort studies included in the updated meta-analysis.

Our study benefited from a large sample size to explore interactions. We found a stronger association between road traffic noise and IHD among current-smokers. Road traffic noise, acting through a stress response and sleep disturbance, may affect lifestyle changes. A recent

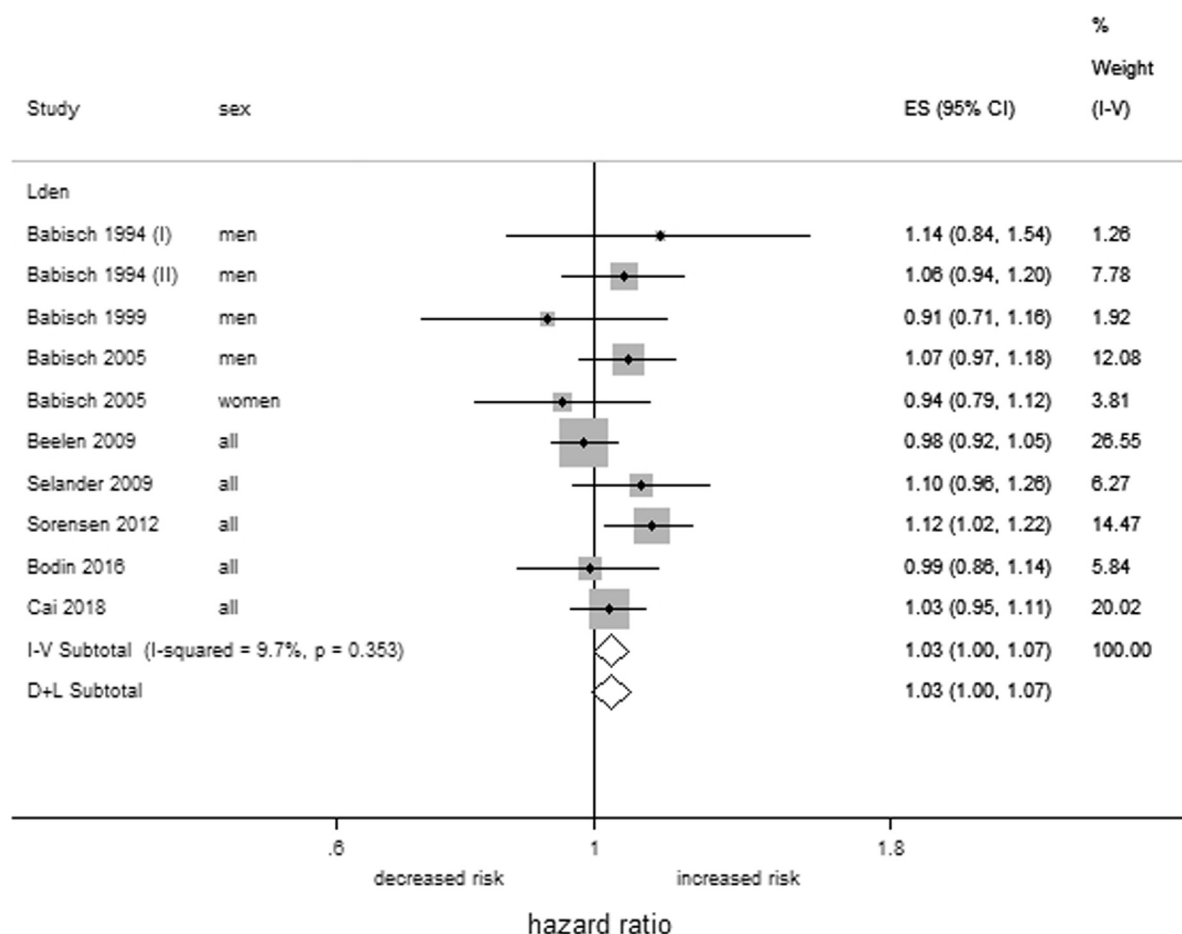


Fig. 2. Updated forest plot of hazard ratios for incident ischemic heart disease per 10 dB(A) higher road traffic noise (Lden) among individual-level cohort studies. I-squared, variation in estimated effect attributable to heterogeneity; I-V, inverse variance weighted fixed effects method; D-L, DerSimonian-Laird random effects method.

Table 4

Association (hazard ratio, 95%CI) between air pollution (per IQR higher) and each incident CVD outcome: pooled analyses of 355,732 participants from three cohorts.

	Crude	Fully adjusted	Fully adjusted + L _{den}
NO₂			
All CVD	1.010 (0.983–1.038)	1.010 (0.982–1.038)	1.010 (0.982–1.038)
Ischemic heart disease	0.978 (0.907–1.055)	0.978 (0.906–1.055)	0.977 (0.906–1.054)
acute coronary events	0.950 (0.842–1.073)	0.940 (0.832–1.061)	0.939 (0.832–1.060)
Cerebrovascular disease	1.029 (0.923–1.148)	1.035 (0.927–1.155)	1.035 (0.927–1.156)
ischemic stroke	1.040 (0.875–1.236)	1.046 (0.879–1.244)	1.045 (0.878–1.244)
Hemorrhagic stroke	0.983(0.801–1.206)	0.981(0.798–1.205)	0.985(0.800–1.212)
PM₁₀			
All CVD	1.060 (1.027–1.094)	1.058(1.025–1.092)	1.058 (1.025–1.093)
Ischemic heart disease	1.054 (0.967–1.149)	1.048(0.961–1.142)	1.046 (0.959–1.140)
acute coronary events	1.003 (0.876–1.150)	0.983 (0.858–1.127)	0.978 (0.853–1.121)
Cerebrovascular disease	1.059 (0.932–1.204)	1.060 (0.932–1.206)	1.065 (0.936–1.211)
ischemic stroke	1.054 (0.862–1.289)	1.054 (0.860–1.291)	1.055 (0.861–1.293)
Hemorrhagic stroke	1.024 (0.807–1.299)	1.013 (0.797–1.287)	1.021 (0.803–1.299)
PM_{2.5}*			
All CVD	1.045 (1.011–1.080)	1.031 (0.997–1.066)	1.037 (1.002–1.074)
Ischemic heart disease	1.048 (0.954–1.151)	1.017 (0.926–1.118)	1.005 (0.912–1.109)
acute coronary events	1.021 (0.877–1.189)	0.978 (0.839–1.140)	0.942 (0.805–1.102)
Cerebrovascular disease	1.063 (0.911–1.242)	1.037 (0.887–1.213)	1.027 (0.874–1.208)
ischemic stroke	1.134 (0.872–1.475)	1.095 (0.839–1.430)	1.092 (0.826–1.442)
Hemorrhagic stroke	0.974 (0.756–1.255)	0.972 (0.753–1.255)	0.957 (0.736–1.243)

Crude model: only adjusted for cohort; Fully adjusted model: further adjusted for employment, education level, smoking status. IQR: inter-quartile range (12.8 µg/m³ for NO₂, 4.1 µg/m³ for PM₁₀ and 1.4 µg/m³ for PM_{2.5}). CVD: cardiovascular disease; PM_{2.5} analysis was based on EPIC-Oxford and UK Biobank only (total N = 289,128). Lden: weighted 24-h road traffic noise.

Bold indicates significance level (P-value < 0.05).

* Indicates analysis of EPIC-Oxford and UK Biobank cohorts only.

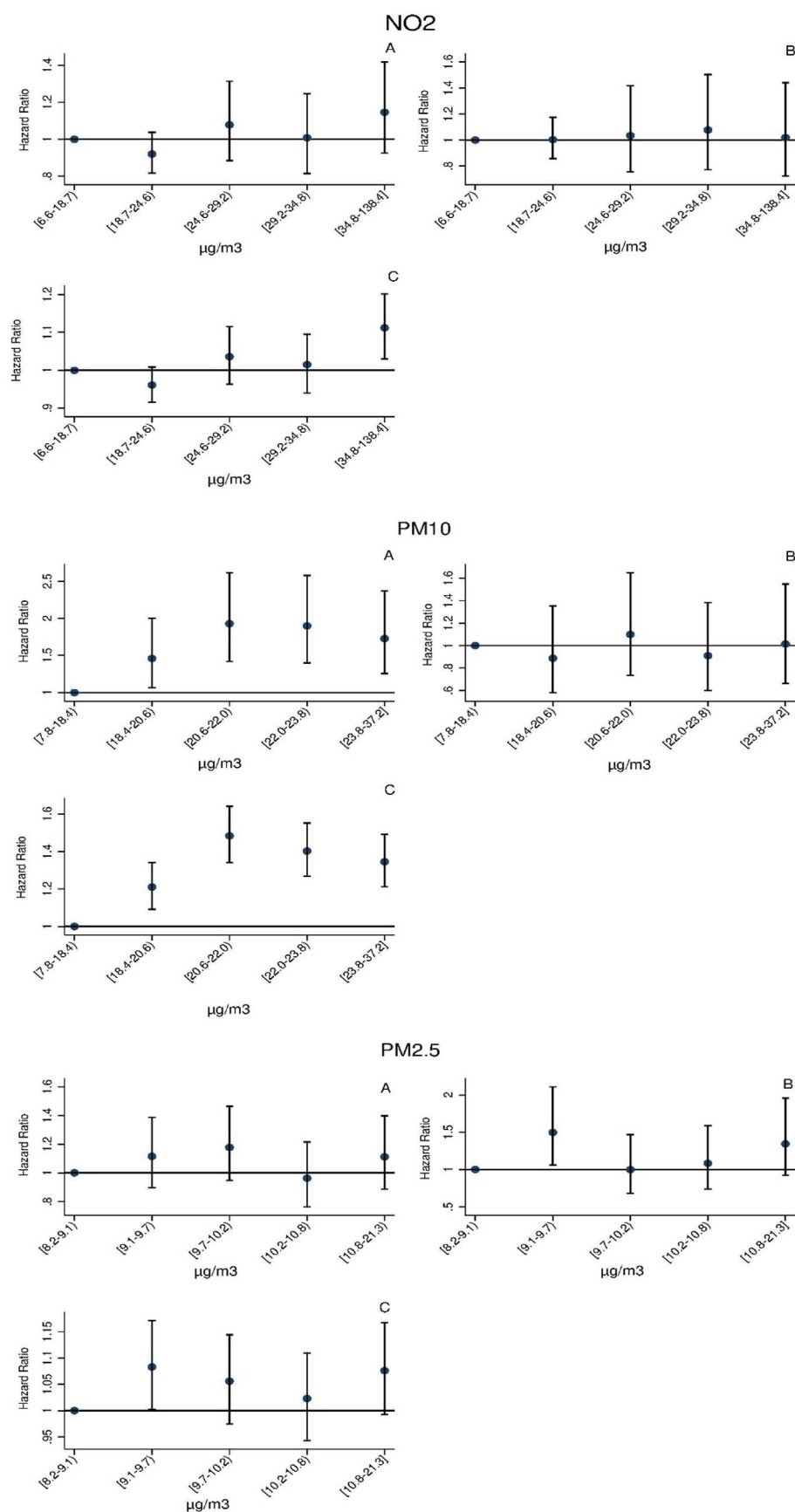


Fig. 3. Associations (hazard ratio, 95%CI) between air pollutants in quintiles and each incident CVD outcome in the fully adjusted model*: A) incident IHD, B) incident cerebrovascular disease, C) incident all CVD.

Fully adjusted model: cohort, employment, education level, smoking status, stratified by sex.

Table 5

Cohort-specific analyses between long-term air pollution (per IQR higher) and incident CVD outcomes based on the fully adjusted model#.

	All CVD	IHD	Acute coronary events	Cerebrovascular disease	Ischemic stroke	Hemorrhagic stroke
NO₂						
HUNT2	0.961 (0.939–0.983)	0.906 (0.858–0.956)	0.914 (0.842–0.0992)	1.025 (0.956–1.098)	1.014 (0.922–1.115)	1.051 (0.866–1.275)
EPIC-Oxford	0.971 (0.927–1.016)	1.035 (0.908–1.180)	1.004 (0.815–1.236)	0.854 (0.702–1.038)	0.839 (0.576–1.222)	0.936 (0.715–1.226)
UK Biobank	1.121 (1.080–1.163)	1.122 (1.014–1.242)	1.054 (0.885–1.256)	1.227 (1.017–1.481)	1.204 (0.889–1.631)	0.944 (0.607–1.470)
Cohort-specific meta-analysis ^a	1.015 (0.919–1.120)	1.012 (0.875–1.170)	0.956 (0.876–1.042)	1.026 (0.875–1.203)	1.020 (0.914–1.138)	1.003 (0.865–1.163)
PM₁₀						
HUNT2	0.972 (0.949–0.996)	0.915 (0.865–0.969)	0.875 (0.803–0.954)	1.053 (0.977–1.134)	1.051 (0.949–1.164)	1.069 (0.869–1.316)
EPIC-Oxford	0.989 (0.941–1.040)	1.112 (0.961–1.287)	1.150 (0.916–1.444)	0.842 (0.690–1.028)	0.720 (0.492–1.053)	0.927 (0.694–1.238)
UK Biobank	1.214 (1.162–1.268)	1.230 (1.091–1.387)	1.176 (0.963–1.437)	1.275 (1.008–1.613)	1.278 (0.878–1.862)	1.083 (0.673–1.743)
Cohort-specific meta-analysis ^a	1.052 (0.916–1.209)	1.071 (0.875–1.311)	1.040 (0.832–1.298)	1.035 (0.862–1.244)	1.006 (0.785–1.290)	1.025 (0.875–1.202)
PM_{2.5}						
EPIC-Oxford	0.974 (0.921–1.029)	0.979 (0.832–1.152)	0.947 (0.734–1.223)	0.970 (0.777–1.212)	1.091 (0.722–1.650)	1.016 (0.740–1.396)
UK Biobank	1.068 (1.026–1.112)	1.042 (0.932–1.165)	1.004 (0.833–1.209)	1.108 (0.889–1.380)	1.073 (0.762–1.512)	0.858 (0.534–1.378)
Cohort-specific meta-analysis ^a	1.022 (0.934–1.118)	1.021 (0.932–1.120)	0.984 (0.846–1.144)	1.037 (0.887–1.213)	1.080 (0.830–1.406)	0.964 (0.741–1.255)

^a Pooled estimates from random-effect models; #fully adjusted model for cohort, employment, education, smoking status, stratified by sex; Inter-quartile range (IQR) for NO₂: 5.0 µg/m³ for HUNT2, 13.1 µg/m³ for EPIC-Oxford, and 10.9 µg/m³ for UK Biobank; IQR for PM₁₀: 1.5 µg/m³ for HUNT2, 3.9 µg/m³ for EPIC-Oxford, and 3.5 µg/m³ for UK Biobank; IQR for PM_{2.5}: 1.5 µg/m³ for EPIC-Oxford and 1.3 µg/m³ for UK Biobank.

cross-sectional study has shown that higher long-term road traffic noise exposure was significantly associated with increased smoking intensity or being a current smoker (Roswall et al., 2017), thus may potentially explain our finding of a stronger association in current-smokers. However, other studies have reported an association in ex-smokers only (Selander et al., 2009) or no effect modification by smoking (Beelen et al., 2009). We also found stronger associations between road traffic noise and IHD among women or obese persons, although these effect modifications were not statistically significant.

Our study is one of the very few studies that have investigated road traffic noise effects on incident stroke. The study by Sorensen and colleagues was the first to report a positive significant association between L_{den} and incident stroke (HR: 1.14, 95%CI: 1.03–1.25, per 10 dB (A) increase) (Sorensen et al., 2011). The same research group later reported that this association was mainly confined to ischemic stroke but not hemorrhagic stroke (Sorensen et al., 2014), results of which are supported by the findings of a recent study in Switzerland (Heritier et al., 2017). Our study did not find an association with any category of stroke events. Similarly, a longitudinal study using linked databases from 211,016 adults aged 40–79 years living across Greater London also found no association between night-time noise and incident stroke (Carey et al., 2016). Heterogeneity was found across previous studies in a recent review, in which the authors suspected that noise effects on stroke may follow a non-linear trend (Dzhambov and Dimitrova, 2016), which is in line with our categorical analyses. The nature of any dose-response relationship however remains to be established.

4.2. Air pollution

Compared to mortality studies, there are relatively fewer studies investigating long-term air pollution effects on overall CVD morbidity. We observed significant positive associations between long-term PM exposure and incident all CVD events, after adjustment for noise. This may be due to the fact that our study was powered by a relatively large number of incident CVD events. It could also be a chance finding among

the many associations studied, but the coherence with the categorical analysis supports this finding. Moreover, emerging studies have reported significant associations between long-term air pollution exposure and adverse changes in established cardiovascular risk factors (Cai et al., 2017; Chuang et al., 2011), which suggest an underlying mechanism between air pollution and development of cardiovascular disease. Although it is difficult to interpret this finding as this category has included a diverse range of cardiovascular diseases which likely have different associations with air pollution, our results suggest that long-term particulate air pollution may have an impact on overall CVD morbidity.

In our study, the direction of the association between long-term PM₁₀ exposure on a continuous scale and incident IHD, is consistent with most other studies (Atkinson et al., 2013; Lipsett et al., 2011; Rosenlund et al., 2009; Gan et al., 2011; Hart et al., 2015; Katsoulis et al., 2014; Madrigano et al., 2013; Maheswaran et al., 2005; Puett et al., 2008; Puett et al., 2011). In particular, the effect size of our estimate was comparable to that from Atkinson et al. (2013), a register-based nationwide study in England. These Western European and North American studies, including ours, shared a similar low level of modelled PM₁₀ exposure and a relatively small exposure contrast among the studied populations, which may be one of the reasons to explain the non-significant findings when the exposure was investigated on a continuous scale. Only three studies to date, each with a different study design, reported a significant positive association (Cesaroni et al., 2014; Miller et al., 2007; To et al., 2015). Of these, the ESCAPE study pooled study-level result estimates from 11 cohorts of > 100,000 participants across Finland, Sweden, Denmark, Germany and Italy and reported a 12% (95%CI: 1%–25%) increased risk of acute coronary events per 10 µg/m³ higher PM₁₀ (Cesaroni et al., 2014). In fact, we also reported the same effect estimate as per 10 µg/m³ higher of PM₁₀ among the three cohorts from UK and Norway, although this did not reach statistical significance. The other two studies in North America were conducted in women-only populations and reported significant associations with PM_{2.5} obtained either on a community level through

monitoring stations (Miller et al., 2007) or on a postal-code level using satellite data (To et al., 2015). Our analysis of the two UK cohorts, in which ESCAPE-modelled individual-level $PM_{2.5}$ estimates were used and for which annual average levels were slightly lower as compared to those two North American studies (10 vs. $13 \mu\text{g}/\text{m}^3$), found a small non-significant increased risk for IHD, an estimate in line with those reported by Cesaroni et al. from the other 11 European cohorts (Cesaroni et al., 2014).

In contrast to the non-significant results using PM_{10} on a continuous scale, we found significant associations with incident IHD in the 2nd–5th quintiles of PM_{10} , following an approximate bell-shaped relationship. It should be noted that the risk started to increase at a level as low as $18 \mu\text{g}/\text{m}^3$ and remained elevated up to a level of $37 \mu\text{g}/\text{m}^3$, a level which is below the current European Union (EU) standard for annual average PM_{10} ($40 \mu\text{g}/\text{m}^3$). However, such a relationship is less obvious for $PM_{2.5}$ in our study.

There was a meta-analysis of 20 studies globally up to year 2015 reporting a pooled HR of 1.06 (95%CI: 1.02–1.10) for all stroke events for each $10 \mu\text{g}/\text{m}^3$ higher in PM_{10} (Scheers et al., 2015). When only pooling European studies, the respective estimate was 1.06 (95%CI: 0.97–1.15). Our estimate for PM_{10} -incident cerebrovascular disease was broadly consistent with most other European studies included in the meta-analysis by Scheers and colleagues.

Most previous studies, consistent with ours, did not find any association between NO_2 and incident IHD (Atkinson et al., 2013; Bodin et al., 2016; Carey et al., 2016; Cesaroni et al., 2014; Gan et al., 2011; Katsoulis et al., 2014; Lipsett et al., 2011; Maheswaran et al., 2005), or incident cerebrovascular events (Katsoulis et al., 2014; Korek et al., 2015; Lipsett et al., 2011; Stafoggia et al., 2014). The independent role of long-term exposure to NO_2 , a common surrogate pollutant relating to near-road traffic exhaust, on cardiovascular morbidity is still a debatable subject given that it is usually closely correlated with traffic-related PM.

It should be noted that in the cohort-specific analyses, we found significant positive associations between air pollution (NO_2 and PM_{10}) and incident IHD or incident cerebrovascular disease in UK Biobank. These results will nevertheless need to be replicated in future studies with longer periods of follow-up and/or improved exposure estimates.

4.3. Strengths and limitations

Strengths of this study include its prospective design, a large sample size with harmonised exposure, health and covariate data, and mutual adjustment of noise and air pollution exposures in relation to CVD morbidity.

We acknowledge limitations of this study. First, our model-based exposure assessment approaches at baseline residential address is inevitably associated with exposure misclassification, for example, due to time spent away from home, housing characteristics, window-opening habits and hearing impairment. These misclassifications are believed to be non-differential for cases and non-cases and therefore likely bias the risk estimates towards null. In addition, the current noise model used in this study tends to over-estimate noise exposures for those at low exposure levels due to the assumed national traffic flow baseline value and to under-estimate exposure for those living in areas with heavily trafficked minor roads. Both scenarios contribute to the uncertainty of continuous noise estimates and limit our ability to detect a noise effect, if present. The European harmonised LUR model for air pollution was likely less accurate for the HUNT cohort, as compared to the two UK cohorts, because for Norway the road networks only had major roads, but not minor roads, included. However, we adopted common LUR air pollution and noise models developed for Europe to minimise differences between cohorts that would otherwise be introduced by having different exposure assessment methods. Indeed, this cross-cohort harmonised approach is crucial to identify the usually small risk in population-based environmental research. Second, noise from railway,

aircraft and occupation may all have impacts on health (Munzel et al., 2014), and by not considering these noise sources, our risk estimates may have been biased. However, aircraft and other sources of community noise are qualitatively different from road noise and may not have similar exposure-response relationships, which is an argument against examining effects of combined exposures. Third, noise and air pollution exposure was estimated using traffic data input from year 2009 and then applied to participants' home addresses across the three cohorts for which baseline occurred during the period 1993–2010. We made an assumption that whilst the absolute traffic volumes will have changed between earlier baseline periods and 2009, the relative difference in road traffic noise/air pollution between areas would likely have been stable over time. This assumption is supported by findings for NO_2 air pollution, for which road traffic is a major source (Gulliver et al., 2013). We were not able to consider the impact on exposure of residential changes during follow-up, which will contribute to misclassification of long-term exposure relevant to the development of CVD. Fourth, we cannot rule out the possibility of residual confounding by other unaccounted factors such as physical activity, diet, medication use, family history of CVD and area-level deprivation. Finally, selection bias may exist as we only included 57% of the original sample in this analysis. Across the three cohorts, participants included in the analyses were younger and in relatively better socioeconomic positions in terms of employment and education, which may be protective against adverse effects of environmental exposures.

4.4. Implications for public health policy

All participants in our study were exposed to an annual average PM_{10} level at residence lower than the current EU standard ($40 \mu\text{g}/\text{m}^3$), and yet we still observed a significant 15% increased risk for incident all CVD events for each $10 \mu\text{g}/\text{m}^3$ higher PM_{10} exposure within our exposure range. Using the more stringent WHO standard for annual PM_{10} ($20 \mu\text{g}/\text{m}^3$), in combining with the European threshold for L_{den} (55 dB(A)), we also found significant increased risks for incident IHD and all CVD among participants who were exposed to levels above these threshold values for both pollutants. Given the ubiquitous presence of air pollution and the fact that > 125 million people are exposed to road traffic noise > 55 dB(A) across Europe (European Environment Agency, 2014), these results, if confirmed, have important implications for public health, and indicate that more stringent environmental policy on these exposures is warranted.

5. Conclusions

This study provides suggestive evidence of a possible association between road traffic noise and incident IHD, consistent with current literature. Our study also suggested that long-term PM_{10} exposure, even at a concentration lower than current European air quality standard, was significantly associated with incident CVD.

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Conflicts of interests

The authors declare that they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2018.02.048>.

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