Long-Term Exposure to Road Traffic Noise and Nitrogen Dioxide and Risk of Heart Failure

A Cohort Study

Sørensen, Mette; Wendelboe Nielsen, Olav; Sajadieh, Ahmad; Ketzel, Matthias; Tjønneland, Anne; Overvad, Kim; Raaschou-Nielsen, Ole

Published in:
Environmental Health Perspectives

DOI (link to publication from Publisher):
10.1289/EHP1272

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP1272.

Long-Term Exposure to Road Traffic Noise and Nitrogen Dioxide and Risk of Heart Failure: A Cohort Study

Mette Sørensen,[1] Olav Wendelboe Nielsen,[2] Ahmad Sajadieh,[2] Matthias Ketzel,[3] Anne Tjønneland,[1] Kim Overvad,[4,5] and Ole Raaschou-Nielsen[1,3]

[1]Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark
[2]Department of Cardiology, Copenhagen University Hospital of Bispebjerg, Bispebjerg, Denmark
[3]Department of Environmental Science, Aarhus University, Roskilde, Denmark
[4]Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark
[5]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

Background: Although air pollution and road traffic noise have been associated with higher risk of cardiovascular diseases, associations with heart failure have received only little attention.

Objectives: We aimed to investigate whether long-term exposure to road traffic noise and nitrogen dioxide (NO_2) were associated with incident heart failure.

Methods: In a cohort of 57,053 people 50–64 y of age at enrollment in the period 1993–1997, we identified 2,550 cases of first-ever hospital admission for heart failure during a mean follow-up time of 13.4 y. Present and historical residential addresses from 1987 to 2011 were found in national registers, and road traffic noise (L_{den}) and NO_2 were modeled for all addresses. Analyses were done using Cox proportional hazard model.

Results: An interquartile range higher 10-y time-weighted mean exposure for L_{den} and NO_2 was associated with incidence rate ratios (IRR) for heart failure of 1.14 (1.08–1.21) and 1.11 (1.07–1.16), respectively, in models adjusted for gender, lifestyle, and socioeconomic status. In models with mutual exposure adjustment, IRRs were 1.08 (1.00–1.16) for L_{den} and 1.07 (1.01–1.14) for NO_2. We found statistically significant modification of the NO_2–heart failure association by gender (strongest association among men), baseline hypertension (strongest association among hypertensive), and diabetes (strongest association among diabetics). The same tendencies were seen for noise, but interactions were not statistically significant.

Conclusions: Long-term exposure to NO_2 and road traffic noise was associated with higher risk of heart failure, mainly among men, in both single- and two-pollutant models. High exposure to both pollutants was associated with highest risk. https://doi.org/10.1289/EHP1272

Introduction

Heart failure is a common disease, associated with morbidity and mortality. Although the incidence has been stable over the last two decades, it still ranks as the most frequent reason for hospitalization among older people, affecting approximately one in five persons (Jencks et al. 2009; Roger 2013). Heart failure is a complex syndrome, with several subtypes that may respond different to therapeutic interventions (McMurray et al. 2012). Heart failure represents the end stage of various cardiovascular diseases, and risk factors include coronary diseases, hypertension, and diabetes, as well as lifestyle habits, such as smoking and alcohol consumption.

Road traffic noise and ambient air pollution are environmental exposures that coexist, especially in urban environments. They have both been associated with higher risk of cardiovascular diseases, including hypertension, myocardial infarction, and stroke (Brook et al. 2010; van Kempen and Babisch 2012; Vienneau et al. 2015). A recent meta-analysis found a positive association between short-term increases in air pollutants and risk of heart failure–related hospitalization or death (Shah et al. 2013). With regard to long-term exposure, an expert position paper recently concluded that studies of long-term exposure to air pollution and incidence of chronic heart failure were still missing (Newby et al. 2015), as only one English national cohort study investigated and found long-term exposure to PM_{10} and NO_2 to be positively associated with incident heart failure (Atkinson et al. 2013). This study included no information on road traffic noise. In addition, few studies have indicated that long-term exposure to NO_2 and $PM_{2.5}$ is positively associated with heart failure mortality (Beelen et al. 2009; Raaschou-Nielsen et al. 2012). Both studies also included information on road traffic noise: Beelen et al. found similar risk estimates before and after adjustment for noise, whereas Raaschou-Nielsen et al. found noise adjustment to reduce risk estimates. Three studies have addressed the relationship between traffic noise and heart failure, indicating that transportation noise increases risk for heart failure, both incident heart failure (Seidler et al. 2016) and heart-failure mortality (Beelen et al. 2009; Heritier et al. 2017). Adjustment for air pollution was included in the two mortality studies and indicated only minor effect of adjustment on risk estimates. Air pollution adjustment was not included in the study on noise and incident heart failure.

The external pathways through which the two exposures act are very different. Particles and other air pollutants enter the body through inhalation, whereas noise is believed to be hazardous through activation of a general stress response and the disturbance of nighttime sleep (Donaldson et al. 2005; Miedema and Vos 2007). However, the suggested pathophysiologic pathways of the two exposures share some characteristics: *a*) effects on the autonomic nervous system, including activation of the hypothalamus–pituitary–adrenaline axis and the sympathetic–adrenal–medulla axis; *b*) modulation of the immune system, in which air pollution stimulates local and systemic inflammation, whereas noise, through disturbance of sleep, may weaken the immune system, as sleep is known to have a strong regulatory influence on the immune system, and disturbances in sleep have been associated with reduced immune function and a proinflammatory state; *c*) endothelial dysfunction; and *d*) oxidative stress (Irwin et al. 2015; Lange et al. 2010; Miller et al. 2012; Mullington et al.

Address correspondence to M. Sørensen. Diet, Genes and Environment, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen, Denmark. Telephone: +45 35257626. Email: mettes@cancer.dk

Supplemental Material is available online (https://doi.org/10.1289/EHP1272).

The authors declare they have no actual or potential competing financial interests.

Received 25 October 2016; Revised 9 August 2017; Accepted 9 August 2017; Published 26 September 2017.

2010; Münzel et al. 2016; Schmidt et al. 2015; Tørnqvist et al. 2007; Wellenius et al. 2013). These pathways may vary in importance according to exposure to either noise or air pollution.

Our aim was to study the association between long-term residential exposure to air pollution (estimated as NO_2) and road traffic noise and risk of incident heart failure in a large Danish cohort, investigating the association of each of the pollutants alone, the effects of mutual confounding, and combined associations. Furthermore, we aimed to investigate whether persons with known pre-existing cardiovascular disease, chronic obstructive pulmonary disease (COPD), and/or diabetes were more susceptible than persons without such disease diagnoses.

Methods

Study Population

The study was based on the Danish Diet, Cancer and Health cohort (Tjønneland et al. 2007). Briefly, 160,725 Danes were invited to participate from 1993 to 1997. The inclusion criteria were between 50 and 64 y of age, resided in the greater Copenhagen or Aarhus area; and had no previous cancer diagnosis registered in the Danish Cancer Registry. In total, 57,053 participants accepted the invitation and were enrolled in the study. All participants completed self-administered and interviewer-checked questionnaires at enrollment covering education, hypertension, and lifestyle habits. Trained staff members measured height, weight, waist circumference, and blood pressure according to standard protocols. The study was conducted in accordance with the Helsinki Declaration, approved by local ethical committees, and all participants provided written informed consent.

Identification of Outcome

Heart failure cases diagnosed before death, emigration, or the end of follow-up period (31 December 2011) were identified by linking the unique personal identification number of each cohort member to the nationwide Danish National Patient Register (Lynge et al. 2011). Cases were identified using discharge diagnosis according to the *International Classification of Diseases* (ICD) 8 codes 4,270 and 4,271 or ICD-10 codes I50, I11.0, I42.0, I42.9, and I42.9. We excluded all participants with a diagnosis of heart failure before 1 July 1997 because *a*) we considered only incident heart failure (all diagnoses before enrollment excluded); *b*) we wanted to ensure at least 10 y of previous exposure for all (recording of exposure from 1 July 1987); and *c*) the first Danish guidelines for diagnosis and managing of failure were published in 1997.

Exposures

Residential address history for all cohort members between 1 July 1987 and event or end of follow-up period at 31 December 2011 were collected from the Danish Civil Registration System. All addresses were geocoded.

Annual levels of road traffic noise were estimated at all addresses using SoundPLAN (version 7.1; SoundPLAN Nord ApS), which is a calculation program that implements the joint Nordic prediction method for road traffic noise. The Nordic prediction method is the standard method for noise calculation in Scandinavia and has been applied for many years (Bendtsen 1999). The noise model requires information on a number of variables, including geocode and height for each address (at most-exposed façade); information on annual average daily traffic for all Danish road links, distribution of light and heavy vehicles for all road links, travel speed, and road type for all road links (motorway, express road, road wider than 6 m, road less than 6 m and more than 3 m, and other road); and polygons (3D) for all buildings in Denmark, obtained from the Danish Geodata Agency. All information on traffic was obtained from a national road and traffic database (Jensen et al. 2009a). The database is based on four different data sources, rated as follows: *a*) traffic data collected from the 140 Danish municipalities with most residents and traffic, covering 97.5% of the addresses in the present study (period from 1995 to 1998); included roads typically have >1,000 vehicles per day and are based on traffic counts and estimated numbers; *b*) traffic data for all major state and county roads; *c*) traffic data for 1995–2000 for all major roads in the Greater Copenhagen Area; and *d*) smoothed traffic data for 1995 for all smaller roads based on estimated numbers for distribution of traffic by road type and by urban/rural zone. Subsequently, the traffic data were extrapolated forward and backward in time based on historical traffic trends for different street types. In the model, we assumed that the terrain was flat. Furthermore, we assumed that roads, urban areas, and areas with water were hard surfaces, and all other areas were assumed acoustically porous. We did not have information on noise barriers and road surfaces. We calculated road traffic noise as the equivalent continuous A-weighted sound pressure levels at the most exposed facade of each residence during day, evening, and night, and expressed noise exposure as L_{den} by applying a 5-dB penalty for the evening and a 10-dB penalty for the night.

We used the Danish AirGIS dispersion modeling system to calculate exposure to annual levels of ambient NO_2 for all addresses (Berkowicz et al. 2008). This modeling system calculates NO_2 at each address as the sum of: *a*) NO_2 from the nearest street, calculated using information on traffic, car fleet emission factors, geometry of streets and buildings, as well as daily information on meteorology; *b*) urban background, which is calculated using information on emission density, city dimensions, and heights of buildings; and *c*) regional background, estimated from rural monitoring data and national vehicle emissions (Berkowicz et al. 2008). For traffic input data, the information used were the same as described above for noise. Several studies have successfully validated and applied the modeled NO_2 estimates obtained using AirGIS (Jensen et al. 2009b; Ketzel et al. 2011); NO_2 is a well-recognized surrogate for a mix of traffic-related air pollutants (Levy et al. 2014).

Statistical Methods

Analyses were based on Cox proportional hazards model with age as underlying time. We used left truncation at age of 1 July 1997, such that people were considered at risk from the exact age they had reached at that date (delayed entry), and right censoring at the age of heart failure, death, emigration, or end of follow-up period (31 December 2011), whichever came first. Exposure to road traffic noise (L_{den}) and NO_2 were modeled as time-weighted means 1-, 5-, and 10-y preceding diagnosis, taking all then-current and historical addresses in these periods into account. The exposure windows were entered as time-dependent variables into the statistical risk model, thus for each case of heart failure recalculating exposure for all cohort participants at exactly the same age as the case at the time of diagnosis.

Incidence rate ratios (IRR) for heart failure in association with noise and NO_2 were analyzed in three models: Model 1 with adjustment for age (by design) and sex; Model 2 with further adjustment for baseline information on lifestyle and socioeconomic status (SES); and Model 3, where we further adjusted models of road traffic noise for NO_2 and vice versa, (for same exposure time-windows, 1-, 5-, and 10 y). The included lifestyle and SES covariates were smoking status (never, former, current); smoking intensity (g tobacco/day, linear); smoking duration

(years, linear); intake of vegetables (g/day, linear); intake of red meat (g/day, linear); years of school attendance (<8, 8–10, >10 y); alcohol intake (yes/no, g/day among those drinking alcohol, linear); sport during leisure time (yes/no; hours of sport per week among active, linear); calendar year (5-y categories, entered as time-dependent variable); and area level SES of the participant's enrollment municipality (or district for Copenhagen; 10 districts in total), classified as low, medium, or high, based on municipality/district-level, information on education, work-market affiliation, income, and occupational status. Covariates were selected *a priori*, based on existing literature, biological plausibility, and availability of data. We also generated six exposure categories of the 10-y exposures to road traffic noise, with 425 cases in each, and estimated IRR (Model 2) of the five higher exposure categories (52.7–56.0 dB; 56.0–59.2 dB; 59.2–62.2 dB; 62.2–66.5 dB; and ≥66.5 dB) in comparison with the lowest exposure category (<52.7 dB; reference category). The same approach was used for NO_2 (<11.2 $\mu g/m^3$; 11.2–12.7 $\mu g/m^3$ 12.7–14.8 $\mu g/m^3$; 14.8–17.7 $\mu g/m^3$; 17.7–22.1 $\mu g/m^3$; and ≥22.1 $\mu g/m^3$).

Linearity of continuous exposures and covariates were evaluated by graphical evaluation using linear spline models with boundaries at deciles among cases. Deviation from linearity was only found for alcohol consumption, which was therefore included in the model after allowance for different slopes below and above 40 g/day.

We estimated the association between noise/NO_2 and heart failure in predefined subgroups by sex, baseline hypertension, baseline obesity, baseline waist circumference, and a diagnosis of myocardial infarction, atrial fibrillation, COPD, or diabetes (before censoring). Potential modifications were evaluated by introducing an interaction term into the model and tested by Wald test. Baseline hypertension was defined as systolic blood pressure >140 mm Hg or diastolic pressure >90 mm Hg at enrollment and/or answering yes to the question "Do you suffer, or have you ever suffered, from high blood pressure?" in the baseline questionnaire. Blood pressure was measured by an automatic blood pressure device (Takeda Medical UA 751 or UA-743). The measurement was conducted in supine position after 5 min rest. If systolic blood pressure was ≥160 mm Hg, or diastolic blood pressure was ≥95 mm Hg, the measurement was repeated and the lowest measurement used. We found that only 7% of the participants were defined as hypertensive solely based on self-reported hypertension. Information on diagnosis of myocardial infarction, atrial fibrillation, or COPD before censoring was obtained by linkage with the Danish National Patient Registry; myocardial infarction: ICD-8 (410) and ICD-10 (DI21, DI22); atrial fibrillation: ICD-8 (427.93, 427.94) and ICD-10 (I48.9); and COPD: ICD-8 (490–493) and ICD-10 (J40–J46). Diabetes cases were identified by linkage with the Danish National Diabetes Registry.

To investigate the effect of high exposure to both pollutants on risk for heart failure, we combined tertiles of the two exposures (10-y mean exposure) into nine categories, using the category of low noise and NO_2 as reference group (categorical analysis). All analyses were performed using SAS® version 9.3 (SAS Institute Inc.).

Results

Of the study cohort of 57,053, we excluded 574 with cancer before baseline (no previous cancer was an enrollment criteria); 329 with heart failure before 1 July 1997; 316 who died or emigrated before start of follow-up period (1 July 1997); 3,119 without information on exposure; and 1,780 without information on one or more potential confounders, leaving a study population of 50,935 participants, of whom 2,550 developed heart failure within a mean follow-up period of 13.4 y (8.5 y among cases).

Table 1. Baseline characteristics of the diet, cancer, and health cohort by heart failure status.

Characteristic at enrollment	Total cohort (n = 50,954)	Heart failure cases (n = 2,550)
Men, %	47.1	63.6
Age (years)	56.2 (50.7–64.2)	59.3 (51.3–64.7)
Years of school attendance, %		
≤7	33.0	43.9
8–10	46.4	40.8
>10	20.6	15.3
Area level SES, %		
Low	21.2	18.9
Medium	64.6	59.7
High	14.2	21.5
Smoking status, %		
Never	36.2	23.3
Former	27.5	28.1
Current	36.2	48.6
Smoking intensity (g/day)[a]	14.7 (3.8–34.2)	17.2 (6.0–37.6)
Smoking duration (years)[a]	33 (7–46)	37 (11–48)
Intake of vegetables (g/day)	161 (49–367)	142 (41–353)
Drink alcohol, %	97.8	96.7
Alcohol intake (g/day)	13.3 (1.1–64.5)	15.1 (0.9–80.7)
Intake of red meat (g/day)	78.1 (32.0–64.5)	86.5 (36.6–181.9)
Sport during leisure time		
Yes, %	54.3	42.6
Hours among active	2.0 (0.5–7.0)	2.0 (0.5–7.5)
Hypertension, %	50.7	69.1
Obese (BMI >30), %	14.5	27.3
Road traffic noise, L_{den} (dB)	57.0 (49.0–70.6)	58.3 (49.3–71.2)
Air pollution, NO_2 ($\mu g/m^3$)	15.7 (12.2–33.5)	16.9 (12.3–34.6)

Note: Values are medians (5–95 percentiles) unless otherwise stated.
[a]Among present and ex-smokers.

In comparison with the total cohort, we found that cases with heart failure were more often men than women; they had fewer years of school attendance; they smoked more; they eat fewer vegetables and more red meat; they drank more alcohol; they were less physically active and more obese; and they were more likely to have hypertension (Table 1). Similar trends were seen when investigating men and women separately (see Table S1). Furthermore, when comparing participants exposed to over- and below-median NO_2 or noise, we found the highly exposed participants to be more often women than men, smokers, hypertensive, obese, slightly less educated, and less physically active (see Table S2). Similar trends were seen when investigating men and women separately (see Tables S3 and S4). The correlation ($R_{Spearman}$) between average 10-y exposure of road traffic noise and NO_2 preceding start of follow-up (July 1997) for the total study population was 0.65. Distributions of road traffic noise and NO_2 are shown in Figure S1. We found that 68% of the cases and 71% of the noncases lived at the same address 10 y or longer before censoring.

Table 2 shows associations between exposure to noise and NO_2 and risk of heart failure. In crude analyses and with further adjustment for lifestyle, SES, and calendar-year, we found both exposures to be associated with a statistically significant higher risk of heart failure for all three exposure time-windows. For example, an interquartile range increase in 10-y exposure for noise and NO_2 was associated with a 14% (8–21%) and 11% (7–14%) higher risk of heart failure in the adjusted model, respectively. The association appeared to follow a linear exposure–response relationship for both exposures; however, for noise, there were indications of a threshold around 55 dB, under which no increase in risk was observed (Figure 1; see Table S5). In two-pollutant models with mutual noise/NO_2 adjustment, the IRRs were lower, but there was still a statistically significant

Table 2. Associations between mean 1-, 5-, and 10-y residential exposure [linear, per interquartile range (IRR)] to road traffic noise and NO_2 and risk for heart failure [IRR (95% CI)].

Exposures	Model 1 Adjusted for age and sex	Model 2 Adjusted for age, sex, lifestyle,[a] SES,[b] and calendar year	Model 3 Adjusted for age, sex, lifestyle,[a] SES,[b] calendar year, and mutual noise/NO_2 adjustment
1-y exposure[c]			
Road traffic noise (L_{den}, per IQR: 10.0 dB)	1.22 (1.15, 1.29)	1.13 (1.07, 1.19)	1.06 (0.98, 1.14)
Air pollution (NO_2, per IQR: 6.6 $\mu g/m^3$)	1.17 (1.13, 1.21)	1.10 (1.06, 1.14)	1.07 (1.02, 1.12)
5-y exposure[c]			
Road traffic noise (L_{den}, per IQR: 9.8 dB)	1.23 (1.17, 1.30)	1.14 (1.08, 1.21)	1.07 (0.99, 1.15)
Air pollution (NO_2, per IQR: 7.1 $\mu g/m^3$)	1.19 (1.14, 1.23)	1.11 (1.07, 1.16)	1.08 (1.02, 1.14)
10-y exposure[c]			
Road traffic noise (L_{den}, per IQR: 9.9 dB)	1.24 (1.18, 1.31)	1.14 (1.08, 1.21)	1.08 (1.00, 1.16)
Air pollution (NO_2, per IQR: 7.5 $\mu g/m^3$)	1.20 (1.15, 1.25)	1.11 (1.07, 1.16)	1.07 (1.01, 1.14)

Note: CI, confidence interval; IQR, interquartile range; IRR, incidence rate ratio.
[a]Lifestyle: smoking status, duration and intensity; intake of vegetables, red meat, and alcohol; and sport during leisure time.
[b]SES, socioeconomic status: length of school attendance and municipality SES.
[c]Mean time-weighted exposures calculated 1-, 5-, or 10-y preceding heart-failure diagnosis taking all addresses in that period into account.

association with heart failure for both exposures for the 10-y exposure time-window: IRR of 1.08 (1.00, 1.16) for road traffic noise and of 1.07 (1.01, 1.14) for NO_2.

In analyses of effect modification of the NO_2–heart failure association by gender, baseline characteristics and comorbidity (Table 3), we found statistically significant modification by gender (only association among men), baseline hypertension (only association among hypertensive) and diabetes (strongest association among patients with existing diabetes). The same tendencies were seen with regard to the noise–heart failure association, although the interactions were not statistically significant. We found no significant effect modification of the exposure–heart failure association by obesity, waist circumference, or existing myocardial infarction, atrial fibrillation, or COPD for either noise or NO_2, although results indicated a stronger association between noise and heart failure among participants without COPD and a stronger association between NO_2 and heart failure among participants with myocardial infarction. When investigating incident heart disease in the present cohort, defined as the first case of either myocardial infarction, atrial fibrillation, or heart failure, we found that heart failure contributed with ~20% of the incident cases.

Table 4 shows combined association between road traffic noise and NO_2 in relation to heart failure risk. The strongest association was found for the combination of high exposure to both noise and NO_2 (IRR = 1.31; 95% CI = 1.15,1.49). Also, combinations of medium-medium and medium-high exposures yielded increased estimates (IRRs from 1.15–1.27).

We investigated the exposure–heart failure association with regard to time of diagnosis and found no marked differences. For diagnoses between 1997 and 2004, the IRR was 1.12 for noise and 1.13 for NO_2 (1,030 cases); for diagnoses between 2005 and 2011, the IRR was 1.17 for noise and 1.10 for NO_2 (1,520 cases).

Discussion

We found long-term exposure to road traffic noise and NO_2 to be associated with higher risk of incident heart failure, both before and after mutual adjustment. For both exposures, the associations followed an exposure–response relationship. For NO_2, we found the association with heart failure to be strongest among men, among people with baseline hypertension, and among people with diabetes. The same tendencies were seen for noise, although not statistically significant. The strongest association with heart failure was seen when both noise and NO_2 levels were high.

Research in air pollution and heart failure has focused on showing an association between short-term changes in air pollution and risk of hospitalization and death for heart failure (Shah et al. 2013). However, heart failure is a condition that can develop slowly over time, and it is, therefore, also relevant to investigate whether long-term exposure increases the risk of incident heart failure. We found long-term exposure to NO_2 and road traffic noise to be associated with a higher risk of heart failure both before and after mutual adjustment. This finding indicates that both these coexisting traffic pollutants affect the risk of developing heart failure. For air pollution, our results are supported by one other study, which found long-term exposure to different air pollutants, PM_{10}, NO_2, and SO_2, to be associated with a statistically significant increase in risk of heart failure (Atkinson et al. 2013). Interestingly, Atkinson et al. (2013) found an IRR of 1.06 per IQR higher NO_2, which is very similar to the IRR found in the present study. For noise, our result is supported by one recent study that found that aircraft, railway, and road traffic noise to be associated with increased risk for heart failure, although in that study, the risk estimates were found to be considerably lower than observed in the present study, with an odds ratio of 1.024 per 10.0 dB road traffic noise (Seidler et al. 2016). Also, the few studies that have addressed long-term exposure to noise and/or NO_2 in relation to cardiac dysfunction (Leary et al. 2014) and heart failure mortality (Beelen et al. 2009; Heritier et al. 2017; Raaschou-Nielsen et al. 2012) provide support to our findings.

For both pollutants, mutual adjustment reduced the risk estimates. Noise and NO_2 correlate, reflecting that road traffic is an input variable in both exposure models. However, the correlation is moderate, with an R^2 of 0.42, and thus a 58% unexplained variation. Reasons include that the NO_2 model uses information on regional and urban background contribution, which is not relevant for noise modeling, as well as differences in dispersion of the two exposures, as the NO_2 model includes information on street canyons, wind, and chemistry, whereas the noise model includes information on sound reflection and absorption. It is, however, not possible to disentangle the effects of the two exposures completely.

Heart failure is a condition that represents the end stage of other conditions, such as hypertension, coronary artery diseases, and arrhythmias. We have previously found associations between the two pollutants and myocardial infarction, stroke, and atrial fibrillation in the present cohort, whereas we found no clear relationship with blood pressure (Monrad et al. 2016; Roswall et al. 2017; Sørensen et al. 2011, 2014). When investigating whether a known existing cardiovascular condition modified

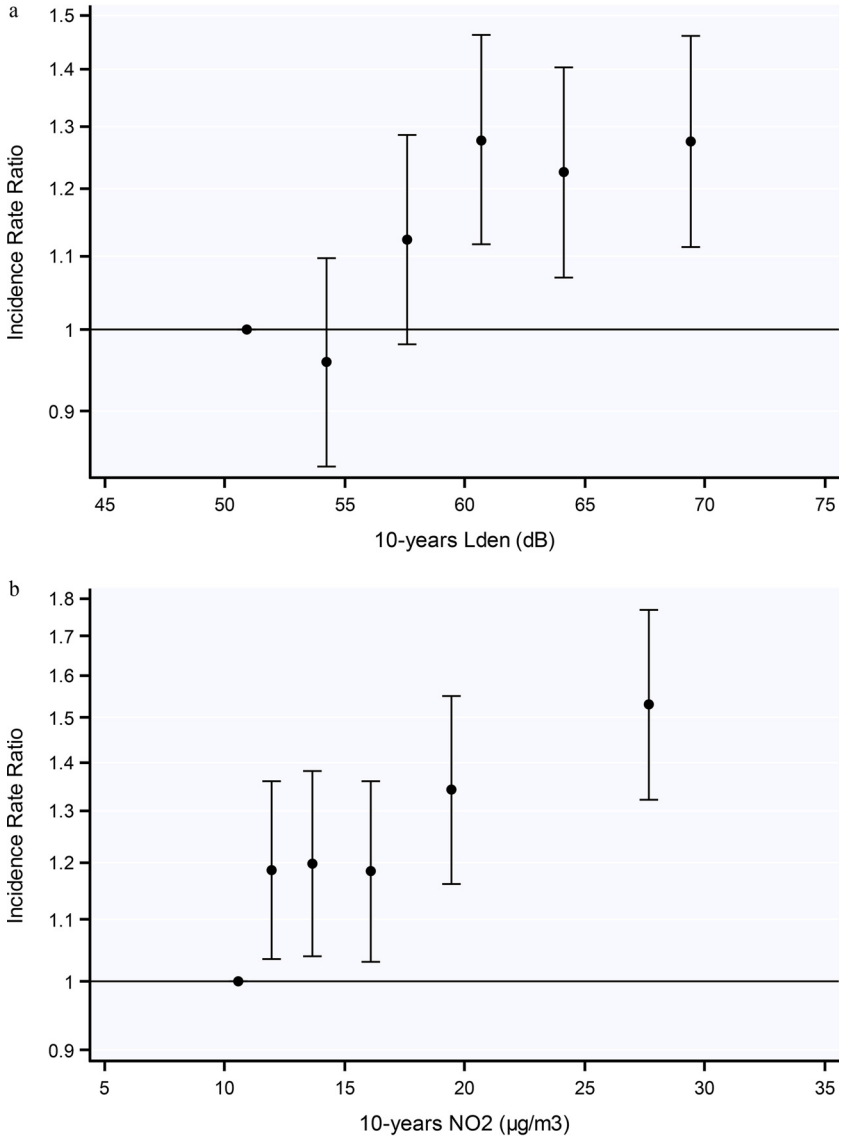

Figure 1. Association between residential exposure to road traffic noise (*a*) and NO_2 (*b*) 10-y preceding diagnosis and risk of heart failure adjusted for age, sex, lifestyle, socioeconomic status, and calendar year. The vertical whiskers show incidence rate ratios with 95% confidence interval (CI) at the median of the exposure categories compared with the reference category (six categories, see Table S5 for IRRs and CI values).

the relationship between the exposures and risk of heart failure, we found that especially people who were hypertensive at baseline were susceptible to the hazardous effects of air pollution and, potentially, also noise, on risk of heart failure. We also found indications of a stronger association between air pollution and heart failure among people with a previous myocardial infarction (though not statistically significant), whereas for noise, the results surprisingly indicated no effect modification by myocardial infarction. Atrial fibrillation did not seem to affect the exposure–heart failure association for either noise or air pollution. This finding indicates that air pollution may increase risk of heart failure among persons whose vascular systems are already known to be challenged by other factors, whereas for noise, the picture was not clear.

Similarly, we found the association with air pollution and possibly noise to be more evident among people with preexisting diabetes. Hyperglycemia and insulin resistance have been associated with systemic inflammation and oxidative stress, and diabetics are known to have an accelerated development of atherosclerosis and high risk of hypertension and cardiovascular disease (Bornfeldt and Tabas 2011; Emerging Risk Factors et al. 2010). Furthermore, we found the association between both exposures and heart failure to be stronger in men in comparison with the association in women. For noise, a few previous studies have suggested that men may be more sensitive to noise in relation to risk for cardiovascular disease (Eriksson et al. 2010; Evrard et al. 2016), but for air pollution, the picture is not clear (Beelen et al. 2014; Kaufman et al. 2016). Again, this finding fits with the concept of an association among persons with a challenged vascular system, as men are known to have more advanced atherosclerosis than women have, possibly due to the beneficial effects of estrogen on the vascular system, because research has shown that atherosclerosis rises in women after menopause (Mathur et al. 2015).

Surprisingly, we found no interactions with baseline obesity, which might be expected as high BMI and waist circumference are known to be associated with a higher atherosclerotic burden. However, BMI and waist circumference were measured at baseline, and it is possible that changes in weight during follow-up may have blurred the result. Overall, our results indicate that air

Table 3. Modification of associations between 10-y exposure (linear, per interquartile range) of road traffic noise and NO_2 and risk for incident heart failure by gender, baseline characteristics and co-morbidity from other major cardiovascular diseases, diabetes and chronic obstructive pulmonary disease at the time of heart failure.

	Road traffic noise (10-y L_{den}, per IQR[a])			Air pollution (10-yNO_2, per IQR[a])	
Covariates	*n* cases	IRR (95% CI)[b]	*p*-Value[c]	IRR (95% CI)[b]	*p*-Value[c]
Gender			0.053		0.007
Men	1,622	1.19 (1.11,1.28)		1.16 (1.10,1.22)	
Women	928	1.06 (0.96,1.17)		1.03 (0.96,1.11)	
BMI[d]			0.88		0.92
Obese (BMI ≥30)	696	1.12 (1.01,1.25)		1.10 (1.02,1.19)	
Nonobese (BMI <30)	1,854	1.13 (1.06,1.21)		1.11 (1.05,1.16)	
Waist circumference[d]			0.37		0.39
Above WHO recommendations	1,673	1.12 (1.04,1.20)		1.10 (1.04,1.16)	
Below WHO recommendations	877	1.18 (1.07,1.30)		1.14 (1.06,1.22)	
Hypertension[d]			0.21		0.04
Yes	1,793	1.17 (1.09,1.25)		1.14 (1.09,1.20)	
No	757	1.08 (0.97,1.20)		1.04 (0.96,1.12)	
Myocardial infarction[e]			0.81		0.19
Yes	787	1.12 (1.01,1.24)		1.15 (1.07,1.23)	
No	1,763	1.13 (1.06,1.21)		1.09 (1.03,1.14)	
Atrial fibrillation[e]			0.85		0.90
Yes	825	1.17 (0.97,1.42)		1.13 (0.98,1.30)	
No	1,725	1.15 (1.08,1.22)		1.12 (1.07,1.17)	
Diabetes[e]			0.30		0.03
Yes	573	1.20 (1.06,1.35)		1.20 (1.11,1.30)	
No	1,977	1.12 (1.05,1.19)		1.09 (1.03,1.14)	
Chronic obstructive pulmonary disease[e]			0.17		0.79
Yes	514	1.06 (0.93,1.21)		1.11 (1.01,1.22)	
No	2,036	1.17 (1.10,1.25)		1.12 (1.07,1.18)	

[a]IQR, Interquartile range (9.9 dB for noise; 7.5 $\mu g/m^3$ for air pollution).
[b]Adjusted for age; sex; length of school attendance; municipality SES; smoking status, duration and intensity; intake of vegetables, red meat, and alcohol; sport during leisure time, and calendar year (Model 2). IRR: incidence rate ratio.
[c]*p*-Value for interaction (test for differences in slopes).
[d]Baseline information.
[e]A diagnosis before censoring; included as time-dependent variable.

pollution increases the risk of developing cardiac dysfunction in people with a vascular system that is already impaired by other conditions. For noise, neither preexisting myocardial infarction, atrial fibrillation, or baseline hypertension played a major role in the associations between noise and heart failure, which is unexpected, because noise has been associated with these diseases (van Kempen and Babisch 2012; Vienneau et al. 2015).

We found indications of a combined effect of the two exposures in the highest exposure categories. Some of the suggested biological mechanisms linking exposure to risk for cardio-vascular disease are similar for noise and air pollution, including endothelial dysfunction, increased blood pressure, and atherosclerosis (Münzel et al. 2016). Therefore, it seems plausible that high levels of exposure to noise renders the body more sensitive to the hazardous effects of air pollution and vice versa.

The strengths of the present study include the prospective design with information on various potential lifestyle and socioeconomic confounders, the large number of cases, inclusion of only the first hospitalization of heart failure, and access to residential address history, allowing us to estimate long-term exposure to air pollution and noise. Road traffic noise and air pollution were estimated using high- quality input data and state-of-the-art exposure models. Furthermore, cases with heart failure were identified using a high-quality nationwide hospital register, which has been found to have a high positive predictive value with regard to the heart failure diagnosis (81%) (Kümler et al. 2008).

A major limitation of the present study is that, although we know that urban air contains a mix of pollutants, we have information on only one air pollutant, NO_2, which is not thought to be the main causative agent in relation to cardiovascular disease. However, as indicated by a recent study, nitrogen oxide species (NO, NO_2 and NO_x) appear to be the best available proxy measures of urban-scale variability in chronic exposures to complex urban air pollution mixtures (Levy et al. 2014). Although NO_2 is a well-recognized surrogate for a mix of traffic-related air pollutants, inclusion of other pollutants, especially $PM_{2.5}$, would have been a major strength. Furthermore, estimation of air pollution and road traffic noise were based on exposure models, and although both models are state-of-the-art models, estimation of exposure is inevitably associated with some degree of uncertainty. As the exposure model does not distinguish between cases and noncases, such misclassification is likely to be nondifferential. We also lacked information on factors that influence the personal exposure to air pollution and road traffic noise, including time spent at home, information on commuting and occupational exposure, and direction of the bedroom, which may result in exposure misclassification. We would expect such misclassification to be unrelated to our outcome of interest and, therefore, draw the estimates towards the null. Last, we did not have information on exposure to air pollution or noise in the days preceding a

Table 4. Combined effects of 10-y mean road traffic noise (L_{den}) and air pollution (NO_2) in relation to risk of heart failure.

	Road traffic noise (L_{den})[a]		
NO_2[a]	≤56.0 dB	56.0-62.2 dB	>62.2 dB
≤12.7 $\mu g/m^3$ (*n*)	513	248	88
IRR (95% CI)	1.00 (ref)	1.07 (0.92, 1.25)	1.07 (0.85, 1.34)
12.7–17.7 $\mu g/m^3$ (*n*)	264	377	209
IRR (95% CI)	0.92 (0.79,1.08)	1.22 (1.06,1.39)	1.15 (0.97, 1.35)
>17.7 $\mu g/m^3$ (*n*)	73	225	553
IRR (95% CI)	1.19 (0.92,1.53)	1.27 (1.08, 1.50)	1.31 (1.15, 1.49)

Note: CI, confidence interval; IRR, incidence rate ratio; ref, reference. IRRs were adjusted for age, sex, length of school attendance, municipality SES, smoking status, duration and intensity; intake of vegetables, red meat, and alcohol; sport during leisure time and calendar year.
[a]Exposure categories in tertiles among cases.

diagnose of heart failure, which would have been a major strength, as previous studies have found short-term changes in air pollution to be associated with heart failure hospitalization (Shah et al. 2013).

Another limitation is that we identified participants with heart failure based on hospital admissions and/or outpatient visits and thus we may have overlooked participants with a milder form or less validated heart failure. Also, there might have been a higher proportion of underdiagnosis of heart failure in the beginning of the follow-up period in comparison with diagnoses in the later period, due to gradual implementation of guidelines (Kümler et al. 2008). However, associations between the two exposures and heart-failure risk varied only a little when comparing associations in the period 1997–2004 with those of the period 2005–2011, suggesting that this did not affect our results markedly, although this analysis may include selection bias as the most susceptible persons may be diagnosed during the first period (or die). Separate analyses on left- and right-ventricular heart failure would have been a major strength in the present study. However, only 10% of the cases were specified as "left-ventricular heart failure," resulting in very low power to detect associations.

Adjustment by SES and lifestyle habits resulted in a considerable decrease in risk estimates (from Model 1 to Model 2), and residual confounding may be an issue in the present study. However, in this cohort, we had detailed information for each participant on major lifestyle risk factors, for which we adjusted. This information included smoking status, alcohol consumption, and physical activity; alcohol consumption and smoking information was based on lifetime exposure with detailed information back in time. Furthermore, we evaluated effect modification by relevant comorbidities, mainly identified through a nationwide hospital registry, with high validity of most of the investigated comorbidities (except the diagnosis of asthma, which is known to be underreported). Although we had such detailed information, we cannot rule out residual confounding by unmeasured characteristics. Lastly, the study participants are not representative of the general Danish population. The response rate for the cohort was 35%, and participants were found more often to be women and have a higher SES, in comparison with nonparticipants (Tjønneland et al. 2007). Furthermore, our study is based on a selected urban cohort of elderly people, and results may, therefore, not be readily generalizable to the general population.

In conclusion, we found an association between air pollution and road traffic noise and risk of incident heart failure, which seemed strongest among persons with a vascular system that was already impaired by other conditions. Furthermore, there were indications of combined effects of noise and air pollution.

Acknowledgment

This work was supported by the European Research Council (grant 281760).

References

Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. 2013. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24(1):44–53, PMID: 23222514, https://doi.org/10.1097/EDE.0b013e318276ccb8.

Beelen R, Hoek G, Houthuijs D, van den Brandt PA, Goldbohm RA, Fischer P, et al. 2009. The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. Occup Environ Med 66(4):243–250, PMID: 19017691, https://doi.org/10.1136/oem.2008.042358.

Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, et al. 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383:785–795, PMID: 24332274, https://doi.org/10.1016/S0140-6736(13)62158-3.

Bendtsen H. 1999. The Nordic prediction method for road traffic noise. Sci Total Environ 235(1-3):331–338, https://doi.org/10.1016/S0048-9697(99)00216-8.

Berkowicz R, Ketzel M, Jensen SS, Hvidberg M, Raaschou-Nielsen O. 2008. Evaluation and application of OSPM for traffic pollution assessment for a large number of street locations. Environ Modell Softw 23(3):296–303, https://doi.org/10.1016/j.envsoft.2007.04.007.

Bornfeldt KE, Tabas I. 2011. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab 14(5):575–585, PMID: 22055501, https://doi.org/10.1016/j.cmet.2011.07.015.

Brook RD, Rajagopalan S, Pope CA, III, Brook JR, Bhatnagar A, ez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121(21):2331–2378, PMID: 20458016, https://doi.org/10.1161/CIR.0b013e3181dbece1.

Donaldson K, Tran L, Jimenez LA, Duffin R, Newby DE, Mills N, et al. 2005. Combustion-derived nanoparticles: a review of their toxicology following inhalation exposure. Part Fibre Toxicol 2:10, PMID: 16242040, https://doi.org/10.1186/1743-8977-2-10.

Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. 2010. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375:2215–2222, PMID: 20609967, https://doi.org/10.1016/S0140-6736(10)60484-9.

Eriksson C, Bluhm G, Hilding A, Ostenson CG, Pershagen G. 2010. Aircraft noise and incidence of hypertension–gender specific effects. Environ Res 110(8):764–772, PMID: 20880521, https://doi.org/10.1016/j.envres.2010.09.001.

Evrard AS, Lefevre M, Champelovier P, Lambert J, Laumon B. 2016. Does aircraft noise exposure increase the risk of hypertension in the population living near airports in France? Occup Environ Med 74(2):123–129, PMID: 27481872, https://doi.org/10.1136/oemed-2016-103648.

Heritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, et al. 2017. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. Eur J Epidemiol 32(4):307–315, PMID: 28280950, https://doi.org/10.1007/s10654-017-0234-2.

Irwin MR, Olmstead R, Carroll JE. 2015. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biol Psychiatry 80(1):40–52, PMID: 26140821, https://doi.org/10.1016/j.biopsych.2015.05.014.

Jencks SF, Williams MV, Coleman EA. 2009. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 360:1418–1428, PMID: 19339721, https://doi.org/10.1056/NEJMsa0803563.

Jensen SS, Hvidberg M, Pedersen J, Storm L, Stausgaard L, Becker T, et al. 2009a. "GIS-based national street and traffic data base 1960-2005." [In Danish with English summary]. National Environmental Research Institute, Aarhus University, Roskilde NERI Technical Report No. 678. http://www2.dmu.dk/Pub/FR678.pdf [accessed 25 August 2017].

Jensen SS, Larson T, Deepti KC, Kaufman JD. 2009b. Modeling traffic air pollution in street canyons in New York City for intra-urban exposure assessment in the US Multi-Ethnic Study of atherosclerosis and air pollution. Atmos Environ 43(30):4544–4556, https://doi.org/10.1016/j.atmosenv.2009.06.042.

Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. 2016. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet 388(10045):696–704, PMID: 27233746, https://doi.org/10.1016/S0140-6736(16)00378-0.

Ketzel M, Berkowicz R, Hvidberg M, Jensen SS, Raaschou-Nielsen O. 2011. Evaluation of AirGIS: a GIS-based air pollution and human exposure modelling system. IJEP 47(1/2/3/4):226–238, https://doi.org/10.1504/IJEP.2011.047337.

Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, et al. 2008. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail 10(7):658–660, PMID: 18539522, https://doi.org/10.1016/j.ejheart.2008.05.006.

Lange T, Dimitrov S, Born J. 2010. Effects of sleep and circadian rhythm on the human immune system. Ann N Y Acad Sci 1193:48–59, PMID: 20398008, https://doi.org/10.1111/j.1749-6632.2009.05300.x.

Leary PJ, Kaufman JD, Barr RG, Bluemke DA, Curl CL, Hough CL, et al. 2014. Traffic-related air pollution and the right ventricle. The multi-ethnic study of atherosclerosis. Am J Respir Crit Care Med 189(9):1093–1100, PMID: 24593877, https://doi.org/10.1164/rccm.201312-2298OC.

Levy I, Mihele C, Lu G, Narayan J, Brook JR. 2014. Evaluating multipollutant exposure and urban air quality: pollutant interrelationships, neighborhood variability, and nitrogen dioxide as a proxy pollutant. Environ Health Perspect 122(1):65–72, PMID: 24225648, https://doi.org/10.1289/ehp.1306518.

Lynge E, Sandegaard JL, Rebolj M. 2011. The Danish National Patient Register. Scand J Public Health 39(7 suppl):30–33, PMID: 21775347, https://doi.org/10.1177/1403494811401482.

Mathur P, Ostadal B, Romeo F, Mehta JL. 2015. Gender-related differences in atherosclerosis. Cardiovasc Drugs Ther 29(4):319–327, PMID: 26006701, https://doi.org/10.1007/s10557-015-6596-3.

McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. 2012. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 14(8):803–869, PMID: 22828712, https://doi.org/10.1093/eurjhf/hfs105.

Miedema HM, Vos H. 2007. Associations between self-reported sleep disturbance and environmental noise based on reanalyses of pooled data from 24 studies. Behav Sleep Med 5(1):1–20, PMID: 17313321, https://doi.org/10.1207/s15402010bsm0501_1.

Miller MR, Shaw CA, Langrish JP. 2012. From particles to patients: oxidative stress and the cardiovascular effects of air pollution. Future Cardiol 8(4):577–602, PMID: 22871197, https://doi.org/10.2217/fca.12.43.

Monrad M, Sajadieh A, Christensen JS, Ketzel M, Raaschou-Nielsen O, Tjonneland A, et al. 2016. Residential exposure to traffic noise and risk of incident atrial fibrillation: a cohort study. Environ Int 92-93:457–463, PMID: 27164554, https://doi.org/10.1016/j.envint.2016.04.039.

Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. 2010. Sleep loss and inflammation. Best Pract Res Clin Endocrinol Metab 24(5):775–784, PMID: 21112025, https://doi.org/10.1016/j.beem.2010.08.014.

Münzel T, Sørensen M, Gori T, Schmidt FP, Rao X, Brook FR, et al. 2016. Environmental stressors and cardio-metabolic disease: part II-mechanistic insights. Eur Heart J In press 38(8):557–564, PMID: 5381593, https://doi.org/10.1093/eurheartj/ehw294.

Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, et al. 2015. Expert position paper on air pollution and cardiovascular disease. Eur Heart J 36(2):83–93b, PMID: 25492627, https://doi.org/10.1093/eurheartj/ehu458.

Raaschou-Nielsen O, Andersen ZJ, Jensen SS, Ketzel M, Sørensen M, Hansen J, et al. 2012. Traffic air pollution and mortality from cardiovascular disease and all causes: a Danish cohort study. Environ Health 11:60, PMID: 22950554, https://doi.org/10.1186/1476-069X-11-60.

Roger VL. 2013. Epidemiology of heart failure. Circ Res 113(6):646–659, PMID: 23989710, https://doi.org/10.1161/CIRCRESAHA.113.300268.

Roswall N, Raaschou-Nielsen O, Ketzel M, Gammelmark A, Overvad K, Olsen A, et al. 2017. Long-term residential road traffic noise and NO2 exposure in relation to risk of incident myocardial infarction - a Danish cohort study. Environ Res 156:80–86, PMID: 28334645, https://doi.org/10.1016/j.envres.2017.03.019.

Schmidt F, Kolle K, Kreuder K, Schnorbus B, Wild P, Hechtner M, et al. 2015. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. Clin Res Cardiol 104(1):23–30, PMID: 25145323, https://doi.org/10.1007/s00392-014-0751-x.

Seidler A, Wagner M, Schubert M, Droge P, Romer K, Pons-Kuhnemann J, et al. 2016. Aircraft, road and railway traffic noise as risk factors for heart failure and hypertensive heart disease - a case-control study based on secondary data. Int J Hyg Environ Health 219(8):749–758, PMID: 27667192, https://doi.org/10.1016/j.ijheh.2016.09.012.

Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, et al. 2013. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 382(9897):1039–1048, PMID: 23849322, https://doi.org/10.1016/S0140-6736(13)60898-3.

Sørensen M, Hvidberg M, Hoffmann B, Andersen ZJ, Nordsborg RB, Lillelund KG, et al. 2011. Exposure to road traffic and railway noise and associations with blood pressure and self-reported hypertension: a cohort study. Environ Health 10:92, PMID: 22034939, https://doi.org/10.1186/1476-069X-10-92.

Sørensen M, Lühdorf P, Ketzel M, Andersen ZJ, Tjønneland A, Overvad K, et al. 2014. Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke? Environ Res 133:49–55, PMID: 24906068, https://doi.org/10.1016/j.envres.2014.05.011.

Tjønneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, et al. 2007. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. Scand J Public Health 35(4):432–441, PMID: 17786808, https://doi.org/10.1080/14034940601047986.

Törnqvist H, Mills NL, Gonzalez M, Miller MR, Robinson SD, Megson IL, et al. 2007. Persistent endothelial dysfunction in humans after diesel exhaust inhalation. Am J Respir Crit Care Med 176(4):395–400, PMID: 17446340, https://doi.org/10.1164/rccm.200606-872OC.

van Kempen E, Babisch W. 2012. The quantitative relationship between road traffic noise and hypertension: a meta-analysis. J Hypertens 30(6):1075–1086, PMID: 22473017, https://doi.org/10.1097/HJH.0b013e328352ac54.

Vienneau D, Schindler C, Perez L, Probst-Hensch N, Röösli M. 2015. The relationship between transportation noise exposure and ischemic heart disease: a meta-analysis. Environ Res 138:372–380, PMID: 25769126, https://doi.org/10.1016/j.envres.2015.02.023.

Wellenius GA, Boyle LD, Wilker EH, Sorond FA, Coull BA, Koutrakis P, et al. 2013. Ambient fine particulate matter alters cerebral hemodynamics in the elderly. Stroke 44(6):1532–1536, PMID: 23709640, https://doi.org/10.1161/STROKEAHA.111.000395.