Meta-Analysis

ISEE ENVIRONMENTAL EPIDEMIOLOGY

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Road traffic noise and incident ischemic heart disease, myocardial infarction, and stroke

A systematic review and meta-analysis

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Background: This systematic review aimed to estimate relative risks for incident ischemic heart disease (IHD), myocardial infarction (MI), and stroke in relation to long-term road traffic noise exposure and to evaluate exposure–response functions.

Methods: We systematically searched databases for longitudinal studies in humans on incident IHD, MI, and/or stroke, including quantitative estimates on individual exposure to residential road traffic noise based on validated models or measurements. Risk of bias was evaluated in each study based on predefined criteria. Pooled linear exposure–response functions were generated from random-effect models in meta-analyses of study-specific risk estimates. Restricted cubic spline models were used to capture potential non-linear associations.

Results: Twenty eligible studies were identified based on more than 8.4 million individuals, mostly from Europe, including between 160,000 and 240,000 cases for each of the outcomes. Pooled relative risk estimates were 1.017 (95% confidence interval [CI]: 0.990, 1.044) for IHD, 1.029 (95% CI: 1.011, 1.048) for MI, and 1.025 (95% CI: 1.009, 1.041) for stroke per 10 dB L_{den} in road traffic noise exposure. Risk estimates appeared higher in combined analyses of studies with a low risk of exposure assessment bias. Restricted cubic spline analyses of these studies showed clear risk increases with exposure for all three cardiovascular outcomes.

Conclusions: The evidence indicates that long-term exposure to road traffic noise increases the incidence of IHD, including MI, and stroke. Given the abundant exposure, traffic noise is a cardiovascular risk factor of public health importance. High-quality assessment of noise exposure appears essential for the risk estimation.

Keywords: Road traffic noise; Ischemic heart disease; Myocardial infarction; Stroke; Systematic review; Risk estimation

Introduction

Transportation noise is an increasing environmental exposure, primarily due to ongoing urbanization and the growth of the transport sector. In 2017, it was estimated that at least 20% of the population in the European Union (EU) was exposed to road traffic noise exceeding 55 dB L_{den}, which is the indicator level set by the European Environment Agency and linked to adverse health effects.[1] Corresponding exposure to railway and aircraft noise affected 4% and 0.7%, respectively.[1] Long-term exposure to environmental noise was estimated to cause 12,000 premature deaths and contribute to 48,000 new cases of ischemic heart disease (IHD) yearly in the EU.[1] In addition, 22 million people were estimated to be highly annoyed and 6.5 million highly sleep disturbed by transportation noise.[1] Most of the health impact was related to road traffic noise. The burden of disease from noise was considered the second highest in Europe, after air pollution, among evaluated environmental exposures.[2,3] In view of the growing evidence on adverse health effects, the World Health Organization (WHO) proposed stricter environmental noise guidelines in 2018.[4]

Current health risk assessments of the cardiovascular effects attributable to road traffic noise, such as those carried out by the European Environment Agency and the European Commission,[1,5] are generally based on risk estimates developed

What this study adds:
The systematic review indicates that long-term exposure to road traffic noise increases the incidence of ischemic heart disease (IHD), myocardial infarction (MI), and stroke. Risk estimates are provided for quantifying the cardiovascular health impacts of road traffic noise, valid within the exposure range of 40–80 dB L_{den}. It extends risk estimates previously provided by World Health Organization to also include MI and stroke and to levels below 53 dB L_{den}, affecting large parts of the population. High-quality assessment of noise exposure appears essential for the risk estimation, as imprecise exposure estimation may result in erroneously low risk estimates.

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The analyses were based on publicly available data in the publications specified in the reference list.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.environepidem.com).

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Environmental Epidemiology (2025) 9:e400

Received 7 February, 2025; Accepted 3 May, 2025

Published online 28 May 2025

DOI: 10.1097/EE9.0000000000000400

for the WHO Environmental Noise Guidelines.[4,6] For IHD, an excess relative risk (RR) of 8% per 10 dB L_{den} was estimated in a meta-analysis of studies published until 2015 and assumed a linear increase in risk from 53 dB L_{den}, which constituted the weighted average exposure level in the reference category of the included studies. Only European studies were available, and the evidence was not considered sufficient to propose a risk estimate for stroke.

Since the WHO Environmental Noise Guidelines, a substantial number of epidemiological studies on transportation noise and cardiovascular outcomes have been published, mostly covering IHD, including myocardial infarction (MI), and stroke. The evidence is primarily based on studies from Europe and North America and has been evaluated in several systematic reviews.[7–11] Unfortunately, many of the meta-analyses have severe limitations, which may impact the combined risk estimates, including incomplete literature search,[9,11] data extraction errors,[8,11] double counting of cohorts,[8,9,11] mixing of ecological, cross-sectional, and longitudinal designs,[7,9,11] and not separating mortality and morbidity outcomes.[8] Furthermore, most recent meta-analyses did not evaluate exposure–response functions (ERFs) in detail, although this is crucial for health risk assessments. Finally, potential confounding by air pollution exposure of the association between transportation noise and cardiovascular outcomes was evaluated in one recent systematic review, unfortunately mixing evidence from studies with longitudinal and cross-sectional design, and those based on incidence and mortality.[12]

The aim of this systematic review was to evaluate the epidemiological evidence on the association between road traffic noise and the incidence of IHD, MI, and stroke. We focused on the estimation of ERFs and evaluation of the influence of several quality features on risk estimates, including study design, exposure assessment, bias, and inclusion of air pollution adjustment.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] The review and analysis protocols were defined a priori and registered in the PROSPERO database (CRD42024563176).

Eligibility criteria

Only studies in humans were considered. Quantitative estimates on individual exposure to residential road traffic noise had to be available based on validated models or measurements. Examples of validated noise prediction methods are provided in Table 1, describing our criteria for evaluating bias. Studies solely based on subjective noise assessment were excluded. Data on incident IHD, MI, or stroke had to be available, and studies strictly based on mortality were not included. Only longitudinal studies with individual data were included, that is, cohort and case–control studies, whereas cross-sectional and ecological studies were excluded. Finally, each publication was required to include quantitative estimates on associations between road traffic noise exposure and risk of incident IHD, MI, or stroke, or detailed data making it possible to calculate such estimates.

Literature search

We performed literature searches in PubMed and Web of Science of studies published until 31 December 2023, using the search terms shown in Supplement Table 1; https://links.lww.com/EE/A350. The search results were first screened to remove duplicate references. Subsequently, title and abstract of all papers were screened independently by two authors (G.P. and G.M.A. for IHD/MI, and M.S. and T.L. for stroke) according to the eligibility criteria, and any disagreements regarding inclusion were discussed and settled. A final consensus on publications eligible for meta-analysis was reached following careful consideration by each of the two groups. We focused on studies providing original data and scanned reviews to identify studies with original data not appearing in the literature searches specified earlier.

Data extraction

Two authors performed independent extraction of data from the eligible publications according to a predefined scheme (G.P. and G.M.A. for IHD/MI, and M.S. and T.L. for stroke). Some articles overlapped since they contained information on both IHD and stroke, which meant that data from these articles were extracted independently by four authors. Furthermore, an additional extraction of relevant noise information was performed by M.Ö. for all eligible publications. Emphasis was put on the assessment of the risk of different types of bias for each study, according to criteria described later. When initial disagreements occurred in the bias assessment, consensus was reached following discussion among all five authors engaged in the data extraction.

Supplement Table 2; https://links.lww.com/EE/A350 provides an example of the type of data extracted from each publication. In some instances, crucial data were lacking in the published articles, and the authors were contacted directly to obtain supplementary information. Furthermore, efforts were made to avoid double counting, by carefully checking that each study population only appeared once (for each outcome) in the meta-analyses. If a cohort appeared in more than one publication, we included data from the one based on the longest follow-up of the cohort in our analyses.

Evaluation of bias

We assessed bias in each eligible study based on criteria described by van Kempen et al for the WHO Environmental Noise Guidelines and by the WHO Global Air Quality Guidelines Working Group on Risk of Bias Assessment,[4,6,14] but with important modifications and specifications. Our ambition was to use objective and quantifiable criteria. Four types of bias were considered: confounding, selection, exposure assessment, and outcome assessment bias. The detailed criteria for evaluation of bias in individual studies are described in Table 1. The evaluation resulted in a categorization of either high or low risk of bias for each type of bias. In addition, an assessment was made of publication bias, as described in detail later.

Statistical analysis

Different noise indicators were used in the included studies, such as L_{den}, $L_{Aeq\ 24\ h}$, and L_{night}. As a rule, the studies calculated noise exposure at the most exposed facade (the highest facade noise level) of the residential building or address. However, some studies assigned both the highest (L_{denMax}) and the lowest (L_{denMin}) facade noise level to the study participants. If results for more than one noise measure were present, we prioritized as follows:

(1) $L_{den} > L_{Aeq\ 24\ h} > L_{day} > L_{night}$
(2) L_{denMax} over L_{denMin}
(3) The longest exposure time window for which relevant risk estimates were available.

We converted the indicators for road traffic noise in all studies to L_{den} according to Brink et al.[15] These are empirically derived, based on data from Western Europe.

Odds ratios and hazard ratios were treated as estimates of RRs (rate ratios) in the meta-analyses. Risk estimates from linear models were expressed per 10 dB L_{den}. If nonlinear functions

Table 1.

Criteria for evaluating bias in studies included in the meta-analyses

Type of bias	Criteria	Risk of bias
A. Bias due to confounding	• Adjustment by a minimum set of confounders defined as: age, sex, individual SES (education and/or income and/or occupational status), and smoking. *Exception*: If empirical evidence exists for a specific study showing that after adjustment for age, sex, and individual SES, little or no residual confounding by smoking is expected then adjustment for age, sex, and individual SES is accepted as minimum set of confounders. • Lack of the above-defined minimum set of confounders.	Low High
B. Selection bias	• Loss to follow-up less than 20% in cohort studies and response rate over 80% in recruitment of study subjects in case–control studies. Also, less than 20% excluded due to missing confounder information. If information on percentage loss to follow-up is not provided, but evaluation reveals that follow-up is conducted using a high-coverage registry, then loss to follow-up is expected to be below 20%. • If the above criteria for low risk of bias are not met or if there are indications that loss to follow-up or nonresponse rates are related to both exposures and outcomes under study.	Low High
C. Bias due to exposure assessment	• All the following three criteria are met: ➢ Better than 100 m spatial resolution on receiver point position. ➢ Calculations should be based on detailed traffic flow data, preferably based on measured traffic, alternatively based on high-quality road traffic flow modeling. ➢ Calculations should be performed using validated and standardized noise prediction method, such as CoRTN (UK), TNM (USA), Cnossos-EU (EU), Nordic methods 1996 or 2000 (Nordic countries), or similar. Land use regression methods can be considered high quality if they meet criteria 1 and 2 and provide similar accuracy as standard methods in validated test cases. • If all the three criteria above are not met.	Low High
D. Bias due to outcome assessment	• Outcome identified in high-quality registries or medical records with full coverage of the study population. • Outcome solely relying on self-report.	Low High

SES indicates socioeconomic status.

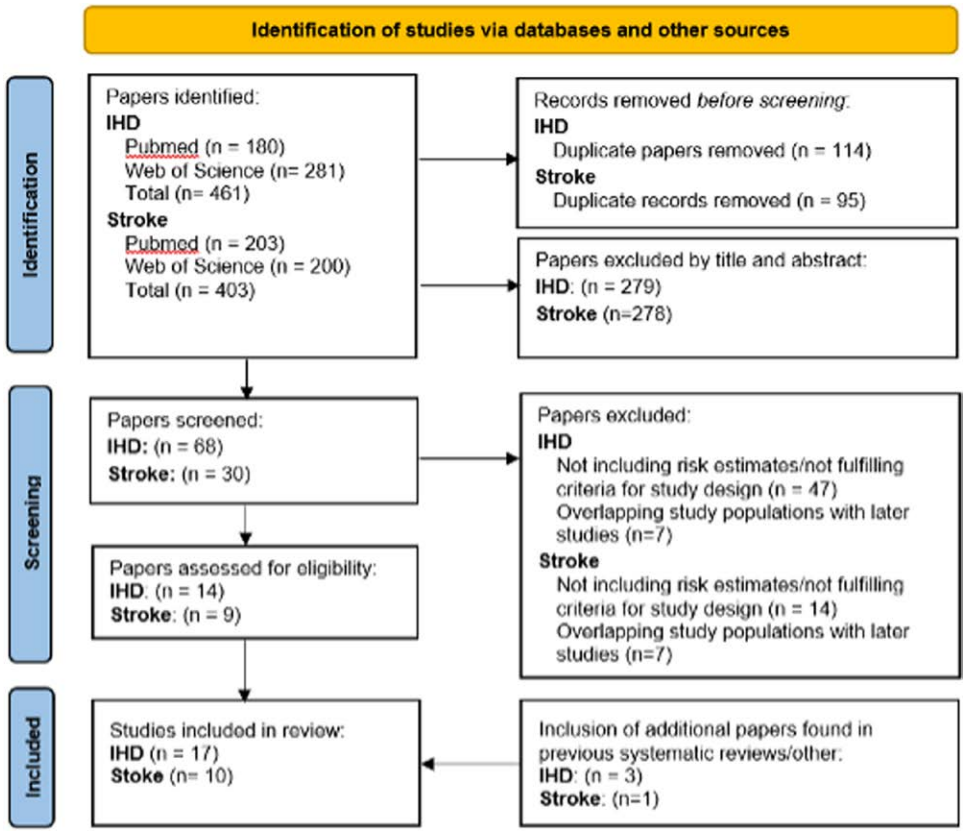

Figure 1. PRISMA 2020 flowchart of assessment of eligible studies on road traffic noise exposure and ischemic heart disease (IHD), including myocardial infarction, and stroke.

were presented, and risk estimates were not reported or available otherwise, numeric estimates were generated based on digitalization of presented illustrations and expressed per 1 dB L_{den} within the study-specific exposure range using apps.automeris.io software.[16,17] Generation of risk estimates per noise category (such as 5 dB intervals) included attribution of such estimates to a specific exposure value (e.g., middle point in each category) with subsequent linear interpolation between the estimates (more details of the procedure are provided in Supplement Table 3; https://links.lww.com/EE/A350).

Table 2.

Characteristics of studies on road traffic noise and incident ischemic heart disease and myocardial infarction

Study	Outcome	Location	Study design	Population[a]	Outcome assessment	Adjustment in selected model[b]	Noise assessment, metric, and average	Effect size
Babisch et al[14]	MI	Berlin, Germany	Case–control Questionnaire	$N_{controls}$: 3,390 N_{cases}: 645 Enrollment: unclear Age range: 31–70 years Male population	ICD9: 410. Patient records from hospital clinics	Age, social class, employment status, family status, smoking, BMI, shift work, area (inner/ suburban districts)	DIN 18005 $L_{Aeq\,6–22\,h}$ Noise distribution[c]: ≤60 dB: 83.4% 61–65 dB: 5.7% 66–70 dB: 5.5% 71–75 dB: 4.2% 76–80 dB: 1.3%	OR (95% CI): ≤60 dB: 1.0 (ref) 61–65 dB: 1.2 (0.8, 1.7) 66–70 dB: 0.9 (0.6, 1.4) 71–75 dB: 1.1 (0.7, 1.7) 76–80 dB: 1.5 (0.8, 2.8)
Babisch et al[19]	IHD	Caerphilly, Wales	Cohort Questionnaire	N: 2,512 N_{cases}: 312 Enrollment: 1979–1983 Mean age (SD): 52.1 years (4.4 years) Male population	ICD9: 410–414 Hospital and outpatient records and death certificates	Age, social class, marital status, unemployment, smoking, physical activity, BMI, prevalence of preexisting disease, family history of IHD	CoRTN $L_{Aeq\,6–22\,h}$ Noise distribution: 51–55 dB: 73.6% 56–60 dB: 8.4% 61–65 dB: 12.7% 66–70 dB: 5.3%	OR (95% CI): 51–55 dB: 1.00 (ref) 56–60 dB: 1.07 (0.68, 1.68) 61–65 dB: 0.87 (0.58, 1.30) 66–70 dB: 1.07 (0.60, 1.91)
Babisch et al[19]	IHD	Speedwell, England	Cohort Questionnaire	N: 2,348 N_{cases}: 291 Enrollment: 1979–1983 Mean age (SD): 54.2 years (4.4 years) Male population	ICD9: 410–414 Hospital and outpatient records and death certificates	Age, social class, marital status, unemployment, smoking, physical activity, BMI, prevalence of preexisting disease, family history of IHD	CoRTN $L_{Aeq\,6–22\,h}$ Noise distribution: 51–55 dB: 69.5% 56–60 dB: 11.2% 61–65 dB: 9.1% 66–70 dB: 10.2%	OR (95% CI): 51–55 dB: 1.00 (ref) 56–60 dB: 0.67 (0.42, 1.07) 61–65 dB: 0.76 (0.48, 1.22) 66–70 dB: 0.92 (0.61, 1.41)
Babisch et al[25]	MI	Berlin, Germany	Case–control Questionnaire	$N_{controls}$: 2,234 N_{cases}: 1,881 Enrollment: 1998–2001 Mean age (SD): Men: 56 years (8.5 years) Women: 58 years (8.7 years)	ICD9: 410 Hospital admission diagnosis	Age, <12 years at school, employment status, cohabitation, smoking, hypertension, diabetes, family history of MI, BMI, noise sensitivity, work noise, aircraft, and railway noise	RLS90 $L_{Aeq\,6–22\,h}$ Noise distribution: Men ≤60 dB: 73.1% 61–65 dB: 11.6% 66–70 dB: 9.8% >70 dB: 5.5% Women ≤60 dB: 71.5% 61–65 dB: 11.2% 66–70 dB: 12.3% >70 dB: 4.9%	OR (95% CI): Men ≤60 dB: 1.00 (ref) 61–65 dB: 1.01 (0.77, 1.31) 66–70 dB: 1.13 (0.86, 1.49) >70 dB: 1.27 (0.88, 1.84) Women ≤60 dB: 1.00 (ref) 61–65 dB: 1.14 (0.70, 1.85) 66–70 dB: 0.93 (0.57, 1.52) >70 dB: 0.66 (0.32, 1.35)
Bai et al[26]	MI	Toronto, Canada	Cohort Administrative	N: 1,005,214 N_{cases}: 37,441 Enrollment: 2001 Mean age (SD): 56.1 years (14.5 years)	ICD9: 410; ICD10: I21 Hospital registry	Age, sex, area-level education, employment, immigrants, and household income	TNM $L_{Aeq\,24\,h}$ Median (IQR): 54 dB (10.7 dB)	HR (95% CI): 1.07 (1.06, 1.09) per 10.7 dB
Bustaffa et al[27]	IHD	Pisa, Italy	Cohort Administrative	N: 139,710 N_{cases}: approximately 3,700[d] Enrollment: 2001–2013 Age: 0–44 years: 50.3%, ≥45 years: 49.7%	ICD9: 410–414 Hospital registry	Age, area-level socioeconomic deprivation index, NO_2	Not reported $L_{Aeq\,1\,day}$ Median (IQR): 56.7 (9.6) dB	HR (95% CI): 0.999 (0.994, 1.003) per 1 dB

(*Continued*)

Table 2.
(*Continued*)

Study	Outcome	Location	Study design	Population[a]	Outcome assessment	Adjustment in selected model[b]	Noise assessment, metric, and average	Effect size
Bustaffa et al[27]	MI	Pisa, Italy	Cohort Administrative	N: 139,710 N_{cases}: approximately 1,900[c] Enrollment: 2001–2013 Age: 0–44 years: 50.3%, ≥45 years: 49.7%	ICD9: 410 Hospital registry	Age, area-level socioeconomic deprivation index, NO_2	Not reported $L_{Aeq,day}$ Median (IQR): 56.7 (9.6) dB	HR (95% CI): 1.002 (0.995, 1.008) per 1 dB
Cai et al[20]	IHD	Nord-Trøndelag, Norway	Cohort Questionnaire	N: 43,267 N_{cases}: 2,764 Enrollment: 1995–1997 Mean age (SD): 45.7 years (15.3 years)	ICD9: 410–414; ICD10: I20–I25 Hospital and mortality registries	Age, sex, education, employment, smoking status	Cnossos-EU L_{den} Mean (SD): 49.2 (4.3) dB	HR (95% CI): 1.011 (0.961, 1.065) per IQR (6 dB)
Cai et al[20]	IHD	UK	Cohort Questionnaire	N: 23,909 N_{cases}: 307 Enrollment: 1993–1999 Mean age (SD): 40.2 years (12.1 years)	ICD9: 410–414; ICD10: I20–I25 Hospital and mortality registries	Age, sex, education, employment, smoking status	Cnossos-EU L_{den} Mean (SD): 56.3 (4.3) dB	HR (95% CI): 1.013 (0.919, 1.116) per IQR (3.6 dB)
Carey et al[28]	MI	Greater London, UK	Cohort Administrative	N: 207,042 N_{cases}: 2,582 Enrollment: 2005 Mean age (min, max): 55.4 years (40 years, 79 years)	ICD10: I20–I23 GP records and hospital registry	Age, sex, smoking status, BMI	CoRTN/TRANEX $L_{Aeq,16}$ Mean (SD) given for Lnight: 52.1 (4.6) dB	HR (95% CI): 1.01 (0.92, 1.10) per 10 dB $L_{Aeq,16}$[e]
Dimakopoulou et al[29]	MI	Around Athens airport, Greece	Cohort Questionnaire	N: 420 N_{cases}: 18 Enrollment: 2004–2006 Mean age (SD): 58 years (9.1 years)	Self-reported.	Age, sex, education, smoking status, physical activity, alcohol, salt use, BMI.	Not reported $L_{Aeq,24\,h}$ Mean (SD): 38.7 (12.6) dB	OR (95% CI): 0.96 (0.60, 1.53) per 10 dB
Hao et al[9]	IHD	Across UK	Cohort Questionnaire	N: 342,566 N_{cases}: 22,722 Enrollment: 2006–2010 Mean age (SD): Men: 56.2 years (8.2 years) Women: 55.8 years (8.0 years)	ICD10: I21–I25 Hospital registry	Age, sex, education, ethnicity, smoking, alcohol, physical activity, fruit and vegetable intake, sleep duration, family history of CVD, hypertension, diabetes, and high cholesterol	Cnossos-EU $L_{Aeq,24\,h}$ Mean (IQR): 54.9 (3.5) dB	HR (95% CI): 1.00 (0.97, 1.03) per 10 dB
Hao et al[9]	MI	Across UK	Cohort Questionnaire	N: 342,566 N_{cases}: 6,537 Enrollment: 2006–2010 Mean age (SD): Men: 56.2 years (8.2 years) Women: 55.8 years (8.0 years)	Unclear which ICD10 codes were used Hospital registry	Age, sex, education, ethnicity, smoking, alcohol, physical activity, fruit and vegetable intake, sleep duration, family history of CVD, hypertension, diabetes, and high cholesterol	Cnossos-EU $L_{Aeq,24\,h}$ Mean (IQR): 54.9 (3.5) dB	HR (95% CI): 0.99 (0.94, 1.05) per 10 dB
Hoffmann et al[30]	Coronary events	Ruhr area, Germany	Cohort Questionnaire	N: 4,350 N_{cases}: 135 Enrollment: 2000–2003 Mean age (SD): 59.3 years (7.8 years)	ICD10: I20.0, I21, I23, I24 (disease); ICD10: I20–I25 (death) Medical records, death certificates	Age, sex, recruitment year, education, marital status, employment, area-level unemployment, smoking status, duration, and intensity	Cnossos-EU Lnight Mean (SD): 45.3 (8.6) dB	HR (95% CI): 1.40 (0.79, 2.49) per 26 dB

(*Continued*)

Table 2.
(*Continued*)

Study	Outcome	Location	Study design	Population[a]	Outcome assessment	Adjustment in selected model[b]	Noise assessment, metric, and average	Effect size
Lekavičiūtė[31]	MI	Kaunas, Lithuania	Case–control Questionnaire	$N_{controls}$: 1,099 N_{cases}: 496 Enrollment: 1999–2005 Age range: 25–64 years Male population	ICD10: I21 Hospital registry	Smoking, blood pressure, BMI, psychological (stress) status, current address for >10 years, noise annoyance at home	IDW interpolation $L_{Aeq,24\ h}$ Mean (SD): 71.4 (6.0) dB in 2001–2002 in 10 districts in Kaunas	OR (95% CI): <60 dB: 1.00 (ref) 60–65 dB: 0.71 (0.53, 0.96) >65 dB: 1.29 (0.55, 3.04)
Magnoni et al[32]	MI	Milan, Italy	Cohort Administrative	N: 1,087,110 N_{cases}: 13,201 Enrollment: 2011–2018 Mean age (SD): 54 years (17 years)	ICD9: 410 Hospital registry	Age, sex, citizenship, area-level deprivation index	NMPB L_{den} Median: ~68 dB[c]	HR (95% CI): <65 dB: 1.00 (ref) 65–69 dB: 0.994 (0.951, 1.040) 70–74 dB: 1.005 (0.958, 1.053) ≥75 dB: 0.999 (0.951, 1.050)
Pyko et al[23,f]	IHD	Across Denmark, Stockholm, Malmö, Gothenburg, Sweden	Pooled cohort Questionnaire	N: 132,801 N_{cases}: 22,459 Enrollment: 1970–2004 Median age (P5–P95): 55.4 years (45.7 years–69.7 years)	ICD8, ICD9: 410–414 ICD10: I20–I25 Hospital and mortality registries	Age, sex, education, marital status, area-level income, smoking, physical activity, cohort, railway and aircraft noise	Nordic 1996 L_{den} Median (P5–P95): 54.5 (40.0–68.1) dB	HR (95% CI): 1.02 (0.99, 1.04) per 10 dB Recalculated HR (95% CI)[f]: 1.003 (0.978, 1.029) per 10 dB
Pyko et al[23,f]	MI	Across Denmark, Stockholm, Malmö, Gothenburg, Sweden	Pooled cohort Questionnaire	N: 132,801 N_{cases}: 7,682 Enrollment: 1970–2004 Median age (P5–P95): 55.4 years (45.7 years–69.7 years)	ICD8, ICD9: 410 ICD10: I21–I23 Hospital and mortality registries	Age, sex, education, marital status, area-level income, smoking, physical activity, cohort, railway and aircraft noise	Nordic 1996 L_{den} Median (P5–P95): 54.5 (40.0–68.1) dB	HR (95% CI): (0.97, 1.04) per 10 dB Recalculated HR (95% CI)[f]: 1.010 (0.972, 1.049) per 10 dB
Seidler et al[33]	MI	Around Frankfurt airport, Germany	Case–control Administrative	N: 834,734 N_{cases}: 19,632 Enrollment: 2006–2010 Median age (P25–P75) controls: 60 years (48–72 years)	ICD10: I21 Hospital diagnoses from health insurance registries	Age, sex, area-level SES	VBUS $L_{Aeq,24\ h}$ Median: ~49 dB[c,d]	OR (95% CI): 1.028 (1.012, 1.045) per 10 dB
Selander et al[34]	MI	Stockholm County, Sweden	Case–control Questionnaire	$N_{controls}$: 2,095 N_{cases}: 1,571 Enrollment: 1992–1994 Age: 45–60 years: 41%, 61–70 years: 59%[c]	ICD9: 410 Hospital clinics, and hospital and mortality registries	Age, sex, area, smoking, physical inactivity, diabetes	Nordic 1996 $L_{Aeq,24\ h}$[c]: <50 dB: 66.7% 50–54 dB: 18.7% 55–59 dB: 10.4% ≥60 dB: 4.1%	OR (95% CI): 1.06 (0.95, 1.16) per 5 dB
Thacher et al[21]	IHD	All of Denmark	Cohort Administrative	N: 2,538,395 N_{cases}: 122,523 Enrollment: 2005 Mean age (SD): 59 years (10 years)	ICD8: 410–414, 427.5 ICD10: I20–I25, I46 Hospital and mortality registries	Age, sex, education, income, civil status, occupation, country of origin, area-level SES (low income, low education, manual labor, unemployment, single parent)	Nordic 1996 L_{den} Mean (SD): 55.0 (8.1) dB[f]	HR (95% CI): 1.052 (1.044, 1.059) per 10 dB
Thacher et al[21]	MI	All of Denmark	Cohort Administrative	N: 2,538,395 N_{cases}: 76,825 Enrollment: 2005 Mean age (SD): 59 years (10 years)[e]	ICD8: 410 ICD10: I21 Hospital and mortality registries	Age, sex, education, income, civil status, occupation, country of origin, area-level SES (low income, low education, manual labor, unemployment, single parent)	Nordic 1996 L_{den} Mean (SD): 55.0 (8.1) dB[e]	HR (95% CI): 1.041 (1.032, 1.051) per 10 dB

(*Continued*)

Table 2.
(Continued)

Study	Outcome	Location	Study design	Population[a]	Outcome assessment	Adjustment in selected model[b]	Noise assessment, metric, and average	Effect size
Yankoty et al[35]	MI	Island of Montreal, Canada	Cohort Administrative	N: 1,065,414 N_{cases}: 40,718 Enrollment: 2000 Age: 45–64 years: 64.1%, ≥65 years: 35.9%	ICD9: 410; ICD10: I21–I22 Health insurance, medical services, hospital, death, pharmaceutical registers	Age, sex, area-level SES (education, income, employment)	Not reported $L_{Aeq,24\,h}$ Mean: 54.5 dB	HR (95% CI): 1.01 (1.00, 1.02) per 10 dB

[a]Unless otherwise specified the population consists of both men and women.
[b]Criteria for selecting the main adjustment model: (1) most comprehensive adjustment model for SES and lifestyle though, if possible, not including BMI, and (2) no adjustment for air pollution (in Bustaffa et al[27] risk estimates without adjustment for NO_2 were not provided).
[c]The distribution refers to the distribution among controls.
[d]Exact number not given. The number, therefore, represents the authors estimation based on available information in the paper.
[e]Results provided after contacting the main authors, as the results needed for the present review were not provided in the original paper.
[f]For the Pyko et al,[23] we have recalculated HRs and CIs after excluding all cases diagnosed after 2000 for the two Danish cohorts (Diet Cancer and Health cohort and Danish Nurses Cohort) to avoid overlap with Thacher et al.[21] The recalculated HRs were based on 11,089 and 5017 cases of IHD and MI, respectively.
BMI indicates body mass index; CVD, cardiovascular disease; HR, hazard ratio; IDW, inverse distance weighting; IQR, interquartile range; OR, odds ratio; P5–P95, 5th–95th percentiles; P25–P75, 25th–75th percentiles; ref, reference; SD, standard deviation; SES, socioeconomic status.

We initially generated a pooled linear ERF by conducting a meta-analysis of risk estimates from linear models. This analysis utilized a random effects model to derive pooled RRs, accompanied by I^2 and Q statistics for evaluating study heterogeneity.[18] Pooled nonlinear ERFs were produced employing the dosresmeta package in R. Two estimation methods, Maximum Likelihood (ML) and restricted ML, were used to evaluate model fit and variance components. The analysis utilized a restricted cubic spline model with three or four knots to capture potential nonlinear associations. Models with three knots provided a better fit and were used in the analyses. The model selection was performed using ML based on Akaike information criterion, with subsequent re-estimation using restricted ML to obtain unbiased variance estimates. The Wald test was applied to assess the deviation from linearity of the spline model, allowing comparison between linear and nonlinear model fits.

Additional analyses were conducted by selectively including or excluding studies based on risk of bias or other predefined criteria. Furthermore, assessment of publication bias was performed using funnel plots, Egger test, and the Trim-and-Fill method.

Results

From the literature search, we identified a total of 461 and 403 publications for IHD/MI and stroke, respectively (Figure 1). Following exclusions according to the eligibility criteria, only 17 publications for IHD/MI and 10 for stroke remained for meta-analyses and quality assessment. Seven of these publications included data on both IHD/MI and stroke. The publication by Babisch et al[19] included two cohorts from different geographical areas, for which the results were reported separately, and we kept these apart in the analysis. In view of differences in the classification of bias, two cohorts in the pooled analysis of Cai et al[20] were analyzed separately (EPIC-Oxford and HUNT2). We used the study by Hao et al[9] instead of the third cohort (UK-Biobank) in Cai et al,[20] because it was based on a longer follow-up. All in all, the publications were based on 28 different study populations.

One publication on IHD/MI[21] and one on stroke[22] covered the entire Danish population, which implied some overlap with the two Danish cohorts included in both Pyko et al[23] and Roswall et al,[24] respectively. In all meta-analyses, we therefore used reanalyzed data for Pyko et al[23] and Roswall et al,[24] excluding the overlapping population in the two Danish cohorts. The studies by Pyko et al[23] and Roswall et al[24] were based on pooled analyses of nine Scandinavian cohorts, for which data on road traffic noise and IHD, MI, and/or stroke were published earlier for some of the cohorts. However, as the populations in Pyko et al[23] and Roswall et al[24] had longer follow-up times than in previous studies, results from these two studies were used in our analyses.

The 19 studies on IHD and/or MI included 14 with cohort and five with case–control design (Table 2). The total study population comprised more than 7.3 million individuals, including 163,843 and 208,464 cases of IHD and MI, respectively. Seventeen of the studies were based in Europe and two in Canada; 12 included information on lifestyle and other individual characteristics from questionnaires, while seven were strictly based on registry data. Eight studies reported data on IHD and 14 on MI. The study by Hoffmann et al[30] used coronary events as outcome and was included in the IHD category because of the similarities in International Classification of Diseases (ICD) codes. The study by Babisch et al[25] only reported separate risk estimates for men and women, and these were used in the meta-analysis.

Table 3 summarizes the characteristics of the 11 studies on road traffic noise and stroke. Ten were cohorts and one

Table 3.

Characteristics of studies on road traffic noise and incident stroke

Study	Outcome	Location	Study design[a]	Population	Outcome assessment	Adjustment in selected model[b]	Noise assessment, metric, and average	Effect size
Bustaffa et al[27]	Stroke	Pisa, Italy	Cohort Administrative	N: 139,710 N_{cases}: approximately 2,450[c] Enrollment: 2001–2013 Age: 0–44 years: 50.3%, ≥45 years: 49.7%	ICD9: 434, 435, 437, 446 Hospital registry	Age, area-level socioeconomic deprivation index, NO_2	Not reported $L_{Aeq,day}$ Median (IQR): 56.7 (9.6) dB	HR (95% CI): 0.999 (0.994, 1.004) per 1 dB
Cai et al[20]	Cerebrovascular disease	Nord-Trøndelag, Norway	Cohort Questionnaire	N: 43,267 N_{cases}: 1,559 Enrollment: 1995–1997 Mean age (SD): 45.7 years (15.3 years)	ICD9: 430–438, ICD10: I60–I69 Hospital and mortality registries	Age, sex, education, employment, smoking status	Cnossos-EU L_{den} Mean (SD): 49.2 (4.3)	HR (95% CI): 0.952 (0.890, 1.019) per IQR (6 dB)
Cai et al[20]	Cerebrovascular disease	UK	Cohort Questionnaire	N: 23,909 N_{cases}: 169 Enrollment: 1993–1999 Mean age (SD): 40.2 years (12.1 years)	ICD9: 430–438, ICD10: I60–I69 Hospital and mortality registries	Age, sex, education, employment, smoking status	Cnossos-EU L_{den} Mean (SD): 56.3 (4.3) dB	HR (95% CI): 0.976 (0.853, 1.118) per IQR (3.6 dB)
Carey et al[28]	Stroke	Greater London, UK	Cohort Administrative	N: 207,047 N_{cases}: 3,716 Enrollment: 2005 Mean age (min, max): 55.4 years (40 years, 79 years)	ICD10: I61, I63–I64 GP records and hospital registry	Age, sex, smoking status, BMI	CoRTN/ TRANEX $L_{Aeq,16}$ Mean (SD) only given for Lnight: 52.1 (4.6) dB	HR (95% CI): 0.96 (0.88, 1.04) per 10 dB $L_{Aeq,16}$[d]
Dimakopoulou et al[29]	Stroke	Around Athens airport, Greece	Cohort Questionnaire	N: 420 N_{cases}: 5 Enrollment: 2004–2006 Mean age (SD): 58 years (9.1 years)	Self-reported	Age, sex, education, smoking status, physical activity, alcohol, salt use, BMI	Not reported $L_{Aeq,24\ h}$ Mean (SD): 38.7 (12.6) dB	OR (95% CI): 1.33 (0.59, 3.03) per 10 dB
Hao et al[9]	Stroke	Across UK	Cohort Questionnaire	N: 342,566 N_{cases}: 6,319 Enrollment: 2006–2010 Mean age (SD): Men: 56.2 years (8.2 years) Women: 55.8 years (8.0 years)	ICD10: I60–I64 Hospital registry	Age, sex, education, ethnicity, smoking, alcohol, physical activity, fruit and vegetable intake, sleep duration, family history of CVD, hypertension, diabetes, and high cholesterol	Cnossos-EU $L_{Aeq,24\ h}$ Mean (IQR): 54.9 (3.5) dB	HR (95% CI): 1.05 (0.99, 1.11) per 10 dB
Hoffmann et al[30]	Stroke	Ruhr area, Germany	Cohort Questionnaire	N: 4,350 N_{cases}: 71 Enrollment: 2000–2003 Mean age (SD): 59.3 years (7.8 years)	ICD10: I61, I63–I64 (disease); ICD10: I61–I64 (death) Medical records, death certificates	Age, sex, recruitment year, education, marital status, employment, area-level unemployment, smoking status, duration, and intensity	Cnossos-EU Lnight Mean (SD): 45.3 (8.6) dB	HR (95% CI): 1.01 (0.45, 2.24) per 26 dB
Magnoni et al[32]	Ischemic stroke	Milan, Italy	Cohort Administrative	N: 1,087,110 N_{cases}: 10,419 Enrollment: 2011–2018 Mean age (SD): 54 years (17 years)	ICD9: 433.x1, 434.x1, 436 Hospital registry	Age, sex, citizenship, area-level deprivation index	NMPB L_{den} Median: ~68 dB[c]	HR (95% CI): <65 dB: 1.00 (ref) 65–69 dB: 0.995 (0.946, 1.047) 70–74 dB: 1.048 (0.994, 1.105) ≥75 dB: 1.032 (0.976, 1.091)

(*Continued*)

Table 3.
(*Continued*)

Study	Outcome	Location	Study design[a]	Population	Outcome assessment	Adjustment in selected model[b]	Noise assessment, metric, and average	Effect size
Roswall et al[24,e]	Stroke	Across Denmark, Stockholm, Malmö, Gothenburg, Sweden	Pooled cohort Questionnaire	N: 135,951 N_{cases}: 11,056 Enrollment: 1970–2004 Median age (P5–P95): 55.6 years (45.7 years–70.3 years)	ICD8, ICD9: 431–434, 436 ICD10: I61–I64 Hospital and mortality registries	Age, sex, year, education, cohabiting status, area-level income, smoking status, physical activity, BMI, railway and aircraft noise, cohort	Nordic 1996 L_{den} Median (P5–P95): 54.5 (40.0–68.1) dB	HR (95% CI): 1.05 (1.02–1.07) per 10 dB Recalculated HR (95% CI)[e]: 1.042 (1.005, 1.081) per 10 dB
Seidler et al[36]	Stroke	Around Frankfurt airport, Germany	Case–control Administrative	$N_{controls}$: 827,601 N_{cases}: 25,495 Enrollment: 2006–2010 Age: 35–60 years: 49.2%, >60 years: 50.8%	ICD10: I61, I63, I64 Hospital diagnoses from health insurance registries	Age, sex, area-level unemployment	VBUS $L_{Aeq,24\ h}$ Median: ~49 dB[c]	OR (95% CI): 1.017 (1.003, 1.032) per 10 dB
Sørensen et al[22]	Stroke	All of Denmark	Cohort Administrative	N: 3,616,893 N_{cases}: 184,524 Enrollment: 2000 Median (P5–P95): 47 years (35 years–80 years)[d]	ICD8: 431–434, 436; ICD10: I61–I64 Hospital and mortality registries	Age, sex, year, education, income, civil status, employment status, country of origin, area-level SES (low income, low education, manual labor, unemployment, single parent and criminal record, railway noise)	Nordic1996 L_{den} Mean (SD): 56.2 (7.9) dB[d]	HR (95% CI): 1.039 (1.033, 1.046) per 10 dB

[a]All stroke studies were based on populations consisting of both men and women.
[b]Criteria for selecting the main adjustment model: (1) most comprehensive adjustment model for SES and lifestyle though, if possible, not including BMI, and (2) no adjustment for air pollution (in Bustaffa et al[27] risk estimates without adjustment for NO_2 were not provided).
[c]Exact number not given. The number therefore represents the authors estimation based on available information in the paper.
[d]Results provided after contacting the main authors, as the results needed were not provided in the original paper.
[e]For the Roswall et al study, we have recalculated HR and CI after excluding all cases diagnosed after 2000 for the two Danish cohorts (Diet Cancer and Health cohort and Danish Nurses Cohort) to avoid overlap with Sørensen et al.[22] The recalculated HR was based on 5408 stroke cases in total.
BMI indicates body mass index; CVD, cardiovascular disease; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; P5–P95, 5th–95th percentiles; ref, reference; SD, standard deviation; SES, socioeconomic status.

Table 4.
Risk of bias in studies included in the IHD, MI, and stroke meta-analyses

		Risk of bias[a]			
		A	B	C	D
Study	Disease	Confounding	Selection	Exposure	Outcome
Babisch et al[14]	MI	Low	High	High	Low
Babisch et al, Caerphilly[19]	IHD	Low	Low	Low	Low
Babisch et al, Speedwell[19]	IHD	Low	Low	Low	Low
Babisch et al[25]	MI	Low	Low	High	Low
Bai et al[26]	MI	High	Low	High	Low
Bustaffa et al[27]	IHD, MI, stroke	High	Low	High	Low
Cai et al, EPIC-OXFORD[20]	IHD, cerebrovascular disease	Low	High	High	Low
Cai et al, HUNT2[20]	IHD, cerebrovascular disease	Low	Low	High	Low
Carey et al[28]	MI, stroke	High	Low	High	Low
Dimakopoulou et al[29]	MI, stroke	Low	High	High	High
Hao et al[9]	IHD, MI, stroke	Low	Low	High	Low
Hoffmann et al[30]	Cardiac events, stroke	Low	Low	High	Low
Lekavičiūtė[31]	MI	Low	High	High	High
Magnoni et al[32]	MI, ischemic stroke	High	Low	High	Low
Pyko et al[23]	IHD, MI	Low	Low	Low	Low
Roswall et al[24]	Stroke	Low	Low	Low	Low
Seidler et al[33]	MI	High	Low	Low	Low
Seidler et al[36]	Stroke	High	Low	Low	Low
Selander et al[34]	MI	Low	High	Low	Low
Sørensen et al[22]	Stroke	Low	Low	Low	Low
Thacher et al[21]	IHD, MI	Low	Low	Low	Low
Yankoty et al[35]	MI	High	Low	High	Low

[a]See Table 1 for a comprehensive description of the criteria used when assessing risk of bias.

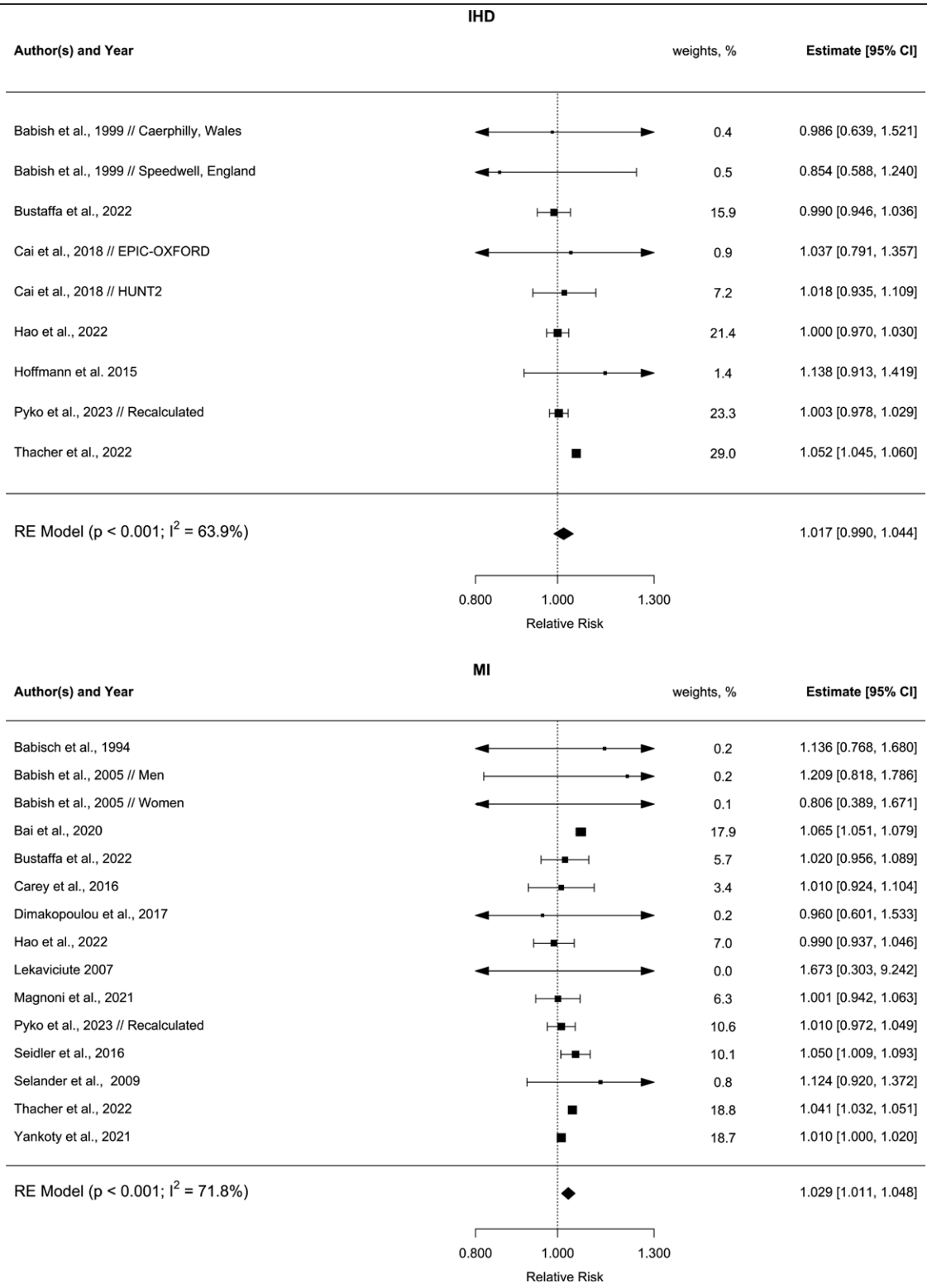

Figure 2. Individual study and combined relative risks calculated in meta-analyses of ischemic heart disease (IHD), myocardial infarction (MI), and stroke per 10 dB higher (L_{den}) road traffic noise exposure.

a case–control study. In total, 240,135 stroke cases were included in our analyses from a study population of about 6.3 million individuals. All studies originated from Europe and seven included questionnaire data on covariates, while four were only based on registry data. The studies focusing on cerebrovascular disease[20] (two cohorts) and ischemic stroke[32] were analyzed together with the studies using stroke as outcome.

Our evaluation of potential bias in the 22 studies included in the meta-analyses is shown in Table 4. Most studies were considered to have a high risk of at least one type of bias. The most common type was exposure assessment bias, where we considered that 13 studies had a high risk of bias. Supplement Table 4; https://links.lww.com/EE/A350 provides a detailed description of the basis for the classification of exposure assessment bias in each study. Furthermore, seven studies were classified as having

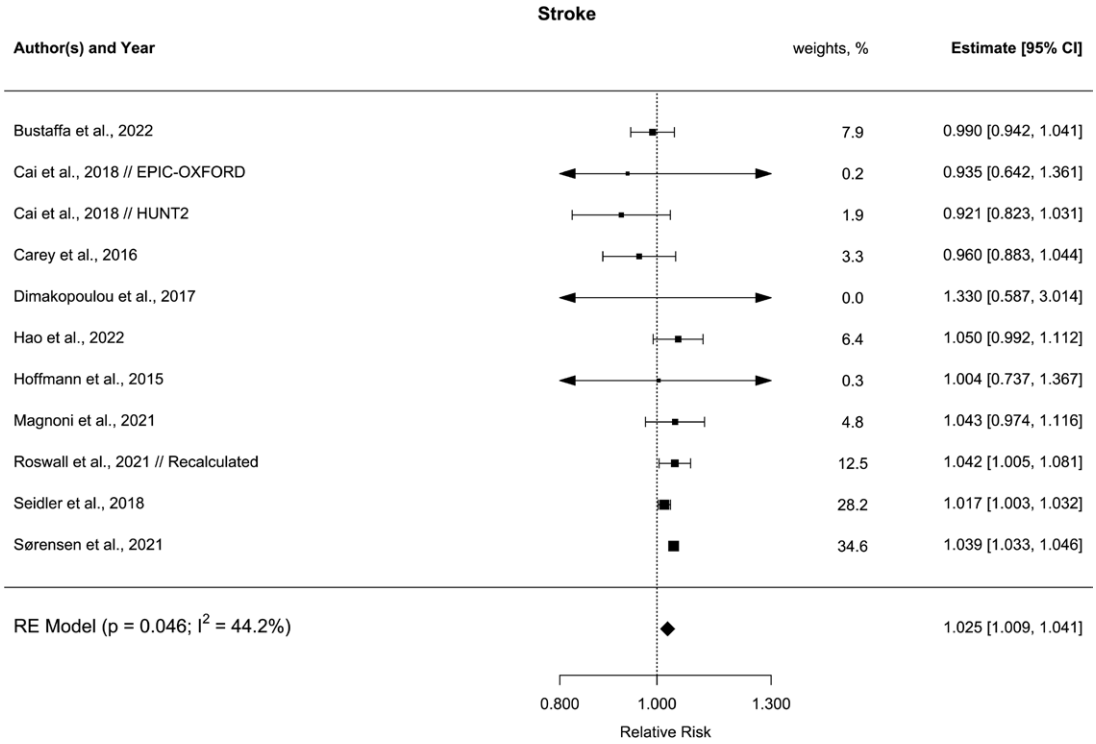

Figure 2. Continued

a high risk of confounding, five of selection bias, and two of outcome assessment bias. Only five studies were considered to have a low risk of all four types of bias.

Results of the meta-analyses assuming a linear exposure–response trend for road traffic noise and each of the health outcomes are provided in Figure 2. The combined RR estimates were 1.017 (95% confidence interval [CI]: 0.990, 1.044) for IHD, 1.029 (95% CI: 1.011, 1.048) for MI, and 1.025 (95% CI: 1.009, 1.041) for stroke, per 10 dB L_{den}, with substantial heterogeneity in estimates between studies, particularly for IHD and MI (I^2 >50%, *P* value of chi-squared test <0.001). Strictly registry-based studies were most influential for the risk estimates because of their larger size.

Positive trends in RRs with noise exposure were suggested for the three cardiovascular outcomes in the restricted cubic spline models, especially at the highest exposures (Figure 3). However, risk estimates were uncertain at the highest noise levels because of lower numbers of exposed, and there was no statistically significant departure from a linear model for any of the outcomes.

Risk estimates for IHD, MI, and stroke (per 10 dB L_{den} higher road traffic noise exposure) in relation to study type, adjustment for air pollution, and risk of bias are shown in Figure 4 and Supplement Table 5; https://links.lww.com/EE/A350. No consistent pattern of change in risk estimates appeared for type of study (questionnaire/strictly registry-based) or with adjustment for NO_2. However, adjustment for $PM_{2.5}$ seemed to lower the risk estimates, particularly for IHD. Consistency of the evidence across cardiovascular outcomes according to cohort or case–control design could not be evaluated because of too few case–control studies. There seemed to be an influence of exposure assessment bias. Studies considered to have a low risk of exposure bias showed risk estimates of 1.026 (95% CI: 0.980, 1.074), 1.040 (95% CI: 1.031, 1.049), and 1.031 (95% CI: 1.014, 1.048) per 10 dB L_{den} for IHD, MI, and stroke, respectively. Overall, the lower heterogeneity of the risk estimates for stroke than for IHD or MI was confirmed in most of the subgroup analyses.

Restricting the cubic spline analyses to studies with low risk of exposure assessment bias indicated clearer risk increases for all three cardiovascular outcomes compared with results of corresponding analyses based on all studies (Figure 5). Furthermore, the ERFs for IHD and MI significantly deviated from a linear model, which was not the case for stroke.

There was little support for publication bias regarding each of the three health outcomes, as suggested by low asymmetry in the Funnel plots (Supplement Figure 1; https://links.lww.com/EE/A350). This was confirmed by the Egger test *P* values, which were 0.68 for IHD, 0.98 for MI, and 0.25 for stroke. The Trim-and-Fill method estimated one missing study each for IHD and MI, and two missing studies for stroke.

Discussion

Our systematic review identified a total of 20 eligible publications on road traffic noise and IHD, MI, and/or stroke, which were based on 28 different study populations, primarily from Europe. Most studies were considered to have a high risk of bias, especially related to the exposure assessment. The meta-analyses revealed increasing risks with long-term exposure to road traffic noise for all three health outcomes, particularly when studies with a high risk of exposure assessment bias were excluded.

In 2018, WHO concluded that there was high-quality epidemiological evidence supporting an association between exposure to road traffic noise and IHD (no separate assessment was made for MI), while the corresponding evidence for stroke was considered as being of moderate quality.[4] Our review shows that substantial new evidence on road traffic noise and IHD, MI, and stroke has appeared since the WHO review. The meta-analyses assuming a linear exposure–response trend showed excess RRs of 1.7, 2.9, and 2.5% per 10 dB L_{den} in long-term road traffic noise exposure for IHD, MI, and stroke, respectively. These estimates are in general agreement with those reported in recent systematic reviews,[7,11] suggesting similar excess risks in incidence related to road traffic noise exposure for the three cardiovascular outcomes.

Our risk estimates, as well as those in other recent reviews,[7,11] appeared lower than the risk estimate of 1.08 (95% CI: 1.01,

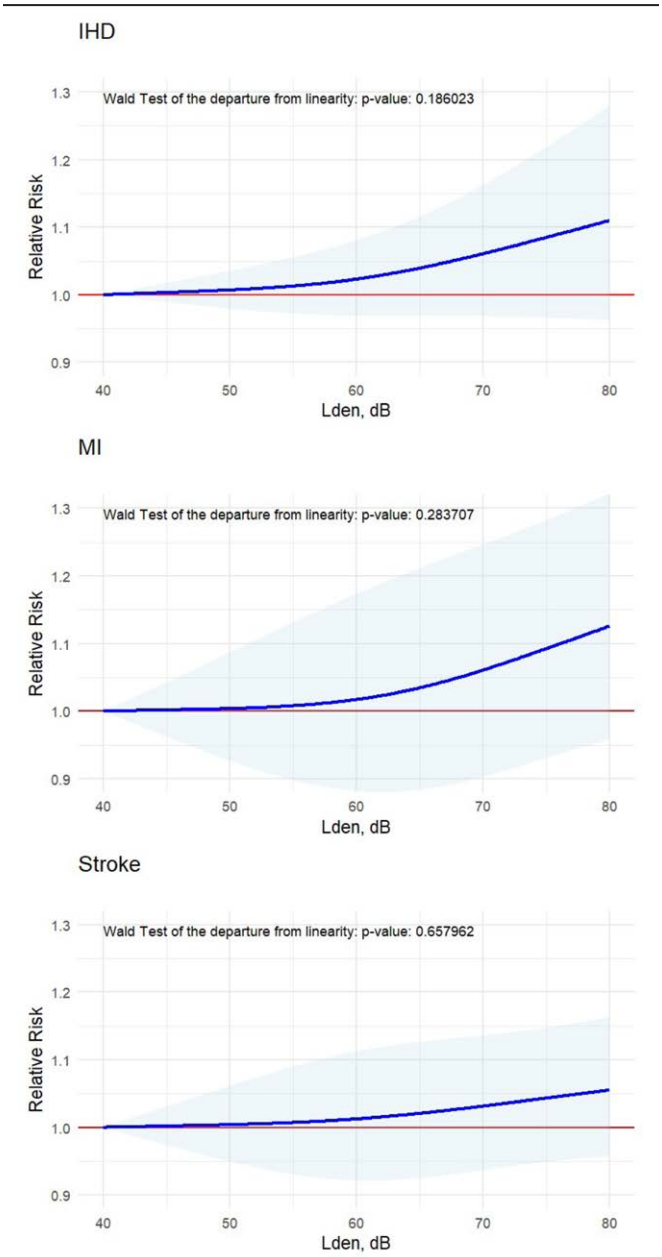

Figure 3. Exposure–response functions expressed as relative risks with 95% confidence intervals for ischemic heart disease (IHD), myocardial infarction (MI), and stroke in relation to exposure to road traffic noise in combined analyses of the epidemiological studies.

1.15) per 10 dB L_{den} reported by WHO for IHD, including MI, which was calculated for exposures of 53 dB L_{den} and above.[4] The reasons behind the discrepancy are unclear. One contributing explanation may be an influence by exposure assessment bias. In our evaluation, only 33% of the studies included in the WHO review were classified as having a high risk of exposure assessment bias, compared with 79% of the newer studies included in our meta-analyses, which may have led to more attenuation of the risk estimates in recent studies. However, when restricting our analyses to studies with low risk of exposure assessment bias, our risk estimates seemed lower than those calculated by WHO. Heterogeneity in the risk estimates between studies, particularly for IHD and MI, also complicates the interpretation.

Earlier reviews on transportation noise and cardiovascular disease, including the one conducted by WHO,[4] have often lumped together IHD and MI. However, noise-related risks may differ between different subgroups of IHD.[23,21] MI generally constitutes a minority of the cases of IHD, as evident from the studies in our review, and angina pectoris cases often make up a larger group. However, the distribution of subtypes depends on the source of diagnostic information, age group, sex distribution, etc.[37] An advantage with MI is that the diagnostic validity is higher than for other IHD subgroups, and angina pectoris is less well captured in national registries compared with other IHD diagnoses.[38] However, we did not find substantial differences in the risk estimates related to noise exposure for IHD and MI, which suggests that these may be grouped together in the risk assessment.

Our evaluation showed that most studies on road traffic noise and IHD, MI, and/or stroke had a high risk of at least one type of bias. The most common type was bias in the exposure assessment, primarily expected to lead to imprecision of the exposure estimates. Coarse geographical resolution was a major contributor to our assessment of high risk of bias in the exposure assessment. This can lead to substantial errors in the assessment of transportation noise exposure and result in marked attenuation of risk estimates, for example, since the noise level can vary substantially over relatively short distances.[39] When including only studies with low risk of exposure assessment bias in our analyses, the risk estimates assuming a linear trend appeared higher for all three health outcomes. Furthermore, corresponding analyses of nonlinear ERFs indicated clear risk increases for IHD, MI, and stroke, primarily at high exposure levels. There was a significant departure from linearity for IHD and MI, lending some support for a threshold at lower levels, such as used by WHO for IHD.[4] A higher imprecision in the road traffic noise estimates at low levels[40] could also have contributed to attenuation of the risk estimates at these levels. Unfortunately, only few studies fulfilled the criteria for low exposure assessment bias in our meta-analyses, and most of these came from Scandinavia, which may affect the generalizability of the findings.

There is ample evidence from experimental studies in animals and humans on mechanisms for noise-induced effects on the cardiovascular system.[41] Noise-related stress may induce inflammation, oxidative stress, and adverse redox signaling. Furthermore, epidemiologic studies have found stress reactions and sleep disturbance resulting from transportation noise exposure, which both constitute risk factors for cardiovascular disease, such as IHD and stroke. Other cardiovascular outcomes have also been linked to transportation noise exposure, including atrial fibrillation, heart failure, and cardiovascular mortality.[11,42] Furthermore, growing evidence indicates that long-term exposure to road traffic noise is associated with overweight/obesity and type 2 diabetes,[43,44] which both increase the risk of cardiovascular disease. Overall, the large body of evidence on various interrelated cardiovascular and metabolic effects of transportation noise strengthens the interpretation of causality of individual health outcomes and points to a substantial public health burden of this abundant exposure.

The risk estimates for the association between road traffic noise and the three cardiovascular outcomes did not differ consistently between administrative studies (strictly based on registry data) and corresponding estimates in studies based on questionnaires. The risk of confounding bias may be lower in questionnaire studies, which also include individual information on lifestyle factors.[4,45] On the other hand, selection bias is expected to be less prominent in administrative studies, which generally have a better coverage of the population. Overall, the combined risk estimates in our meta-analyses were more influenced by the administrative studies, which were considerably larger than the questionnaire-based studies.

Adjustment for $PM_{2.5}$ consistently reduced the risk estimates for road traffic noise. Long-term exposure to $PM_{2.5}$ has been linked to several cardiovascular outcomes[46,47] and could

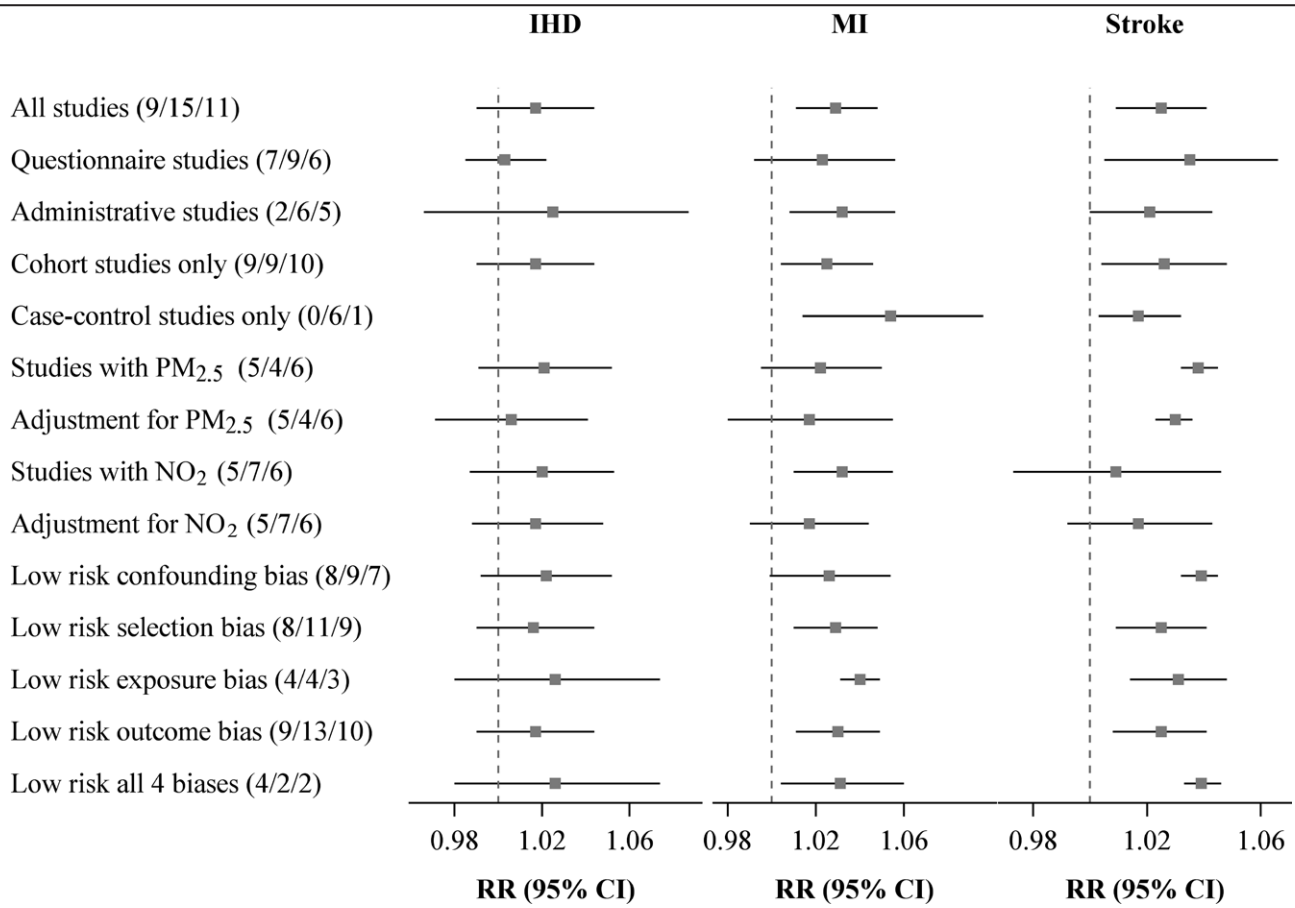

Figure 4. Relative risks for road traffic noise per 10 dB and ischemic heart disease (IHD), myocardial infarction (MI), and stroke calculated in meta-analyses according to study design, adjustment for air pollution, and risk of bias. The numbers in parentheses show the number of studies in each meta-analysis for IHD, MI, and stroke, respectively. Air pollution adjusted estimates for the HUNT2 and EPIC-Oxford cohorts in Cai et al[20] were obtained after contact with the main author.

therefore be a confounder for the road traffic noise-related associations, although the excess risk for stroke remained after adjustment for $PM_{2.5}$. However, the results should be interpreted with caution since only about half of the studies included data on both road traffic noise and air pollution. Furthermore, our findings differ from those of Eminson et al,[12] who concluded that air pollution did not appear to confound associations between traffic noise and cardiovascular health, including IHD, MI, and stroke. One reason for the discrepancy could be that we were more restrictive in the inclusion of studies, for example, by exclusion of cross-sectional and mortality studies.

There was little support for publication bias regarding road traffic noise and each of the three health outcomes. However, only eight studies were available for IHD, which makes the Egger test less reliable. Caution is necessary in the interpretation of publication bias using funnel plots and symmetry indices, since there may be several other reasons for asymmetry than publication bias.[48] Overall, the funnel plots for each of the outcomes showed rather unusual patterns with several large, precise studies and few small, imprecise ones. In addition, two of the three smallest studies for each outcome showed point estimates below one, also speaking against publication bias.

Our systematic review has several strengths. We avoided some weaknesses in earlier reviews on road traffic noise and cardiovascular outcomes, influencing the possibility to draw conclusions on how exposure affects disease incidence, such as combining results of overlapping studies (populations), mixing studies with ecological, cross-sectional, and longitudinal design, and/or including studies strictly focusing on mortality.[7–11] Furthermore, we made efforts to include all studies in both the meta-analyses, assuming linear and nonlinear ERFs, even if the original studies did not provide such data. We also developed transparent and objective criteria for the assessment of bias and applied these in the meta-analyses to explore the possible impact of various types of bias.

One limitation of the evidence is that substantial imprecision exists in the estimation of exposure in the included studies, even after exclusion of studies with a high risk of bias in the exposure assessment. For example, the included studies generally did not have information on residential floor or noise levels on the least exposed facade, which may affect noise exposure and the corresponding risk estimates.[21,39] Furthermore, most included studies were performed in Western Europe, including Scandinavia, and it is unclear how generalizable results are to other regions, with different building techniques and behavioral patterns, etc. Overall, a limitation is the small number of studies, particularly in the subgroup analyses, which complicates the interpretation of heterogeneity and publication bias. Finally, the exact definition of outcome varied between the included studies. However, the majority of the studies applied very similar outcome definitions, and we therefore expect this to have only a minor influence on the risk estimates.

Conclusions

Our systematic review showed increased risks of IHD, MI, and stroke in relation to long-term exposure to road traffic noise, particularly when studies with a high risk of bias in the exposure assessment were excluded. The risk estimates provide a basis for quantifying the cardiovascular health impacts of road

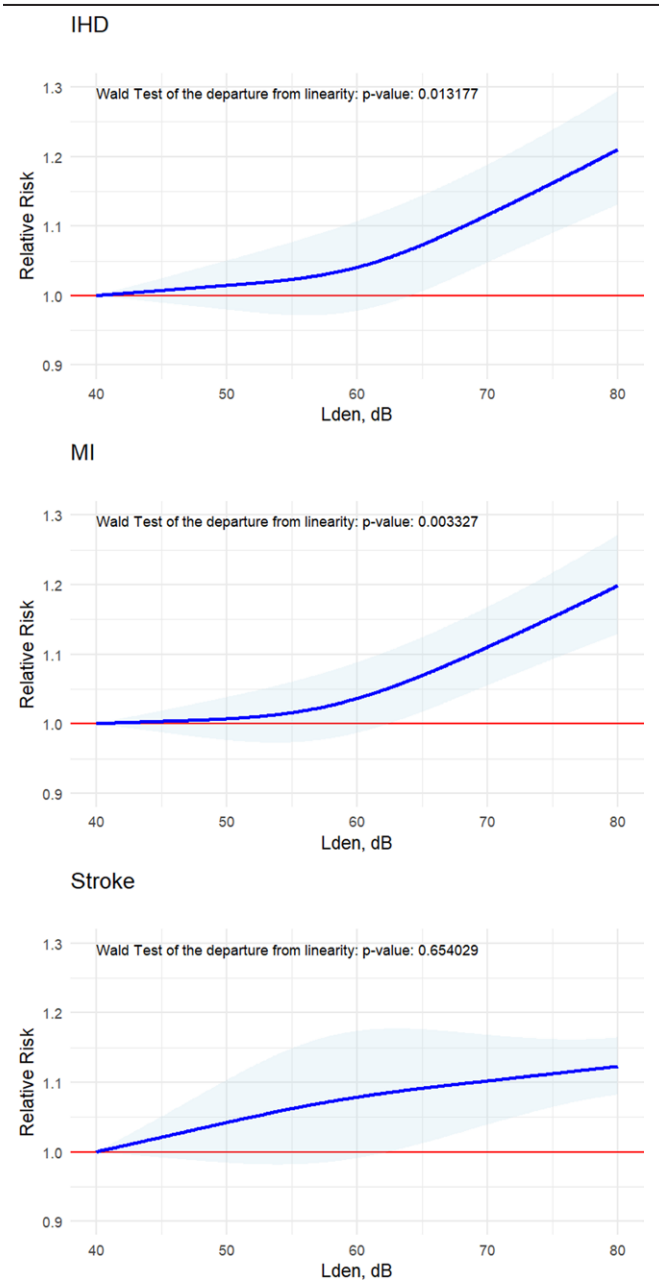

Figure 5. Exposure–response functions expressed as relative risks with 95% confidence intervals for ischemic heart disease (IHD), myocardial infarction (MI), and stroke in relation to exposure to road traffic noise in combined analyses of studies with low risk of exposure assessment bias.

traffic noise, such as in terms of disability-adjusted life years. The associations appear linear, and the risk estimates are valid within the exposure range of 40–80 dB L_{den}.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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