Original article DOI: 10.1515/aiht-2016-67-2751

Exposure-response relationship between traffic noise and the risk of stroke: a systematic review with meta-analysis

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[Received in November 2015; CrossChecked in November 2015; Accepted in May 2016]

Traffic noise is an established risk factor for some cardiovascular diseases such as hypertension and ischaemic heart disease, but the evidence regarding stroke is still limited. In this study we aimed to systematically review the related epidemiological data and make a meta-analysis of the risk of stroke morbidity associated with road and air traffic noise exposure. We searched articles in English, Spanish, and Russian indexed in MEDLINE, EMBASE, and Google Scholar on 24 November 2015. Qualitative synthesis was made for 13 studies, and 11 studies were included in quality effects meta-analyses. Overall, they were of high quality. Based on six studies (n≈8,790,671 participants) for road traffic noise, we found a pooled relative risk (RR) of stroke per 10 dB to be 1.01 (95 % CI: 0.96, 1.06). In the 70-75 dB noise range (versus <55 dB) RR increased to 1.29 (95 % CI: 0.74, 2.24). For air traffic noise we pooled five studies (n≈16,132,075 participants) and the $RR_{per\ 10\ dB}$ was1.01 (95 % CI: 1.00, 1.02). Road traffic group showed high heterogeneity whereas the air traffic group had none. Both groups showed evidence of publication bias. In conclusion, we have established a small but elevated risk of stroke to be associated with both road and air traffic noise exposure, but the association was statistically significant only with the latter. The effect of road traffic noise followed a non-linear trend.

KEY WORDS: *aircraft; cerebrovascular disease; cardiovascular disease; noise exposure; road traffic; transportation*

Traffic noise is already a recognised risk factor for cardiovascular disease (1). It acts as a general environmental stressor, adversely affecting the neuroendocrine system and sleep architecture, which ultimately leads to increased levels of plasma catecholamine and cortisol, impaired carbohydrate and lipid metabolism, and increase in blood pressure and vascular reactivity (2). Meta-analyses have found that the pooled risk of ischaemic heart disease is 1.04 (95 % CI: 1.00, 1.10) per 10 dB increase in road traffic day-evening-night sound level (L_{den}) and 1.06 (95 % CI: 1.04, 1.08) per 10 dB increase in air traffic L_{den} (3). With respect to the air traffic noise, the odds ratio (OR) for the exposed population to develop hypertension is 1.63 (95 % CI: 1.14, 2.33) (4). Burden-of-disease analyses have shown that traffic-noise-attributed myocardial infarction is associated with 61 000 disability-adjusted life-years in Western Europe (5).

Stroke can be defined as central nervous system infarction or cell death attributed to ischaemia or intracerebral/subarachnoid haemorrhage (6). It is a leading mortality cause worldwide associated with considerable social and economic costs (7, 8). The number of stroke victims has increased in the past twenty years, with most of the burden in middle-to-low income countries and an alarming rise in stroke morbidity and mortality in young people and even children (9). However, little is known about the effects of traffic noise on the risk of stroke (2). This would be particularly important, given that some studies point towards an increased risk (10, 11), whereas others show little or no effect (12, 13). Quantitative risk data are necessary not only to delineate the effect of noise on this specific cardiovascular outcome but also to assess the burden of disease associated with it. As far as we are aware, there has been only one ad-hoc attempt to quantitatively synthetize the results from primary studies (14), and it estimated a pooled relative risk (RR) per 10 dB of 1.04 (95 % CI: 1.00, 1.09) (14). However, the validity of this finding is uncertain.

Therefore, in this study we aimed to systematically review the epidemiological data and to run a meta-analysis on the risk of stroke associated with exposure to noise from road and air traffic.

MATERIALS AND METHODS

Systematic review

Search strategy

Our systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses (PRISMA) guidelines (15) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement (16). The research question was defined as the exposure-response relationship between traffic noise exposure (road and air traffic) and the risk of stroke. Railway noise was not considered for this review. We developed an *a priori* review protocol and data extraction forms.

Two independent electronic searches were carried out in MEDLINE (PubMed), EMBASE (ScienceDirect), and the Internet (Google Scholar) on 24 November 2015. The search string included the following free-term keywords in different combinations: stroke, cerebrovascular, road traffic noise, aircraft noise. Language restrictions were English, Spanish, and Russian. Articles were screened on three levels: titles, abstracts, and full-texts.

Duplicate publications were excluded. Only peer-reviewed epidemiological studies exploring the risk of stroke/cerebrovascular disease in adults associated with objectively measured traffic noise exposure were eligible. We excluded experimental studies, studies using self-reported exposure, and reviews. Authors and experts in the field were contacted in order to identify additional records. Hand-searching of the reference lists of included articles complemented the search.

Data extraction

Different estimates of the relative risk (e.g. hazard ratio, odds ratio, incidence rate ratio, mortality ratio) were considered for the meta-analysis, assuming that they were empirically similar enough to be pooled together (17, 18). The outcome of interest was stroke or cerebrovascular disease and was assessed either objectively (ICD codes) or it was self-reported in a questionnaire. If possible, we extracted morbidity estimates but, for studies reporting only mortality estimates, those were taken as a conservative proxy for risk of morbidity. Studies analysing a summary health outcome (stroke + other cardiovascular disease) were not included in the meta-analysis. Studies using combined traffic noise exposure indicator were also excluded from it. Risks were generally extracted for the fully adjusted models. In some cases educated choice was done; for example from the Evrard et al. study (19) we took the risk adjusted for NO_2 instead of $PM_{2.5}$ (to ensure comparability with other studies). From cohort studies we extracted data for the longest follow-up. When results had been stratified by age, such as in Sørensen et al. (20), we included both age groups in the meta-analysis, if no summary result for all age groups had been reported. The selected noise indicator was L_{den}, but when it was not available we extracted data associated with daytime noise exposure to achieve uniformity across studies. The only extracted estimate associated with night-time noise exposure (L_{night}) was that from Hoffmann et al. (21), who did not report results for daytime noise, but, given the high correlation between daytime and night-time traffic flow and noise, this is not a problem in linear trend estimation (12).

Quality assessment

The methodological quality of each study included in the qualitative synthesis was rated according to the *a priori* criteria listed in Appendix 1. They were developed based on a previously used protocol (22) and expert discussions.

Meta-analysis

Studies selected for quantitative synthesis were allocated into two groups: road and air traffic exposure. In the road traffic group two types of risks were used and meta-analysed: linear trend of risk per 10 dB increase in noise exposure and categorical risk in the range 50-75 dB (reference <55 dB). In the air traffic group we pooled only the trend of risk per 10 dB.

For the trend meta-analysis we either used already reported estimates per 10 dB or transformed the categorical risks. When the number of stroke cases and the size of the total population in each exposure group were reported in addition to the risk estimates (10, 23), we used the generalised least squares (STATA "glst") (24), as previously done by Babisch (1) and Vienneau et al. (3). When only the risk estimates for each category were available, we instead used the variance-weighted least squares command (STATA "vwls") (24), employed by Vienneau et al. (3). To estimate the trend per 10 dB for Hoffmann et al. (21), we used the exponential approximation proposed by van Kempen et al. (25), assuming that the difference in compared exposure categories was 26 dB. Command lines for "glst" and "vwls" are shown below:

Trend estimation without correction for covariance of risk estimates ("vwls")

```
gen double logRR=log(RR)
gen double loglci=log(lci)
gen double loguci=log(uci)
gen double logse=((loguci - loglci)/(2*invnorm(.975)))
vwls logRR Noise, noconstant sd(logse)
lincom Noise*10, eform
```

where "log" is natural logarithm; "RR" is the risk estimate in exposure category; "lci" is the lower limit of the confidence interval of the risk estimate; "uci" is the upper limit of the confidence interval of the risk estimate; "logse" is the standard error of the log-transformed risk estimate; and "Noise" is the midpoint of exposure category. Note that the reference exposure level was omitted from the trend estimation because it had a standard error of zero!

Trend estimation with correction for covariance of risk estimates ("glst")

```
gen double logRR=log(RR)
gen double loglci=log(lci)
gen double loguci=log(uci)
gen double logse=((loguci - loglci)/(2*invnorm(.975)))
glst logRR Noise, se (logse) cov (N Cases) ci
```

lincom Noise*10, eform
where "N" is the total number of cases in the exposure category and "Cases" is the number of stroke cases. The reference exposure level was set to 0 dB to comply with the algorithm!

For dichotomous comparisons, we used the following exponential approximation formula (25):

$RR_{per\ 10\ dB}$=log(RR)*(10/ΔdB),

logse=(log(uci)-log(lci)/3.92)*(10/ΔdB),

95 % CI for $RR_{per\ 10\ dB=}$exp(logRR$_{\pm}$1.96*logse)

where "ΔdB" is the difference in noise levels between the exposed and the reference group.

The range of open-ended categories was assumed to be the same as that of the adjacent category, and the exposure level in them was fixed at the midpoint when applying transformations (e.g., 55-60 dB and >60 dB → 55-60 dB and 62.5 dB). Noise indicators were entered in the analyses after conversion to L_{den} using the following approximations: $L_{Aeq,16h}$+2 dB, L_{dn}+0.3 dB (1, 3). However, when the effect was already reported per 10 dB, noise indicators were not transformed to L_{den} because it would not affect the risk estimate.

Even so, transforming categorical to linear trend estimates loses some information. This is why we also conducted a categorical meta-analysis using only high quality studies (with fewer sources of bias) reporting categorical risks. Categories for the pooled results were delineated as follows: <55 dB (reference), 55-60 dB, 60-65 dB, 65-70 dB, and 70-75 dB. After converting the exposure levels from each study to the L_{den} metric, we pooled together the estimates for each of the five exposure categories. Finally, we plotted the pooled risks from each category against its midpoint (e.g. 55-60 dB → 57.5 dB) and compared linear, quadratic, and cubic polynomials through the data points to select the best fitting function. For the reference category (<55 dB), a value of 52.5 dB was assigned.

For the meta-analysis we preferred the quality-effects model (26, 27) over the random-effects model, as the latter underestimates the error of the effects and may produce spuriously significant results (28). The quality-effects model uses an artificial quality index (Qi) to correct for study-specific information about its methodological rigor and thus give more weight to studies with higher quality (fewer sources of bias). We used the quality score for each study as input to generate the Qi. For comparison, we also report results from the random-effect model. Doi plots were used to check for possible publication bias, as they are more sensitive than the funnel plots (29). A symmetrical mountain-like plot with Luis Furuya-Kanamori (LFK) index <|1| indicates no asymmetry; LFK index between |1| and |2| suggests minor asymmetry; and LFK index >|2| suggests major asymmetry (29). Statistical heterogeneity can be suspected when Cochran's Q is significant at $p<0.1$, I^2 is >30 %, and/or tau-squared is >1.

For the meta-analyses we used MetaXL v. 3.1 (EpiGear International Pty Ltd, Sunrise Beach, Queensland, Australia).

RESULTS

Literature search results

We identified 18 records in PubMed, 182 in ScienceDirect, 3,040 in Google Scholar, and three from the reference lists of the reviews we consulted. The study of Babisch et al. (23) was identified through Google Scholar and missed by the other search engines. Having removed duplicates and applied stroke and traffic noise exposure filters, we screened the titles of the remaining 3,062 records. Twenty-three of the 43 abstracts were excluded. Twenty full-texts were read and seven excluded because they were either irrelevant to the research question or contained no useful data regarding the relationship between traffic noise and stroke. No additional articles were retrieved after hand-searching the reference lists of already included articles. Figure 1 shows the flow diagram of the searches.

Road traffic noise

Qualitative synthesis

All the seven studies included in this group (See Table 1) were conducted in European countries with a high socio-economic standard. The study of Floud et al. (30) was, in fact, an international survey across six countries. Except for Babisch et al. (23) and Beelen et al. (12), the collected data span after the year 2000 [Sørensen et al. (31) spanned 1993-2009 and Kluizenaar et al. (32)-1991-2004]. Four studies were cohort (12, 21, 31, 32), two were cross-sectional (23, 30), and one was ecological (using aggregate data) (10). The average follow-up in the cohort studies was around 10 years.

Sample sizes ranged from 2,512 (23) to 8.61 million (10) people and from 35 (23) to 62,513 stroke cases (10). All samples included both men and women from the general population, except for Babisch et al. (23), which included only men. The participants were middle aged in Babisch et al. (23), Beelen et al. (12), Hoffmann et al. (21) and Sørensen et al. (31). Halonen et al. (10) reported separate estimates for those aged ≥25 years and those aged ≥75 years.

The definition of the outcome varied across studies. Three studies looked at the ICD-code-defined stroke (10, 21, 31), while Beelen et al. (12) used ICD codes for the more general cerebrovascular disease. (See Table 1) Babisch et al. (23) and Floud et al. (30) relied on self-reported stroke. Sørensen et al. (31) studied different subtypes of stroke and reported the main results for ischemic stroke. Kluizenaar et al. (32) used combined outcome (ischemic heart disease + cerebrovascular disease). Beelen et al. (12), in fact,

Table 1 *Characteristics of studies included in the systematic review*

Study	Design	Population	Outcome	Noise assessment	Follow-up	Analysis	Adjustments	Noise categories (dB)
ROAD TRAFFIC GROUP								
Beelen et al. (12); Quality score=33	Cohort; Netherlands Cohort Study on Diet and Cancer (1987-1996)	Total/ cases=117 528/1 175; M (47.2 %) + F; 55-69 yrs.	Cerebrovascular disease (mortality)-ICD-9: 430-438, ICD-10: I60-I69; Death certificates	Modelling (EMPARA)-25 m grid; Indicator similar to L_{den}	9 yrs.	Cox regression (HR)	A, G, S, SES, TI, BS	<50, 50-55, 55-60, 60-65, >65
Floud et al. (30)-road traffic; Quality score=32	Cross-sectional; Hypertension and Environmental Noise near Airports study (2004-2006); six countries	Total/cases=4 712/62; M (49.6 %) + F; 45-70 yrs.	Self-reported doctor-diagnosis (morbidity)	Modelling (INM)-10 m grid; $L_{Aeq,24h}$	n/a	Logistic regression (OR)	A, G, BMI, E, Eth, aircraft noise	Trend per 10 dB
Halonen et al. (10)-adults; Quality score=33	Ecological; London, UK (2003-2010)	Total=8.61 million; Morbidity: cases= 62 513; M + F; ≥25 yrs.	Stroke morbidity-ICD-10: I61, I63, I64; Hospital admissions and death certificates	Modelling (TRANEX); $L_{Aeq,16h}$	n/a	Poisson regression (RR)	A, G, SES, Eth, S, $PM_{2.5}$	<55, 55-60, >60
Sørensen et al. (31); Quality score=38	Cohort; Danish Diet, Cancer and Health cohort (1993-2009)	Total/cases=51 569/1 999; M (47 %) + F; 56.2 yrs. (50.7-64.2)	Ischemic stroke morbidity-ICD-10: I63; Medical records + expert validation	Modelling (SoundPLAN); L_{den}	10 yrs.	Cox regression (IRR)	A, G, E, SES, S, D, Al, PA, BMI, calendar-year, NO_2	Trend per 10 dB
Hoffmann et al. (21); Quality score=34	Cohort; Heinz Nixdorf Recall study (2000-2009); Germany	Total/cases=4 350/71; M (47.9 %) + F; 45-74 yrs.	Stroke morbidity-ICD-10: I61, I63, I64; Medical records	Modeling (END); L_{night}	Average of 7.9 yrs. (± 1.5)	Cox regression (HR)	A, G, recruitment year, MS, E, Em, S, SES, PA, BMI, Al	Trend per 10 dB
Babisch et al. (23); Quality score=22	Cross-sectional; Caerphilly study; UK	Total/cases= 2 512/35; M; 45-59 yrs.	Self-reported stroke morbidity	Measurements; $L_{Aeq,6-22h}$ ($L_{Aeq,16h}$) at 10 m from the center of the road	n/a	RR calculated from raw data	None	51-55, 56-60, 61-65, 66-70

Study	Design	Population	Outcome	Noise assessment	Follow-up	Analysis	Adjustments	Noise categories (dB)
*Kluizenaar et al. (32); Quality score=35	Cohort; GLOBE study; Netherlands (1991-2004)	Total/ cases=18 213/1 547; M (47 % and 63.9 %) + F; 46.4 yrs. (± 15.9) and 59.3 yrs. (± 9.1)	Ischemic heart disease (ICD-9: 410-414) + cerebrovascular disease (ICD-9: 430-438) morbidity; Hospital admission registry	Modelling (SKM2); L_{den}	13 yrs.	Cox regression (RR)	A, G, BMI, S, E, PA, MS, Al, SES, employment, PM_{10}	Trend per 10 dB
**Sørensen et al. (20)-<64.5 yrs.; Quality score=36	Cohort; Danish Diet, Cancer and Health cohort (1993-2006)	Total/cases=51 485/952; M + F; <64.5 yrs.	First hospitalization for stroke (morbidity)-ICD-8: 431.0, 431.9, 432.0, 432.9, 433.09, 433.99, 434.09, 434.99, 436.0, 436.9 and ICD-10: I61, I63, I64; Hospital discharge register	Modelling (SoundPLAN); L_{den}	Average of 10.1 yrs. among cohort members and 6 yrs. among cases	Cox regression (IRR)	A, G, calendar-year, S, D, BMI, PA, Al, E, SES, AN, RN, NO_x	Digitized from graph: <55, 55-58, 58-61, 61-64, 64-67, 67-70, 70-73
**Sørensen et al. (20)->64.5 yrs.; Quality score=36	Cohort; Danish Diet, Cancer and Health cohort (1993-2006)	Total/cases=51 485/929; M + F; ≥64.5 yrs.	First hospitalization for stroke (morbidity)-ICD-8: 431.0, 431.9, 432.0, 432.9, 433.09, 433.99, 434.09, 434.99, 436.0, 436.9 and ICD-10: I61, I63, I64; Hospital discharge register	Modelling (SoundPLAN); L_{den}	Average of 10.1 yrs. among cohort members and 6 yrs. among cases	Cox regression (IRR)	A, G, calendar-year, S, D, BMI, PA, Al, E, SES, AN, RN, NO_x	Digitized from graph: <55, 55-58, 58-61, 61-64, 64-67, 67-70, 70-73
AIR TRAFFIC GROUP								
Evrard et al. (19); Quality score=37	Ecological; France (2007-2010)	Total=1.9 million; M + F	Stroke mortality-ICD-10: I60-I64, excluding I63.6; Mortality register	Modelling (INM); L_{den}	n/a	Poisson regression (MRR)	A, G, SES, lung cancer mortality, NO_2	Trend per 10 dB
Floud et al. (30)-aircraft; Quality score=32	Cross-sectional; Hypertension and Environmental Noise near Airports study (2004-2006); six countries	Total/cases=4 712/62; M (49.6 %) + F; 45-70 yrs.	Self-reported doctor-diagnosis (morbidity)	Modelling (INM)-10 m grid; $L_{Aeq,16h}$	n/a	Logistic regression (OR)	A, G, BMI, E, Eth, road traffic noise	Trend per 10 dB

Study	Design	Population	Outcome	Noise assessment	Follow-up	Analysis	Adjustments	Noise categories (dB)
Hansell et al. (11); Quality score=33	Ecological; UK (2001-2005)	Total/cases=3.6 million/16 983; M + F	Main reason for hospitalization is stroke (morbidity)-ICD-10: I61, I63-I64; National registry	Modelling (ANCON)-10 m grid; $L_{Aeq,16h}$	n/a	Poisson regression (RR)	A, G, Eth, SES, lung cancer	≤ 51, 51-54, 54-57, 57-60, 60-63, >63
Huss et al. (13); Quality score=33	Cohort; Swiss National Cohort (2000-2005)	Total/cases=4.6 million/12 102; M + F; ≥30 yrs.	Primary or concomitant stroke mortality-ICD-10: I60-I64 excluding I63.6; Death certificate	Modelling-100 m grid; L_{dn}	5 yrs.	Cox regression (HR)	A, G, MS, Eth, nationality, urban/rural, language region, type of building, SES (non-movers for >15 yrs.)	<45, 45-49, 50-54, 55-59, ≥60
Correia et al. (33); Quality score=31	Ecological; US (2009)	Total/cases=6 million/1343.3 (1 092.5-1 652.2); M + F; ≥65 yrs.	Cerebrovascular disease morbidity-ICD-9: 430-438; Hospitalization records	Modelling (INM); L_{dn}	n/a	Poisson regression (RR)	A, G, race, SES, Eth, $PM_{2.5}$, ozone	Trend per 10 dB (digitized from graph)
COMBINED TRAFFIC GROUP								
*Gan et al. (34);Quality score = 39	Cohort; Canada (1994-2002)	Total/cases = 445 868/1 288; M (45-46%) + F; 45-85 yrs.	Stroke mortality-ICD-9: 430-434, 436-438 and ICD-10: I60-I69 excluding I63.6; Death registration database	Modelling (CadnaA)-6-digit postal code area; Lden; Combined road + air & railway traffic noise	4 yrs.	Cox regression (HR)	A, G, SES, $PM_{2.5}$, NO_2, black carbon, diabetes, COPD	Trend per 10 dB

*M-male, F-female, A-age, G-gender, S-smoking, SES-socio-economic status, BMI-body mass index, TI-traffic intensity, BS-black smoke, E-education, Eth-ethnicity, AN-aircraft noise, $PM_{2.5}$ fine particulate matter, NO_2-nitrogen dioxide, D-diet, PA-physical activity, MS-marital status, Em-employment, Al-alcohol, RN-railway noise, NO_x-nitrogen oxide, COPD-chronic obstructive pulmonary disease; *not included in meta-analysis, **included only in categorical meta-analysis* estimated the risk of cerebrovascular disease mortality, whereas the others reported morbidity estimates. Most studies employed noise modelling approaches, while Babisch et al. (23) carried out field measurements. Selected noise indicators differed: three studies used L_{den} (12, 31, 32), one used $L_{Aeq,24h}$ (30), two used $L_{Aeq,16h}$ (10, 23), and one used L_{night} (21).

All four cohort studies fitted the Cox proportional hazards model to study the risk of stroke (12, 21, 31, 32). Halonen et al. (10) used Poisson regression, and Floud et al. (30) logistic regression. Adjustment sets included the core demographics (age, gender) and the rest controlled for dietary habits or body mass index, except for two studies (10, 12). Beelen et al. (12), Sørensen et al. (31), Kluizenaar et al. (32), and Halonen et al. (10) adjusted for indicators of air pollution, while Floud et al. (30) adjusted for air traffic noise. Babisch et al. (23) reported unadjusted data. Overall, Beelen et al. (12), Kluizenaar et al. (32), and Hoffmann et al. (21) did not find elevated risk associated with noise exposure in the adjusted models. In Kluizenaar et al. (32) the risk per 10 dB was elevated (RR=1.09, 95 % CI: 0.90, 1.32) only in the subgroup with a history of cardiovascular disease, whereas the relative risk in the whole sample was 1.00 (95 % CI: 0.91, 1.10). Others did find the risk above 1.00, but it was statistically significant only in Sørensen et al. (31) and Halonen et al. (10). There were no risks for haemorrhagic strokes in the study of Sørensen et al. (31), and the risk was higher for those exposed for one year (IRR=1.19, 95 % CI: 1.09, 1.31). In Halonen et al. (10) the elderly (≥75 years) had a slightly higher risk than the whole sample of adults (≥25 years). Night-time noise exposure >60 dB was associated with a lower risk than daytime exposure: RR=1.01 (95 % CI: 0.98, 1.05) in those aged ≥25 years and RR=1.02 (95 % CI: 0.97, 1.08) in those aged ≥75 years. The risk estimates in Beelen et al. (12) and Halonen et al. (10) were categorical, in Hoffmann et al. (21) they were reported per one interquartile range increase in L_{night}, and Babisch et al. (23) reported only the prevalence of stroke across noise categories, from which we derived a linear trend per 10 dB. The rest reported risks per 10 dB. Overall, the studies were of high quality, with the score of Sørensen et al. (31) being the highest.

We included Hoffmann et al. (21), Halonen et al. (10), Sørensen et al. (31), Floud et al. (30), Beelen et al. (12), and Babisch et al. (23) in the linear trend meta-analysis. The categorical meta-analysis included Beelen et al. (12), Halonen et al. (10), and two coefficients from another study by Sørensen et al. (20) based on the same cohort, which reported results from categorical analysis stratified by the age threshold of 64.5 years. Those two subgroups were included separately in the meta-analysis. Kluizenaar et al. (32) was included in neither of the two quantitative syntheses because the outcome included ischemic heart disease.

Meta-analysis

The meta-analysis was based on the most comparable effect sizes. Appendix 2 reports the input data for linear trend estimation. Figure 2 presents a forest plot of the risk

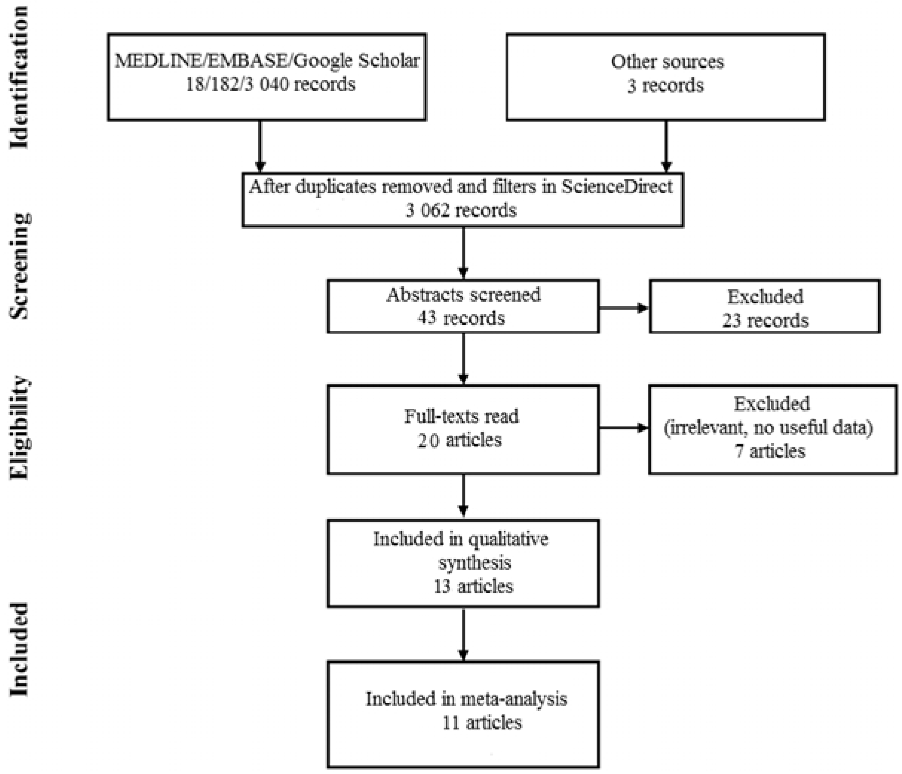

Figure 1 *Study selection flow-chart*

of stroke morbidity associated with 10 dB increase in road traffic noise exposure. The pooled risk was 1 % (95 % CI: -4 %, 6 %). The coefficient from Halonen et al. (10) was associated with the highest weight (84.5 %). There was high statistical heterogeneity (tau-squared=0.0008, significant Cochran's Q at p=0.00, I^2=79 %). The Doi plot in Figure 3 was asymmetrical with LFK index >|2|, suggesting gross publication bias. For comparison, under the random effects model the pooled risk was similar (RR=1.01, 95 % CI: 0.98, 1.05), but the weight of Halonen et al. (10) dropped to 41.4 % and that of Beelen et al. (12) increased from 6.6 % to 37.6 %.

Results from sensitivity analysis, shown in Table 2, reveal that, upon exclusion of most studies one-at-a-time, the pooled effect remained unchanged but the study of Halonen et al. (10) was driving the effect, which dropped <1.00 when it was excluded. If only cohort studies were pooled (three studies), the relative risk would be 0.99 (95 % CI: 0.81, 1.20). If the analysis was limited to studies originally reporting linear trend estimates per 10 dB (three studies), the relative risk would be 1.15 (95 % CI: 1.05, 1.25).

Figure 4 shows individual study risks included in the categorical meta-analysis (see Appendix 3 for risk estimates).

The pooled categorical risk is given in Figure 5. Although it failed in statistical significance, it was elevated in the categories 55-60 dB (RR=1.04, 95 % CI: 0.87, 1.24), 60-65 dB (RR=1.05, 95 % CI: 0.75, 1.46), 65-70 dB (RR=1.21, 95 % CI: 0.81, 1.81) and 70-75 dB (RR=1.29, 95 % CI: 0.74, 2.24). The linear function explained only 89 % of the variance in the risk of stroke. The cubic polynomial did not provide substantial improvement (R^2=96 %) to the quadratic function. Therefore, the best fitting and most parsimonious approximation of the risk as a function of L_{den} in the range <55-75 dB was the following unweighted quadratic polynomial:

$$Risk=0.00066295186571*(L_{den})^2-0.06779154098343*(L_{den})+2.73847143171073,\ R^2=0.95$$

Table 2 *Sensitivity of road traffic noise estimates (linear trend meta-analysis)*

Excluded study	Pooled Risk estimate (95 % CI)	I^2 %
Hoffmann et al. (21)	1.01 (0.96, 1.07)	83.07
Halonen et al. (10)	0.99 (0.85, 1.15)	74.66
Sørensen et al. (31)	1.01 (0.97, 1.05)	72.56
Floud et al.-road traffic (30)	1.01 (0.96, 1.06)	83.03
Beelen et al. (12)	1.01 (0.91, 1.13)	60.85
Babisch et al. (23)	1.01 (0.96, 1.06)	82.23

Because the reference category <55 dB represented a wide range of exposure levels below 55 dB, we tested the function in several scenarios, changing the reference exposure level from 47.5 to 50, and finally to 52.5 dB, and found only a marginal impact on the slope or the coefficient of determination.

Air traffic noise

Qualitative synthesis

Five studies were included in this group. Three of those were ecological (11, 19, 33), one cross-sectional (30), and one cohort (13). The only non-European study was that of Correia et al. (33), as it was carried out in the United States. Sample sizes ranged from 4,712 (30) to 6 million (33) people. All samples included men and women, and that of Correia et al. (33) was limited to the elderly (≥65 years).

Only Correia et al. (33) defined the outcome as cerebrovascular events, while the rest specified it as types of stroke. Only Floud et al. (30) used self-reported doctor diagnosis. Two of the studies examined the risk of stroke mortality (13, 19). All studies assessed noise exposure objectively through validated models. Selected indicators were L_{den} (19), L_{dn} (13, 33), and $L_{Aeq,16h}$ (11, 30). Ecological studies analysed their data with Poisson regression; Huss et al. (13) used Cox proportional hazards model; and Floud et al. (30) used logistic regression. Adjustments were made for key demographics, but some important individual-level factors could not be measured in the ecological studies. All studies were of high quality, with Evrard et al. (19) scoring the top 37 of 42 points. All found some increase in the risk of stroke with increasing exposure, ranging from 1.001 (95% CI: 0.99, 1.01) (13) to 1.08 (95% CI: 0.82, 1.41) (19). Evrard et al. reported elevated risk in men (MRR=1.10, 95 % CI: 0.90, 1.33) but not in women (MRR=1.00, 95 % CI: 0.85, 1.19) (19). Some authors found lower risk of night-time in comparison to daytime noise (10), whereas others reported higher relative risk (1.29; 95 % CI: 1.14, 1.46) for L_{night} >55 dB (11) and higher odds ratio per 10 dB L_{night} (1.18; 95 % CI: 0.89, 1.57) (30). All studies were included in quantitative synthesis.

Meta-analysis

Figure 6 shows the results of the linear trend meta-analysis. The pooled effect was 1 % (0.2 %, 2 %) when the quality effects model was used. There was no heterogeneity (tau-squared=0.00, non-significant Cochran's Q at p=0.76, I^2=0.00 %), but there was evidence of major asymmetry in the Doi plot (LFK >|2|) (Figure 7). When the random effects model was used, the effect remained virtually the same (RR=1.01; 95 % CI: 1.00, 1.01).

In sensitivity analysis the pooled risk remained unchanged upon exclusion of each study one-at-a-time (Table 3). If only studies reporting stroke morbidity were analysed, the risk would remain unchanged (RR=1.01; 95 %

CI: 1.00, 1.01). Restriction to studies originally reporting linear trend estimates would raise the relative risk per 10 dB to 1.03 (95 % CI: 0.97, 1.09).

Combined traffic noise

Table 3 *Sensitivity of air traffic noise estimates (linear trend meta-analysis)*

Excluded study	Pooled Risk estimate (95 % CI)	I^2 %
Evrard et al. (19)	1.01 (1.00, 1.01)	0.00
Hansell et al. (11)	1.01 (0.99, 1.02)	0.00
Floud et al.-air traffic (30)	1.01 (1.00, 1.02)	0.00
Correia et al. (33)	1.01 (1.00, 1.02)	0.00
Huss et al. (13)	1.01 (1.00, 1.02)	0.00

Qualitative synthesis

Only one study was included in this group (34). Gan et al. used linked administrative health insurance databases to assemble this population-based cohort from Vancouver in Canada. People aged 45-85 years were enrolled and followed for four years. Data about stroke were obtained from death registry and cases were defined by ICD codes. The authors used CadnaA software to model L_{den} for combined traffic noise (road, air, and railway) (34).

The risk of stroke mortality per 10 dB increase in that study was 1.03 (95% CI: 0.91, 1.16). For ischaemic and haemorrhagic stroke, the risk was 1.02 (95% CI: 0.78, 1.33) and 1.14 (95% CI: 0.91, 1.44), respectively. The analysis relied on Cox regression, adjusted only for some important covariates, since the authors lacked individual-level questionnaire data (34). This study received high-quality score (39 of 42 points), but since the exposure indicator did not differentiate between road and air traffic noise, we did not include in our meta-analysis.

DISCUSSION

Main findings

With respect to road traffic noise, the risk of stroke increased 1 % (95 % CI: -4 %, 6 %) with every 10 dB increase in L_{den}. This finding was driven by the study of Halonen et al. (10), because it included all London area residents. In categorical analysis we found non-linearity in the effect, and the pooled risk reached 29 % (-26 %, 24 %) in the category 70-75 dB. Overall, road traffic noise studies were methodologically heterogeneous, which may be expected to lead to differences in the observed effects.

As far as the air traffic noise is concerned, the pooled risk per 10 dB was also 1 % (95 % CI: 0.2 %, 2 %). However, these studies were more consistent in their effects and methodologies.

Even so, both groups showed gross asymmetry in the Doi plots as evidence of publication bias, which may be skewing the pooled results, if primary studies are being published selectively, depending on the effect they find.

For the only study using a combined traffic noise indicator (34), the overall effect was similar to those for road and air traffic noise. Previously Vienneau et al. (3) argued that ignoring the type of noise source might not be much of an issue because the pooled risks of ischemic heart disease in relation to road and air traffic noise were close. While we also found no difference in the pooled point estimates associated with either type of traffic noise, the precision of the estimates in our meta-analysis was higher for air traffic and there was no heterogeneity in that group. Therefore, we do not recommend combining studies investigating the effects of different noise sources, as the

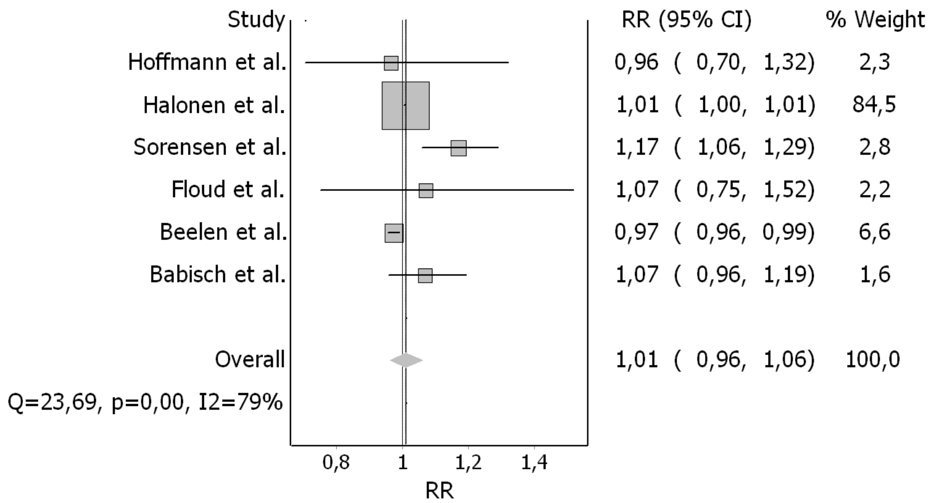

Figure 2 *Forest plot of studies included in the meta-analysis of the linear trend of stroke risk per 10 dB increase in road traffic noise exposure*

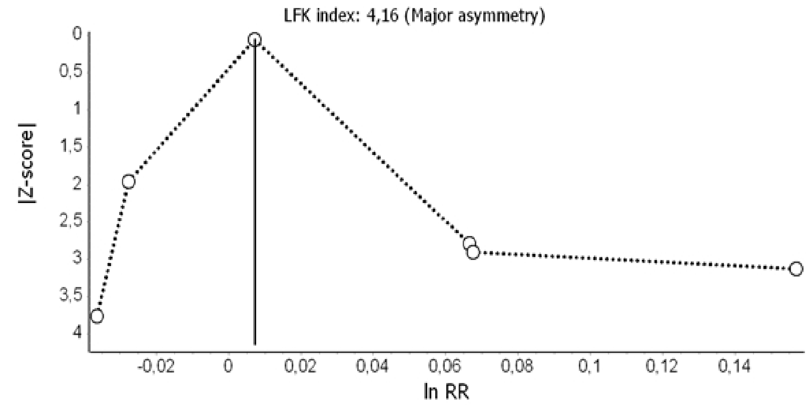

Figure 3 *Doi plot with Luis Furuya-Kanamori index for the detection of publication bias in the road traffic group (linear trend meta-analysis)*

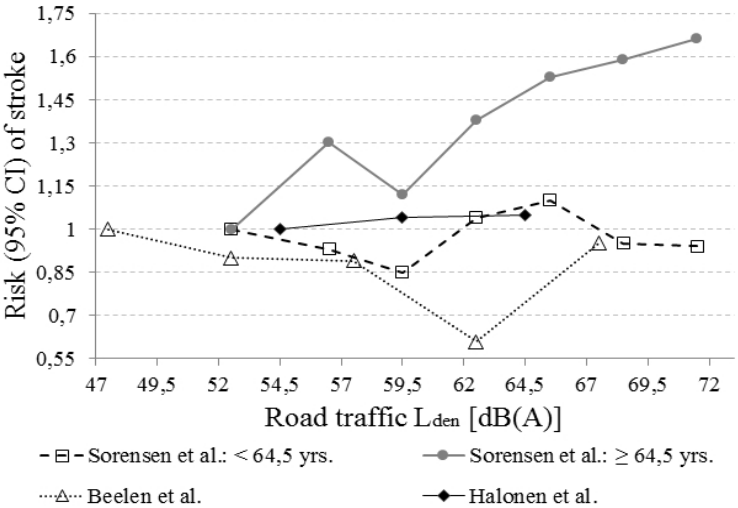

Figure 4 *Individual risk estimates for stroke reported in studies included in the categorical meta-analysis*

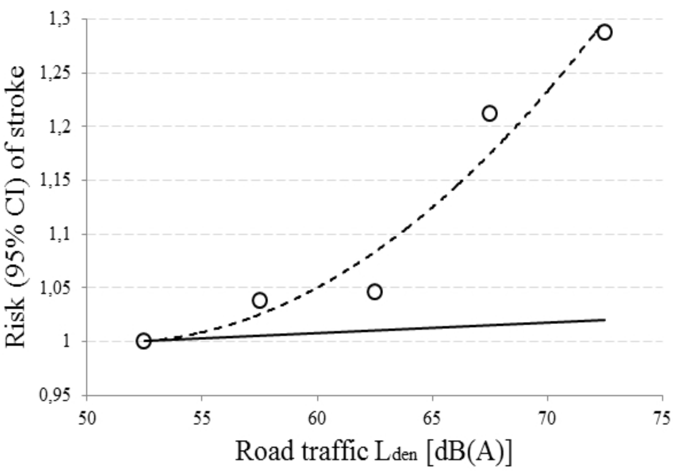

Figure 5 *Pooled categorical risk of stroke associated with road traffic noise exposure*
The solid line represents the pooled linear trend of the risk per 10 dB (based on 6 estimates). The dashed line represents a quadratic polynomial approximation of the categorical risk: 50-55 dB (reference); 55-60 dB is based on 4 estimates; 60-65 dB is based on 4 estimates; 65-70 dB is based on 3 estimates; 70-75 dB is based on 2 estimates

issues of heterogeneity and precision should not be taken lightly. Based on our findings, we contend that the risk of 4 % (96 % CI: 0 %, 9 %) per 10 dB reported by Houthuijs et al. (14) might be an overestimation.

Limitations

The first limitation of our systematic review and meta-analysis is that it should have included more studies to have sufficient power for subgroup analysis and formal publication bias tests. However, our meta-analysis included a greater number of studies than are usually included in this type of meta-analysis (35)and it also included a higher number of participants. After all, the meta-analysis that has served as the basis for ischemic heart disease burden of disease estimation in Europe also included but a few studies (36). As for the environmental noise research, there are not enough studies to begin with, as it has only recently turned its focus to stroke as an endpoint.

Another issue might be pooling together different point estimates. This choice can be justified due to the empirical similarity of those estimates, especially given the small effect sizes and that there was only one study reporting odds ratio (which is the least conservative estimate), while the others employed Cox proportional hazards or Poisson regression models (17, 18). Therefore those should be reasonable measures of the relative risk.

Taking the risk of stroke mortality as a proxy for the risk of morbidity makes the pooled effect conservative, as it ignores non-fatal cases. On the other hand, we included only one (out of six) mortality estimate in the road traffic group and two (out of five) in the air traffic group, and their exclusion did not affect the pooled risk. The same can be deduced from some studies reporting both morbidity and mortality risks (11); others, however, showed lower risk for noise-attributed stroke mortality than for noise-attributed stroke morbidity (10). The same bias towards the null applies to the cerebrovascular disease when it is used as a proxy for stroke. Therefore the categorical risk, based on Beelen et al. (12), who reported estimates for cerebrovascular disease mortality, is probably underestimated and conservative.

In line with Vienneau et al. (3), we found that studies originally reporting linear trend per 10 dB were associated with higher risk than those for which such a trend was derived by us. Estimating a linear trend per 10 dB from reported categorical risks is associated with information loss. While the generalised least squares approach was specifically designed for this purpose, the assumption of

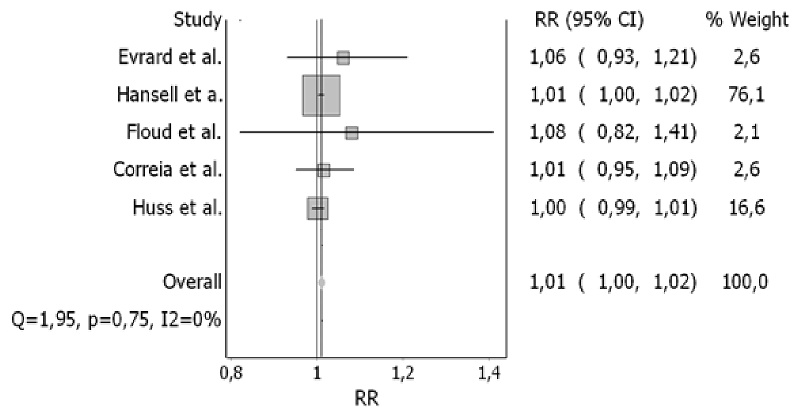

Figure 6 *Forest plot of studies included in meta-analysis of the linear trend of stroke risk per 10 dB increase in air traffic noise exposure*

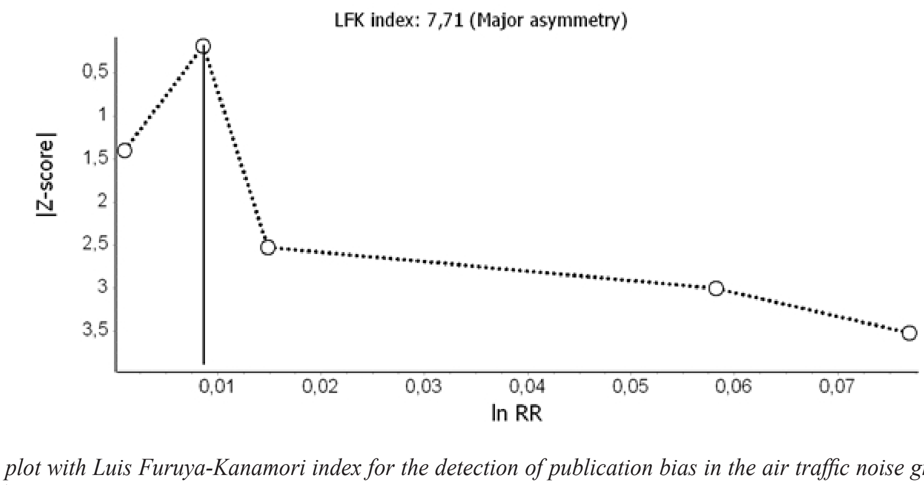

Figure 7 *Doi plot with Luis Furuya-Kanamori index for the detection of publication bias in the air traffic noise group (linear trend meta-analysis)*

the variance-weighted least squares that the log relative risk estimates are independent is never confirmed in practice (24). Even so, when the covariance matrix cannot be specified, the latter is an alternative (3). For studies reporting sufficient information (10, 23) we used generalised least squares but we also estimated the linear trend via variance-weighted least squares and found very similar results.

The categorical approach requires for the included studies to be similar in terms of exposure assessment, noise indicators, and reference levels and to be generally of high quality, because of which few studies are usually fit for this approach (37). This is why we should interpret it with caution. Furthermore, including the two subgroups of Sørensen et al. (20) in the categorical meta-analysis might violate the assumption of statistical independence and, although the subsamples do not share subjects, the fact that the investigators of these effects were the same implies some bias (38). This choice was made only because Sørensen et al. (20) did not report combined categorical risk for the whole sample.

Finally, the high heterogeneity in the road traffic group and the considerable bias associated with some estimates (23) were addressed by using the quality effects model (28, 39) and by excluding Babisch et al. (23) from the categorical meta-analysis.

Future research

The results of this meta-analysis can be used for preliminary calculation of disease burden. However, in order to grow and strengthen the evidence of the exposure-response relationship, additional studies with compatible methodologies need to be reported. Special emphasis should be put on the effect with regards to different types of stroke and comparable ICD definitions of the outcome.

Although ecological studies do provide the opportunity to analyse large samples, they lack control for some important individual and behavioural factors that might be confounding or moderating the effects of noise. Gender, age, and ethnic group stratification is also necessary in order to identify vulnerable subpopulations.

Furthermore, there is no evidence from middle- and low-income countries where both stroke incidence and traffic noise exposure are considerably higher than in Western Europe.

The effect of night-time noise has not been addressed sufficiently either. Studies should report both trend and categorical risk estimates to facilitate data meta-synthesis.

Finally, the issue of the publication bias should be addressed more carefully.

CONCLUSIONS

In conclusion, we found a small but elevated risk of stroke associated with both road and air traffic noise exposure, but it was statistically significant only for the latter. The effect of road traffic noise followed a non-linear trend. As soon as the results from other high-quality studies are published this exposure-response relationship should be updated and adjusted.

Conflict of interest statement

This study was conducted without any relationships that could be construed as potential conflict of interest. We were not financially supported in any way.

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Appendix 1 *Quality scoring checklist*

Design
- a) Cohort: yes (3) / no (0)
- b) Cross-sectional/case-control: yes (2) / no (0)
- c) Ecological: yes (1) / no (0)

Sample
- a) Representative: yes (3) / no or no information (1)
- b) Random: yes (3) / no or no information (1)
- c) Sufficient sample size: yes (3) / no or no information (1)
- d) Response rate: ≥80 % (3) / 60-79 % (2) / <60 % or no information (1)

Outcome
- a) Objective assessment (medical records, death certificates, ICD-classification, etc.): yes (3) / self-reported or no information (1)
- b) Definition: stroke (ischemic/haemorrhagic) (3) / cerebrovascular disease (1)

Noise exposure
- a) Objective assessment (modelling, measurements): yes (3) / no information on the model (1)
- b) Indicator: L_{den} (3) / other or no information (1)

Analysis
- a) Adequate: yes (3) / no or no information (1)
- b) Adjustments: demographics (age, gender, socio-economic status/education/ethnicity) + diet/physical activity/body mass index + smoking + genetics/family history + hypertension/diabetes mellitus/hearth rhythm disorders/kidney disease + blood lipids + other environmental exposures (6) / most of those including age, gender, diet/physical activity/body mass index and smoking (4) / some of those including age and gender (3) / not including age and gender (1)

Extracted effect size
- a) Transformations necessary: no (3) / yes (1)
- b) Extraction: straightforward (3) / no (1)

Maximum=42 points

Appendix 2 *Input data for the estimation of linear trend of stroke risk per 10 dB increase in road traffic and air traffic noise exposure*

Study (method)	Mid-category noise levels (original metric/L_{den}/for trend estimation)	Risk estimates (95 % CI) for trend estimation	Risk per 10 dB
Beelen et al. (12) ("vwls")			0.97 (0.96, 0.99)
	47.5/47.5/omitted	1.00	
	52.5/52.5/52.5	0.90 (0.78, 1.04)	
	57.5/57.5/57.5	0.89 (0.76, 1.05)	
	62.5/62.5/62.5	0.61 (0.44, 0.84)	
	67.5/67.5/67.5	0.95 (0.55, 1.66)	
Halonen et al. (10) ("glst")*			1.01 (1.00, 1.01)
	47.5/49.5/0	1.00	
	52.5/54.5/54.5	1.04 (1.02, 1.07)	
	62.5/64.5/64.5	1.05 (1.02, 1.09)	
Hoffmann et al. (21) (exponential fit)	Reported per 26 dB	0.91 (0.40, 2.06)	0.96 (0.70, 1.32)
Floud et al.-road traffic (30)	Reported per 10 dB		1.07 (0.75, 1.52)
Floud et al.-aircraft (30)	Reported per 10 dB		1.08 (0.82, 1.41)
Sørensen et al. (31)	Reported per 10 dB		1.17 (1.06, 1.29)
Babisch et al. (23) ("glst")*			1.07 (0.96, 1.19)
	53/55/0	1.00	
	58/60/60	1.20 (0.36, 3.96)	
	63/65/65	1.06 (0.37, 3.05)	
	68/70/70	2.53 (0.88, 7.23)	
Hansell et al. (11) ("vwls")			1.01 (1.003, 1.02)
	49.5/51.5/omitted	1.00	
	52.5/54.5/54.5	1.03 (0.98, 1.09)	
	55.5/57.5/57.5	1.04 (0.98, 1.12)	
	58.5/60.5/60.5	1.04 (0.95, 1.14)	
	61.5/63.5/63.5	1.10 (0.96, 1.25)	
	64.5/66.5/66.5	1.24 (1.08, 1.43)	
Evrard et al. (19)	Reported per 10 dB		1.06 (0.93, 1.21)
Huss et al. (13) ("vwls")			1.001 (0.99, 1.01)
	42/42.3/omitted	1.00	
	47/47.3/47.3	1.03 (0.92, 1.14)	
	52/52.3/52.3	1.02 (0.90, 1.15)	
	57/57.3/57.3	0.96 (0.82, 1.13)	
	62/62.3/62.3	0.88 (0.58, 1.34)	
Correia et al. (33)	Reported per 10 dB		1.02 (0.95, 1.09)

**linear trend estimates generated with "vwls" are similar to the first decimal place; "vwls"-variance-weighted least squares; "glst"-generalized least squares*

Appendix 3 *Input data for the estimation of categorical risk of stroke associated with road traffic noise exposure*

Study	Original noise category/trend category (L_{den})	Risk estimates (95 % CI)
Sørensen et al. <64.5 yrs. (20)	<55/reference	1.00
	55-58/55-60	0.93 (0.77, 1.12)
	58-61/omitted	0.85 (0.68, 1.05)
	61-64/60-65	1.04 (0.84, 1.29)
	64-67/omitted	1.10 (0.86, 1.41)
	67-70/65-70	0.95 (0.70, 1.28)
	70-73/70-75	0.94 (0.64, 1.39)
Sørensen et al. >64.5 yrs. (20)	<55/reference	1.00
	55-58/55-60	1.30 (1.07, 1.58)
	58-61/omitted	1.12 (0.89, 1.41)
	61-64/60-65	1.38 (1.12, 1.71)
	64-67/omitted	1.53 (1.19, 1.95)
	67-70/65-70	1.59 (1.19, 2.10)
	70-73/70-75	1.66 (1.17, 2.36)
Beelen et al. (12)	≤50/reference	1.00
	50-55/omitted	0.90 (0.78, 1.04)
	55-60/55-60	0.89 (0.76, 1.05)
	60-65/60-65	0.61 (0.44, 0.84)
	>65/65-70	0.95 (0.55, 1.66)
Halonen et al. (10)	<55/reference	1.00
	55-60/55-60	1.04 (1.02, 1.07)
	>60/60-65	1.05 (1.02, 1.09)

Odnos između izloženosti prometnoj buci i rizika od moždanog udara: sustavni pregled s metaanalizom

Prometna je buka rizični čimbenik za nastanak bolesti krvožilja poput povišenoga krvnog tlaka i ishemijske bolesti srca, ali su saznanja vezana uz moždani udar još uvijek ograničena. Cilj je ovoga istraživanja bio napraviti sustavni pregled epidemioloških podataka i metaanalizu rizika od moždanog udara povezanoga s izloženošću buci cestovnog i zračnog prometa. Pretraživanje je provedeno 24. studenoga 2015., a obuhvatilo je članke na engleskom, španjolskom i ruskom jeziku koji su odgovarali kriterijima pretrage u bazama MEDLINE, EMBASE i Google Scholar. Kvalitativna sinteza obuhvatila je 13 istraživanja, od kojih je 11 obuhvaćeno metaanalizom kvalitativnih učinaka. U prosjeku su svi članci bili visokokvalitetni. Na temelju rezultata šest istraživanja (n ≈ 8.790.671 sudionik) vezanih uz buku cestovnog prometa, utvrdili smo da ukupni relativni rizik (RR) od moždanog udara prilikom porasta buke od 10 dB iznosi 1,01 (95 % CI: 0,96, 1,06). U rasponu buke od 70 do 75 dB (prema <55 dB) RR se povećao na 1,29 (95 % CI: 0,74; 2,24). Prema objedinjenim podacima o buci zračnoga prometa iz pet istraživanja (n ≈ 16.132.075 sudionika), RR za porast buke od 10 dB iznosio je 1,01 (95 % CI: 1,00; 1,02). Podaci iz istraživanja cestovne buke, za razliku od onih iz istraživanja zračne buke, bili su statistički izrazito heterogeni. Obje su skupine istraživanja iskazale odstupanje podataka zbog pretežitog objavljivanja određenog tipa istraživanja (tzv. *publication bias*). Ovim smo istraživanjem utvrdili donekle povišeni rizik od moždanog udara zbog izloženosti buci cestovnog i zračnog prometa, ali je ta povezanost bila statistički značajna samo kod potonjega. Učinci cestovne buke slijedili su nelinearni trend.

KLJUČNE RIJEČI: *bolest krvožilja; cerebrovaskularna bolest; cestovni promet; prijevoz; zračni promet*