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Residential traffic noise and Mammographic Breast Density in the Diet, Cancer and Health cohort

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Abstract

Objectives:

Traffic is the most important source of community noise, and it has been proposed to be associated with a range of disease outcomes, including breast cancer. As mammographic breast density (MD) is one of the strongest risk factors for developing breast cancer, the present study investigated whether there is an association between residential exposure to traffic noise and MD in a Danish cohort.

Methods:

We included women with reproductive and lifestyle information available from the Diet, Cancer and Health cohort, who also participated in the Copenhagen Mammography Screening Programme (N = 5,260). Present and historical addresses from 1987-2011 were found in national registries, and traffic noise was modelled 5 years before mammogram. Analyses between residential traffic noise and MD were performed using logistic regression.

Results:

We found no association between residential road and railway noise exposure 5 years before mammogram, and having a mixed/dense vs. a fatty mammogram, and no interaction with menopausal status, BMI, HRT use, and railway noise exposure, for analyses on road traffic noise.

Conclusion:

The present study does not suggest an association between residential traffic noise exposure and subsequent MD in a cohort of middle-aged Danish women.

Background

Traffic noise exposure has been associated with estrogen receptor (ER) negative breast cancer [1, 2]. Proposed mechanisms for this association include sleep disturbance, as it disrupts the circadian rhythm and entails suppression of melatonin, which holds anti-carcinogenic properties, including DNA repair and modulation of the immune response [3-6]. Furthermore, traffic noise may act as a stressor; provoking a typical stress-response by activation of the hypothalamus-pituitary-adrenal axis [7]. This entails increased levels of cortisol, catecholamines, and oxidative stress [8-10].

One of the strongest risk factors for breast cancer is mammographic breast density (MD); referring to the amount of radiologically dense breast consisting of epithelial or stromal tissue, that appears light on a mammogram, whereas fat tissue appears dark [11]. Women with highly dense breasts (>75% density) have a four-to-six fold increased breast cancer risk compared to women with fatty breasts with low density (<25%) [12]. MD decreases with age, number of childbirths, and increasing Body Mass Index (BMI), and increases with hormone therapy (HT) use [11, 13]. Little is known about other determinants of MD, including environment, and how high MD contributes to breast cancer risk [12].

MD has been found to be higher among women living in urban compared to non-urban areas, but the mechanism behind this association is unknown [14-16]. Whereas one study has suggested that air pollution may be the causal factor [17], two other studies have not found an association between air pollution and MD [16, 18]. No study has, to the best of our knowledge, examined a possible association between traffic noise and MD, but given that traffic noise is more prevalent in urban areas, this could potentially be another causal agent explaining the higher MD found here.

This study investigated the association between exposure to residential traffic noise and MD. Furthermore, we examined effect modification by menopausal status, BMI, HT, and railway noise.

Methods and material

Study population

A detailed description of the Diet, Cancer and Health (DCH) cohort is published in Tjønneland, 2007 [19]. Briefly, 79,729 women were invited to participate from 1993-97. Inclusion criteria were 50-64 years of age, residence in the greater Copenhagen or Aarhus area, and no previous cancer diagnosis in the Danish Cancer Registry. In total, 29,875 women accepted the invitation and filled in a baseline questionnaire. Trained personnel collected anthropometrics.

Using the personal identification number, we linked the cohort to the Copenhagen Mammography Screening Program, which started in 1991 and targeted approximately 40,000 women aged 50-69 years at initiation of each biennial screening round [20]. 7,507 DCH-participants were subsequently invited into the Program. Of these, 1,158 women did not participate, and 646 had breast cancer detected at their first screening and did therefore not have MD assessed. Thus, the study population consisted of 5,703 women.

Exposure assessment

Detailed description of exposure assessment is available in Sørensen, 2014 [1]. Briefly, residential address history was collected for all participants between July 1987 and 2011, using the Danish civil registration system. Road traffic and railway noise exposure was calculated using SoundPLAN, implementing the Nordic prediction method. This calculates equivalent continuous A-weighted sound pressure level (L_{Aeq}) for each address, when information on a series of traffic and topographic parameters is available. Input variables were: points for noise estimation (geographical coordinates and height (floor) for each residential address), building polygons, and traffic information on road (annual average daily traffic, vehicle distribution (light/heavy), travel speed and road type) [21] and railway (annual average daily train lengths, train types, travel speed (obtained from BaneDanmark, which is operating and developing the Danish state railway network)) links.

Traffic noise was calculated at the most exposed facade of the dwelling at each address for day (L_d ; 07:00–19:00h), evening (L_e ; 19:00–22:00h), and night (L_n ; 22:00–07:00h), and expressed as L_{den} (den=day, evening, night). A 5 and 10 dB penalty was applied to evening and night, respectively. For railway noise, all noise barriers along the railway were included in the model, and the daily train lengths are given for 1997 and 2011. For road traffic noise, no information was available on noise barriers or road surfaces. Exposure to road traffic noise was calculated for the years 1990, 1995, 2000, 2005 and 2010. Traffic noise for the year 1990 was used as a proxy for the period July 1st, 1987 to June 30th, 1992, the year 1995 was a proxy of the period July 1st, 1992 to June 30th, 1997, etc.

Outcome

Mammography screening in the municipality of Copenhagen was a centralized program. All screens were taken by radiographers or X-ray nurses, and evaluated independently by two radiologists. A two-view mammography, craniocaudal and oblique, was performed at the initial screening. MD was dichotomized into fatty breast, equivalent to Breast Imaging Reporting and Data System (BI-RADS) [22] density code 1 and part of code 2, and mixed/dense breast, equivalent to part of BI-RADS code 2, and code 3 or 4. Women with a negative screening test and fatty breasts were scheduled to have only an oblique view at their next screening, whereas women with a negative screening test and mixed/dense breasts were scheduled for another two-view mammogram. MD was not coded for positive screening mammograms. This dichotomous outcome for MD has previously been successfully utilized in earlier studies, showing the expected association with cancer risk [23], and it has been validated against the BI-RADS density scores, with good agreement [24]. We used MD from first screening after cohort baseline.

Statistical analyses

We investigated the association between residential traffic noise exposure and mixed/dense MD with logistic regression. Results are presented as odds ratios (OR) with 95% confidence intervals (CI).

Exposure to road and railway noise was modelled as 5-year mean exposure before mammography, taking all present and historical addresses in that period into account.

Analyses were conducted in three models with increasing adjustment: Model 1) Crude, adjusted for age only; Model 2) As model 1, and additionally adjusted for opposite noise source (road/railway) and known MD determinants: BMI (continuous, kg/m²), use of hormone replacement therapy (HRT) (categorical: never/former/current), duration of HRT use (continuous, years), nulliparous (categorical: yes/no), number of children (continuous), history of benign breast disease (categorical: yes/no), and menopausal status (categorical: premenopausal / postmenopausal); Model 3) As model 2, and additionally adjusted for breast cancer risk factors: alcohol use (categorical: yes / no), alcohol intake (continuous: g/day), leisure time physical activity (categorical: yes/no), and education (categorical: ≤7 years/8-10 years/> 10 years). Additional adjustment for air pollution (NO₂ and NO_x in µg/m³), smoking status (current / former / never), smoking duration (years), smoking intensity (g/day), and age at first birth did not affect the results, and were therefore not included in the final models.

Since an association has been proposed between traffic noise and obesity [25], which is strongly inversely associated with MD [26], including BMI as a covariate could result in over-adjustment, as BMI may in fact be a mediating variable. Hence, as a sensitivity analysis, we conducted the analyses both with and without adjustment for BMI. Effect modification by

menopausal status, BMI, HT-use, and railway noise exposure was investigated by introducing an interaction-term into the model and tested by the likelihood ratio test statistic.

The GENMOD procedure in SAS version 9.3 (SAS Institute Inc., Cary, NC) was used to conduct the analyses. P-values < 0.05 were considered statistically significant. Results are presented as odds ratios (OR) with 95 % confidence intervals. For road traffic noise, they were calculated in continuous analyses per 10 dB higher level of exposure to road traffic noise, as well as in categorical analyses, based on quartiles of exposure. For railway noise, the association was investigated categorically in categories of 0 dB, <55 dB and ≥ 55 dB.

Results

Of the 5,703 women available for the study, we excluded 121 with a cancer diagnosis before baseline, 106 with missing exposure information, and 216 with missing information on covariates, leaving 5,260 women in the analytical cohort.

Women with mixed/dense breasts were younger and less likely to be postmenopausal. They had a lower median BMI, and consumed more alcohol. They were more likely to have a long education, smoke, currently use HT, be physically active, nulliparous, and have a history of benign breast disease. The magnitude of road traffic noise exposure was similar across MD-status. Railway noise exposure was somewhat less frequent among women with mixed/dense breasts (**Table 1**). The correlation (R_{Spearman}) between railway and road traffic noise was low: -0.03, whereas the correlation between L_{den} , L_d , L_e , and L_n road was very high; with all $R_s > 0.99$.

We did not find an association between traffic noise and MD for either road or railway traffic noise: The linear estimate for road traffic noise per 10 dB increment was OR 0.99, 95% confidence interval (CI) (0.91-1.08) in the crude model, and OR 0.94, 95% CI (0.86-1.03) in both Models 2 and 3. Results of Model 2 and 3 for the categorical analyses are presented in **Figure 1**. These also showed no association. . Finally, there was no effect modification of the association between road traffic noise and MD by menopausal status, BMI, HT-use, or railway noise (all $p > 0.05$).

We investigated the association between traffic noise and MD without BMI adjustment, since this could potentially be a mediating variable. However, this did not affect the association

(E.g. linear estimate, model 2, road traffic noise with adjustment for BMI: OR 0.94, 95% CI (0.86-1.03), without adjustment for BMI: OR 0.95, 95% CI (0.88-1.04).

Discussion

The results of the present study does not suggest an association between residential traffic noise exposure and subsequent MD in middle-aged women, neither overall, nor for subgroups defined by menopausal status, BMI, HT-use, or railway noise exposure.

This is the first study of its kind. Hence, the findings require reproduction. The only two studies on traffic noise and breast cancer, for which MD is a strong risk factor [11], found that traffic noise was associated with an increased risk of ER-negative tumors, which account for 20% of all breast cancers [1, 2]. Our findings do not suggest that traffic noise operates via MD as an intermediary phenotype in relation to ER-negative breast cancer. There is no convincing evidence that the association between MD and breast cancer differ by ER status in postmenopausal women [27]. Our results of no association is, however, in accordance with the fact that these two previous studies does not find an association with overall or ER-positive breast tumors.

Since an association has been proposed between traffic noise and obesity [25, 28], which is strongly inversely associated with MD [26, 29], including BMI as a covariate might result in over-adjustment. However, excluding BMI resulted in associations of similar magnitude as models with adjustment.

We excluded 646 women who were diagnosed with breast cancer at the initial screening, as they were never assigned an MD-value, but instead referred to additional testing. These women have likely had a high MD, since this is directly associated with breast cancer risk [11]. As traffic noise has been found associated with breast cancer [1, 2], one could speculate that they also had higher traffic noise exposure. Thus, selection bias could affect the study. This is, however, speculative and since we have no MD information available for the excluded women, we cannot account for how this affect the results. However, given the

consistent null-results across sub-groups in the present study, as well as across exposure categories in the categorical analyses, it seems unlikely that including these women would have completely reversed the findings.

The detailed traffic noise modeling is a prominent study strength. Furthermore, covariate information was collected before mammography, and is thus unaffected by MD-status. Women participating in the DCH cohort are better educated and have higher income than women who chose not to accept the invitation into the study cohort [19]. They also have a lower mortality, including cancer-specific mortality, over time [30]. Women participating in the Copenhagen Mammography Screening Programme have previously been shown to be older, more likely to not be in contact with a primary care physician or to attend dental care, and more likely to have a medium rather than a high or low education, and less likely to be married/cohabiting, and a Danish citizen [31]. Thus, selection bias may affect the results of the present study, as both cohorts are most likely affected by a healthy participant effect, with inclusion primarily of participants with a generally healthy lifestyle. This self-selection bias is merely a problem, if a third factor, related to both exposure and outcome is also determinative of participation [32]. Unfortunately, however, we do not have information on differences in traffic noise exposure between participants and non-participants, but only of these demographic covariates, rendering it difficult to assess the magnitude of this bias in our study. However, selection into the cohort is merely a problem in relation to the external validity. For the present study, representativeness of participants may also be affected by the fact that we included only Copenhagen residents, who have higher residential traffic noise exposure than the remainder of Danish women: The median (5; 95 percentiles) road traffic noise exposure 5 years before mammogram in the present study population was 61.3 (50.6; 72.5) dB, compared to a median (5; 95 percentiles) exposure of 57.1 (48.8; 70.1) dB 5 years before baseline among all women participating in the Diet, Cancer and Health cohort. However, this is an

advantage if an association exists only above a certain threshold. A major study limitation is the simplified, MD-data, reducing a more complex outcome to a binary variable. The binary classification of MD has been validated previously; showing the expected associations with cancer risk [23], as well as good agreement with the BI-RADS density scores [24]. However, we cannot preclude that this simplified classification of MD entails outcome misclassification to a degree disallowing us to detect a potential association. Future studies on traffic noise and MD would thus benefit from using the BI-RADS density scores. Lack of information on bedroom orientation, time spent at home, and window opening habits, which affects actual noise exposure, could result in exposure misclassification. However, this is most likely unrelated to MD, and is thus expected to be non-differential; drawing the estimates towards the null.

In conclusion, the study does not suggest an association between residential traffic noise exposure and subsequent MD in middle-aged women. A potential association between traffic noise and ER-negative breast cancer does not seem to operate via a pathway of MD.

Acknowledgements

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The authors declare no conflicts of interest.

Compliance with ethical standards:

The study complies with the current laws of Denmark, in which the study was performed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Table and Figure Legends

Table 1. *Characteristics of study participants¹.*

	Total cohort	Mammographic Breast Density	
	N = 5,260	Low (fatty) N = 2,298	High (Mixed/dense) N = 2,962
Age at mammogram, years	57.4 (51.9-65.2)	58.8 (52.0-65.6)	56.2 (51.8-64.9)
Postmenopausal,%	83.8	88.0	80.6
BMI (kg/m ²)	25.1 (19.7-34.7)	26.8 (20.9-37.4)	24.1 (19.3-31.9)
Education, years %			
≤7	35.3	41.4	30.7
8-10	49.1	47.6	50.3
>10	15.6	11.1	19.1
Alcohol intake, g/day ²	7.9 (0.6-44.8)	6.9 (0.5-43.1)	9.9 (0.6-46.8)
Abstainers,%	3.4	3.7	3.2
Smoking status,%			
<i>Never</i>	36.8	37.1	36.6
<i>Former</i>	21.8	22.2	21.5
<i>Current</i>	41.4	40.7	41.9
Leisure-time physically active,%	48.2	46.2	49.7
Nulliparous,%	14.7	11.1	17.5
Number of children	2 (0-4)	2 (0-4)	2 (0-3)
History of benign breast disease,%	12.3	8.5	16.1

HT user,%			
<i>Never</i>	53.3	57.9	49.7
<i>Former</i>	16.0	18.2	14.4
<i>Current</i>	30.7	24.0	36.0
Duration of HT-use ³	4 (0.5-18.0)	4.0 (0.5-18.0)	4.0 (0.5-18.0)
Road traffic noise exposure, dB ⁴	61.3 (50.6-72.5)	61.3 (50.5-72.6)	61.3 (50.6-72.4)
Railway noise exposed,% ⁵	23.8	24.5	23.3
¹ Median and 5-95 percentile, unless otherwise stated.			
² Among drinkers			
³ Among ever users			
⁴ 5-year mean exposure before mammogram			
⁵ During 5 year period before mammogram			

Figure 1: Association between time-weighted mean exposure to traffic noise during the 5-year period before mammogram, and OR for mixed/dense mammogram. A) Road traffic noise in quartiles (N = 1,315 for each quartile). B) Railway noise in categories (Non-exposed, N = 4,042; Exposed ≤ 55 dB, N = 817; Exposed > 55 dB, N = 401). Model 1) Crude, adjusted for age only; Model 2) As model 1, and additionally adjusted for opposite noise source (road/railway) and known MD determinants: BMI (continuous, kg/m²), use of hormone replacement therapy (HRT) (categorical: never/former/current), duration of HRT use (continuous, years), nulliparous (categorical: yes/no), number of children (continuous), history of benign breast disease (categorical: yes/no), and menopausal status (categorical: premenopausal / postmenopausal); Model 3) As model 2, and additionally adjusted for breast cancer risk factors: alcohol use (categorical: yes / no), alcohol intake (continuous: g/day), leisure time physical activity (categorical: yes/no), and education (categorical: ≤ 7 years/8-10 years/ > 10 years)