

## **A systematic analysis of mutual effects of transportation noise and air pollution exposure on myocardial infarction mortality: a nationwide cohort study in Switzerland**

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## **Abstract**

**Aims:** The present study aimed to disentangle the risk of the three major transportation noise sources – road, railway and aircraft traffic– and the air pollutants NO<sub>2</sub> and PM<sub>2.5</sub> on myocardial infarction (MI) mortality in Switzerland based on high quality/fine resolution exposure modelling.

**Methods and Results:** We modelled long term exposure to outdoor road traffic, railway and aircraft noise levels, as well as NO<sub>2</sub> and PM<sub>2.5</sub> concentration for each address of the 4.40 million adults (>30y) in the Swiss National Cohort (SNC). We investigated the association between transportation noise/air pollution exposure and death due to MI during the follow-up period 2000 to 2008, by adjusting noise (L<sub>den</sub>(Road), L<sub>den</sub>(Railway), L<sub>den</sub>(Air)) estimates for NO<sub>2</sub> and/or PM<sub>2.5</sub> and vice versa by multipollutant Cox regression models considering potential confounders. Adjusting noise risk estimates of MI for NO<sub>2</sub> and/or PM<sub>2.5</sub> did not change the hazard ratios per 10 dB increase in road traffic (without air pollution: 1.032, 95% CI: 1.014-1.051, adjusted for NO<sub>2</sub> and PM<sub>2.5</sub>: 1.034, 1.014-1.055), railway traffic (1.020, 1.007-1.033 vs. 1.020, 1.007-1.033) and aircraft traffic noise (1.025, 1.006-1.045 vs. 1.025, 1.005-1.046). Conversely, noise adjusted hazard ratios for air pollutants were lower than corresponding estimates without noise adjustment. HR per 10 µg/m<sup>3</sup> increase with and without noise adjustment were 1.024 (1.005-1.043) vs. 0.990 (0.965-1.016) for NO<sub>2</sub> and 1.054 (1.013-1.093) vs. 1.019 (0.971-1.071) for PM<sub>2.5</sub>.

**Conclusion:** Our study suggests that transportation noise is associated with MI mortality, independent from air pollution. However, air pollution studies not adequately adjusting for transportation noise exposure may overestimate the cardiovascular disease burden of air pollution.

**Keywords:** Noise, Road traffic, Railway, Aircraft, Air pollution

## Introduction

Several meta-analyses have highlighted the link between transportation noise and cardiovascular health. Babisch<sup>1</sup> reported a risk increase of 1.08 (95% CI; 1.04-1.13) for coronary heart diseases per 10 dB(A) increase in road traffic noise levels, and positive associations between myocardial infarction (MI) and exposure to road traffic and to aircraft noise have also been reported by Vienneau.<sup>2</sup> Air pollutants have also been shown to impact cardiovascular health. A recent meta-analysis focusing on MI reported a relative risk of 1.011 (95% CI; 1.006-1.016) and 1.025 (95% CI; 1.015-1.036) per 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$  and  $\text{PM}_{2.5}$  concentrations, respectively.<sup>3</sup> Transportation noise and air pollution impact health through different pathways,<sup>4</sup> though they share many biologic pathways.

Mutual confounding is also of concern, since transportation noise and air pollution mainly originate from traffic.  $\text{NO}_2$  and road traffic noise are often highly spatially correlated; aircraft and railway noise are less correlated with air pollution<sup>5,6</sup> and thus offer the potential to elucidate their mutual independent impact on health. Correlations between long-term traffic noise and air pollution ranging from 0.16 to 0.72 were reported in a systematic review.<sup>7</sup> However, Fecht and colleagues<sup>8</sup> found that correlation depends on the spatial unit, with largest ranges seen when comparing across smaller vs. larger spatial units. Finally, correlation between transportation noise and air pollution has been shown to decrease with decreasing measurement error demonstrating the need of high quality exposure modeling.<sup>9</sup> Various studies have investigated the link between co-exposure to air pollution and noise, and CVD mortality. Some report independent noise effects<sup>6, 10-14</sup> while others suggest attenuation of the noise effect estimates after adjustment for air pollution thus indicating confounding or antagonistic interaction<sup>15, 16</sup> or did not adjust for exposure to air pollutants.<sup>17, 18</sup> A limitation in many of these studies, including our own previous analysis on this cohort,<sup>19</sup> is the fact that they do not model exposure at the same spatial scale. Depending on the main interest of a

study, the model used for adjustment may be less accurate than the main exposure model which would then yield partial confounding adjustment. A systematic review of nine studies comprising outcomes such as hospital discharge registers, self-reported medication intake, and mortality found that less than 10% of the effect estimate of noise was attenuated after adjustment for air pollution or vice versa<sup>7</sup> and thus concluded that confounding of cardiovascular effects by noise or air pollution is low. However, improvements in exposure assessment may change the situation.

As per our previous cohort study,<sup>20, 21</sup> we developed high-quality models to assess road, railway, and aircraft noise. In this study, we further included highly detailed NO<sub>2</sub> and PM<sub>2.5</sub> exposures to investigate the independent associations between transportation noise and air pollution at the participants' residence with MI mortality.

## **Methods**

### ***Study population***

The SNC probabilistically links national census data with mortality and emigration records.<sup>22</sup> The data used in our study is based on the 4 December 2000 census and on mortality and emigration data for the period 5 December 2000 to 31 December 2008 and contains 7.28 million observations. We excluded subjects below 30 years of age (n=2.59 million) as myocardial mortality is very rare in this age group, observations for which residential coordinates were missing (n=0.19 million) or no buffers for the prediction of the air pollution levels could be calculated (n=0.01 million), subjects living in an institution such as special-care homes (n=0.25 million), and observations for which the cause of death was imputed (0.03 million) leaving 4.40 million observations for the analyses. The outcome under investigation was primary causes of death from MI (ICD-10: I21-I22). Immediately after death, primary and underlying causes of deaths are recorded by a physician, possibly verified

later by autopsy. Eventually, coding of causes is done centrally by the Federal Statistical Office using the German Modification of the ICD-10 system. The SNC was approved by the cantonal ethics boards of Bern and Zurich.

### ***Noise exposure data***

Within the framework of the SiRENE project (Short and Long Term Effects of Transportation Noise Exposure), we built a Swiss-wide noise exposure database for the year 2001 which included the three major transportation noise sources in Switzerland: road traffic, railway and aircraft noise.

The noise exposure database is described in detail elsewhere.<sup>23</sup> In brief, road traffic noise emissions were calculated using sonROAD<sup>24</sup> while propagation was computed via the propagation model of StL-86<sup>25</sup>. For railway noise, the emissions were calculated using sonRAIL<sup>26</sup> and propagation was computed using the Swiss railway noise model SEMIBEL.<sup>27</sup> Aircraft noise exposure estimates were calculated via FLULA2.<sup>28</sup>

For each building in Switzerland, transportation noise exposure was estimated at pre-defined façade points with a maximum of 3 per facade.<sup>23</sup> For each façade point, we calculated the  $L_{den}$  for each noise source. Using the available geocodes and the information about floor of residence, we linked participants to their respective dwelling unit to assign noise exposure. Exposure was assigned on the basis of the façade point per dwelling unit with the highest  $L_{den}$  value. If information on the floor of residence was not available, we assigned the noise estimates corresponding to the middle floor of the building.

### ***NO<sub>2</sub> exposure***

The fine scale NO<sub>2</sub> model was based on data from cantonal air pollution monitoring authorities of Genève, Vaud, Neuchâtel, Jura, Fribourg, Berne, Basel-City, Basel-Country, Solothurn, Aargau, Ticino, the Inluft and Ostluft network, and the Sapaldia team.<sup>29</sup> The data

comprised 9,469 data points from 14-days passive measurements collected from 2000–2008 at a total of 1,834 locations. Missing data was imputed by considering available values from other monitoring sites within the same network based on inverse distance weighting. Subsequently, annual mean concentration for each year and site were calculated, and were regressed against various spatial predictors as outlined in the supplementary material including table S1.

The prediction for the SNC at residential address was performed for each year, from 2000–2008, and then averaged to obtain a long-term NO<sub>2</sub> exposure estimate for each participant.

### ***PM<sub>2.5</sub> exposure***

Daily PM<sub>2.5</sub> at 100 m grid cells across Switzerland was predicted for 2003–2008 from satellite, land use and meteorological data as described in detail in de Hoogh et al, 2017.<sup>30</sup> We used aerosol optical depth (AOD) data for the period of 2003–2008 at 1×1 km resolution and combined it in 4-staged modelling approach<sup>31</sup> with various predictors (see supplementary material) and with PM<sub>2.5</sub> ground measurements to refine model resolution to address level. The annual models for the period 2003–2008 were used to predict PM<sub>2.5</sub> exposure for each SNC study participant, and the average over the whole period was used as a long term PM<sub>2.5</sub> exposure measure in the epidemiological analysis.

### ***Statistical Analysis***

We analysed the data using the Cox proportional hazards model with age at date of entry into the cohort as the underlying time variable. Participants were followed until emigration, death or end of follow-up. In order to capture long term effects of noise and air pollution, exposure values representing the average during the follow-up period as described above were added as static covariate into the model. L<sub>den</sub> variables were left censored at 35 dB (road traffic) or 30

dB (railway and aircraft noise). Linear hazard ratios (HR) were computed using multipollutant models adjusted for potential confounders excluding NO<sub>2</sub> and PM<sub>2.5</sub> in a first step, and stepwise including them in a second step. Additional potential confounders included in the model were sex, neighborhood index of socio-economic position,<sup>32</sup> civil status, educational level, nationality, and mother tongue using the categories depicted in Table 1. The latter was selected as it is expected to represent cultural variability in health behaviour in Switzerland.<sup>33</sup> To satisfy the Cox proportional hazard assumption, we stratified the baseline hazard function on the following variables; sex, neighbourhood index of socio-economic position, civil status, and education level. Potential multicollinearity between exposure variables in the Cox proportional hazards models was evaluated using the variance inflation factor (VIF).

In addition to linear HRs, we also conducted categorical noise analyses using L<sub>den</sub>(Road) in 5 dB and L<sub>den</sub>(Railway) and L<sub>den</sub>(Air) in 10 dB categories to explore the effect of combined exposures of noise respectively with NO<sub>2</sub> and PM<sub>2.5</sub>. All analyses were conducted with the statistical software R and the package “survival”.<sup>34, 35</sup>

## Results

The cohort contained 4.40 million observations amounting to 33.67 million person-years. There were 19,261 deaths from MI. The characteristics of the study population are displayed in table 1.

For the NO<sub>2</sub> exposure model, R<sup>2</sup> values independently validated with NABEL data for each year, ranged from 0.70 to 0.82 with highest value for the year 2002 (table S2). R<sup>2</sup> values for 10 fold cross-validated elastic net models were  $\geq 0.60$  and the R<sup>2</sup> values for elastic net combined with kriged residuals were  $\geq 0.84$  (table S2). For the PM<sub>2.5</sub> model, cross validated temporal and spatial R<sup>2</sup> values ranged from 0.81 to 0.92 and 0.59 to 0.80.<sup>30</sup>

Mean NO<sub>2</sub> and PM<sub>2.5</sub> exposure concentrations were 26.1 and 20.2 µg/m<sup>3</sup> as depicted in figure S1 of supplemental material. The highest Spearman's correlation coefficient between the noise and the air pollution variables was 0.44, observed between L<sub>den</sub>(Road) and NO<sub>2</sub> (table 2). Correlation between PM<sub>2.5</sub> and road (0.27), railway (0.20) and aircraft noise (0.24) was rather low. The correlation coefficient between NO<sub>2</sub> and PM<sub>2.5</sub> was 0.62.

Without considering air pollution exposure, the hazard ratio for MI mortality per 10 dB noise increase was 1.032 (1.014-1.051) for road traffic, 1.020 (1.007-1.033) for railway traffic and 1.025 (1.006-1.045) for aircraft traffic (Table S3). Adjustment for air pollution exposure had little impact on the HR of the linear exposure-response relationship for all three transportation noise sources (Figure 1). Categorical models showed a slight attenuation of the noise estimates for MI in all road traffic noise exposure categories after adjustment for both air pollutants (table S4). A similar pattern was seen for the association between MI mortality and railway noise (table S5) but not aircraft noise (table S6).

Without considering noise exposure, the hazard ratio for MI mortality per 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> was 1.024 (1.005-1.043) and per 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> 1.052 (1.013-1.093) (table S7). In this case risk estimates for air pollution exposure unadjusted for noise tended to decrease upon adjustment for all noise sources (Figure 2).

Multicollinearity between noise and air pollution exposure measures was not critical. In fully adjusted multipollutant models VIF was 1.25 for road traffic noise, 1.06 for railway traffic noise, 1.10 for aircraft noise, 1.65 for PM<sub>2.5</sub> and 1.92 for NO<sub>2</sub>.

Synergistic or antagonistic effects between road traffic noise and PM<sub>2.5</sub> or NO<sub>2</sub> could not be seen in linear-exposure response models including interaction terms. Similarly, testing interactions in categorical models to evaluate potential thresholds for interaction did not reveal any relevant interactions for PM<sub>2.5</sub> (table 3) or NO<sub>2</sub> (table S8) with road traffic noise



exposure. For instance, interaction terms were close to unity for people exposed to high levels of noise and air pollutants.

## **Discussion**

Using fine scale exposure modelling, this study demonstrates that the association between transportation noise and death from MI is stable to air pollution adjustment but not vice versa.

NO<sub>2</sub> originates mainly from road traffic while PM<sub>2.5</sub> arises from multiple sources including those not related to traffic such as industrial areas, power plants and wood burning and is thus less correlated to road traffic noise than NO<sub>2</sub>. In multipollutant air pollution studies, the impact of NO<sub>2</sub> on mortality was independent from PM<sub>2.5</sub>.<sup>36</sup> Strikingly many of the air pollution studies have not adjusted for transportation noise and thus noise as confounder in these studies cannot be ruled out, in particular for associations with NO<sub>2</sub>. In the present study we found that the effect estimates of both air pollutants were attenuated upon inclusion of the noise variables in the models, which indicates a confounding effect of transportation noise on air pollution. This finding would imply that many air pollution studies, which have not adjusted for transportation noise, may have overestimated the effects of air pollution on MI mortality.

On the other hand, our associations between noise and MI mortality were robust to PM<sub>2.5</sub> adjustment and only slightly attenuated if NO<sub>2</sub> was considered in the analyses. However, we were not able to evaluate the effects of ultrafine particles (UFP) due to lack of a national model. Of all air pollutants, UFP may have the most similar propagation behaviour to noise. Ultrafine particles are moderately correlated to road traffic noise<sup>37-41</sup> and are a known risk factor for cardiovascular morbidity.<sup>42, 43</sup> Ultrafine particles, however, are poorly correlated with PM<sub>2.5</sub> and we cannot fully rule out that road traffic noise exposure is confounded by UFP. However, UFP are expected to be poorly correlated with railway noise in Switzerland,

since railways are electrified, and thus the corresponding risk estimates are unlikely to suffer from such a bias.

Noise and air pollution exposure were both estimated at the residential address and thus bias due to different spatial resolution is expected to be minimized. Such bias may have occurred in our previous analysis<sup>20,21</sup> and other studies.<sup>7, 44-46</sup> The models are further comparable in that both the noise and air pollution estimates reflect the ambient exposure, rather than indoor exposure, and therefore suffer similar bias. Nevertheless, bias cannot be completely excluded if accuracy of the models would differ; although  $R^2$  in external validations available for NO<sub>2</sub> and road traffic noise were found to be similar (0.70-0.82 for all models).

In previous analyses conducted with the same cohort and noise data,<sup>19</sup> the noise effect models were adjusted for NO<sub>2</sub> derived from PolluMap, a 200×200m dispersion model for the year 2010. Here we improved the spatial resolution of the NO<sub>2</sub> exposure estimate, from the grid level to the address level, by further modelling with an extensive passive sampling network distributed across the country. PolluMap was included in this new NO<sub>2</sub> model as a predictor variable, and was found to be the most relevant predictor for NO<sub>2</sub>. However including additional factors like road and population density around the place of residence produced improved NO<sub>2</sub> exposure estimates (Table S1). The correlation between NO<sub>2</sub> estimates from PolluMap used in our previous study<sup>19</sup> and from the NO<sub>2</sub> estimates used here is 0.83. In contrast to our previous analyses we did not consider the intermittency ratio - a measure of noise eventfulness - as an additional noise metric to the Leq.

Our results for noise are in line with most of the criteria for evaluating causality proposed by Sir Arthur Hill<sup>47</sup> such as consistency,<sup>48, 49</sup> temporality, biological gradient, plausibility<sup>50</sup> and coherence<sup>51</sup>, although specificity cannot be expected for the multifactorial disease MI. The effect sizes are small and not of clinical relevance for an individual. Overall, however, public health burden is relevant as many people are exposed to transportation noise and air pollution.

A previous health impact assessment for Switzerland concluded that transportation noise and air pollution caused 6,000 and 14,000 years of life lost in 2010.<sup>52</sup>

### ***Strength and limitations***

The strengths of this study include the large study population and the long follow-up time. We developed a detailed noise exposure model, which allowed for an individual exposure assessment at the address and floor level. Our air pollution models for NO<sub>2</sub> and PM<sub>2.5</sub> were both based on novel approaches using high resolution input data. Potential selection bias is minimal in this nationwide study based on census data. Finally, both the noise and air pollution models have been validated with independent data. The road traffic noise model for 2011 has been validated using 99 weekly measurements conducted in 2016 yielding an average difference between modelling and measurements of +0.5 dB(A) with a standard deviation of 4.0 dB(A).<sup>53</sup> This good agreement was obtained despite a time lag of five years between modelling and measurements demonstrating stable noise exposure in our study area. Similar stability is also expected for the time between baseline, time at which the noise exposure was assigned, and follow-up of this cohort study.

Though our models are adjusted for socioeconomic status and other demographic variables, we could not adjust for lifestyle and smoking as this information is not available in the SNC. We therefore cannot rule out that residual confounding of lifestyle may play a role for our analyses, although no indications for this were seen in a previous SNC noise study.<sup>6</sup> However, the non-significant effect estimates observed for NO<sub>2</sub> and PM<sub>2.5</sub> after noise adjustment may suffer from residual confounding. In Switzerland, mortality from cardiovascular diseases has been shown to be higher in rural areas,<sup>33</sup> where air pollution is lower on average. This mortality pattern is likely due to individual risk factors and the number of health facilities associated with urban areas, and thus correlated with NO<sub>2</sub> and PM<sub>2.5</sub>, which may not be fully

considered in our adjustment set. Since noise exposure varies on a very small scale, this type of bias is likely less relevant for these estimates.

Further, despite high quality exposure modelling, exposure misclassification is unavoidable due to uncertainty in the input data. For noise, uncertainty may arise from exposure assignment based on estimates for the loudest outdoor facade point while no information was available regarding indoor noise levels and noise attenuation factors. However, the impact of such misclassification on the study results are similar for noise and air pollution, and are more likely to dilute the association than introduce a spurious effect.

## **Conclusion**

In this analysis on MI, mutually adjusted with fine-scale noise and air pollution modelling at address level, a consistent exposure-response association between long term transportation noise exposure and MI mortality was observed. This association was independent from the effects observed for air pollution. Conversely, air pollution effects decreased upon adjustment for transportation noise exposure. Future studies need high quality exposure models for both air pollution and transportation noise to better understand their clinical and public health relevance for cardiovascular disease in various settings.

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## **Conflict of interests**

The authors declare no conflict of interests.

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## References

1. Babisch W. Updated exposure-response relationship between road traffic noise and coronary heart diseases: A meta-analysis. *Noise and Health* 2014; **16**:1-9.
2. Vienneau D, Schindler C, Perez L, Probst-Hensch N, Rössli M. The relationship between transportation noise exposure and ischemic heart disease: a meta-analysis. *Environmental research* 2015; **138**:372-380.
3. Mustafić H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, Périer MC, Marijon E, Vernerey D, Empana JP, Jouven X. Main air pollutants and myocardial infarction: A systematic review and meta-analysis. *JAMA* 2012; **307**:713-721.
4. Münzel T, Sørensen M, Gori T, Schmidt FP, Rao X, Brook J, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part I—epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. *European Heart Journal* 2016:ehw269.
5. Dratva J, Phuleria HC, Foraster M, Gaspoz J-M, Keidel D, Künzli N, Liu LS, Pons M, Zemp E, Gerbase MW. Transportation noise and blood pressure in a population-based sample of adults. *Environmental health perspectives* 2012; **120**:50.
6. Huss A, Spoerri A, Egger M, Roosli M. Aircraft noise, air pollution, and mortality from myocardial infarction. *Epidemiology* 2010; **21**:829-36.
7. Tetreault LF, Perron S, Smargiassi A. Cardiovascular health, traffic-related air pollution and noise: are associations mutually confounded? A systematic review. *International journal of public health* 2013; **58**:649-66.
8. Fecht D, Hansell AL, Morley D, Dajnak D, Vienneau D, Beevers S, Toledano MB, Kelly FJ, Anderson HR, Gulliver J. Spatial and temporal associations of road traffic noise and air pollution in London: Implications for epidemiological studies. *Environment international* 2016; **88**:235-242.
9. Foraster M, Künzli N, Aguilera I, Rivera M, Agis D, Vila J, Bouso L, Deltell A, Marrugat J, Ramos R. High blood pressure and long-term exposure to indoor noise and air pollution from road traffic. *Environmental health perspectives* 2014; **122**:1193.
10. Correia AW, Peters JL, Levy JI, Melly S, Dominici F. Residential exposure to aircraft noise and hospital admissions for cardiovascular diseases: multi-airport retrospective study. 2013.
11. Floud S, Blangiardo M, Clark C, de Hoogh K, Babisch W, Houthuijs D, Swart W, Pershagen G, Katsouyanni K, Velonakis M, Vigna-Taglianti F, Cadum E, Hansell AL. Exposure to aircraft and

- road traffic noise and associations with heart disease and stroke in six European countries: a cross-sectional study. *Environmental Health* 2013; **12**:89.
12. Gan WQ, Davies HW, Koehoorn M, Brauer M. Association of long-term exposure to community noise and traffic-related air pollution with coronary heart disease mortality. *Am J Epidemiol* 2012; **175**:898-906.
  13. Hansell AL, Blangiardo M, Fortunato L, Floud S, de Hoogh K, Fecht D, Ghosh RE, Laszlo HE, Pearson C, Beale L, Beevers S, Gulliver J, Best N, Richardson S, Elliott P. Aircraft noise and cardiovascular disease near Heathrow airport in London: small area study. *BMJ : British Medical Journal* 2013; **347**.
  14. Sorensen M, Andersen ZJ, Nordsborg RB, Jensen SS, Lillelund KG, Beelen R, Schmidt EB, Tjonneland A, Overvad K, Raaschou-Nielsen O. Road traffic noise and incident myocardial infarction: a prospective cohort study. *PLoS One* 2012; **7**:e39283.
  15. Beelen R, Hoek G, Houthuijs D, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Armstrong B, Brunekreef B. The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. *Occupational and environmental medicine* 2009; **66**:243-50.
  16. Tonne C, Halonen JI, Beevers SD, Dajnak D, Gulliver J, Kelly FJ, Wilkinson P, Anderson HR. Long-term traffic air and noise pollution in relation to mortality and hospital readmission among myocardial infarction survivors. *Int J Hyg Environ Health* 2016; **219**:72-8.
  17. Seidler A, Wagner M, Schubert M, Dröge P, Pons-Kühnemann J, Swart E, Zeeb H, Hegewald J. Myocardial Infarction Risk Due to Aircraft, Road, and Rail Traffic Noise. *Deutsches Ärzteblatt international* 2016; **113**:407.
  18. Seidler A, Wagner M, Schubert M, Dröge P, Römer K, Pons-Kühnemann J, Swart E, Zeeb H, Hegewald J. Aircraft, road and railway traffic noise as risk factors for heart failure and hypertensive heart disease—A case-control study based on secondary data. *International Journal of Hygiene and Environmental Health* 2016; **219**:749-758.
  19. Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Köpfli M, Pieren R, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Rössli M. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *European Journal of Epidemiology* 2017:1-9.
  20. Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Köpfli M, Pieren R, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Rössli M, group SNCs. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Eur J Epidemiol* 2017; **32**:307–315.
  21. Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Köpfli M, Pieren R, Schmidt-Trucksäss A, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Rössli M, group SNCs. Diurnal variability of transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *International journal of hygiene and environmental health* 2018:epub ahead of print.
  22. Spoerri A, Zwahlen M, Egger M, Bopp M. The Swiss National Cohort: a unique database for national and international researchers. *International journal of public health* 2010; **55**:239-242.
  23. Karipidis I, Vienneau D, Habermacher M, Köpfli M, Brink M, Probst-Hensch N, Rössli M, Wunderli J-M. Reconstruction of historical noise exposure data for environmental epidemiology in Switzerland within the SiRENE project. *Noise mapping* 2014; **1**.
  24. Heutschi K. SonRoad: New Swiss road traffic noise model. *Acta Acustica united with Acustica* 2004; **90**:548-554.
  25. BAFU *Computermodell zur Berechnung von Strassenlärm, Teil 1, Bedienungsanleitung zum Computerprogramm StL-86*; Bundesamt für Umweltschutz: Bern, 1987.
  26. Thron T, Hecht M. The sonRAIL emission model for railway noise in Switzerland. *Acta Acustica United with Acustica* 2010; **96**:873-883.
  27. FOEN *SEMIBEL: Schweizerisches Emissions- und Immissionsmodell für die Berechnung von Eisenbahnlärm*; Swiss Federal Office for the Environment: Berne, 1990.
  28. Thomann G, Bütikofer R, Krebs W. FLULA2 Ein Verfahren zur Berechnung und Darstellung der Fluglärmbelastung, Technische Programm-Dokumentation Version 2.1. In EMPA report, April: 2005.

29. Wüthrich B, Schmid-Grendelmeier P, Schindler C, Imboden M, Bircher A, Zemp E, Probst-Hensch N, Team S. Prevalence of atopy and respiratory allergic diseases in the elderly SAPALDIA population. *International archives of allergy and immunology* 2013; **162**:143-148.
30. de Hoogh K, Héritier H, Stafoggia M, Künzli N, Kloog I. Modelling daily PM<sub>2.5</sub> concentrations at high spatio-temporal resolution across Switzerland. *Environmental Pollution* 2017.
31. Kloog I, Chudnovsky AA, Just AC, Nordio F, Koutrakis P, Coull BA, Lyapustin A, Wang Y, Schwartz J. A new hybrid spatio-temporal model for estimating daily multi-year PM<sub>2.5</sub> concentrations across northeastern USA using high resolution aerosol optical depth data. *Atmospheric Environment* 2014; **95**:581-590.
32. Panczak R, Galobardes B, Voorpostel M, Spoerri A, Zwahlen M, Egger M. A Swiss neighbourhood index of socioeconomic position: development and association with mortality. *Journal of epidemiology and community health* 2012:jech-2011-200699.
33. Chammartin F, Probst-Hensch N, Utzinger J, Vounatsou P. Mortality atlas of the main causes of death in Switzerland, 2008-2012. *Swiss Med Wkly* 2016; **146**:w14280.
34. Therneau Terry M. GPM, *Modeling Survival Data: Extending the Cox Model*. Springer: New York, 2000.
35. TM T *A package for Survival Analysis in S*, 2015.
36. Faustini A, Rapp R, Forastiere F. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. *European Respiratory Journal* 2014; **44**:744-753.
37. Allen RW, Davies H, Cohen MA, Mallach G, Kaufman JD, Adar SD. The spatial relationship between traffic-generated air pollution and noise in 2 US cities. *Environmental research* 2009; **109**:334-342.
38. Can A, Rademaker M, Van Renterghem T, Mishra V, Van Poppel M, Touhafi A, Theunis J, De Baets B, Botteldooren D. Correlation analysis of noise and ultrafine particle counts in a street canyon. *The Science of the total environment* 2011; **409**:564-72.
39. Kheirbek I, Ito K, Neitzel R, Kim J, Johnson S, Ross Z, Eisl H, Matte T. Spatial Variation in Environmental Noise and Air Pollution in New York City. *Journal of Urban Health : Bulletin of the New York Academy of Medicine* 2014; **91**:415-431.
40. Meier R, Cascio WE, Ghio AJ, Wild P, Danuser B, Riediker M. Associations of Short-Term Particle and Noise Exposures with Markers of Cardiovascular and Respiratory Health among Highway Maintenance Workers. *Environmental Health Perspectives* 2014; **122**:726-732.
41. Morelli X, Foraster M, Aguilera I, Basagana X, Corradi E, Deltell A, Ducret-Stich R, Phuleria H, Ragettli MS, Rivera M, Thomasson A, Künzli N, Slama R. Short-term associations between traffic-related noise, particle number and traffic flow in three European cities. *Atmospheric Environment* 2015; **103**:25-33.
42. Du Y, Xu X, Chu M, Guo Y, Wang J. Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. *Journal of Thoracic Disease* 2016; **8**:E8-E19.
43. Lanki T, Pekkanen J, Aalto P, Elosua R, Berglind N, D'Ippoliti D, Kulmala M, Nyberg F, Peters A, Picciotto S, Salomaa V, Sunyer J, Tiittanen P, von Klot S, Forastiere F. Associations of traffic related air pollutants with hospitalisation for first acute myocardial infarction: the HEAPSS study. *Occupational and Environmental Medicine* 2006; **63**:844.
44. Cai Y, Hansell AL, Blangiardo M, Burton PR, BioShaRe, de Hoogh K, Doiron D, Fortier I, Gulliver J, Hveem K, Mbatchou S, Morley DW, Stolk RP, Zijlema WL, Elliott P, Hodgson S. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. *European heart journal* 2017; **38**:2290-2296.
45. Cai Y, Hodgson S, Blangiardo M, Gulliver J, Morley D, Fecht D, Vienneau D, de Hoogh K, Key T, Hveem K, Elliott P, Hansell AL. Road traffic noise, air pollution and incident cardiovascular disease: A joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. *Environ Int* 2018; **114**:191-201.
46. Fuks KB, Weinmayr G, Basagana X, Gruzieva O, Hampel R, Oftedal B, Sorensen M, Wolf K, Aamodt G, Aasvang GM, Aguilera I, Becker T, Beelen R, Brunekreef B, Caracciolo B, Cyrus J, Elosua R, Eriksen KT, Foraster M, Fratiglioni L, Hilding A, Houthuijs D, Korek M, Kunzli N, Marrugat J, Nieuwenhuijsen M, Ostenson CG, Penell J, Pershagen G, Raaschou-Nielsen O, Swart WJR, Peters A, Hoffmann B. Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). *European heart journal* 2017; **38**:983-990.

47. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965; **58**:295-300.
48. Babisch W. Updated exposure-response relationship between road traffic noise and coronary heart diseases: a meta-analysis. *Noise & health* 2014; **16**:1-9.
49. Vienneau D, Schindler C, Perez L, Probst-Hensch N, Rösli M. The relationship between transportation noise exposure and ischemic heart disease: a meta-analysis. *Environmental research* 2015; **138**:372-80.
50. Münzel T, Sörensen M, Gori T, Schmidt FP, Rao X, Brook J, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part I-epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. *European heart journal* 2016.
51. Münzel T, Daiber A, Steven S, Tran LP, Ullmann E, Kossmann S, Schmidt FP, Oelze M, Xia N, Li H, Pinto A, Wild P, Pies K, Schmidt ER, Rapp S, Kroller-Schon S. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. *European heart journal* 2017; **38**:2838-2849.
52. Vienneau D, Perez L, Schindler C, Lieb C, Sommer H, Probst-Hensch N, Kunzli N, Rösli M. Years of life lost and morbidity cases attributable to transportation noise and air pollution: A comparative health risk assessment for Switzerland in 2010. *International journal of hygiene and environmental health* 2015; **218**:514-21.
53. Schlatter F, Piquerez A, Habermacher M, Ragettli M, Rösli M, Brink M, Cajochen C, Probst-Hensch N, Foraster M, Wunderli J-M. Validation of large scale noise exposure modelling by long-term measurements. *Noise Mapping* 2017; **4**:75-86.



## Figure Captions

**Figure 1: linear HRs for associations between road, railway, and aircraft noise exposure and myocardial infarction per 10 dB increase in  $L_{den}$ , not adjusted for air pollution (no AP), adjusted for  $PM_{2.5}$  only ( $PM_{2.5}$ ), adjusted for  $NO_2$  only ( $NO_2$ ), and adjusted for  $PM_{2.5}$  and  $NO_2$  ( $PM_{2.5}+NO_2$ ). All models were adjusted for age, sex, neighborhood index of socio-economic position, civil status, education level, mother tongue, nationality and the other noise sources.**

**Figure 2: linear HRs for associations between  $PM_{2.5}$  (left side) and  $NO_2$  (right side) per  $10 \mu g/m^3$  and myocardial infarction in single exposure models, adjusted additionally for all noise sources, and adjusted for all noise sources and the complimentary air pollutant. All models were adjusted for age, sex, neighbourhood index of socio-economic position, civil status, education level, mother tongue, and nationality.**

**Table 1: Study population characteristics**

| <b>Characteristics at baseline</b>                                   |             |                                     |   |   |
|--|-------------|-------------------------------------|---|---|
|  |             | Lden Road above<br>median (54.1 dB) | NO <sub>2</sub> above median<br>(27.0 µg/m <sup>3</sup> ) | PM <sub>2.5</sub> above median<br>(18.7 µg/m <sup>3</sup> ) |
| <b>Number of participants at baseline</b>                            | 4404046     | 2202848                             | 2202744   | 2202025   |
| <b>Males (%)</b>   | 48          | 48                                  | 47  | 48  |
| <b>Age: mean (SD)</b>  | 52.4 (15.1) | 52.47 (15.44)                       | 52.57 (15.49)   | 52.51 (15.37)   |
| <b>Education level (%)</b>   |             |                                     |   |   |
| Compulsory education or less   | 24          | 26                                  | 25  | 25  |
| Upper secondary level education                                      | 52          | 50                                  | 50  | 50  |
| Tertiary level education   | 22          | 21                                  | 23  | 22  |
| Not known  | 2           | 3                                   | 3   | 3   |
| <b>Civil status (%)</b>  |             |                                     |   |   |
| Single   | 14          | 15                                  | 17  | 16  |
| Married  | 70          | 67                                  | 65  | 66  |
| Widowed  | 8           | 8                                   | 8   | 8   |
| Divorced   | 8           | 9                                   | 10  | 10  |
| <b>Neighbourhood socio-economic position</b>                         |             |                                     |   |   |
| low  | 33          | 37                                  | 32  | 33  |
| medium   | 33          | 33                                  | 32  | 33  |
| high   | 33          | 29                                  | 36  | 34  |
| <b>Mother tongue (%)</b>   |             |                                     |   |   |
| German and Rhaeto-Romanic  | 65          | 59                                  | 60  | 60  |
| French   | 19          | 22                                  | 19  | 19  |
| Italian  | 7           | 9                                   | 10  | 10  |
| Other  | 8           | 10                                  | 11  | 11  |
| <b>Nationality (%)</b>   |             |                                     |   |   |
| Swiss  | 82          | 78                                  | 76  | 77  |
| Rest of Europe (inclusive ex-USSR)                                   | 16          | 19                                  | 21  | 20  |
| Other /unknown   | 2           | 2                                   | 3   | 3   |
|  |             |                                     |   |   |
| <b>NO<sub>2</sub> concentration in µg/m<sup>3</sup>: mean (SD)</b>   | 27.7 (7.6)  | 30.3 (7.8)                          | 33.7 (5.6)  | 31.5 (7.2)  |
| <b>PM<sub>2.5</sub> concentration in µg/m<sup>3</sup>: mean (SD)</b> | 19.4 (3.7)  | 20.2 (4.1)                          | 21.1 (4.1)  | 22.1 (3.1)  |

**Table 2: Spearman's rank correlation coefficients and variance inflation factor (VIF) for road traffic, railway, and aircraft noise as well as for PM<sub>2.5</sub> and NO<sub>2</sub>**

|                         | <b>Lden Road</b> | <b>Lden Railway</b> | <b>Lden Air</b> | <b>PM<sub>2.5</sub></b> | <b>NO<sub>2</sub></b> |
|-------------------------|------------------|---------------------|-----------------|-------------------------|-----------------------|
| <b>Lden Road</b>        | 1                |                     |                 |                         |                       |
| <b>Lden Railway</b>     | 0.13             | 1                   |                 |                         |                       |
| <b>Lden Air</b>         | 0.09             | -0.04               | 1               |                         |                       |
| <b>PM<sub>2.5</sub></b> | 0.27             | 0.20                | 0.24            | 1                       |                       |
| <b>NO<sub>2</sub></b>   | 0.44             | 0.18                | 0.27            | 0.62                    | 1                     |

**Table 3: Adjusted\* HR (95% confidence intervals) and number of deaths (N=) for PM<sub>2.5</sub> and road traffic noise for MI in categorical (quartiles) interaction exposure models. Cells with interaction terms are shown in italics.**

|  |                                  | Road traffic noise [dB]          |  |  |  |
|--|----------------------------------|----------------------------------|--|--|--|
|  |                                  | ≤49.0<br>(main effect)<br>N=4249 | 49.0-54.1<br>N=4775                                  | 54.1-60.3<br>N=5016                                  | >60.3<br>N=5221                                      |
| PM <sub>2.5</sub> [µg/m <sup>3</sup> ] | ≤16.9<br>(main effect)<br>N=4524 | 1.00<br>(reference)<br>N=1509    | 1.04<br>(0.97-1.13)<br>N=1135                        | 1.06<br>(0.98-1.15)<br>N=986                         | 1.07<br>(0.98-1.16)<br>N=894                         |
|  | 16.9-18.7<br>N=4667              | 1.07<br>(0.99-1.15)<br>N=1198    | <i>0.97</i><br>( <i>0.87-1.08</i> )<br><i>N=1215</i> | <i>0.98</i><br>( <i>0.87-1.1</i> )<br><i>N=1159</i>  | <i>1.01</i><br>( <i>0.90-1.13</i> )<br><i>N=1095</i> |
|  | 18.7-21.1<br>N=5056              | 1.06<br>(0.98-1.15)<br>N=987     | <i>1.02</i><br>( <i>0.91-1.14</i> )<br><i>N=1327</i> | <i>1.03</i><br>( <i>0.92-1.16</i> )<br><i>N=1389</i> | <i>1.04</i><br>( <i>0.92-1.16</i> )<br><i>N=1353</i> |
|  | >21.1<br>N=5014                  | 1.09<br>(0.98-1.21)<br>N=555     | <i>0.96</i><br>( <i>0.85-1.09</i> )<br><i>N=1098</i> | <i>0.97</i><br>( <i>0.86-1.11</i> )<br><i>N=1482</i> | <i>0.93</i><br>( <i>0.82-1.06</i> )<br><i>N=1879</i> |

\* Age as the underlying time scale and additionally adjusted for sex, neighborhood index of socio-economic position, civil status, education level, mother tongue, nationality, railway and aircraft noise, PM<sub>2.5</sub>.



