# (Un)Healthy in the city

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# The association of air pollution and depressed mood in 70,928 individuals from four European cohorts

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## ABSTRACT

### Background

Exposure to ambient air pollution may be associated with impaired mental health, including depression. However, evidence originates mainly from animal studies and epidemiological studies in specific subgroups. We investigated the association between air pollution and depressed mood in four European general population cohorts.

### Methods

Data were obtained from LifeLines (the Netherlands), KORA (Germany), HUNT (Norway), and FINRISK (Finland). Residential exposure to particles ($PM_{2.5}$, $PM_{2.5}$absorbance, $PM_{10}$) and nitrogen dioxide ($NO_2$) was estimated using land use regression (LUR) models developed for the European Study of Cohorts for Air Pollution Effects (ESCAPE) and using European wide LUR models. Depressed mood was assessed with interviews and questionnaires. Logistic regression analyses were used to investigate the cohort specific associations between air pollution and depressed mood.

### Results

A total of 70,928 participants were included in our analyses. Depressed mood ranged from 1.6% (KORA) to 11.3% (FINRISK). Cohort specific associations of the air pollutants and depressed mood showed heterogeneous results. For example, positive associations were found for $NO_2$ in LifeLines (odds ratio [OR]= 1.34; 95% CI: 1.17, 1.53 per 10 $\mu g/m^3$ increase in $NO_2$), whereas negative associations were found in HUNT (OR= 0.79; 95% CI: 0.66, 0.94 per 10 $\mu g/m^3$ increase in $NO_2$).

### Conclusions

Our analyses of four European general population cohorts found no consistent evidence for an association between ambient air pollution and depressed mood.

## INTRODUCTION

It is well established that exposure to air pollution can lead to a wide variety of adverse health effects [1]. Air pollution is for example associated with increased risks of pulmonary [2] and cardiovascular disease [3], and mortality [4,5]. Exposure to ambient air pollution has also been suggested to increase the risk of depressive symptoms, but few epidemiological studies have investigated these effects. So far, mainly short-term studies have been conducted and found relations with increased suicide risk [6] and depressive symptoms in Korean populations [7], and short-term increases in ambient air pollution were associated with emergency department visits for depression in Canada [8] and Korea [9]. However, no evidence for an association between both short- and long-term air pollution exposure and depressive symptoms could be seen in an US study [10]. Another US study among women reported that long-term and short-term exposure to air pollution was related to anxiety symptoms [11], which are often comorbid with depression [12].

Recently, studies on air pollution in relation to neuropsychological effects were reviewed. The authors concluded that the two are probably linked, but acknowledged that these results are not conclusive, as the number of studies was limited, and their sample sizes were small [13]. Another limitation in the current literature is the lack of studies investigating the possible confounding and synergistic effects of air pollution and noise on depressed mood. Individuals exposed to traffic related air pollution are probably also exposed to traffic related noise, and both exposures may be related to the pathogenesis of depression [13]. A systematic review of the effects of air pollution and ambient noise on different aspects of mental health concluded that both exposures may be associated with mood disorders [14]. The simultaneous analysis of air pollution and noise has not been undertaken extensively, and is required in future research [13,14].

In summary, most prior studies have provided limited evidence for the relation between air pollution and depression, and did not analyze exposure to noise in addition to air pollution. Previous studies were mainly undertaken in Asian [6,7,9] and American populations [8,10], while relations have not yet been studied in Europe. We investigated the association between air pollution exposure and depressed mood in four general population cohorts from Europe, while taking into account exposure to road traffic noise.

## METHODS

### Study population

This study is an analysis of cohort data obtained by BioSHaRE (Biobank Standardisation and Harmonisation for Research Excellence in the European Union), a collaborative project that aims to facilitate harmonization and standardization of data, and the sharing and pooling of data across multiple biobanks and databases. The present study included the BioSHaRE cohorts with information about air pollution exposure and depression prevalence. The cohorts were: LifeLines (three Northern provinces of the Netherlands) [15,16], HUNT3 (Nord-Trøndelag area, Norway) [17], KORA (F3 and F4) (Augsburg area, Germany) [18], and FINRISK2007 (Helsinki, Vantaa and Turku areas, Finland) [19]. All cohorts are general population based. Air pollution exposure estimation and depressed mood assessments were undertaken within overlapping periods (LifeLines, HUNT), or with a few years in between (KORA, FINRISK). We assume that the spatial contrasts in the measured and modelled annual average levels were stable over these periods [20]. Additional information about the study designs and populations is provided in Table 1. Ethical approval was obtained from the local authorized institutional review boards and written informed consent was obtained from all participants.

**Table 1.** Cohort characteristics

| | LifeLines | KORA | HUNT | FINRISK |
|---|---|---|---|---|
| Study region | Three Northern provinces of the Netherlands | Augsburg area, Germany | Nord-Trøndelag area, Norway | Helsinki, Vantaa and Turku, Finland |
| Period of study measurements | 2007-2013 (baseline) | 2004-2005 (F3) and 2006-2008 (F4) | 2006-2008 (HUNT3) | 2007 (FINRISK 2007) |
| Air pollution LUR model (measurement period) | ESCAPE (2009-2010) and EU-wide (2007) | ESCAPE (2008-2009) and EU-wide (2005-2007) | EU-wide (2006-2007) | ESCAPE (2010-2011) |
| Depression measure | MINI diagnostic interview | PHQ-9 interview version | HADS-D questionnaire | CES-D questionnaire |

Abbreviations: ESCAPE = European Study of Cohorts for Air Pollution Effects; EU-wide = European wide; MINI = Mini-International Neuropsychiatric Interview; PHQ-9 = depression module of the patient health questionnaire; HADS-D = depression subscale of the Hospital Anxiety Depression Scale; CES-D = Center for Epidemiological Studies Depression scale; LUR = land use regression

### Air pollution exposure assessment

Air pollution estimates for the participant's address locations were derived from two types of land use regression (LUR) models. For LifeLines, KORA, and FINRISK, estimates of particulate matter ($PM_{2.5}$, $PM_{2.5}$ absorbance (reflectance on $PM_{2.5}$

filters, i.e. a marker of black carbon), and $PM_{10}$) and nitrogen dioxide ($NO_2$) were calculated using LUR models that were previously developed in ESCAPE (European Study of Cohorts for Air Pollution Effects) [21,22]. The HUNT study area (Nord-Trøndelag area, Norway) was not included in the ESCAPE project and hence no ESCAPE LUR model was available to be linked to the HUNT cohort. Therefore, for HUNT (and in addition for LifeLines and KORA), estimates of $PM_{10}$ and $NO_2$ were calculated using Western European-wide (EU-wide) LUR models enhanced with satellite-derived estimates of ground level air pollution [23]. Detailed descriptions of model development and validation can be found in Supplemental Digital Content, including tables S1-S2, and elsewhere [21–23]. Briefly, ESCAPE LUR models were developed for $NO_2$, $PM_{2.5}$, $PM_{2.5}$ absorbance, and $PM_{10}$ based on estimated annual average concentrations from intensive monitoring campaigns, taking place in each study area between October 2008 and April 2011 [24,25]. Measurements were undertaken in three two-week periods in the cold, warm and intermediate season. For each measurement site the annual average concentration was calculated, with adjustment for temporal variation using measurements from centrally located reference sites with year-round measurement data. The air pollution concentrations obtained from the measurement campaign were then used as outcome variables for LUR model development for each of the areas. Geographic Information System (GIS)-derived land use, road network, and other topographic data were used as predictors of the spatial variation in annual average air pollution levels. LUR models were developed locally, but followed a standardized protocol [21,22].

The EU-wide model incorporates GIS-derived land use, road network and topographic data, as well as satellite-derived estimates of ground level concentrations for $PM_{2.5}$ (as an indicator of $PM_{10}$) and $NO_2$. In these multiple linear regression equations, ambient concentrations of $NO_2$ and $PM_{10}$ (years 2005-2007) obtained from regulatory monitoring were used as dependent variables. Model development followed the ESCAPE procedure to construct the multiple linear regression equations for Western Europe (17 countries) [23]. The main difference between the ESCAPE and EU-wide models is that the ESCAPE models are region specific, while EU-wide models are developed for a much larger area. ESCAPE models were developed for specific European regions, while the EU-wide models were developed for 17 countries in Western Europe. In addition, monitoring data used in ESCAPE models originated from a monitoring campaign specifically conducted for the ESCAPE-project with monitoring sites selected for this purpose, whereas monitoring data for the EU-wide models were obtained from regulatory monitoring networks.

**Depressed mood assessment**

Depressed mood was assessed with standardized face-to-face interviews (LifeLines and KORA) or with questionnaires (HUNT and FINRISK). LifeLines participants were interviewed by trained medical professionals when they visited the research facilities. Depressed mood was assessed with a psychiatric interview (the Mini-International Neuropsychiatric Interview; MINI) [26]. The MINI is a brief structured interview for diagnosing psychiatric disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Participants were asked to indicate whether they experienced symptoms of depression in the last two weeks (yes/no). These 9 symptoms were based on the DSM-IV criteria for the diagnosis of major depressive disorder (MDD), and a cut off of ≥5 symptoms, of which at least one of the key symptoms (depressed mood or anhedonia) was used in accordance with DSM-IV [26]. KORA participants were interviewed by trained medical professionals during their visit to the study center. Depressed mood was assessed with the interview version of the 9 item depression module of the Patient Health Questionnaire-9 (PHQ-9) [27]. Participants rated the frequency of symptoms of depression over the past two weeks on a scale ranging from not at all (0) to nearly every day (3). As with the MINI, the 9 items are based on the 9 DSM-IV criteria for diagnosis of MDD, and the same cut off was used. In HUNT, depressed mood was assessed with the depression subscale of the Hospital Anxiety Depression Scale (HADS) [28]. The HADS depression subscale is a self-administered questionnaire consisting of seven symptoms, each scored from not present (0) to highly present (3) in the previous week. A cut off of 10 or more points was chosen for the current study. This is different from the cut off of ≥8, which was most often used in previous studies [29]. We chose for ≥10 because this cut off was found to be more specifically related to a clinical diagnosis of MDD [30]. In FINRISK, the 20 item Center for Epidemiological Studies Depression Scale (CES-D) [31] was administered. The CES-D assesses feelings of depression in the previous week. Participants rated the frequency of these symptoms on a scale ranging from rarely or none of the time (0) to most or all of the time (3). A cut off of ≥16 is recommended and used by many studies. However, we chose a cut off of ≥21, as this cut off has shown to identify cases of severe depression [32], which is more related to MDD as measured by the MINI and the PHQ-9.

**Covariates**

The covariates were chosen a priori based on prior knowledge [13,14,33–37]. Data on covariates including sex, age, level of education, household income, history of myocardial infarction (MI), history of asthma, and current chronic obstructive pulmonary disease (COPD) were available from questionnaires. Data were harmonized across cohorts where possible according to the DataSHaPER methodology [38]. Level of education and household income data were not available to us from HUNT, and could therefore not be used in the HUNT-specific analyses. COPD data were not available in KORA. Household equivalent income was calculated as net household income per month divided by the square root of the number of persons in the household. For FINRISK, data on household income before taxes was used in the analyses, since information of the tax rate for each household was not available. Household disposable income seems rather similar for the Netherlands, Germany, Norway, and Finland during the period of study measurements [39]. Urbanity was available for LifeLines, KORA and FINRISK, and was operationalized as household density per square kilometer (KORA and FINRISK) or address density per square kilometer (LifeLines). Urbanity was not available for the HUNT cohort, and was therefore not included in the HUNT-specific analyses.



The noise exposure indicators were derived from recent noise maps for home addresses of study participants. Road traffic noise was operationalized as day-evening-night time ($L_{den}$) annual average in decibels A (dB(A)). Road traffic noise estimates for LifeLines and HUNT were derived from a new implementation of the Common Noise Assessment Methods in Europe (CNOSSOS-EU) noise model [40]. For KORA, road traffic noise was calculated by the interim calculation method for environmental noise at roads (VBUS) [41], which is based on the German standard RLS-90 ("Richtlinien für den Lärmschutz an Strassen") [42]. In FINRISK, road traffic noise was estimated in accordance with the Environmental Noise Directive (2002/49/EC) and using the Nordic prediction method [43]. The road traffic noise models typically contain empirically derived equations to determine the initial noise level based on traffic flow and sound propagation based on known environmental factors and physical processes. Quantitative data of road networks, traffic flows, land cover, and building height were obtained from local sources.

### Statistical analyses

Data were analyzed on the cohort level following a common protocol (described below). Data analyses were undertaken at the University Medical Center Groningen, the Netherlands for LifeLines, HUNT and FINRISK using SPSS (version 22). Analyses for KORA were done locally, using R (version 3.1.0). For each cohort, logistic regression analyses with depressed mood (yes/no) as dependent variable were used to analyze associations between air pollution and depressed mood. Separate regression models were constructed for each of the air pollutants and separately for air pollution estimates derived from the ESCAPE and EU-wide model. Models were firstly adjusted for sex, age, level of education, and household income (minimum confounder model); additionally for MI, asthma, COPD, and urbanity (extended confounder model); and finally additionally for road traffic noise (main model). In addition, an alternative confounder model, with adjustment for age, sex, asthma, MI, COPD, and road traffic noise was fitted for the analyses with EU-wide air pollution estimates. This was decided because those analyses included HUNT data for which no data on socioeconomic status and urbanity was available. Data was analyzed for participants from whom we had complete data on all covariates that were available in the cohorts. Effect estimates are presented as odds ratios (OR) for depressed mood, with 95% confidence intervals (CI), per 10 $\mu g/m^3$ for $NO_2$ and $PM_{10}$, 1 $10^{-5}$/m for $PM_{2.5}$ absorbance, and 5 $\mu g/m^3$ for $PM_{2.5}$. The fixed increments were chosen according to ESCAPE and are based on the exposure contrasts to enable broad comparisons between the pollutants [5].

## RESULTS

A total of 70,928 participants was included in our analyses (LifeLines n=32,145; KORA n=5,314; HUNT n=32,102; and FINRISK n=1,367). Population characteristics are summarized in Table 2. Prevalence of depressed mood ranged from 1.6% (KORA) to 11.3% (FINRISK). Mean age was highest in KORA (55.3 years, standard deviation (SD)=12.3 years) and lowest in LifeLines (43.8 years, SD=11.7 years), and ranged from 18 to 96 years across the four cohorts. All cohorts included more women than men, ranging from 51.5% women in KORA, to 56.9% women in LifeLines (Table 2). Distributions of estimated annual average air pollution

**Table 2.** Population characteristics in LifeLines, KORA, HUNT and FINRISK

| Characteristic | LifeLines | KORA | HUNT | FINRISK |
|---|---|---|---|---|
| N | 32,145 | 5,314 | 32,102 | 1,367 |
| Depressed mood (%) | 681 (2.1) | 87 (1.6) | 1,226 (3.8) | 155 (11.3) |
| Age, years (mean±SD) | 43.8±11.7 | 55.3±12.3 | 54.7±15.3 | 51.9±14.0 |
| Women (%) | 18,276 (56.9) | 2,736 (51.5) | 17,875 (55.7) | 771 (56.4) |
| Educational level (%) | | | | |
| Primary or secondary | 7,743 (24.1) | 597 (11.2) | NA | 673 (49.2) |
| Post-secondary, non-tertiary | 21,745 (67.6) | 3,885 (73.1) | NA | 282 (20.6) |
| Tertiary | 2,657 (8.3) | 832 (15.7) | NA | 412 (30.1) |
| Household equivalent income, euros/month (mean±SD) | 1,551±540[a] | 1,097±569[a] | NA | 2,388±1159[b] |
| Myocardial infarction (%) | 252 (0.8) | 128 (2.4) | 1,094 (3.4) | 22 (1.6) |
| Asthma (%) | 2,607 (8.1) | 421 (7.9) | 3,745 (11.7) | 58 (4.3) |
| Chronic obstructive pulmonary disease (%) | 1,494 (4.6) | NA | 1,076 (3.4) | 25 (1.8) |

SD = standard deviation; NA = not available for the cohort.

[a] after taxes [b] before taxes

levels, degree of urbanity, and road traffic noise are presented in Figure 1. Median concentrations of $NO_2$ and $PM_{2.5}$absorbance were highest in KORA (18.8 (interquartile range (IQR) 4.9) µg/m$^3$ and 1.66 (IQR 0.21) $10^{-5}$/m respectively, based on ESCAPE models), while median $PM_{10}$ and $PM_{2.5}$ concentrations were highest

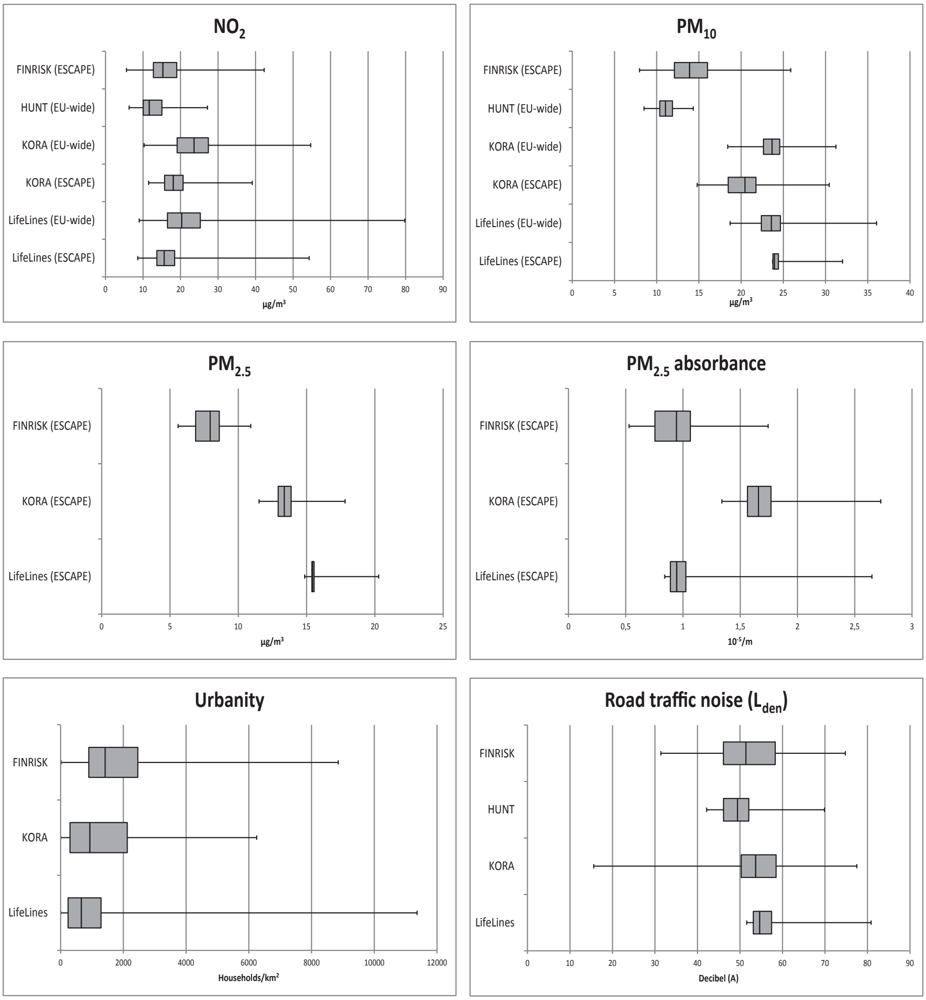


**Figure 1.** Distribution of estimated annual average air pollution levels, degree of urbanity, and estimated 24 hour average road traffic noise for LifeLines, KORA, HUNT and FINRISK. Median, 25th and 75th percentiles are shown in the box, whiskers indicate minimum and maximum estimates. Urbanity is operationalized as household density per square kilometer (KORA and FINRISK) or address density per square kilometer (LifeLines).

Abbreviations: ESCAPE = European Study of Cohorts for Air Pollution Effects; EU-wide = European wide; $NO_2$ = nitrogen dioxide; $PM_{10}$ = particulate matter with aerodynamic diameter ≤10 µm; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤2.5 µm; $PM_{2.5}$absorbance = reflectance on $PM_{2.5}$ filters, i.e. a marker of black carbon; $L_{den}$ = day-evening-night time annual average road traffic noise.

in LifeLines (23.95 (IQR 0.65) μg/m$^3$ and 15.4 (IQR 0.16) μg/m$^3$ respectively, based on ESCAPE models). Median levels of air pollution and noise were lowest in HUNT (median $NO_2$ 11.7 (IQR 5.0) μg/m$^3$ and $PM_{10}$ 11.0 (IQR 1.5) μg/m$^3$, based on EU-wide models; $L_{den}$ 49.4 (IQR 5.9) dB(A)). As our data from FINRISK only included participants from urban areas, median degree of urbanity was highest for the FINRISK cohort. Correlations between air pollution levels, urbanity and road traffic noise within each cohort are presented in the Supplemental Digital Content, Table S3. For $NO_2$ and $PM_{10}$ in LifeLines and KORA, correlations between estimated levels from both the ESCAPE and EU-wide models were calculated. $NO_2$ estimates were highly correlated (Spearman's rho = 0.86 in LifeLines and 0.76 in KORA), while correlations between $PM_{10}$ estimates were less strong (Spearman's rho = 0.54 in LifeLines and 0.39 in KORA). Correlations between air pollution levels, urbanity, and road traffic noise ranged from moderate to high, depending on the pollutant and the cohort. Correlations between road traffic noise and air pollution estimates in HUNT were low, probably because traffic data sets for HUNT were less detailed as for the other cohorts.

**Results from cohort specific logistic regression analyses**

Cohort specific associations of air pollution and depression are presented in Table 3. Odds ratios for air pollution levels (ESCAPE and EU-wide models) and depressed mood, adjusted for age, sex, education, and household income (minimal confounder model), all indicated higher odds for depressed mood in the LifeLines cohort, except for $PM_{2.5}$. When regression models were additionally adjusted for asthma, MI, COPD, and urbanity (extended confounder model), associations were no longer statistically significant, except the associations of EU-wide modelled $NO_2$ (OR 1.31, 95% CI 1.06, 1.63) and $PM_{10}$ (OR 2.92, 95% CI 1.47, 5.79) and depressed mood. Associations between air pollution levels from the EU-wide models and depressed mood in LifeLines remained positive and significant after additional adjustment for road traffic noise (main model), and only a small attenuation of the ORs was observed for $NO_2$ (OR 1.31, 95% CI 1.04, 1.66) and $PM_{10}$ (OR 2.89, 95% CI 1.43, 5.85) (Table 3). None of the associations in the KORA and FINRISK cohorts were statistically significant. Associations from the main model were negative for ESCAPE modelled $NO_2$ (both cohorts), negative (KORA) and positive (FINRISK) for ESCAPE modelled $PM_{10}$, and positive for $PM_{2.5}$ and $PM_{2.5}$absorbance (both cohorts). A positive ($NO_2$) and a negative ($PM_{10}$) association was found in KORA for the EU-wide modelled pollutants. In HUNT, $NO_2$ and $PM_{10}$ (EU-wide models) were significantly associated with lower odds for depressed mood. These associations remained statistically significant after adjustment for age, sex, asthma, myocar-

**Table 3.** Cohort-specific associations of air pollution and depressed mood.
Associations are presented in exposure increments of 10 μg/m$^3$ ($NO_2$ and $PM_{10}$); 5 μg/m$^3$ ($PM_{2.5}$); or 1 $10^{-5}$/m ($PM_{2.5}$absorbance). LifeLines n=32,145; KORA n=5,314; HUNT n=32,102; FINRISK n=1,367.

| | Odds ratio (95% confidence interval) | | | |
|---|---|---|---|---|
| **Study** | **Minimal confounder model** | **Extended confounder model** | **Main model** | **Alternative confounder model** |
| **$NO_2$ (ESCAPE)** | | | | |
| LifeLines | 1.49 (1.23, 1.81) | 1.09 (0.77, 1.56) | 1.04 (0.69, 1.57) | NA |
| KORA | 1.18 (0.68, 2.06) | 1.16 (0.67, 2.03) | 0.76 (0.34, 1.70) | NA |
| FINRISK | 0.89 (0.61, 1.29) | 0.93 (0.57, 1.52) | 0.96 (0.57, 1.63) | NA |
| **$PM_{10}$ (ESCAPE)** | | | | |
| LifeLines | 4.18 (1.45, 12.04) | 0.70 (0.15, 3.31) | 0.43 (0.07, 2.62) | NA |
| KORA | 1.08 (0.44, 2.64) | 0.93 (0.36, 2.37) | 0.81 (0.31, 2.13) | NA |
| FINRISK | 0.89 (0.51, 1.54) | 1.05 (0.50, 2.21) | 1.08 (0.50, 2.33) | NA |
| **$PM_{2.5}$ (ESCAPE)** | | | | |
| LifeLines | 2.47 (0.94, 6.52) | 1.20 (0.41, 3.54) | 1.04 (0.32, 3.40) | NA |
| KORA | 1.60 (0.46, 5.54) | 1.54 (0.44, 5.38) | 1.06 (0.25, 4.51) | NA |
| FINRISK | 1.22 (0.59, 2.51) | 1.32 (0.62, 2.80) | 1.39 (0.64, 3.05) | NA |
| **$PM_{2.5}$absorbance (ESCAPE)** | | | | |
| LifeLines | 1.91 (1.13, 3.25) | 0.79 (0.37, 1.70) | 0.56 (0.22, 1.44) | NA |
| KORA | 2.09 (0.62, 7.02) | 2.05 (0.61, 6.89) | 1.44 (0.33, 6.33) | NA |
| FINRISK | 1.18 (0.55, 2.54) | 1.30 (0.58, 2.95) | 1.44 (0.60, 3.46) | NA |
| **$NO_2$ (EU-wide)** | | | | |
| LifeLines | 1.39 (1.21, 1.60) | 1.31 (1.06, 1.63) | 1.31 (1.04, 1.66) | 1.34 (1.17, 1.53) |
| KORA | 1.11 (0.76, 1.63) | 1.23 (0.84, 1.79) | 1.01 (0.54, 1.89) | 1.01 (0.67, 1.54) |
| HUNT | 0.78 (0.65, 0.93)[a] | 0.77 (0.65, 0.93)[b] | NA | 0.79 (0.66, 0.94) |
| **$PM_{10}$ (EU-wide)** | | | | |
| LifeLines | 3.35 (2.14, 5.26) | 2.92 (1.47, 5.79) | 2.89 (1.43, 5.85) | 2.66 (1.63, 4.35) |
| KORA | 1.06 (0.26, 4.56) | 1.41 (0.33, 6.09) | 0.48 (0.06, 3.91) | 0.74 (0.16, 3.47) |
| HUNT | 0.38 (0.21, 0.68)[a] | 0.39 (0.21, 0.70)[b] | NA | 0.36 (0.20, 0.66) |

Abbreviations: ESCAPE = European Study of Cohorts for Air Pollution Effects; EU-wide = European wide; $NO_2$ = nitrogen dioxide; $PM_{10}$ = particulate matter with aerodynamic diameter ≤10 μm; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤2.5 μm; $PM_{2.5}$absorbance = reflectance on $PM_{2.5}$ filters, i.e. a marker of black carbon; NA=not available for cohort

[a] Not adjusted for education and household income; [b] Not adjusted for education, household income, and urbanity

Minimal confounder model: age, sex, education, household income

Extended confounder model: age, sex, education, household income, asthma, myocardial infarction, COPD, urbanity

Main model: age, sex, education, household income, asthma, myocardial infarction, COPD, urbanity, road traffic noise

Alternative confounder model: age, sex, asthma, myocardial infarction, COPD, road traffic noise dial infarction, COPD and road traffic noise (alternative confounder model: $NO_2$ OR 0.79, 95% CI 0.66, 0.94; $PM_{10}$ OR 0.36, 95% CI 0.20, 0.66, Table 3).

In summary, statistically significant associations between EU-wide modelled $NO_2$ and $PM_{10}$, and depressed mood were observed in LifeLines and HUNT. These pollutants were related to higher odds for depressed mood in LifeLines, but were related to lower odds for depressed mood in HUNT. Since urbanity and road traffic noise are exposures that might co-occur with air pollution, we evaluated the effect sizes of these covariates. In the main models, odds ratios for urbanity were consistently 1.000 and statistically non-significant, except for the main models with ESCAPE air pollution in LifeLines. In these models, odds ratios were also 1.000, but were statistically significant. None of the associations between road traffic noise and depressed mood were statistically significant, and odds ratios were close to 1. Small positive odds ratios were observed in LifeLines, HUNT, and KORA, and small negative odds ratios were observed in FINRISK (data not shown).

## DISCUSSION

We found no clear evidence for a relation between air pollution and depressed mood. Results were heterogeneous between and sometimes within cohorts, and in some cases sensitive to adjustment for urbanity and road traffic noise. Statistically significant results from the cohort specific analyses were found for $NO_2$ and $PM_{10}$ (EU-wide models) in LifeLines and HUNT; these air pollutants were however associated with higher (LifeLines) and lower (HUNT) odds for depressed mood. Another notable contrast is that for LifeLines, significant relations with depressed mood were observed with air pollution estimates from the EU-wide models, but not with air pollution estimates from the ESCAPE models.

Strengths of our study include the very large sample size, the standardized analyses protocol, and the adjustment of our analyses for road traffic noise. Despite these strengths, our results fit into the literature of inconsistent findings on the association between air pollution and depression. One possible explanation for lack of clear associations is the air pollution level in our cohorts. Studies undertaken in Asia did find relations between short-term air pollution exposure and suicide risk [6], depressive symptoms [7], and emergency department visits for depression [9]. Ambient air pollution levels in Asia are generally much higher than in Europe, which may explain these conflicting results. For example, in one of these studies levels of $PM_{10}$ were almost twice as high as the highest average concentration in our study (43.7 μg/m$^3$ in Korea vs. 24.2 μg/m$^3$ in the LifeLines cohort from the Netherlands) [7]. Notably, the only cohort in which air pollution was significantly associated with increased depression prevalence was the LifeLines cohort. The findings in the cohorts in which air pollution was not related to depression are consistent with one prior study undertaken in the United States [10]. No evidence for a relation between air pollution and depressive symptoms was found. The authors suggested that higher concentration levels would have been needed to detect am association between air pollution and depressive symptoms [10]. Several studies suggest that an effect of air pollution could be via neuroinflammation, a process proposed to be involved in depression [44,45]. Animal studies showed that inhaled ultrafine particles (<100 nm) and $PM_{2.5}$ can induce neuroinflammation, either by entering the brain directly, or by inducing immune mediators which reach the brain [46–50]. Observations in human subjects highly exposed to air pollution showed that air pollution components may reach the brain and cause neuroinflammation in humans as well [51].

Our study did not provide a clear answer to the question regarding the association between air pollution and depressed mood. However, the heterogeneous results have important implications for the interpretation of other studies, by showing how the same question approached with the same statistical analytical strategy can lead to different answers. One obvious source of this heterogeneity is differences in the populations studied, including genetic variations, or other cohort- or region-specific differences that we did not assess in this study. However, we identified heterogeneity also within the cohort specific results, associated with the exposure modeling. Associations between $NO_2$ and $PM_{10}$ from EU-wide models and depressed mood in LifeLines were consistently positive and significant, but associations between these same pollutants from ESCAPE models in LifeLines were not significant. The main difference between the ESCAPE and EU-wide models is that ESCAPE models were constructed locally, whereas the EU-wide models were developed for a much larger area in Western Europe. Furthermore, ESCAPE models used more local predictors (e.g. traffic counts) than the EU-wide models, but ESCAPE as well as EU-wide models have shown to explain a large fraction of the spatial variability in annual average air pollution concentrations [21–23]. However, $NO_2$ and $PM_{10}$ estimates from EU-wide models had larger variation among the LifeLines participants than $NO_2$ and $PM_{10}$ estimates from ESCAPE models. We speculate that the larger variation in the EU-wide estimated air pollution exposures may be an explanation for the discrepancy in results from the ESCAPE and EU-wide models in LifeLines.

We adjusted our analyses for urbanity and road traffic noise because these exposures may co-occur with air pollution. However, overfitting of the statistical models may occur, especially for urbanity which is often used as a predictor variable in LUR models for estimation of air pollution concentrations. LUR models that used population density as a predictor were $NO_2$ (ESCAPE: LifeLines and KORA) and $PM_{10}$ (ESCAPE: LifeLines, FINRISK; and EU-wide). However, inspection of the variance inflation factors indicated no multicollinearity. Although to a lesser extent, the same may be applicable to road traffic noise.

A general limitation that applies to all air pollution models is that they provide estimates of exposure at each participant's residential address. Since we have no data on the participants daily mobility and workplace exposure, this could have led to bias due to exposure misclassification. Such bias may have underestimated the relation between air pollution and depressed mood. Our study may not have detected potential short-term effects, since long-term (annual average) air pollution was modelled. Short-term effects could be studied with time-series or panel studies investigating short- or intermediate-term associations. An additional source of heterogeneity is related to the outcome measure. The cohorts included various depression measures, which was probably reflected in the varying depression prevalence, with 1.6% in KORA and 11.3% in FINRISK. Although it is conceivable that depression prevalence differs between countries [52], comparing face-to-face interviews with questionnaires must have undoubtedly played a role in these varying prevalence rates. Outcome misclassification may be present in our study, for example due to the cut offs used to determine depressed mood in this study. We used higher cut offs than usual for the HADS and CES-D in order to harmonize with the other depression measures in our study. Sensitivity analyses were undertaken in HUNT and FINRISK to investigate whether different cut offs of the HADS and CES-D changed the results. Using the cut off 8 for HADS in HUNT and cut off 16 for CES-D in FINRISK did not change the overall conclusions (results available upon request). Apart from the main outcome, heterogeneity might also be related with the fact that not all covariates were available for all cohorts, and also the available data were heterogeneous. We did not have access to data about socioeconomic status and degree of urbanity from the HUNT cohort, making it not possible to adjust the HUNT analyses for these factors. For FINRISK, we only had data on household income before taxes. A limitation that applies to all cohorts is that we did not take into account the use of antidepressants. Participants that use antidepressants, may have less symptoms of depression, and may not be classified as having depressed mood because they have a lower score for the depression assessment. This might have led to an underestimation of the association between air pollution exposure and depressed mood.

In this large multi-cohort study, we found no consistent evidence for an association between ambient air pollution and depressed mood. Regardless of whether there is a true effect of air pollution on depressed mood, our study highlights the importance of multi-cohort studies, where results from multiple cohorts are used for answering research questions. The heterogeneous results observed in this study illustrate how various study methods can lead to various results. Had the relation of air pollution and depressed mood been studied in only one cohort, conclusions might have been different. Moreover, inclusion of data from additional cohorts might have changed our conclusions. Given these contradicting results, investigation of the relation between air pollution and depressed mood in cohort studies from other geographical areas is needed.

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# CHAPTER 4 SUPPLEMENTAL MATERIAL

## Description of ESCAPE land use regression (LUR) models for ambient air pollution

Exposure to ambient air pollution was estimated using land use regression (LUR) models developed for the European Study of Cohorts for Air Pollution Effects (ESCAPE). Within the ESCAPE project, LUR models for 38 European study areas were developed using a standardized approach. ESCAPE LUR models were developed for $NO_2$ (nitrogen dioxide), $NO_2$ background, $PM_{2.5}$ (particulate matter with a diameter ≤2.5 μm), $PM_{2.5}$ absorbance (reflectance on $PM_{2.5}$ filters, i.e. a marker of black carbon), and $PM_{10}$ (particulate matter with a diameter ≤10 μm). A harmonized measurement campaign was conducted in each of the study areas during 2008-2011. In each study area 40 NOx and 20 additional PM measurements were conducted. Measurements were undertaken in three two-week periods in the cold, warm and intermediate season. For each measurement site the annual average concentration was calculated, with adjustment for temporal variation using measurements from centrally located reference sites with year-round measurement data. The air pollution concentrations obtained from the measurement campaign were then used as outcome variables for LUR model development for each of the areas. GIS (geographic information system) derived variables (e.g. distance to nearest road, traffic intensity, built-up land, population density, altitude) were used as predictor variables, to explain these measured concentrations. LUR models were developed locally, but followed a standardized protocol. A supervised forward stepwise procedure was used with pre-specified predictor variables. First, univariate regression models with all potential predictor variables were conducted, and the predictor with the highest adjusted explained variance was selected to be included in the model. Subsequently, all remaining predictor variables were added to the model consecutively, while the change in adjusted explained variances was recorded. The variable with the highest increase in adjusted explained variance was retained if the associated regression coefficient was in the pre-specified direction of the effect; if the additional predictor variables increased the adjusted explained variance by >1%; if the direction of the regression coefficient for the already included predictors remained the same. The addition of variables was repeated until there were no variables that added more than 1% to the adjusted explained variance of the previous model. Finally, variables with p-values larger than 0.1 were sequentially removed from the model. For the final models, diagnostic tests were applied to assess model fit (Variance Inflation Factors, Cook's D, Moran's I). Leave-one-out cross validation (LOOCV) was used to evaluate model performance. The final model was fitted to all sites, but one, while leaving the included variables constant. The predicted air pollution concentrations from the model were compared with the concentrations from the measurement campaign at the left-out site. The procedure was repeated for all sites, and the adjusted explained variance between the predicted and measured concentrations was calculated as for evaluation of model performance. $NO_2$, $PM_{2.5}$, and $PM_{2.5}$absorbance LUR models for the models included in the current study included at least one traffic variable (e.g. traffic intensity). $NO_2$ and $PM_{10}$ LUR models included indicators of population density, while these were not included in the $PM_{2.5}$, and $PM_{2.5}$absorbance LUR models (Supplemental Material Table S1). Adjusted explained variances for the LUR models included in the current study ranged between 83-86% ($NO_2$), 67-83% ($PM_{10}$), 67-88% ($PM_{2.5}$), and 65-92% ($PM_{2.5}$absorbance) [21,22].

**Description of EU-wide land use regression (LUR) model for ambient air pollution**

Exposure to ambient air pollution was estimated using European (EU)-wide LUR models enhanced with satellite derived air pollution estimates. These EU-wide models incorporate GIS-derived land use, road network, and topographic data, as well as satellite-derived estimates of ground level concentrations for $PM_{2.5}$ (as a proxy for $PM_{10}$ because $PM_{10}$ satellite measurements were not available) and $NO_2$ [23]. Model development follows the ESCAPE procedure to construct the multiple linear regression equations. In these multiple linear regression equations, annual mean ambient concentrations of $NO_2$ and $PM_{10}$ (years 2005-2007) obtained from regulatory monitoring were used as dependent variables. Independent variables (predictors), including GIS-derived land use, road network, and topographic data, as well as satellite-derived estimates of ground level concentrations for $PM_{2.5}$ and $NO_2$ were used to construct the multiple linear regression equations. Models were developed according to the ESCAPE supervised stepwise selection of predictor variables. Models were evaluated against measured $PM_{10}$ and $NO_2$ concentrations at an independent subset of 20% sites that were reserved for this purpose. For $NO_2$, all models included satellite-derived surface $NO_2$, the length of minor roads, length of major roads, percentage total built up land, and percentage semi natural land (Supplement Material, Table S2). $NO_2$ LUR models explained 55-60% of the variation in ambient $NO_2$ concentrations based on regulatory monitoring. For $PM_{10}$, all models included satellite-derived $PM_{2.5}$, the Y coordinate (because of a general decreasing trend in $PM_{10}$ concentrations from south to north), and the length of major roads. $PM_{10}$ LUR models explained 38-47% of the variation in ambient $PM_{10}$ concentrations based on regulatory monitoring [23].

**Table S1.** Predictor variables for ESCAPE land use regression models (based on [21,22]).

| | $NO_2$ | | | $PM_{10}$ | | | $PM_{2.5}$ | | | $PM_{2.5}$ absorbance | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LifeLines | KORA | FINRISK | LifeLines | KORA | FINRISK | LifeLines | KORA | FINRISK | LifeLines | KORA | FINRISK |
| Traffic load_25 | | | x | | | | | | | | | |
| Traffic load_25_100 | | | x | | | | | | | | | |
| Traffic load_50 | x | x | | | | | | | | | x | x |
| Traffic load_500 | | | | | | | | | | x | | |
| Heavy traffic load_25 | x | | | | | | | | | | | |
| Heavy traffic load_25_500 | x | | | | | | | | | | | |
| Heavy traffic load_50 | | | | | | | | | | x | | |
| Traffic major load_50 | | | | | | x | | | x | | | |
| Traffic major load_500 | | | | x | | | | | | | | |
| Traffic major load_1000 | | | | | | | x | x | | | x | |
| Distinvnearc1 | x | | | | | | | | | | | |
| Intmajorinvdis | | x | | | | | | | | | | |
| Road length_25 | | | x | | | | | | | | | |
| Road length_25_300 | | | x | | | | | | | | | |
| Road length_50 | | x | | | x | | | | | | x | |
| Road length_300 | | | | | | | | x | | | | |
| Road length_1000 | x | | | | | | | | | | | |
| Major road length_50 | | x | | x | x | | x | x | | x | | |
| Urban green_500 | | | x | | | | | | | | | |
| Urban green_5000 | | | | | | | | x | | | | |
| Natural_100 | | | | | x | | | | | | | |
| Natural_500 | | | | | | x | | | x | | | x |
| Population_5000 | x | x | | x | | | | | | | | |
| Households_100 | | | | | | x | | | | | | |
| Hld_res_500 | | x | | | | | | | | | | |
| Hld_res_5000 | | | | | | | | | | x | | |
| Regional estimate $NO_2$ | x | | | | | | | | | | | |
| Regional estimate $PM_{2.5}$ | | | | | | | x | | | | | |
| Regional estimate $PM_{2.5}$ absorbance | | | | | | | | | | x | | |

Explanation of the variable names (some variables are buffers with _X indicating the radius of the buffer in meters):
The surface area ($m^2$) of all residential land (hld_res_x), urban green space (urban green_X), natural land (natural_X); population (N) (population_X) or number (N) of households (households_X); a regional concentration estimate (μg/m3 or 10−5m−1); total length (m) of all road and all major road segments (road length_x, major road length_x); inverse distance (m−1) to the nearest road of the central road network (distinvnearc1); the product of inverse/inverse squared distance to the nearest major road and the traffic intensity on this road (vehicles·day−1m−1/vehicles·day−1m−2) (intmajorinvdist); the sum of (traffic intensity × the length of all road segments) within a buffer (vehicles·day−1·m) for all roads (traffic load_x), for major roads (traffic major load_X), and for heavy traffic (heavy traffic load_X).

**Table S2.** Predictor variables for EU-wide land use regression models (based on [23])

| | $NO_2$ | | | | $PM_{10}$ | | | |
|---|---|---|---|---|---|---|---|---|
| | **2005** | **2006** | **2007** | **2005-2007** | **2005** | **2006** | **2007** | **2005-2007** |
| Minor road length_200 | | | | | | | x | |
| Minor road length_200-2500 | | | | | | | x | |
| Minor road length_1500 | | x | x | x | | | | |
| Minor road length_1800m | x | | | | | | | |
| Minor road length_1800-10000 | x | | | | | | | |
| Minor road length_1500-10000 | | x | x | x | | | | |
| Major road length_100 | x | x | x | x | | x | | x |
| Major road length | | | | | x | | x | |
| Population_1800 | | | | | | x | | x |
| Impervious surface_1000 (% area) | | | | | x | | | |
| Total built up land_300 | x | x | x | x | | | | |
| Total built up land_400 | | | | | | | | x |
| Total built up land_600 | | | | | | x | | |
| Semi-natural land_500 | | x | | | | | | |
| Semi-natural land_600 | x | | x | x | | | | |
| Semi-natural land_1000 | | | | | | x | | |
| Semi-natural land_1200 | | | | | | | | x |
| Tree canopy 100m (% area) | | | | | | | x | |
| Tree canopy 500m (% area) | | | | | x | | | |
| Satellite-derived surface $NO_2$ 2005 | x | | | | | | | |
| Satellite-derived surface $NO_2$ 2006 | | x | | | | | | |
| Satellite-derived surface $NO_2$ 2007 | | | x | | | | | |
| Satellite-derived surface $NO_2$ 2005-2007 | | | | x | | | | |
| Satellite-derived surface $PM_{2.5}$ 2001 | | | | | x | x | x | x |
| Altitude | | | | | | | x | |
| Distance to sea | | | | | x | x | | x |
| Y coordinate | | | | | x | x | x | x |

Explanation of the variable names (some variables are buffers with _X indicating the radius of the buffer in meters):
Total built up land (% area): residential areas, industrial areas, ports, transport infrastructure, airports, mines, dumps and construction sites.

**Table S3.** Spearman's correlations between air pollution levels, urbanity and road traffic noise

| | $NO_2$ ESCAPE | | | $NO_2$ EU-wide | | | $PM_{10}$ ESCAPE | | | $PM_{10}$ EU-wide | | | $PM_{2.5}$ ESCAPE | | | $PM_{2.5abs}$ ESCAPE | | | $L_{den}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Spearman's rho** | **LL** | **KO** | **FR** | **LL** | **KO** | **HU** | **LL** | **KO** | **FR** | **LL** | **KO** | **HU** | **LL** | **KO** | **FR** | **LL** | **KO** | **FR** | **LL** | **KO** | **FR** |
| **$NO_2$ EU-wide** | 0.86 | 0.76 | NA | | | | | | | | | | | | | | | | | | |
| **$PM_{10}$ ESCAPE** | 0.74 | 0.67 | 0.67 | 0.67 | 0.38 | | | | | | | | | | | | | | | | |
| **$PM_{10}$ EU-wide** | 0.77 | 0.68 | NA | 0.77 | 0.85 | 0.78 | 0.54 | 0.39 | NA | | | | | | | | | | | | |
| **$PM_{2.5}$ ESCAPE** | 0.52 | 0.44 | 0.45 | 0.53 | 0.33 | NA | 0.71 | 0.43 | 0.69 | 0.51 | 0.29 | | | | | | | | | | |
| **$PM_{2.5abs}$ ESCAPE** | 0.79 | 0.67 | 0.49 | 0.71 | 0.35 | NA | 0.93 | 0.66 | 0.72 | 0.58 | 0.34 | NA | 0.67 | 0.48 | 0.99 | | | | | | |
| **$L_{den}$** | 0.56 | 0.43 | 0.36 | 0.43 | 0.37 | -0.06 | 0.57 | 0.29 | 0.21 | 0.38 | 0.31 | 0.06 | 0.46 | 0.38 | 0.24 | 0.61 | 0.46 | 0.31 | | | |
| **Urbanity** | 0.88 | 0.69 | 0.66 | 0.92 | 0.86 | NA | 0.70 | 0.34 | 0.67 | 0.78 | 0.76 | NA | 0.52 | 0.26 | 0.21 | 0.71 | 0.28 | 0.25 | 0.42 | 0.26 | 0.16 |

Abbreviations: ESCAPE = European Study of Cohorts for Air Pollution Effects; EU-wide = European wide; $NO_2$ = nitrogen dioxide; $PM_{10}$ = particulate matter with aerodynamic diameter ≤10 μm; $PM_{2.5}$ = particulate matter with aerodynamic diameter ≤2.5 μm; $PM_{2.5}$abs = reflectance on $PM_{2.5}$ filters, i.e. a marker of black carbon; $L_{den}$ = 24 hour average road traffic noise; LL = LifeLines; KO = KORA; HU = HUNT; FR = FINRISK; NA = not available for cohort.