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http://dx.doi.org/10.1289/ehp.1307725
Received: 1 October 2013
Accepted: 15 May 2014
Advance Publication: 16 May 2014

NIH National Institute of Environmental Health Sciences

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Running title: Long-Term Air Pollution and Hypertension in Europe

Acknowledgments: We thank Martin Adam, Dirk Keidel, Evi Samoli and members of ESCAPE Statistics Working Group for their kind help with analysis code writing. We thank all cohort participants and the dedicated study personnel. For the cohort-specific information, see Supplemental Material, Cohort-Specific Information, Funding and Acknowledgements.

Grant information: *ESCAPE:* The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2011) under grant agreement number: 211250.

Competing financial interests: Authors declare no competing financial interests.

Abstract

Background: Long-term exposure to air pollution is hypothesized to elevate arterial blood pressure (BP). The existing evidence is scarce and country-specific.

Objectives: We investigated the cross-sectional association of long-term traffic-related air pollution with BP and prevalent hypertension in European populations.

Methods: Fifteen population-based cohorts, participating in the European Study of Cohorts for Air Pollution Effects (ESCAPE), were analysed. Residential exposure to particulate matter and nitrogen oxides was modelled with land use regression using a uniform protocol. Traffic exposure was assessed with traffic indicator variables. We analysed systolic and diastolic BP in participants medicated and non-medicated with BP lowering medication (BPLM) separately, adjusting for personal and area-level risk factors and environmental noise. Prevalent hypertension was defined as ≥ 140 mmHg systolic, or ≥ 90 mmHg diastolic BP, or intake of BPLM. We combined cohort-specific results using random-effects meta-analysis.

Results: In the main meta-analysis of 113,926 participants, traffic load on major roads within 100 m of the residence was associated with increased systolic and diastolic BP in non-medicated participants (0.35 mmHg [95% CI: 0.02–0.68] and 0.22 mmHg [95% CI: 0.04–0.40] per 4,000,000 vehicles × m/day, respectively). The estimated odds ratio for prevalent hypertension was 1.05 [95% CI: 0.99–1.11] per 4,000,000 vehicles × m/day. Modelled air pollutants and BP were not clearly associated.

Conclusions: In this first comprehensive meta-analysis of European population-based cohorts we observed a weak positive association of high residential traffic exposure with BP in non-medicated participants, and an elevated OR for prevalent hypertension. The relationship of modelled air pollutants with BP was inconsistent.

Introduction

Long-term exposure to traffic-related air pollution (TRAP) increases risk of cardiovascular events and mortality (HEI 2010). High blood pressure (BP), a major risk factor worldwide, could mediate the cardiovascular effects of TRAP (Brook et al. 2009). It is hypothesized that long-term exposure to TRAP could raise BP chronically, increase the risk of hypertension (Brook 2007), and thereby contribute to the deleterious effects of air pollution on cardiovascular morbidity and mortality.

The evidence is very scarce so far. In two American studies with selected populations (elderly men and black women, respectively) TRAP was linked to higher BP or hypertension (Coogan et al. 2012; Schwartz et al. 2012). In our previous study with a German population-based cohort, we found a positive association of ambient particulate matter (PM) with BP, and an increased prevalence of hypertension among those living near a major road (Fuks et al. 2011). Long-term exposure to PM and gaseous air pollutants were associated with high BP and hypertension in two large Asian cohorts (Chuang et al. 2011; Dong et al. 2013). Long-term PM concentrations were positively related to self-reported hypertension among white American adults (Johnson and Parker 2009). However, not all findings are positive. In a large population-based Danish cohort of older adults, long-term exposure to nitrogen oxides, indicators of traffic-related air pollution, was associated with decreased BP and lower prevalence of self-reported hypertension (Sørensen et al. 2012).

In view of the sparse and partially controversial evidence, we aimed to study the effects of long-term exposure to TRAP on BP and hypertension in 15 European population-based cohorts, using a uniform methodology. We investigated the cross-sectional association of particulate air pollutants, nitrogen oxides, and traffic indicators with arterial blood pressure, as well as with the prev-

alence of hypertension and intake of blood pressure lowering medication (BPLM). This work was performed as a part of the European Study of Cohorts for Air Pollution Effects (ESCAPE 2008).

Methods

General setting

Existing cohort studies of mortality and chronic diseases in Europe have been selected based on their potential to quantify relationships between long-term exposure and health response. Cohorts were eligible to participate in the analysis of blood pressure and hypertension, if following data were available:

1. BP values, measured according to the World Health Organization (WHO) MONICA protocol (Hense et al. 1995) or a study-specific standard.
2. Information on BPLM use.
3. Long-term residential TRAP concentrations at the residence, assessed with the ESCAPE land use regression model.

Fifteen cohorts from 9 countries were eligible to participate in this study: the national FINRISK study (FINRISK, Finland); the Danish Cancer Study (DCH, Denmark); the population-based Oslo Health Study (HUBRO, Norway); the Stockholm 60-year olds cohort (60-year-olds, Sweden); Stockholm diabetes preventive program (SDPP; Sweden); the Swedish National study of Aging and Care in Kungsholmen (SNAC-K; Sweden); the Swedish Twin Registry (TwinGene); the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Umeå (EPIC-Umeå, Sweden); the EPIC Monitoring Project on Risk Factors for Chronic Diseases (EPIC-MORGEN, the Netherlands); the EPIC Prospect cohort (EPIC-Prospect, the Netherlands); the EPIC Oxford cohort (EPIC-Oxford, the United Kingdom); the Heinz Nixdorf Risk Factors, Evaluation of Coronary Calcification, and Lifestyle (Recall) study (HNR, Germany); the Cooperative Health Research in the Region of Augsburg (KORA, Germany); the Swiss Study on Air Pollution and Lung and Heart Disease In Adults (SAPALDIA, Switzerland);

Registre Gironí del Cor – Girona's heart registry (REGICOR, Spain). Further details on each cohort can be found in Supplemental Material, Cohort-Specific Information, Funding and Acknowledgements. Work in all cohorts was conducted in accordance with the Declaration of Helsinki, and with all local ethical requirements.

Air pollution

Concentrations of PM, including particles with diameter ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), >2.5 to ≤10 μm (PM_{coarse}; calculated as PM_{10} minus $PM_{2.5}$), $PM_{2.5}$ absorbance (a marker for black carbon or soot), and nitrogen oxides (NO_2 – nitrogen dioxide and NO_x – nitrogen oxide) were modelled with land use regression (LUR) using a uniform ESCAPE procedure as described in the Supplemental Material, Land Use Regression Model, and elsewhere (Beelen et al. 2013; Eeftens et al. 2012). Briefly, annual averages of measured pollutant concentrations at the monitoring sites and predictor variables, derived from Europe-wide and local Geographic Information System databases were used to develop the study-specific LUR model and to predict concentrations at each participant's address. To evaluate the impact of time-related changes in exposure, the predicted concentrations for PM_{10} and NO_2 were backextrapolated to the time of the BP measurement using data from routine monitoring sites (see Supplemental Material, Extrapolation of Exposure Values Back in Time).

Traffic indicators

We estimated the cumulative traffic exposure with two traffic indicators, selected a priori by the ESCAPE consortium to ensure comparability across all study areas: (1) total traffic load on all major roads (defined as roads with traffic intensity > 5,000 vehicles/day) within a 100 m radius buffer around the residence, defined as the sum of traffic intensity multiplied by the length of

major road fragments within the buffer (vehicles × m/day); (2) traffic intensity on the nearest road (any road type; vehicles/day).Both indicators were based upon study area-specific road networks with traffic intensity data, based on both counted and modelled data. Time of assessment varied between study areas. We aimed to collect traffic data for different years including baseline, current and data for years during relevant windows of exposure. For minor roads, traffic intensity data were missing in some local road networks. In these cases, missing data were imputed with a default value of 500 vehicles/day. As these roads were mainly minor roads, measurement error with regard to defining busy and non-busy roads is likely small. Analyses of traffic indicator variables were adjusted for predicted background concentration of NO_2.

Road traffic noise

We took the concurrent exposure to traffic noise into account. For that, we estimated 24-hour mean road traffic noise level (L_{den}) at the baseline address based on facade points of participants´ residences. Noise assessment was based on mandatory noise modelling according to the Directive 2002/49/EC of the European Parliament and of the Council (see Supplemental Material, Noise Assessment).

Outcome assessment

BP was measured according to the WHO standard procedure (Hense et al. 1995) in 3 studies (KORA, HNR, and SAPALDIA), while other studies applied study-specific standardized procedures (Table 1). Automated oscillometric devices (AOD) were used in nine cohorts: DCH, HUBRO, 60-year-olds, EPIC-MORGEN, EPIC-Prospect, EPIC-Oxford, HNR, SAPALDIA, and REGICOR. Three cohorts used sphygmomanometers (SDPP, SNAC-K, EPIC-Umeå), and two cohorts used either AOD or sphygmomanometer (TwinGene and KORA). In most studies, BP

was measured on the right arm (nine studies), in a seated position (nine studies) and using different cuff sizes according to the upper arm circumference (all except FINRISK). BP was measured at least twice, with a minimum pause of two minutes, in all cohorts but SDPP and a part of EPIC-Oxford. In DCH, if the first measured BP value was considered abnormal, three minutes later a new measurement was taken. The lowest blood pressure measurement was recorded as final.

Intake of BPLM at baseline was assessed by questionnaire or interview and was available in fourteen studies. Twelve cohorts had detailed information on the name of the drug, while two cohorts only had self-reported information on intake of any BPLM (see Supplemental Material, Assessment of BPLM Use). Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or current intake of BPLM (Chobanian et al. 2003). Intake of BPLM was examined as an additional outcome.

Statistical analyses in cohorts

We conducted the analyses in each cohort separately; no pooling of individual data was done. *Cohort-specific analyses* were performed in each study center according to a uniform statistical protocol, which is briefly described below (for more details, see Supplemental Material, Cohort-Specific Analysis). We used STATA versions 10–12 (StataCorp, College Station, TX, USA; www.stata.com). BP readings were treated as continuous outcomes, hypertension and intake of BPLM as dichotomous outcomes. Analyses of systolic and diastolic BP were performed with linear regression. For analyses of BPLM intake ("medication") and hypertension, logistic regression was used. Linear regression model fit and assumptions were tested in each cohort (see Supplemental Material, Cohort-Specific Analysis). Results were presented for the fixed increments of exposures, harmonized across all ESCAPE publications (see Supplemental Material, Exposure Increments in Analyses).

Correcting for the effect of antihypertensive medication

To account for the influence of BPLM intake on the level of measured BP, we assessed the effect of air pollution on BP in participants taking BPLM ("medicated") and in participants not taking BPLM ("non-medicated") separately. To increase power, we calculated results in subgroups of medicated and non-medicated in the whole cohort, using an interaction term exposure × BPLM intake. The analysis model was:

$$BP = \beta_0 + \beta_1 \times Exposure + \beta_2 \times BPLM + \beta_3 \times Exposure \times BPLM + \ldots + \beta_k \times Covariate_k + \varepsilon \quad [1]$$

BPLM intake was coded as 0 (no medication) and 1 (medication). The effect of exposure on BP in medicated (BPLM = 1) participants was therefore estimated as:

$$\beta_1 \times Exposure + \beta_3 \times Exposure \times 1 = (\beta_1 + \beta_3) \times Exposure \quad [2]$$

In non-medicated (BPLM = 0) as:

$$\beta_1 \times Exposure + \beta_3 \times Exposure \times 0 = \beta_1 \times Exposure \quad [3]$$

We used the Z-test for interaction with pooled (meta-analysis) estimates in medicated and non-medicated.

We also conducted a sensitivity analysis with normal right-censored regression to account for BPLM effect. With this method, BP in medicated was censored as right-censored (Tobin et al. 2005). The normal censored regression is fit in equation (1) assuming that the underlying BP in the medicated participants is equal or higher than the measured value under medication:

$$BP_{underlying} \geq BP_{measured} \; if \; BPLM = 1$$

$$BP_{underlying} = BP_{measured} \; if \; BPLM = 0 \quad [4]$$

Covariates included to the analysis

We used harmonized definitions of covariates and adjustment sets.The adjustment sets were defined a priori using causal graphs (Glymour and Greenland 2008). The main model included: age (years), sex (male, female), body mass index (BMI, kg/m²), smoking status (smoker, ex-smoker, non-smoker), pack-years of smoking (total pack-years smoked), passive smoking (yes, no), alcohol consumption (never, 1-3 drinks/week, 3-6 drinks/week, >6 drinks/week; if wine was assessed separately, alcohol consumption excluding wine was calculated), wine consumption (drinks/week; if available), physical activity (<once/month or <1h/week, once/week or 1h/week, 2-3 times/week or >1 and <3 hours/week, >3 times/week or >3 hours/week),individual socioeconomic status (SES) defined as educational level (primary school or less, up to secondary school or equivalent, university degree and postgraduate) and economic activity (employed/self-employed, unemployed, homemaker/housewife, retired).

In case a covariate was not available, of low quality or contained more than 10% missing values, it was replaced by a similar covariate or excluded from the individual cohort-specific model. For example, instead of physical activity in categories, which was not available in REGICOR, a weekly leisure time physical activity variable was used.

Based on existing knowledge of possible non-linear relationships for age, BMI, pack-years of smoking and wine consumption (where available), the corresponding terms were entered as linear and squared, centered on the mean.

Controlling for area-level effects

To adjust for potential clustering of the outcome on a small-scale spatial level, we included a random intercept for neighborhood in the mixed-effects regression models. If area-level variables

were available at different spatial scales, we used the scale corresponding to the spatial scale of the random intercept, which was chosen based on the Akaike Information Criterion of the model. In addition, we controlled for potential confounding on the area-level by including the information on neighborhood SES was as a covariate in the main model. If available, we used unemployment rate in the neighborhood, or, alternatively, welfare rate, average education level or mean income.

Meta-analysis

The ***random effects meta-analysis*** based on the DerSimonian and Laird method (DerSimonian and Laird 1986) was performed. We defined the p-value of Cochrane's Q-test<0.05 or I^2 >50% an indication for heterogeneity (Higgins and Thompson 2002). Forest plots were produced using the package ***metafor*** (Viechtbauer 2010) in R Version 2.13.1.

As ***sensitivity analyses***, we divided cohorts in groups by quality of BP measurement procedure and excluded studies one-by-one to investigate the impact of individual studies on the meta-estimate. We also conducted meta-regression using characteristics of population and exposure in the cohort as independent predictors. For further details, see Supplemental Material, Sensitivity Meta-Analysis and Meta-Regression.

Results

We analysed data from fifteen cohorts in nine European countries, comprising 164,484 individuals with information on exposure, outcome and covariates (Table 2). Cohort-specific baseline examinations ranged from 1992 until 2008. Two cohorts were excluded from the main meta-analysis: EPIC-Oxford, since information on BPLM was not available, and DCH, due to a slightly different BP measurement method in hypertensive participants (see Methods and the Supple-

mental Material, Table S1). This left 13 cohorts with 113,926 participants in the main meta-analysis with NO_x and traffic load, and 12 cohorts with 90,852 participants in the main analysis of PM. All fifteen cohorts were included in the extended meta-analysis.

Out of the 113,926 participants in the main meta-analysis with NO_x and traffic load in a 100 m buffer, 14,943 (13.1%) participants were taking BPLM and 41,067 (36.0%) had hypertension. Mean systolic BP in cohorts ranged from 120.8 mmHg to 142.7 mmHg; mean diastolic BP ranged from 75.0 mmHg to 84.5 mmHg (Table 2). Characteristics of participants included in the main analysis were similar to the extended sample (Table 2).

Mean pollutant concentrations increased from North to South across the studies (Table 3). Correlation between pollutants' concentrations ranged from moderate (Pearson's ρ 0.5 to 0.7) to high (ρ > 0.7; see the Supplemental Material, Table S2). We observed high correlation of PM measures, of PM with NO_x, and of NO_2 with NO_x in most study areas. We observed moderate to high correlations between pollutants, traffic indicators and road traffic noise. The two traffic indicators were weakly (ρ 0.3 to 0.5) to moderately correlated.

Associations with particulate air pollutants

Modelled PM concentrations were not clearly associated with any of the studied outcomes in the single pollutant models (Tables 4–5 and Figure 1). We found a 0.20 mmHg (95% confidence interval (95% CI): -0.76, 1.16) and 0.98 mmHg (95% CI: -0.35, 2.31) increase in systolic BP in non-medicated and medicated participants per 5 μg/m³ increase in $PM_{2.5}$, respectively. The p-value for interaction $PM_{2.5}$ × BPLM intake was 0.25. Similar results were found for diastolic BP: an increase of 0.14 mmHg in non-medicated (95% CI: -0.57, 0.85) and by 0.59 mmHg in medicated (95% CI: -0.19, 1.37) participants per 5 μg/m³ increase in $PM_{2.5}$; the p-value for interaction

was 0.26. The ORs for hypertension and BPLM intake per 5 μg/m³ of $PM_{2.5}$ were 1.07 (95% CI: 0.95, 1.21) and 1.06 (95% CI: 0.96, 1.17), respectively. Similarly, elevated, but non-significant estimates were observed for $PM_{2.5}$ absorbance, PM_{coarse}, and PM_{10}. Results across studies were somewhat heterogeneous for $PM_{2.5}$ and PM_{coarse} (Figure 1), displaying relatively large positive point estimates in some cohorts and inverse associations in others.

Associations with nitrogen oxides

Modelled concentrations of nitrogen oxides were not significantly associated with any of the outcomes, though NO_2 showed a weak inverse relationship with systolic BP in non-medicated participants (-0.29; 95% CI: -0.70, 0.12) mmHg per 10 μg/m³; the p-value for interaction with BPLM intake was 0.64). Results were similar for NO_x (Table 4-5 and Figure 2). Significant heterogeneity was observed in the meta-analysis of NO_2 and NO_x with BP in non-medicated participants and in the analysis with hypertension (Figure 2).

Associations with traffic indicators

Traffic load in a 100 m buffer was associated with elevated BP in non-medicated participants with an increase of 0.35 mmHg (95% CI: 0.02, 0.68) systolic and 0.22 mmHg (95% CI: 0.04, 0.40) diastolic per 4,000,000 vehicles × m/day, respectively, with no evidence for heterogeneity (Table 4 and Figure 2). The p-values for interaction with BPLM intake were 0.14 and 0.15, respectively. No association was found in medicated participants. The estimated odds ratios (OR) for hypertension and BPLM intake were 1.05 (95% CI: 0.99, 1.11) and 1.04 (95% CI: 0.98–1.10) per 4,000,000 vehicles × m/day, respectively, with some evidence for heterogeneity for the outcome hypertension (Table 5). In categorical analyses of traffic load and BP we found the highest effect estimates among most exposed participants, although no consistent exposure-response

relationship was observed (Supplemental Material, Figure S1). Traffic intensity at the nearest road showed no association with the outcomes (Tables 4–5 and Figure 2).

Sensitivity analyses

Results with right-censored regression (censoring by BPLM use) were similar to those in non-medicated (Table 6). We observed a positive association of traffic load with systolic and diastolic BP. Findings for other pollutants were inconsistent.

We observed similar effects in the main analysis as compared to the extended analysis which included DCH and EPIC-Oxford (Supplemental Material, Figure S2 with $PM_{2.5}$, NO_2 and traffic load and systolic BP; not shown with other pollutants and diastolic BP; see also forest plots in main and extended meta-analysis with $PM_{2.5}$ and BP in Supplemental Material, Figure S3). When restricting the analysis to cohorts with at least three consecutive BP measurements, we observed a positive association of $PM_{2.5}$ with systolic BP in medicated participants and an increased estimate in non-medicated (Supplemental Material Figure S2). No consistent differences by body position during measurement and by the BP recording device were observed.

Increasing level of adjustment from the crude to the main model increased the effect estimates of $PM_{2.5}$ with systolic BP (Supplemental Material, Figure S4). Further adjustment with road traffic noise and season in the sensitivity models led to minor decreases in estimates with systolic BP (Supplemental Material, Figure S5 with $PM_{2.5}$, NO_2 and traffic load; not shown with other pollutants). Exclusion of participants who had changed their address recently led to a minor decrease in the estimated change in systolic BP with $PM_{2.5}$, increase with NO_x and no difference with NO_2 and traffic load (Supplemental Material, Figure S5 for $PM_{2.5}$, NO_2, and traffic load; not shown for NO_x). Back extrapolation of exposure estimates for PM_{10} and NO_2 to the time of the baseline

examination slightly increased the estimates for PM_{10} and NO_2 (Supplemental Material, Figure S5 for NO_2; not shown for PM_{10}). Traffic noise was associated with BP only in some of the cohorts (not shown).

In two-pollutant models including both $PM_{2.5}$ and NO_2, estimates were higher for $PM_{2.5}$ and more negative for NO_2 for systolic BP (Supplemental Material, Table S3). This tendency was still observed after we excluded 6 studies with a high correlation of $PM_{2.5}$ and NO_2 (not shown). No difference in estimates was observed for diastolic BP (not shown). A similar but less consistent pattern was observed for PM_{10} and $PM_{2.5}$ absorbance with NO_2 (not shown).

In the meta-regression, mean age of the study participants was positively associated with the study-specific estimate for $PM_{2.5}$ and NO_2 in non-medicated ($p<0.05$; data not shown); no associations with other study characteristics (including leave-one-out cross-validation R^2 of the LUR model) were found.

Discussion

In this comprehensive study of up to fifteen European population-based cohort studies including up to 164,484 participants, high traffic load in a 100 m buffer around the residence was weakly associated with increased arterial BP in participants not taking BPLM, independently of background concentrations of NO_x and road traffic noise levels. We also found a positive, yet imprecise, relationship of high traffic load with the odds for hypertension and intake of BPLM. Modelled exposure to PM was not clearly related to BP, although point estimates were mostly elevated. We found positive associations in the subgroup of studies with at least three consequent measurements of BP per participant. Modelled concentrations of nitrogen oxides were not asso-

ciated with BP, although we found a weak association between higher NO_2 and lower BP. Results for $PM_{2.5}$ and NO_2 were stronger when adjusted for each other.

Living close to a busy road is positively associated with pulse pressure and inflammation markers (Rioux et al. 2010), impaired cardiac function (Van Hee 2009), narrower retinal arteriolar diameter (Adar et al. 2010), coronary heart disease prevalence and mortality (Gan et al. 2010; Hoffmann et al. 2006), and atherosclerosis progression (Hoffmann et al. 2007; Künzli et al. 2010). We have previously reported increased prevalence of hypertension among participants living near major road (Fuks et al. 2011). Our results for traffic load in non-medicated participants were weak, though robust to adjustment for potential confounders such as background air pollution levels, personal cardiovascular risk factors, neighborhood SES, and road traffic noise. We think it is possible that the direct traffic emissions (not estimated with LUR, such as ultrafine particles) could be the reason for the observed associations. A relationship between ultrafine particles and acute changes in cardiovascular function, such as heart rate variability, endothelial vasomotor function and others, was reported in a recent review (Weichenthal, 2012). On the other hand, we found no association of traffic intensity on the nearest road with any of the outcomes. This discordance may be explained by the difference between these two variables: while traffic intensity pertains to the closest road only (regardless of road type and of other highly trafficked roads close by), traffic load takes into account all major roads within 100 m of the residence. As a result the correlation between the two variables was low to moderate.

We observed positive point estimates of PM with BP in medicated participants and no association in non-medicated. Results for long-term $PM_{2.5}$ in medicated participants were generally in accordance with associations reported in prior single-cohort studies in adults, although the confidence intervals were wider in our study despite its large size (Chuang et al. 2011; Coogan et al.

2012; Schwartz et al. 2012). The estimates for PM_{10} with BP in medicated participants were similar or even higher (for diastolic BP) compared to those reported in a recent study from China (Dong et al. 2013). Restriction of the analysis to studies with at least three measurements of BP yielded higher estimates for PM in medicated participants. This finding points to the necessity of reducing the outcome measurement error by repeated and standardized assessments of BP. The observed heterogeneity of the results might also be explained in part by different constituents contributing to the complex PM mixture across the European study areas. Recently, Wu and colleagues have reported positive and inverse short-term associations of different PM constituents with BP (Wu et al. 2013).

We found a weak association between higher NO_2 and lower systolic BP in non-medicated participants, which, although not statistically significant, was robust to the inclusion of traffic noise and to adjustment for temporal changes by using back-extrapolated concentrations. When we included both $PM_{2.5}$ and NO_2 in a two-pollutant model for systolic BP, positive estimate for $PM_{2.5}$ increased, while the negative estimated for NO_2 further decreased in non-medicated participants. NO_2-related BP-decrease has been shown before in a large Danish study, using a different exposure model (Sørensen et al. 2012); however, coherent biological explanations are still missing.

We found partially different results in the groups by BPLM intake While traffic load was associated with BP in non-medicated participants, PM was weakly related to BP only in medicated participants. The proportion of medicated participants differed greatly among the studies. A medication-induced decrease in BP may mask any influences of environmental factors, especially if the prescription of BPLM is in part related to environmentally induced high blood pressure. On the other hand, participants not using BPLM may represent a less susceptible population group,

especially in older cohorts. It is therefore possible that results in non-medicated participants underestimate the true effect in the population.

The suggested biological mechanisms for cardiovascular effects of particulate TRAP include the elicitation of local and systemic inflammation and oxidative stress, autonomic imbalance, and endothelial dysfunction (Brook 2007; Brook et al. 2009). Results from animal hypertension models have shown that $PM_{2.5}$ could potentiate hypertension through modulation of the sensitivity to pressure stimuli (Sun et al. 2008).

The estimated change in BP following exposure to TRAP is rather small. However, even small changes of arterial BP are of high public health importance. A reduction in systolic BP by only 2 mm leads to a reduction in stroke mortality by 5%, in coronary heart disease mortality by 4%, and in total mortality by 3% (Whelton et al. 2002). Reduction of diastolic BP by 2 mmHg has been linked to a 6% decrease in the risk of coronary heart disease and 15% reduction in risk of stroke and transient ischemic attack (Cook et al. 1995).

Assessing exposure with models always implies imprecision, i.e. misclassification, which might have masked or weakened true associations. In addition, TRAP modelling with the ESCAPE protocol was performed on average 5–10 years after BP had been measured. Personal exposure misclassification will likely increase over longer time periods, and possibly mask the small effects. However, in the meta-regression we did not find any influence of the time period between exposure and outcome assessment on the meta-analysis estimate. In addition, it has been shown that LUR models are reliable estimators of spatial air pollution gradients for decades back in time (Eeftens et al. 2011).

Some of estimated odds ratios with hypertension and BPLM intake as high as 1.08. However, given the relatively high prevalence rates of BPLM-intake of 35% to 66% across our cohorts, this prevalence odds ratio likely overstates the magnitude of the effect on the prevalence ratio.

One limitation of our study is that BPLM could be prescribed for conditions other than hypertension. For example, beta blockers are also used for the management of cardiac arrhythmias. To overcome this limitation, we analysed several related outcomes, including measured BP only, intake of BPLM only, and hypertension as a composite outcome. Extended outcome definitions, such as prehypertension, could be added to future analyses, as prehypertension was associated with cardiovascular and cerebrovascular disease (Erbel et al. 2012). A more reliable investigation of the air pollution effect in participants using BPLM will be possible in cohorts with repeated prospective assessment of BP and BPLM.

This is by far the largest study to date to investigate the effect of long-term exposure to TRAP on arterial BP and hypertension. We included up to 164,484 participants from large population-based cohorts in Europe. We used the same protocol for dedicated air pollution measurement campaigns and for LUR modelling across all study areas, underwent great efforts to assess and define outcome variables and covariates in comparable ways, and applied identical statistical analysis procedures accounting for BPLM intake in each cohort. We have used data from all ESCAPE cohorts where BP data were available and of satisfying quality, regardless of whether any effects of air pollution on BP had been investigated or shown in these cohorts previously, therefore, diminishing the probability of publication bias.

Conclusions

This is the largest study on the effect of air pollution on blood pressure and the only meta-analysis to date. Using fifteen European population-based cohorts we observed a weak positive association of high residential traffic exposure with arterial BP in participants without BPLM intake and an elevated OR for prevalent hypertension. The relationship of modelled air pollutants with BP was inconsistent, though positive relationships with BP in medicated participants and in the subgroup of studies with higher quality BP measurements were observed. Due to the importance of arterial blood pressure and hypertension as the major risk factors for premature mortality worldwide, these findings have large public health implications and point to the necessity of refined analyses using information on air pollution components, personal characteristics that may convey differential susceptibility and high quality outcome assessments.

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Table 1. Blood pressure measurement procedure in the participating cohorts.

Study	Measurement period	WHO protocol[a]	Arm used	Different cuff sizes	Body position	Measurement device	Repeated measurements	Final BP
FINRISK	1992, 1997, 2002, 2007	no	right	no	sitting	Manual mercury SM	2–3[b]	mean (1^{st} – 2^{nd})
DCH	1993–1997	no	right	yes	supine	AOD	1-2[c]	1^{st}
HUBRO	2000–2001	no	right	yes	sitting	AOD	3	mean (2^{nd} – 3^{rd})
60-year-olds	1997–1999	no	right	yes	supine	AOD	2	mean (1^{st} – 2^{nd})
SDPP	1992–1994, 1996–1998	no	either	yes	sitting	Manual SM	1	1^{st}
SNAC-K	2001–2004	no	left	yes	sitting, supine, standing	Manual SM	4	2^{nd}
TwinGene	2004–2008	no	right	yes	sitting	AOD, manual SM	2	mean
EPIC-Umeå	1992–1996	no	right	yes	sitting, supine	Manual SM	2	mean
EPIC-MORGEN	1993–1997	no	left	yes	supine	AOD	2	mean
EPIC-Prospect	1993–1997	no	left	no	supine	AOD	2	mean
EPIC-Oxford	1993–2001	no	either	yes	sitting	AOD	1–2[d]	last
HNR	2000–2003	yes	right	yes	sitting	AOD[e]	3	mean (2^{nd} – 3^{rd})
KORA	1994–1995, 1999–2001	yes	right	yes	sitting	random-zero SM, AOD	3	last
SAPALDIA	2001–2002	yes	left	yes	sitting	AOD	2	mean
REGICOR	2003–2006	no	right	yes	sitting	AOD	2[f]	last

BP = blood pressure; SM = sphygmomanometer; AOD = automated oscillometric device.

[a](Hense et al. 1995). [b]Two BP measurements were performed in 1992, 1997, three measurements – in 2002, 2007. [c]If the first measured BP value was considered abnormal, 3 minutes later a new measurement was taken. The lowest blood pressure measurement was recorded as final. [d]BP was measured twice in a subset of 5,241 participants. [e]The missing BP value with AOD was replaced with the value recorded with random-zero SM (in 34 participants, 0.7% of the sample). [f]If the difference between the 1^{st} and the 2^{nd} measurement was >5 mmHg, a 3^{rd} measurement was performed.

Table 2. Description of the study population in the cohorts included in the main and the extended meta-analysis. Studies in the main meta-analysis are ordered from North to South.

Study (country)	N	Systolic BP Mean ± SD	Diastolic BP Mean ± SD	BPLM, %	Hypertension, %	Age Mean ± SD	Men %	BMI, kg/m² Mean ± SD	Smokers %
FINRISK (FI)	10,318	134.1 ± 19.3	80.7 ± 11.6	12.7	41.6	48.1 ± 13.2	47.0	26.4 ± 4.6	26.7
HUBRO (NO)	16,200	130.3 ± 17.8	75.0 ± 11.2	11.8	32.0	47.8 ± 15.1	44.7	25.6 ± 4.1	25.4
60-year-olds (SE)	3,659	138.4 ± 21.8	84.5 ± 10.6	19.6	52.7	60.4 ± 0.1	47.1	26.8 ± 4.2	19.9
SDPP (SE)	7,535	122.8 ± 15.9	77.0 ± 10.0	5.8	24.0	47.1 ± 4.9	38.5	25.7 ± 4.0	26.1
SNAC-K (SE)	2,738	142.7 ± 20.2	81.3 ± 10.6	9.8	66.3	71.1 ± 9.5	41.7	25.7 ± 3.9	13.6
TwinGene (SE)	1,296	135.6 ± 18.8	83.8 ± 11.5	21.4	55.5	60.9 ± 6.0	39.7	25.2 ± 3.7	20.2
EPIC-Umeå (SE)	21,912	126.7 ± 17.2	78.6 ± 10.6	7.5	34.8	46.0 ± 10.2	47.8	25.0 ± 4.0	18.9
EPIC-MORGEN (NL)	16,293	120.8 ± 16.3	76.8 ± 10.7	22.9	20.5	43.9 ± 10.9	45.2	25.2 ± 4.0	34.4
EPIC-Prospect (NL)	16,434	132.5 ± 20.5	78.8 ± 10.8	20.4	43.4	57.7 ± 6.0	0	25.5 ± 4.1	22.2
HNR (DE)	4,615	133.1 ± 20.8	81.4 ± 10.9	35.3	56.9	59.5 ± 7.8	49.9	27.9 ± 4.6	23.2
KORA (DE)	7,501	131.0 ± 19.6	80.7 ± 10.9	18.5	41.0	50.5 ± 13.6	49.0	27.3 ± 4.6	24.4
SAPALDIA (CH)	1,884[a]	126.1 ± 18.3	80.3 ± 10.5	19.3	37.3	53.3 ± 11.4	46.5	25.4 ± 4.2	27.1
REGICOR (ES)	3,541	127.7 ± 19.9	78.4 ± 10.2	25.8	41.7	57.7 ± 12.3	45.2	27.0 ± 4.4	19.8
$TOTAL_{main}$	113,926[b]	130.9	79.8	13.1	36.0	54.1	38.8	26.0	24.2
DCH (DK)	36,829	140.4 ± 20.6	83.4 ± 10.6	13.0	55.19	56.8 ± 4.4	47.1	26.0 ± 4.1	37.0
EPIC-Oxford (GB)	13,729	126.0 ± 19.1	77.1 ± 11.1	–	32.4	49.6 ± 11.6	22.8	24.5 ± 4.1	–
$TOTAL_{extended}$	164,484	131.2	79.8	12.0	40.0	54.0	39.3	25.9	25.0

BP = blood pressure; BPLM = blood pressure lowering medication; SD = standard deviation; BMI = body mass index.

Country abbreviations: FI = Finland, NO = Norway, SE = Sweden, NL= the Netherlands, DE = Germany, CH = Switzerland, ES = Spain, DK = Denmark, GB = the United Kingdom.

[a]Data on NO_x and traffic indicators were available for all three sites of SAPALDIA: Basel, Geneva, Lugano (n=1884). PM exposure concentrations were available only for the Lugano site (n=722). [b]N=90,852 in the analysis of PM exposures. PM was not modelled in EPIC-Umeå and in 2 out of 3 sites of SAPALDIA.

Table 3. Characteristics of the land use regression model (leave-one-out cross-validation R^2) and concentrations of long-term traffic-related air pollution in cohorts (mean ± standard deviation).

Study	R^2 LUR validation: $PM_{2.5}$[a]	R^2 LUR validation: NO_2[b]	$PM_{2.5}$ [μg/m³]	$PM_{2.5}$ absorbance [10^{-5} m^{-1}]	PM_{coarse} [μg/m³]	PM_{10} [μg/m³]	NO_2 [μg/m³]	NO_x [μg/m³]	Traffic load [10^6 vehicles × m/day]
FINRISK	53%	75%	7.7 ± 1.1	0.9 ± 0.2	6.6 ± 2.3	14.0 ± 3.1	15.3 ± 4.9	24.2 ± 8.8	0.6 ± 1.5
HUBRO	68%	66%	9.0 ± 1.3	1.2 ± 0.3	4.0 ± 2.0	13.5 ± 3.1	20.9 ± 7.9	38.3 ± 15.3	0.8 ± 1.9.
60-year-olds	78%[c]	83%	7.3 ± 1.3	0.6 ± 0.2	7.4 ± 2.9	15.0 ± 3.8	10.8 ± 4.2	10.3 ± 3.6	0.5 ± 1.5
SDPP	78%[c]	83%	6.6 ± 1.2	0.5 ± 0.1	6.3 ± 2.4	13.7 ± 3.2	8.4 ± 1.7	14.4 ± 3.3	0.1 ± 0.4
SNAC-K	78%[c]	83%	7.9 ± 1.3	0.8 ± 0.2	8.5 ± 4.7	16.3 ± 6.0	17.4 ± 4.8	33.1 ± 12.3	2.2 ± 3.7
TwinGene	78%[c]	83%	7.3 ± 1.3	0.6 ± 0.2	7.2 ± 3.0	14.8 ± 4.0	10.7 ± 4.0	18.4 ± 8.9	0.6 ± 1.7
EPIC-Umeå	–	83%	–	–	–	–	5.2 ± 2.4	8.7 ± 5.7	0.1 ± 0.4
EPIC-MORGEN	61%	81%	16.9 ± 0.6	1.4 ± 0.2	8.6 ± 1.1	25.4 ± 1.7	23.8 ± 7.0	36.4 ± 11.7	0.9 ± 2.0
EPIC-Prospect	61%	81%	16.8 ± 0.5	1.4 ± 0.2	8.5 ± 0.7	25.3 ± 1.2	26.7 ± 4.7	39.6 ± 10.6	0.7 ± 1.6
HNR	79%	84%	18.4 ± 1.1	1.6 ± 0.4	10.0 ± 1.8	27.8 ± 1.9	30.2 ± 4.9	50.8 ± 12.0	1.0 ± 2.2
KORA	62%	67%	13.6 ± 0.9	1.7 ± 0.2	6.2 ± 1.1	20.3 ± 2.4	18.7 ± 3.9	32.6 ± 7.4	0.4 ± 1.1
SAPALDIA	77%[d]	58%[d], 82%[e]	17.1 ± 1.4[d]	2.0 ± 0.4[d]	6.7 ± 1.2[d]	23.7 ± 2.2[d]	27.5 ± 6.4[f]	46.0 ± 13.8[f]	1.0 ± 1.8[f]
REGICOR	71%	68%	15.0 ± 1.7	2.3 ± 0.7	15.0 ± 2.4	32.0 ± 4.0	35.5 ± 14.2	63.2 ± 29.1	1.6 ± 2.3
TOTAL (main)			12.0	1.2	7.9	20.2	19.3	32.0	0.8
DCH	55%	83%	11.3 ± 0.9	1.15 ± 0.2	5.7 ± 1.0	17.1 ± 1.9	16.3 ± 7.0	26.6 ± 18.3	1.2 ± 2.3
EPIC-Oxford	77%	87%	9.7 ± 1.0	1.05 ± 0.2	6.4 ± 0.9	16.0 ± 2.0	22.9 ± 7.2	38.3 ± 14.0	0.4 ± 1.3
TOTAL (extended)			11.7	1.2	7.6	19.6	19.4	32.1	0.8

[a](Eeftens et al., 2012). [b](Beelen et al., 2013). [c]Common model was developed for the Stockholm cohorts: 60-year-olds, SDPP, SNAC-K, TwinGene. [d]Only Lugano site of SAPALDIA. [e]Only Basel and Geneva sites of SAPALDIA. [f]Three sites of SAPALDIA (Basel, Geneva, Lugano).

Table 4. Adjusted[a] associations of traffic-related air pollution and traffic indicators with blood pressure, estimated with random-effects meta-analysis.

Outcome and exposure (increment)	$N_{(studies)}$	No BPLM Change[b], mmHg (95% CI)	$p_{(het.)}$	I^2 (%)	BPLM intake Change, mmHg (95% CI)	$p_{(het.)}$	I^2 (%)
Systolic blood pressure							
$PM_{2.5}$ (5 µg/m³)	12[c]	0.20 (-0.76, 1.16)	0.09	38	0.98 (-0.35, 2.31)	0.49	0
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	12	0.07 (-0.46, 0.60)	0.42	3	-0.04 (-1.37, 1.29)	0.28	17
PM_{coarse} (5 µg/m³)	12	-0.09 (-0.76, 0.58)	0.01	58	0.30 (-0.44, 1.04)	0.59	0
PM_{10} (10 µg/m³)	12	0.09 (-0.60, 0.78)	0.10	36	0.44 (-0.68, 1.56)	0.36	9
NO_2 (10 µg/m³)	13	-0.29 (-0.70, 0.12)	0.02	50	-0.14 (-0.77, 0.49)	0.26	18
NO_x (20 µg/m³)	13	-0.08 (-0.47, 0.31)	0.03	48	0.04 (-0.43, 0.51)	0.61	0
Traffic load (4 × 10^6 vehicles × m/day)	13[d]	0.35 (0.02, 0.68)	0.35	9	-0.11 (-0.74, 0.52)	0.84	0
Traffic intensity (5,000 vehicles/day)	12[e]	0.08 (-0.06, 0.22)	0.86	0	0.11 (-0.22, 0.45)	0.73	0
Diastolic blood pressure							
$PM_{2.5}$ (5 µg/m³)	12[c]	0.14 (-0.57, 0.85)	0.01	57	0.59 (-0.19, 1.37)	0.88	0
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	12	0.24 (-0.09, 0.57)	0.4	5	0.43 (-0.49, 1.35)	0.14	32
PM_{coarse} (5 µg/m³)	12	0.13 (-0.11, 0.37)	0.25	20	0.34 (-0.23, 0.91)	0.13	32
PM_{10} (10 µg/m³)	12	0.17 (-0.12, 0.46)	0.31	14	0.63 (-0.11, 1.37)	0.23	22
NO_2 (10 µg/m³)	13	0.04 (-0.10, 0.18)	0.62	0	0.21 (-0.12, 0.54)	0.32	13
NO_x (20 µg/m³)	13	0.09 (-0.05, 0.23)	0.62	0	0.32 (-0.01, 0.65)	0.30	14
Traffic load (4 × 10^6 vehicles × m/day)	13[d]	0.22 (0.04, 0.40)	0.72	0	-0.04 (-0.39, 0.31)	0.94	0
Traffic intensity (5,000 vehicles/day)	12[e]	0.08 (0.00, 0.16)	0.80	0	-0.04 (-0.30, 0.21)	0.22	22

BPLM = blood pressure lowering medication; 95% CI = confidence interval at $\alpha = 0.05$; I^2 = measure of heterogeneity between cohorts; $p_{(het.)}$ = p-value for the Q-test of heterogeneity.

[a]Adjusted for age, sex, body mass index, smoking status, pack-years of smoking, passive smoking, alcohol consumption, physical activity, educational level, economic activity, neighborhood socio-economic status (including a random intercept for a neighborhood). [b]Estimated change in blood pressure refers to the indicated exposure increment. [c]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-MORGEN, EPIC-Prospect, HNR, KORA, SAPALDIA (Lugano site), REGICOR. N(total)=91,574; N(non-medicated)=79,404; N(medicated)=12,170. [d]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-Umeå, EPIC-MORGEN, EPIC-Prospect, HNR, KORA, SAPALDIA, REGICOR. N(total)=114,648; N(non-medicated)=99,705; N(medicated)=14,943. [e]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-Umeå, EPIC-MORGEN, EPIC-Prospect, KORA, SAPALDIA, REGICOR. N(total)=110,033; N(non-medicated)==96,717; N(medicated)=13,316.

Table 5. Adjusted[a] associations of traffic-related air pollution and traffic indicators with prevalent hypertension and blood pressure lowering medication use, estimated with random-effects meta-analysis.

Outcome and exposure (increment)	$N_{(studies)}$	Odds ratio[b] (95% CI)	$p_{(het.)}$	I^2
Hypertension				
$PM_{2.5}$ (5 μg/m³)	12[c]	1.07 (0.95, 1.21)	0.13	33
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	12	1.05 (0.95, 1.16)	0.14	31
PM_{coarse} (5 μg/m³)	12	1.00 (0.94, 1.06)	0.07	40
PM_{10} (10 μg/m³)	12	1.01 (0.93, 1.09)	0.25	20
NO_2 (10 μg/m³)	13	0.98 (0.92, 1.04)	0.01	55
NO_x (20 μg/m³)	13	0.98 (0.92, 1.04)	<0.01	64
Traffic load (4×10^6 vehicles × m/day)	13[d]	1.05 (0.99, 1.11)	0.02	51
Traffic intensity (5,000 vehicles/day)	12[e]	1.02 (1.00, 1.04)	0.38	7
BPLM intake				
$PM_{2.5}$ (5 μg/m³)	12[c]	1.06 (0.96, 1.17)	0.85	0
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	12	1.08 (0.98, 1.19)	0.24	20
PM_{coarse} (5 μg/m³)	12	0.99 (0.93, 1.05)	0.63	0
PM_{10} (10 μg/m³)	12	0.98 (0.91, 1.06)	0.54	0
NO_2 (10 μg/m³)	13	1.01 (0.97, 1.05)	0.30	14
NO_x (20 μg/m³)	13	0.98 (0.94, 1.02)	0.60	0
Traffic load (4×10^6 vehicles × m/day)	13[d]	1.04 (0.98, 1.10)	0.12	33
Traffic intensity (5,000 vehicles/day)	12[e]	1.00 (0.98, 1.02)	0.76	0

BPLM = blood pressure lowering medication; 95% CI = confidence interval at $\alpha = 0.05$; I^2 = measure of heterogeneity between cohorts; $p_{(het.)}$ = p-value for the Q-test of heterogeneity.

[a]Adjusted for age, sex, body mass index, smoking status, pack-years of smoking, passive smoking, alcohol consumption, physical activity, educational level, economic activity, neighborhood socio-economic status (including a random intercept for a neighborhood). [b]Odds ratio refers to the indicated exposure increment. [c]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-MORGEN, EPIC-Prospect, HNR, KORA, SAPALDIA (Lugano site), REGICOR. N=91,574. [d]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-Umeå, EPIC-MORGEN, EPIC-Prospect, HNR, KORA, SAPALDIA, REGICOR. N=114,648. [e]FINRISK, HU-BRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-Umeå, EPIC-MORGEN, EPIC-Prospect, KORA, SAPALDIA, REGICOR. N=110,033.

Table 6. Adjusted[a] associations of traffic-related air pollution and traffic indicators with systolic and diastolic blood pressure, estimated with right-censored regression and pooled using random-effects meta-analysis.

Outcome and exposure (increment)	$N_{(studies)}$	Change[b], mmHg (95% CI)	$p_{(het.)}$	I^2
Systolic blood pressure				
$PM_{2.5}$ (5 μg/m³)	12[c]	0.13 (-0.80, 1.07)	0.14	31
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	12	0.03 (-0.94, 0.99)	0.06	42
PM_{coarse} (5 μg/m³)	12	-0.14 (-0.73, 0.45)	0.03	49
PM_{10} (10 μg/m³)	12	-0.06 (-0.57, 0.45)	0.37	8
NO_2 (10 μg/m³)	13	-0.34 (-0.82, 0.13)	0.01	53
NO_x (20 μg/m³)	13	-0.27 (-0.71, 0.17)	0.00	60
Traffic load (4×10^6 vehicles × m/day)	13[d]	0.36 (0.06, 0.67)	0.46	0
Traffic intensity (5,000 vehicles/day)	12[e]	0.05 (-0.10, 0.19)	0.72	0
Diastolic blood pressure				
$PM_{2.5}$ (5 μg/m³)	12[c]	0.12 (-0.52, 0.76)	0.05	44
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	12	0.24 (-0.23, 0.72)	0.16	29
PM_{coarse} (5 μg/m³)	12	0.14 (-0.07, 0.36)	0.35	9
PM_{10} (10 μg/m³)	12	0.12 (-0.15, 0.40)	0.63	0
NO_2 (10 μg/m³)	13	0.03 (-0.11, 0.18)	0.58	0
NO_x (20 μg/m³)	13	0.06 (-0.07, 0.20)	0.55	0
Traffic load (4×10^6 vehicles × m/day)	13[d]	0.25 (0.08, 0.42)	0.56	0
Traffic intensity (5,000 vehicles/day)	12[e]	0.05 (-0.03, 0.13)	0.60	0

95% CI = confidence interval at $\alpha = 0.05$; I^2 = measure of heterogeneity between cohorts; $p_{(het.)}$ = p-value for the Q-test of heterogeneity.

[a]Adjusted for age, sex, body mass index, smoking status, pack-years of smoking, passive smoking, alcohol consumption, physical activity, educational level, economic activity, neighborhood socio-economic status (including a random intercept for a neighborhood). [b]Effect estimate refers to the indicated exposure increment. [c]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-MORGEN, EPIC-Prospect, HNR, KORA, SAPALDIA (Lugano site), REGICOR. N=91,574. [d]FINRISK, HUBRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-Umeå, EPIC-MORGEN, EPIC-Prospect, HNR, KORA, SAPALDIA, REGICOR. N=114,648. [e]FINRISK, HU-BRO, 60-year-olds, SDPP, SNAC-K, TwinGene, EPIC-Umeå, EPIC-MORGEN, EPIC-Prospect, KORA, SAPALDIA, REGICOR. N=110,033.

Figure legends

Figure 1. Cohort-specific and meta-analysis estimates of association of $PM_{2.5,}$ absorbance $PM_{2.5}$, PM_{coarse}, and PM_{10} with systolic blood pressure and hypertension. Results are presented per given increments. ***Legend:*** BP = blood pressure; BPLM = BP lowering medication; I^2 = measure of heterogeneity between cohorts; $p_{(het.)}$ = p-value for the Q-test of heterogeneity.

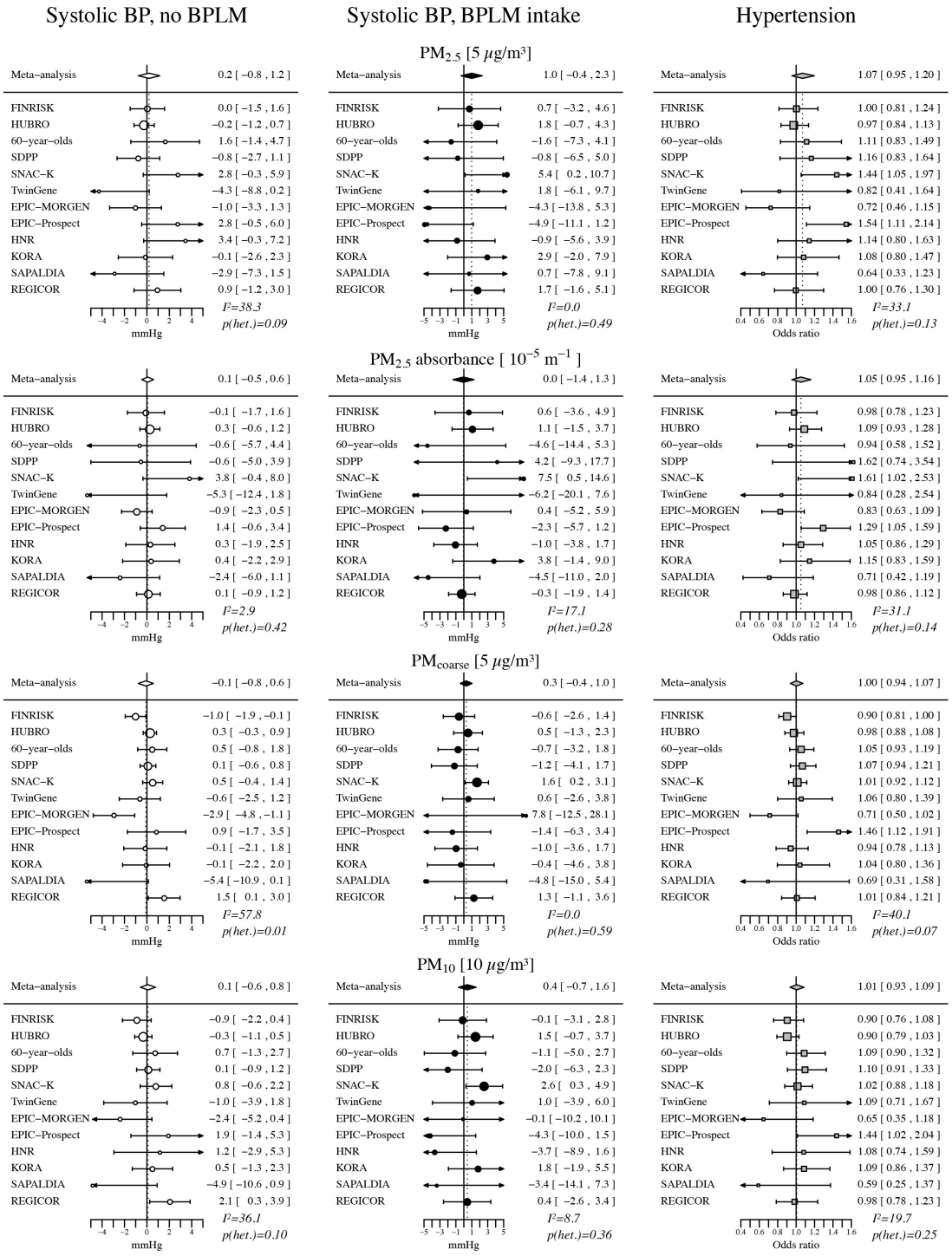

Figure 2. Cohort-specific and meta-analysis estimates of association of NO_2, NO_x, traffic load at major road fragments, and traffic intensity at the nearest road with systolic blood pressure and hypertension. Results are presented per given increments. ***Legend:*** BP = blood pressure; BPLM = BP lowering medication; I^2 = measure of heterogeneity between cohorts; $p_{(het.)}$ = p-value for the Q-test of heterogeneity.