



TRANSPHORM

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3
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39
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1 **Abstract**

2 *Background:* The chemical composition of airborne particulate matter (PM) varies across
3 locations, but associations between exposure to constituents of PM and birth weight have
4 been little examined.

5 *Aim:* We investigated the effect of exposure to elemental composition of PM on birth weight
6 and birth head circumference with standardised fine-scale exposure assessment and extensive
7 control for potential confounders.

8 *Methods:* We pooled data from eight European cohorts comprising 34,923 singleton births in
9 1994–2008. Residential annual average exposure to elemental constituents within PM smaller
10 than 2.5 and 10 μm (PM_{2.5} and PM₁₀) was estimated using land-use regression models at
11 maternal home addresses during pregnancy. Pooled effect estimates for eight elements
12 representing major sources (copper, iron, potassium, nickel, sulfur, silicon, vanadium and
13 zinc) were calculated using random-effects models.

14 *Results:* A 200 ng/m^3 increase in sulfur in PM_{2.5} levels was associated with an increased risk
15 for term low birth weight (<2,500 g among births after 37 weeks of gestation) with an
16 adjusted odds ratio of 1.36 (95% confidence interval: 1.17, 1.58). Risks for term low birth
17 weight were similar for sulfur in PM₁₀ and nickel in PM_{2.5}. Statistically significant reduction
18 in birth weight was found for sulfur in PM_{2.5} as well as in birth head circumference for all
19 elements with exception of potassium. In two-pollutant models the effect estimates for sulfur
20 remained and for mass decreased, suggesting that secondary aerosols contribute to the PM
21 associations.

22 *Conclusions:* Our results suggest that exposure to sulfur in both PM_{2.5} and PM₁₀ were
23 associated with decreased newborn's size.

1 **Introduction**

2 The evidence for associations between exposure to airborne particulate matter (PM) and low
3 birth weight is growing (Pedersen et al. 2013). Most consistently exposure to PM $\leq 2.5 \mu\text{m}$
4 ($\text{PM}_{2.5}$) in aerodynamic diameter has been associated with low birth weight (Fleischer et al.
5 2014; Pedersen et al. 2013; Stieb et al. 2012). Recent meta-analyses show heterogeneity
6 across studies conducted in many different countries (Dadvand et al. 2013; Sapkota et al.
7 2012; Stieb et al. 2012). The observed heterogeneity may be due to differences in the quality
8 of exposure assessment, the study population and the susceptibility to confounding between
9 the individual studies included in these meta-analyses, but the heterogeneity is not easily
10 interpreted. Another possible explanation of the inconsistency could be related to the fact that
11 airborne PM is a complex mixture of solid particles and liquid droplets, which vary spatially
12 and temporally in chemical composition and particle size distribution, related to for instance
13 their sources of origin (Stanek et al. 2011; Kelly and Fussell 2012).

14
15 Associations between various $\text{PM}_{2.5}$ components and risk for low birth weight have reported
16 in four large study populations from the United States (Basu et al. 2014; Bell et al. 2010;
17 2012; Darrow et al. 2011; Ebisu et al. 2012). However, the evidence is mixed and little is
18 known about which PM components are associated with higher risks for low birth weight.
19 Moreover, all these previous studies relied on exposure estimates based on data from the
20 nearest regulatory air monitor, which do not capture within-city exposure contrasts adequately
21 and may result in misclassification of exposure and possibly reduced risk estimates. None of
22 these previous studies have examined associations between particulate constituents and birth
23 head circumference.

24

1 Land-use regression (LUR) has been developed to model the spatial variation of the annual
2 mean concentrations for a range of air pollutants including nitrogen dioxide (NO₂), nitrogen
3 oxides (NO_x) and PM (PM_{2.5}, PM₁₀, PM_{2.5} absorbance) in multiple sites across Europe
4 (Beelen et al. 2013; Eeften et al. 2012). We have recently reported statistical significant
5 associations between temporally adjusted LUR exposure estimates to PM_{2.5}, PM₁₀ and NO₂
6 during pregnancy and low birth weight (Pedersen et al. 2013). Recently, LUR have also been
7 developed for eight a priori selected elements in both PM_{2.5} and PM₁₀ in 20 study areas across
8 Europe (de Hoogh et al. 2013).

9
10 In the present study, we aim to examine the impact of exposures to eight elemental PM
11 constituents on term low birth weight, birth weight and birth head circumference in a large
12 European study population with standardised fine-scale exposure assessment and extensive
13 control for potential confounders.

14
15 The elements included were copper (Cu), iron (Fe), potassium (K), nickel (Ni), sulfur (S),
16 silicon (Si), vanadium (V) and zinc (Z) because they reflected the major anthropogenic
17 particle sources, had evidence for toxicity, had a high percentage of well-detected samples
18 and a good precision of measurements (de Hoogh et al. 2013). We a priori choose to restrict
19 the current analysis to eight key elements to limit false positive associations that could arise
20 from analyzing all measured elements. Though these elemental PM components may have
21 multiple sources, the major sources are road traffic non-tailpipe emissions including brake
22 linings (Cu and Fe); tire wear (Zn); fossil fuel combustion (Ni and V); biomass burning (K);
23 long-range transport (S) and crustal materials (Si) (Viana et al. 2008).

24

1 **Methods**

2 *Study population.*

3 We pooled data from eight European mother-child cohorts in which inclusion exposure to
4 elemental composition of PM was assessed (Pedersen et al. 2013): BAMSE-Sweden (4
5 centres), DNBC-Denmark, KANC-Lithuania, ABCD, and PIAMA (3 centres)-The
6 Netherlands, DUISBURG-Germany, GASPII-Italy and INMA-Spain (Sabadell).

7 Because of financial reasons, GIS modeling was not done everywhere. Therefore, data for
8 elemental PM components are missing for MoBa-Norway, Generation R-The Netherlands,
9 APREG-Hungary and RHEA-Greece.

10 The study population included 34,923 women with singleton deliveries between 1994 and
11 2008. Detailed information on individual characteristics was obtained through interviews of
12 the mother and self-administrated questionnaires during the pregnancy in most cohorts. Data
13 from each cohort were harmonised and pooled centrally. Further information on the study
14 design, the specific eligibility criteria applied in the baseline cohorts for the participation of
15 mothers are summarized in the Supplemental Material (see Supplemental Material, Table S1).
16 Ethical approval was obtained from the ethics committee in each country. Written informed
17 consent was obtained from all participating women.

18

19 *Birth outcomes.*

20 We defined children to be of term low birth weight when the weight was less than 2,500 g and
21 the birth occurred after 37 weeks of gestation. We also assessed continuous measures of birth
22 weight and birth head circumference. Gestational age, birth weight, birth head circumference,
23 sex, and mode of delivery were obtained from birth records and parental reports in PIAMA.
24 Gestational age (weeks) was estimated as the interval between the start of the last menstrual
25 period and delivery when possible (53% of births). Ultrasound-based estimation (10%) was

1 used only if last menstrual period was unavailable; when this was not possible, we used the
2 estimates from the obstetrician (37%).

3

4 *Air pollution exposure assessment.*

5 To estimate exposure we used standardized methods developed within the ESCAPE
6 (European Study of Cohorts for Air Pollution Effects) and TRANSPHORM (Transport
7 related Air Pollution and Health impacts — Integrated Methodologies for Assessing
8 Particulate Matter) projects (Beelen et al. submitted/2014; de Hoogh et al. 2013; Eeftens et al.
9 2012; Wang et al. 2014).

10

11 Briefly, PM concentrations in outdoor air were measured during three two-week
12 measurements during summer, winter and an intermediate season within one year in multiple
13 sites (20-40) within each study area selected to represent spatial variation of air pollution in
14 the residential areas of the participants. Measurements were performed during 2008–2011
15 (see Supplemental Material, Table S1). PM filters were weighed before and after each
16 measurement centrally at IRAS, Utrecht University and were then sent to Cooper
17 Environmental Services (Portland, OR, USA) to detect elements. All filters were analyzed for
18 elemental composition using X-Ray Fluorescence (XRF) (De Hoogh et al. 2013). The three
19 measurements were then averaged, adjusting for temporal trends using data from the nearest
20 background monitoring site with continuous data (De Hoogh et al. 2013). A priori selection of
21 eight out of 48 measured elements was made for further epidemiological evaluation.

22

23 Annual mean concentrations of ambient elemental concentrations, PM_{2.5} and PM₁₀ were
24 estimated at the maternal home addresses during pregnancy with area-specific LUR models
25 (de Hoogh et al. 2013; Eeftens et al. 2012). Predictor variables on nearby traffic intensity,

1 population/household density and land use were derived from Geographic Information
2 Systems (GIS), and were evaluated to explain spatial variation of annual average
3 concentrations using LUR modeling. The LUR models explained 13-94% of variability in the
4 annual average elemental concentrations, depending on the component and study area (see
5 Supplemental Material, Table S2). For PM_{2.5} and PM₁₀ the LUR models explained 60–88%
6 and 50–75% of the variability in the annual average concentrations, respectively (Eeftens et
7 al. 2012). Because of lack of elemental data from routine monitoring stations in each study
8 area we were unable to backextrapolate the annual average elemental concentrations
9 estimated by the LUR models to each individual pregnancy. Data from routine monitoring
10 stations were used to temporally adjust the annual PM_{2.5} and PM₁₀ LUR estimates to the
11 periods corresponding to each individual pregnancy (Pedersen et al. 2013). We accounted for
12 changes of home address during pregnancy when the date of moving and the new address
13 were available for the mass concentration.

14

15 *Statistical analysis.*

16 We followed the same analysis plan as in our first study (Pedersen et al. 2013). Odds ratio
17 (OR) and their 95% confidence intervals (CI) for associations between exposure to air
18 pollution and term low birth weight were determined using logistic regression models. Linear
19 regression models were used for birth weight (g) and birth head circumference (cm). Pooled
20 analyses were conducted using mixed models including a random effect for centre.

21

22 Crude and adjusted models were examined. Adjustment variables were selected a priori; these
23 were gestational age (weeks, continuous and quadratic term), sex, parity (0, 1, 2 and more),
24 maternal height (cm), pre-pregnancy weight (broken stick model with a knot at 60 kg), mean
25 number of cigarettes smoked during second trimester of gestation (cigarettes/day), maternal

1 age (years), maternal education (cohort-specific definition of low, middle, high) and season of
2 conception (January-March, April-June, July-September, October-December).

3 Each exposure variable was entered as a continuous variable separately in regression models.

4 Two-pollutant models were conducted for each element by including particle mass (PM_{2.5},
5 PM₁₀) and the other elements to the model separately.

6

7 Sensitivity analyses included: 1) restriction to women who did not change home address
8 during pregnancy (assuming that residential mobility could result in exposure
9 misclassification); 2) restriction to areas where exposure models had the highest predictive
10 value (defined as a cross-validation R² above 0.6); 3) restricting to women who participated
11 with one pregnancy; 4) further adjustment for maternal ethnicity (born in or nationality as the
12 country of the cohort versus other) and self-reported maternal exposure to second hand smoke
13 (SHS) during pregnancy (no, yes); and 5) finally, analyses stratified on maternal ethnicity
14 (defined as above), maternal age (<25, 25-35, >35 years), sex, parity (0, 1+), maternal active
15 smoking (no, yes), maternal education (low, middle, high) and season of conception to
16 examine potential effect measure modification.

17

18 Interaction models were used to investigate whether associations differed by maternal
19 ethnicity, maternal age, sex, parity, maternal active smoking, maternal education and season
20 of conception when stratified models were suggestive of an interaction. Additionally we
21 performed random-effect meta-analyses of area-specific effects (*results not detailed*).

22

23 We used Stata S.E. version 12.1 S.E. for the statistical analyses (StataCorporation, Texas,
24 USA) and chose an alpha level of 5% (two-sided) to define statistical significance.

1 **Results**

2 Air pollution exposure was estimated for 34,923 mother-child pairs from eight cohorts in
3 seven European countries (Table 1). Mothers were primarily white Europeans, non-smoking,
4 25 to 34 years of age; 84.2% did not change home address during pregnancy. The mean
5 gestational age was 40.0 weeks, and 4.3% of births were preterm. Children weighed on
6 average 3,531 g, mean head circumference at birth was 35.2 cm; the prevalence of low birth
7 weight was 3.2% among all births and 1.2% among term births.

8 On average women from the Northern and Central European cohorts were both taller and
9 heavier and their children weighted more and had larger heads as compared with the means of
10 the Southern European children (Figure S1).

11
12 Air pollution pregnancy exposure levels were on average 17.0 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ and 26.9
13 $\mu\text{g}/\text{m}^3$ for PM_{10} (Table 2, Figure S1). Distributions of estimated particle constituents varied
14 between and within each cohort (Figure 1). It was not possible to estimate all constituents in
15 each study area because LUR models could not be developed. The highest concentrations and
16 exposure gradients of Cu and Fe were observed in the Italian study area. The Italian, German
17 and Dutch study areas were estimated to have the highest mean exposure to S. As shown in
18 Table 2 the S, K, Fe and Si contributed most to the mass of each particle mass fractions. Some
19 elements were mainly contained in the fine fraction (S, Ni, V, Zn), others (Cu, Fe, Si) mainly
20 in the coarse fraction.

21
22 The correlations between elemental concentrations and particle mass concentrations in the
23 same size fraction were modest to high in all cases with exception of Si (Table 2). For
24 example, S had correlations of 0.84 with total mass concentrations, 0.82 and 0.75 with Ni in

1 PM_{2.5} and PM₁₀, respectively (see Supplemental Material, Table S3). Other examples of
2 highly correlated elements include Cu and Fe, Ni and Si, Ni and V as well as Si and V.
3
4 The correlations between elemental and total mass concentrations differed statistically
5 significantly between cohorts and the within-area correlation between mass and elements
6 were smaller than the in the pooled sample (see Supplemental Material, Table S4). This was
7 also the case for correlations between the estimated particle constituents (*results not detailed*).
8
9 Increases in exposure to total particle mass concentrations and all the particle constituents
10 were associated with elevated ORs for term low birth weight with exception of Si (PM_{2.5} and
11 PM₁₀) and K PM₁₀ (Table 3). The associations were statistically significant for S (PM_{2.5} and
12 PM₁₀), Ni PM_{2.5} and mass concentration (PM_{2.5} and PM₁₀). Heterogeneity between cohorts
13 was not statistically significant according to the tests performed as part of the random-effect
14 meta-analyses (*results not detailed*). The combined effect estimates for S (PM_{2.5} and PM₁₀)
15 from random-effect meta-analyses were lower than those from the pooled analysis (*results not*
16 *detailed*), which may suggest that the effects were largely driven by between study area
17 comparisons rather than within study area variation. This was also the case for Ni in PM_{2.5}.
18 The results for S (PM_{2.5} and PM₁₀) were essentially unchanged in two-pollutants models after
19 adjustment for total particle mass concentration (Table 4). In two pollutant-models with PM
20 mass, the ORs for PM mass, but not for S were reduced, especially for PM₁₀. The OR of PM₁₀
21 in one-pollutant model for the study population with S it was 1.23 (1.02, 1.48) and in two-
22 pollutant model with adjustment for S it was reduced to 1.00 (0.80, 1.25) while the OR for S
23 in PM₁₀ in one-pollutant model for the study population with PM₁₀ was 1.27 (1.12, 1.43) and
24 after adjustment for PM₁₀ only the 95% CIs were a bit wider (1.03, 1.56) and the OR was still
25 1.27. The OR for PM_{2.5} in one-pollutant model for the study population with data on S was

1 1.23 (1.05, 1.43) and in two-pollutant model with adjustment for S the OR was reduced to
2 1.08 (0.90, 1.30). The ORs for S in PM_{2.5} and Ni (PM_{2.5} and PM₁₀) were slightly reduced after
3 adjustment for particle mass, but less than the ORs associated with the mass concentration in
4 two-pollutant models. **More?**

5
6 Sensitivity analyses were supportive of an association between S and low birth weight (see
7 Supplemental Material, Table S5). The OR changed very little after exclusion of women from
8 DNBC, who moved or women who participated more than once and after additional
9 adjustment. Only dropping areas with lowest R² of LUR reduces OR but they remain elevated
10 and even significant for PM₁₀. This analysis is anyway difficult to interpret as the change
11 could be due to smaller sample size. Stratified analyses showed that the adjusted ORs for S
12 were somewhat higher for women born elsewhere, women who smoked and gave birth for the
13 first time, nevertheless these differences did not reach statistical significance in additional
14 models with interactions-terms. Associations between S and term low birth weight did not
15 exhibit apparent differences by maternal education level, sex, maternal age and season of
16 conception.

17
18 We also assessed associations with birth weight as a continuous measure (Table 4). PM_{2.5} and
19 S PM_{2.5} were associated with statistically significant reduction in birth weight and in this
20 present study population (N=30, 313) the association for PM₁₀ reached borderline
21 significance. Increases in exposure to Si PM_{2.5}, Fe PM₁₀ and K PM₁₀ were associated with
22 statistically significant increases in birth weight. Si PM₁₀ was associated with higher birth
23 weight at borderline significance (p=0.06). There was no statistically significant evidence of
24 heterogeneity between cohorts according to meta-analyses for S PM_{2.5}, Fe PM₁₀ and K PM₁₀
25 (all p-values>0.10), but p-value was 0.05 and I² was 49.6 for Si PM_{2.5}.

1

2 In two pollutant-models with PM mass, the OR for PM_{2.5} mass, but not for S in PM_{2.5} was
3 reduced. The positive associations for Si PM_{2.5}, Fe PM₁₀ and K PM₁₀ did not change much
4 after mutual adjustment for PM mass or S (Table 4).

5

6 Sensitivity analysis suggested that the results for S PM_{2.5} were relative robust, again not when
7 areas were excluded and the population is reduced from 30,576 to 17,006. Higher reductions
8 of approximately 80 g in association with each 200 ng/m³ increment of S PM_{2.5} were seen in
9 women who smoked, women of first birth and women who had low education.

10

11 Table 5 shows that all pollutants with exception of K (PM_{2.5} and PM₁₀) were associated with
12 significant reductions in birth head circumference. However, random-effect meta-analyses
13 resulted in statistically significant heterogeneity between cohorts for all pollutants (p<0.05).

14

15 As for birth weight, in two pollutant-models with PM mass, the OR for PM mass, but not for
16 S was reduced. Effect estimates for S did not change much after adjustment for Ni or Zn.

17 Sensitivity analysis performed for S (PM_{2.5} and PM₁₀)₅ and Ni PM₂ indicated that the results
18 are robust for these constituents (*results not detailed*).

1 **Discussion**

2 We examined associations between eight key elemental components of the PM_{2.5} and PM₁₀
3 fractions and newborn's size in seven European countries. Our results suggest that especially
4 S in both PM_{2.5} and PM₁₀ and Ni in PM_{2.5} were associated with risk of term low birth weight,
5 reduced birth weight and smaller birth head circumference. The association between S and
6 low birth weight was robust to adjustment for co-pollutants including PM mass. The PM mass
7 effect estimates were reduced and became statistically non-significant after adjustment for S.
8 These findings are based on a large population from eight European cohorts with extensive
9 exposure assessment and detailed control for potential confounders.

10

11 The findings of our study were in consistency with previous findings for low birth weight
12 from the United States (Basu et al. 2014; Bell et al. 2010). The estimated 36% increase in risk
13 of low birth weight at term associated with a 200 ng/m³ for S in PM_{2.5} in our study is,
14 however, larger than those reported by the previous studies; the recalculated OR for a 200
15 ng/m³ increase in pregnancy mean exposure to S in PM_{2.5} was 1.05 (95% CI: 0.97, 1.13) (Bell
16 et al. 2010) and 1.00 (95% CI: 1.00, 1.04) (Basu et al. 2014). The estimated risk for low birth
17 weight found in our study associated with Ni, Cu, K, Fe, V, Zn in PM_{2.5} as well as PM_{2.5} were
18 also larger than those reported previously (Basu et al. 2014; Bell et al. 2010).

19 Likewise, smaller birth weight reduction was observed in the previous studies compared to
20 the reduction associated with S in PM_{2.5} in our study (i.e. recalculated effect estimates: -2 g (-
21 7, -3) in Bell et al. 2010 and -8 g (-10, 7) in Basu et al. 2014, vs. the present study -40 g (-64,
22 -16)). Similarly for this present study population we observe a 21% increase in risk of low
23 birthweight at term associated with a 5 g/m³ increase in exposure to PM_{2.5}, which is also
24 larger than that reported in recent meta-analyses (Dadvand et al. 2013; Sapkora et al. 2012;
25 Stieb et al. 2012).

1 These differences may be explain by differences in study design and the facts that the
2 previous US studies on elemental PM relied on exposure estimates based on data from the
3 nearest regulatory air monitor, which do not capture within-city exposure contrasts adequately
4 and may result in misclassification of exposure and possibly reduced risk estimates. These
5 studies were not always able to adjust for risk factors of low birth weight such as maternal
6 stature, smoking, parity and season of conception. In our study a reduction in birth weight was
7 associated with most elemental component in crude models and models without adjustment
8 for parity. For example a 2 ng/m³ increase for V in PM_{2.5} was associated with -25 g (-42, -7)
9 in models without adjustment for parity, V in PM_{2.5} was not associated with a decrease in
10 birth weight in adjusted models which included parity (Table 5). Opposite to our study
11 previous studies have reported statistically significant reductions in birth weight for V (i.e. the
12 recalculated effect estimate for Bell et al. 2010 was -3 g (-4, -1), for Basu et al. 2014 it was -
13 10 g (-13, -8) and for Ebisu et al. 2012 it was -1 g (-2, 1)). In addition to differences related to
14 adjustment between the studies differences in exposure assessment may explain this
15 inconsistency. Opposite to other elements, V is not easy to model.

16
17 No previous study has examined the associations between PM_{2.5} components and birth head
18 circumference. In our study all the elemental components, with exception of K, were
19 associated with smaller head circumference. In contrast to the findings with low birth weight
20 and birth weight, there was evidence of heterogeneity across study areas and it has to be taken
21 into account for the interpretation of the results. It might be due to the fact that head
22 circumference vary more between study areas than within each study area. Head
23 circumference has been associated with cognitive ability (Heinonen et al. 2008) and child IQ
24 (Eriksen et al. 2013).

25

1 Previous studies (Basu et al. 2014; Bell et al. 2010; Ebisu et al. 2012) did not report results of
2 two-pollutant models with PM mass. Disentangling the effects of various elemental
3 components is challenging because of the covariance among some components due to similar
4 patterns and sources. However, we had no statistically significant co-linearity in the presented
5 two-pollutant models (*results not detailed*). Results for S adjusted for total mass concentration
6 did not differ from those from the single pollutant models. We also investigated whether the
7 previously observed PM_{2.5} effects (Pedersen et al. 2013) were robust to adjustment for S, Ni
8 and Zn. The findings of the current study, which rely on a smaller study population than the
9 full study population as we were unable to estimate elemental PM exposure for each study
10 area, suggest that the effect estimates associated with PM mass for low birth weight, birth
11 weight and head circumference were reduced and became borderline significant in two-
12 pollutant models after adjustment for either S or Ni while the associations for PM mass were
13 robust for adjustment for other elements (*all results not detailed*).

14
15 In our study, most of the variability in S exposure is between areas and the spatial variation of
16 S was mostly explained by various traffic, land use (green) and residential density variables
17 (De Hoogh et al. 2013). S is part of vehicle exhausts, but is mostly determined by secondary
18 aerosol formation. Sulfate is mostly formed in the atmosphere by oxidation of gaseous sulfur
19 dioxide (SO₂) emissions (US Environmental Protection Agency 2004). Sulfate is concentrated
20 in fine particles, which can be transported over long distances, resulting in a high regional
21 background with typically small spatial variation in metropolitan areas (US Environmental
22 Protection Agency 2004). Maternal exposure to ambient PM and combustion related air
23 pollutant gasses such as nitrogen dioxide and SO₂ have been associated with risk of low birth
24 weight (Pedersen et al. 2013; Stieb et al. 2012). Mechanisms are not well understood. Air
25 pollution particles inhaled can trigger enhanced maternal oxidative stress, lipid peroxidation,

1 inflammation, changes in the blood system, damage vascular endothelium and hereby
2 decrease placental blood flow, disrupt transplacental oxygenation and cause placental
3 oxidative stress, inflammation and lead to intrauterine growth restriction (Kannan et al. 2006).
4 Metals such as lead and cadmium have been found to be embryotoxic and teratogenic in a
5 variety of animal species and may also influence human intrauterine growth (Bellinger 2005;
6 Kippler et al. 2012). Data on humans are limited and more mechanistic studies on other PM
7 components are needed.

8

9 The main strengths of our study are the standardised, comprehensive exposure assessment of
10 multiple elements with a high percentage of detected samples (>75%) and good precision of
11 measurements in all eight cohorts, the harmonised and detailed information on potential
12 confounders, and the large population spread over a large geographical area. Detailed
13 information on individual characteristics (e.g. maternal stature, parity, race, education, active
14 and passive smoking during pregnancy) was collected prospectively in a manner that enabled
15 us to reduce potential biases through adjustment in a large study population.

16 A main advantage compared to previous US studies on elemental composition which relied
17 on centralized air monitor data and ignored within-city variation is that we could estimate
18 spatial contrasts at much smaller spatial scales using the LUR models that were developed in
19 a standardized way in all eight cohorts.

20

21 Spatial contrasts of NO₂ have been shown to be stable over time (Cesaroni et al. 2012), but
22 because we used annual LUR estimates to assess pregnancy exposures occurring 2–15 years
23 earlier (with most birth cohorts starting in the start-2000s, we recognize the potential for
24 exposure misclassification. The finding of NO₂ stability over time may be applicable to
25 traffic-related constituents such as Cu, Fe and Zn whereas there is no quantitative evidence

1 for the other constituents, which derive from other sources (e.g. biomass burning, industrial
2 emissions). The LUR prediction varied between the study areas and we poor in certain areas
3 for some constituents (De Hoogh et al. 2013). Moreover, our site selection was designed for
4 estimating especially the health effects on traffic pollution, which may restrict the power to
5 detect other emission sources.

6
7 Our exposure assessment was limited to home address(es), and exposures elsewhere were not
8 estimated, since detailed information on time-activity patterns or personal measures were not
9 available. Incomplete information on residential mobility may introduce exposure
10 misclassification. Most women (84%), however, did not move during pregnancy, and
11 analyses restricted to women who did not change home address during pregnancy gave very
12 similar results to those reported for the full study population.

13
14 We investigated eight a priori selected elements in both the PM_{2.5} and PM₁₀ fraction, so there
15 might be issues related to multiple comparisons, and the correlation between different
16 elements and the extent to which they can act as surrogate for the exposures causing the
17 effect. We think it is unlikely that the associations with S are change findings or can be
18 explained by any of the other measured elements because the associations are evident for all
19 outcomes, there are no sign of heterogeneity between study areas and the effect estimates
20 remain similar to those from single pollutant models in the two pollutant models.

21
22 Currently in the EU and elsewhere, PM is regulated by total mass and size only, without
23 regard to its elemental composition.

24

1 In conclusion, we found that exposure to ambient air pollution with especially S in both PM_{2.5}
2 and PM₁₀, Ni in PM_{2.5} was associated with reduced newborn's size. The effects of S on low
3 birth weight, birth weight and head circumference were robust to adjustment for co-pollutants
4 including PM mass.

References

- Basu R, Harris M, Sie L, Malig B, Broadwin R, Green R. 2014. Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California. *Environ Res* 128:42–51.
- Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X et al. 2013. Development of NO₂ and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. *Atmospheric Environment* 72:10–23.
- Beelen R, Hoek G, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G et al. 2014. Long-Term Exposure to Particle Components and Natural Cause Mortality: An analysis of 19 European Cohorts within the Multi-Center ESCAPE Project. **Submitted**
- Bell ML, Belanger K, Ebisu K, Gent JF, Leaderer BP. 2012. Relationship between birth weight and exposure to airborne fine particulate potassium and titanium during gestation. *Environ Res.*117:83–89.
- Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P et al. 2010. Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. *Epidemiology* 21:884–891.
- Bellinger DC. 2005. Teratogen update: lead and pregnancy. *Birth Defects Res A Clin Mol Teratol* 73:409–420.
- Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K et al. 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health* 11:48.
- Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA et al. 2013 Maternal exposure to particulate air pollution and term birth weight; a multi-country evaluation of effect and heterogeneity. *Environ Health Perspect* 121:267–373.

- Darrow LA, Klein M, Strickland MJ, Mulholland JA, Tolbert PE. 2011. Ambient air pollution and birth weight in full-term infants in Atlanta, 1994-2004. *Environ Health Perspect* 119:731–737.
- de Hoogh K, Wang M, Adam M, Badaloni C, Beelen R, Birk M et al. 2013. Development of land use regression models for particle composition in twenty study areas in Europe. *Environ Sci Technol* 47:5778–5786.
- Ebisu K, Bell ML. Airborne PM_{2.5} chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States. 2012. *Environ Health Perspect* 120:1746–1752.
- Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M et al. 2012. Development of land use regression models for PM_{2.5}, PM_{2.5} absorbance, PM₁₀ and PM_{coarse} in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol* 46:11195–11250.
- Eriksen HL, Kesmodel US, Underbjerg M, Kilburn TR, Bertrand J, Mortensen EL. 2013. Predictors of intelligence at the age of 5: family, pregnancy and birth characteristics, postnatal influences, and postnatal growth. *PLoS One* 13;8(11):e79200.
- Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, Betran AP et al. 2014. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health. *Environ Health Perspect* 122:425–430.
- Heinonen K, Räikkönen K, Pesonen AK, Kajantie E, Andersson S. 2008. Prenatal and postnatal growth and cognitive abilities at 56 months of age: a longitudinal study of infants born at term. *Pediatrics* 121:e1325–1333.
- Kannan S, Misra DP, Dvonch JT, Krishnakumar A. 2006. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework

- for exploring potential effect modification by nutrition. *Environ Health Perspect.* 114:1636–1642.
- Kelly FJ, Fussell JC. 2012. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. *Atmos Environ* 60:504–526.
- Kippler M, Tofail F, Gardner R, Rahman A, Hamadani JD, Bottai M et al. 2012. Maternal cadmium exposure during pregnancy and size at birth: a prospective cohort study. *Environ Health Perspect* 120:284–289.
- Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen AM, Ballester F et al. 2013 Ambient air pollution and low birth weight: A European cohort study (ESCAPE). *Lancet Respir Med* 1:695–704.
- Sapkota A, Chelikowsky, Nachman KE, Cohen AJ, Ritz B. 2012. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Qual Atmos Health* 5:369–381.
- Stanek LW, Sacks JD, Dutton SJ, Dubois JB. 2011. Attributing health effects to apportioned components and sources of particulate matter: An evaluation of collective results. *Atmos Environ* 45:5655–5663.
- Stieb DM, Chen L, Eshoul M, Judek S. 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res*;117:100–111.
- US Environmental Protection Agency. 2004. Air Quality Criteria for Particulate Matter (Final Report, October 2004). Washington, DC: EPA.
- Viana M, Kuhlbusch TAJ, Querol X, Alastuey A, Harrison RM, Hopke PK et al. 2008. Source apportionment of particulate matter in Europe: A review of methods and results. *Journal of Aerosol Science* 39:827–849
- Wang M, Beelen R, Stafoggia M, Raaschou-Nielsen O, Andersen ZJ, Hoffmann B et al. 2014. Long-term exposure to elemental constituents of particulate matter and cardiovascular

2nd draft to be revised by co-authors

mortality in 19 European cohorts: Results from the ESCAPE and TRANSPHORM projects. *Environ Int* 66:97–106.

Table 1. Study population characteristics (N=34,923).

Variable		n (%)	Mean ± SD
Country, city, cohort			
	Sweden, Stockholm, BAMSE	3,860 (11.1)	
	Denmark, Copenhagen, DNBC	17,550 (50.3)	
	Lithuania, Kaunas, KANC	633 (1.8)	
The Netherlands, Amsterdam, ABCD, multiple sites, PIAMA		11,430 (32.7)	
	Germany, Duisburg, DUISBURG	194 (0.6)	
	Italy, Rome, GASPII	684 (2.0)	
	Spain, Sabadell, INMA	572 (1.6)	
Maternal ethnicity (n=34,030) ^a	Born in country of cohort	30,491 (89.6)	
	Born elsewhere	3,539 (10.4)	
Maternal age (years)		34,905	30.4 ± 4.5
Maternal education (n=33,719)	Low	6,609 (19.6)	
	Middle	15,336 (45.5)	
	High	11,774 (34.9)	
Parity (n=34,874)	No children	18,074 (51.8)	
	1 child	12,520 (35.9)	
	2 children	4,280 (12.3)	
Maternal pre-pregnancy weight (kg)		33,822	65.2 ± 11.5
Maternal height (cm)		34,334	168.5 ± 6.6
Maternal smoking during 2 nd trimester (n=34,895)	No	29,689 (85.1)	
	Yes	5,206 (14.9)	
Number of cigarettes per day among smokers		5,206	7.2 ± 5.3
Exposure to secondhand smoke (n=30,900)	No	16,460 (53.3)	
	Yes	14,440 (46.7)	
Moved during pregnancy (n=34,868)	No	29,357 (84.2)	
	Yes	5,511 (15.8)	
Season of conception	January-March	7,612 (21.8)	
	April-June	7,265 (20.8)	
	July-September	9,477 (27.1)	
	October-December	10,569 (30.3)	
Sex	Boy	17,752 (50.8)	
	Girl	17,171 (49.2)	
Birth weight (g)		33,416	3,531 ± 550
	<2500 & 37 weeks	409 (1.2)	
Birth head circumference (cm) ^b		23,840	35.2 ± 1.7
Gestational age (weeks)		33,416	40.0 ± 1.8
	<37 weeks	1,507 (4.3)	

^bTotal in specific variables may be less than 34,923 because of missing values.

^cNot available from KANC, ABCD and DUISBURG.

Table 2. Particle constituent concentrations and correlations between the elemental and total mass concentrations.

	PM _{2.5}			PM ₁₀		
	n	Mean ± SD	r ^a	n	Mean ± SD	r ^a
Mass concentration (g/m ³)	33,882	17.0 ± 4.7		33,882	26.9 ± 7.8	
Elemental concentration (ng/m ³)						
Copper (Cu)	34,923	3.4 ± 2.1	0.43	34,923	14.0 ± 10.6	0.54
Iron (Fe)	34,290	104.0 ± 57.4	0.17	34,923	435.3 ± 276.0	0.59
Potassium (K)	34,096	116.7 ± 27.4	0.20	34,290	224.3 ± 72.2	0.31
Nickel (Ni)	30,430	1.6 ± 0.8	0.67	34,923	1.8 ± 1.2	0.71
Sulfur (S)	34,290	753.9 ± 129.5	0.84	34,290	858.1 ± 171.7	0.84
Silicon (Si)	34,923	83.1 ± 54.4	0.02	34,923	489.7 ± 338.1	0.27
Vanadium (V)	34,923	2.8 ± 1.2	0.62	34,923	3.4 ± 1.5	0.66
Zinc (Zn)	34,290	14.8 ± 4.9	0.60	34,923	25.1 ± 10.9	0.61

^aAll Pearson correlations had a p-value <0.001.

Table 3. Associations between exposure to PM constituents and term low birth weight.

Single pollutant models	PM _{2.5}				PM ₁₀			
	N ^a	n ^b	OR ^c	(95% CIs)	N ^a	n ^b	OR ^c	(95% CIs)
Mass	30,313	381	1.21	(1.08, 1.36)	30,313	381	1.22	(1.03, 1.45)
Cu	31,173	390	1.08	(0.81, 1.44)	31,173	390	1.13	(0.92, 1.39)
Fe	30,576	381	1.14	(0.92, 1.41)	31,173	390	1.06	(0.83, 1.36)
K	30,382	375	1.05	(0.82, 1.33)	30,576	381	0.90	(0.73, 1.11)
Ni	27,339	351	1.14	(1.00, 1.29)	31,173	390	1.29	(0.96, 1.75)
S	30,576	381	1.36	(1.17, 1.58)	30,576	381	1.27	(1.13, 1.43)
Si	31,173	390	0.83	(0.62, 1.12)	31,173	390	0.89	(0.71, 1.13)
V	31,173	390	1.12	(0.86, 1.44)	31,173	390	1.00	(0.72, 1.38)
Zn	30,576	381	1.23	(0.98, 1.54)	31,173	390	1.23	(0.98, 1.53)
Two-pollutant models								
S adjusted for mass	29,716	372	1.24	(0.96, 1.61)	29,716	372	1.27	(1.03, 1.56)
Mass adjusted for S	29,716	372	1.08	(0.90, 1.30)	29,716	372	1.00	(0.80, 1.25)
Ni adjusted for mass	27,337	350	1.11	(0.94, 1.31)	30,313	381	1.14	(0.90, 1.43)
Mass adjusted for Ni	27,337	350	1.05	(0.88, 1.24)	30,313	381	1.15	(0.97, 1.37)
Zn adjusted for mass	29,716	372	1.11	(0.88, 1.40)	30,313	381	1.13	(0.90, 1.42)
Mass adjusted for Zn	29,716	372	1.19	(1.01, 1.40)	30,313	381	1.17	(0.97, 1.42)
S adjusted for Ni	27,339	351	1.08	(0.80, 1.46)	30,576	381	1.10	(0.83, 1.44)
Ni adjusted for S	27,339	351	1.10	(0.91, 1.33)	30,576	381	1.07	(0.85, 1.35)
S adjusted for Zn	30,576	381	1.39	(1.13, 1.70)	30,576	381	1.26	(1.10, 1.45)
Zn adjusted for S	30,576	381	0.96	(0.75, 1.23)	30,576	381	1.02	(0.82, 1.27)

^aN refer number of subjects in each model.

^bn refer number of cases in each model.

^cEffect estimates refer to odds ratio (OR) and 95% confidence interval (CIs) for low birth weight (<2,500 g) among term births (37 weeks of gestation) from pooled analyses using logistic regression models with random effect of centre adjusted for gestational age, sex, parity, maternal height, pre-pregnancy weight, maternal active smoking during 2nd trimester, maternal age, maternal education and season of conception per increments of 5 g/m³ for PM_{2.5}; 5 ng/m³ for Cu PM_{2.5}; 100 ng/m³ for Fe PM_{2.5}; 50 ng/m³ for K PM_{2.5}; 1 ng/m³ for Ni PM_{2.5}; 200 ng/m³ for S PM_{2.5}; 100 ng/m³ for Si PM_{2.5}; 2 ng/m³ for V PM_{2.5}; 10 ng/m³ for Zn PM_{2.5}; 10 g/m³ for PM₁₀; 5 ng/m³ for Cu PM_{2.5}; 10 g/m³ for PM₁₀; 20 ng/m³ for Cu PM₁₀; 500 ng/m³ for Fe PM₁₀; 100 ng/m³ for K PM₁₀; 2 ng/m³ for Ni PM₁₀; 200 ng/m³ for S PM₁₀; 500 ng/m³ for Si PM₁₀; 3 ng/m³ for V PM₁₀; and 20 ng/m³ for Zn PM₁₀.

Table 4. Associations between PM constituents and birth weight.

Single pollutant models	PM _{2.5}			PM ₁₀		
	N ^a	β ^b	(95% CIs)	N ^a	β ^b	(95% CIs)
Mass	30,313	-16	(-29, -3)	30,313	-11	(-25, 2)
Cu	31,173	10	(-8, 27)	31,173	8	(-4, 19)
Fe	30,576	6	(-5, 16)	31,173	14	(1, 28)
K	30,382	11	(-11, 33)	30,576	14	(2, 27)
Ni	27,339	4	(-15, 22)	31,173	1	(-22, 24)
S	30,576	-40	(-64, -16)	30,576	-2	(-21, 17)
Si	31,173	26	(5, 48)	31,173	13	(-1, 27)
V	31,173	5	(-13, 23)	31,173	13	(-8, 35)
Zn	30,576	-4	(-21, 12)	31,173	8	(-6, 21)
Two-pollutant models						
S adjusted for mass	29,716	-35	(-64, -7)	29,716	5	(-17, 27)
Mass adjusted for S	29,716	-6	(-22, 9)	29,716	-11	(-27, 5)
Ni adjusted for mass	27,337	7	(-13, 26)	30,313	-6	(-33, 20)
Mass adjusted for Ni	27,337	-8	(-23, 7)	30,313	7	(-26, 39)
Zn adjusted for mass	29,716	-1	(-18, 16)	30,313	14	(-1, 29)
Mass adjusted for Zn	29,716	-13	(-27, 1)	30,313	-18	(-34, -2)
Fe adjusted for mass	29,716	11	(-1, 22)	30,313	33	(16, 51)
Mass adjusted for Fe	29,716	-19	(-34, -5)	30,313	-34	(-52, -16)
Si adjusted for mass	30,313	36	(13, 60)	30,313	31	(14, 49)
Mass adjusted for Si	30,313	-20	(-34, -7)	30,313	-29	(-45, -13)
K adjusted for mass	29,522	12	(-11, 35)	29,716	24	(9, 39)
Mass adjusted for K	29,522	-14	(-28, 1)	29,716	-21	(-37, -6)
Fe adjusted for S	30,576	15	(4, 26)	30,576	19	(5, 33)
S adjusted for Fe	30,576	-56	(-80, -32)	30,576	-15	(-35, 6)
Si adjusted for S	30,576	33	(12, 54)	30,576	16	(2, 30)
S adjusted for Si	30,576	-45	(-69, -22)	30,576	-11	(-30, 8)
K adjusted for S	30,382	12	(-7, 30)	30,576	15	(2, 27)
S adjusted for K	30,382	-62	(-85, -37)	30,576	-5	(-24, 14)
S adjusted for Ni	27,339	-17	(-50, 16)	30,576	-6	(-33, 20)
Ni adjusted for S	27,339	7	(-50, 16)	30,576	7	(-26, 39)
S adjusted for Zn	30,576	-43	(-69, -16)	30,576	-1	(-21, 19)
Zn adjusted for S	30,576	4	(-14, 22)	30,576	-4	(-22, 13)

^aN refer number of subjects in each model.

^bEffect estimates refer to β coefficient and 95% confidence interval (CIs) for change in birth weight (g) among term births (> 37 weeks of gestation) from pooled analyses using linear regression models with random effect of centre.

See table 3 for adjustment and increments.

Table 4. Associations between PM constituents and birth head circumference.

Single pollutant models	PM _{2.5}			PM ₁₀		
	N ^a	β ^b	(95% CIs)	N ^a	β ^b	(95% CIs)
Mass	21,053	-0.23	(-0.29, -0.18)	21,053	-0.23	(-0.28, -0.17)
Cu	21,923	-0.29	(-0.36, -0.23)	21,923	-0.16	(-0.20, -0.11)
Fe	21,923	-0.19	(-0.22, -0.15)	21,923	-0.17	(-0.22, -0.12)
K	21,923	0.30	(0.22, 0.39)	21,923	0.05	(0.00, 0.09)
Ni	18,604	-0.60	(-0.71, -0.49)	21,923	-0.43	(-0.53, -0.33)
S	21,923	-0.79	(-0.93, -0.66)	21,923	-0.57	(-0.66, -0.47)
Si	21,923	-0.13	(-0.21, -0.05)	21,923	-0.09	(-0.14, -0.04)
V	21,923	-0.45	(-0.56, -0.35)	21,923	-0.46	(-0.57, -0.35)
Zn	21,923	-0.13	(-0.21, -0.05)	21,923	-0.25	(-0.33, -0.18)
Two-pollutant models						
S adjusted for mass	21,053	-0.73	(-0.90, -0.57)	21,053	-0.51	(-0.63, -0.39)
Mass adjusted for S	21,053	-0.06	(-0.14, 0.02)	21,923	-0.06	(-0.13, 0.02)
Ni adjusted for mass	18,602	-0.48	(-0.61, -0.36)	21,053	-0.32	(-0.44, -0.21)
Mass adjusted for Ni	18,602	-0.14	(-0.21, -0.06)	21,053	-0.15	(-0.20, -0.09)
Zn adjusted for mass	21,053	0.03	(-0.06, 0.13)	21,053	-0.09	(-0.19, 0.01)
Mass adjusted for Zn	21,053	-0.24	(-0.31, -0.18)	21,053	-0.18	(-0.25, -0.12)
S adjusted for Ni	18,604	-0.63	(-0.80, -0.46)	21,923	-0.55	(-0.68, -0.42)
Ni adjusted for S	18,604	-0.32	(-0.45, -0.19)	21,923	-0.02	(-0.17, 0.12)
S adjusted for Zn	21,923	-0.92	(-1.07, -0.77)	21,923	-0.63	(-0.73, -0.52)
Zn adjusted for S	21,923	0.18	(0.08, 0.28)	21,923	0.13	(0.03, 0.23)

^aN refers number of subjects in each model.

Birth head circumference is not available from KANC, ABCD and DUISBURG.

^bEffect estimates refer to β coefficient and 95% confidence interval (CIs) for change in birth head circumference (cm) from pooled analyses using linear regression models with random effect of centre.

See table 3 for adjustment and increments.

Figure 1. Distributions of exposure to PM constituents (ng/m³) by cohorts and for the pooled study population.

Upper box-plots are for PM_{2.5} and lower ones for PM₁₀.

The line in the middle of the box represents the median values, the ends of the box refer to the 25th and 75th percentiles and the ends of the whiskers indicate the variability outside the upper and lower quartiles (i.e., within 1.5 interquartile range of the lower quartile and upper quartile). Outliers are plotted as individual dots.

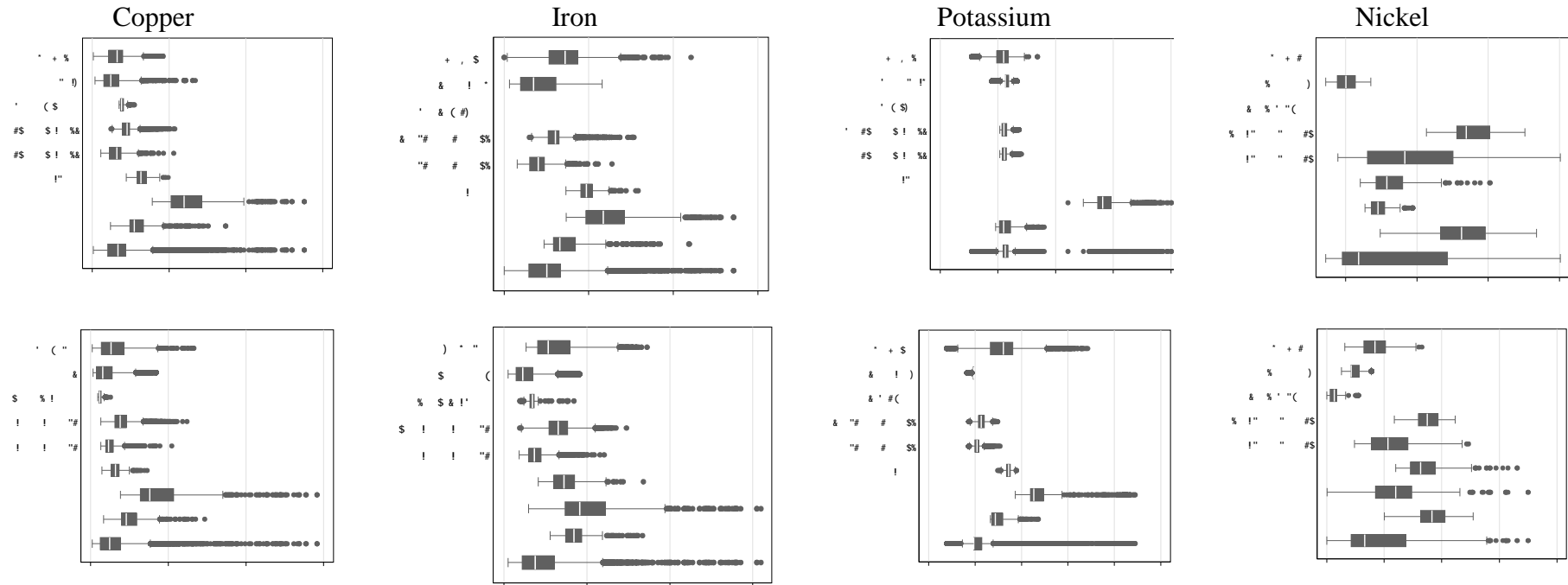
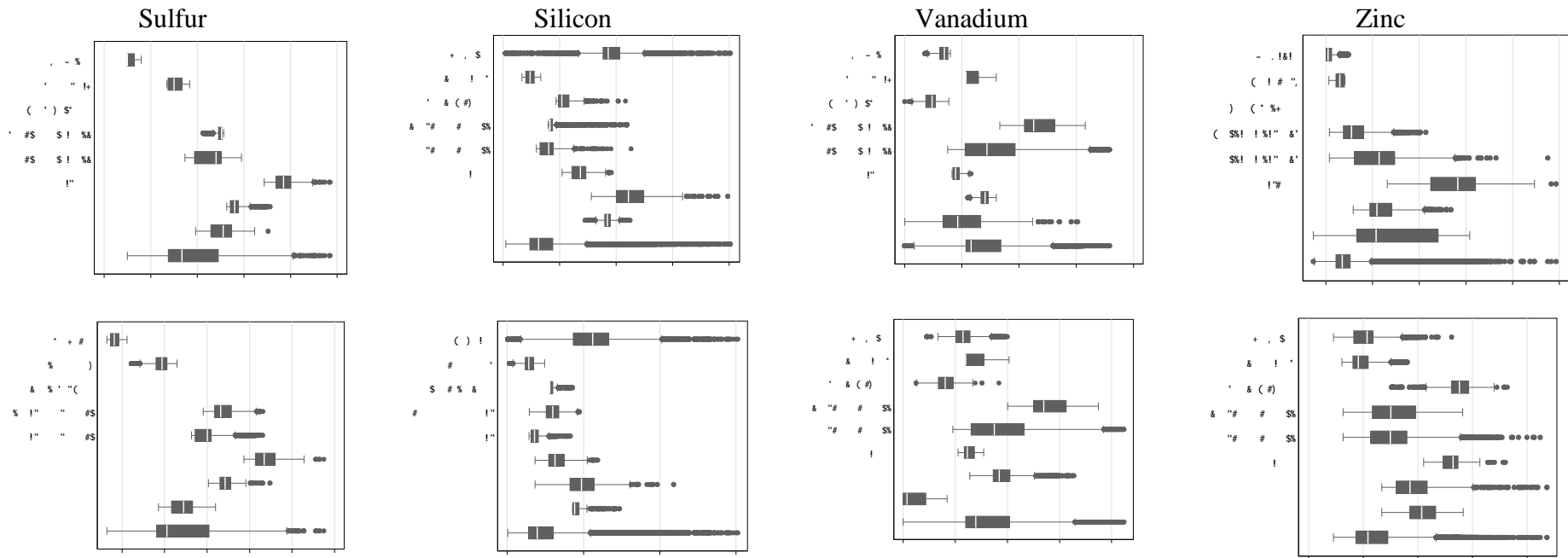


Figure 1. Distributions of exposure to PM constituents (ng/m³) by cohorts and for the pooled study population – cont.



Supplemental Material

Elemental Constituents of Particulate Matter and Newborn's Size in Eight European Cohorts: Results From the ESCAPE and TRANSPHORM Projects.

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List of content

Table S1. Mother-child cohort data collection.

Table S2. Land-use regression model's prediction (R^2) by study area.

Table S3. Correlations between elemental concentrations (ng/m^3).

Table S4. Correlations between elemental (ng/m^3) and PM mass concentration (g/m^3) by cohort.

Table S5. Sensitivity and stratified analyses of sulfur on term low birth weight.

Figure S1. Distributions of $\text{PM}_{2.5}$, PM_{10} , maternal height, pre-pregnancy weight, birth weight, birth head circumference and gestational age by cohorts and for the pooled study population.

Table S1. Mother-child cohort data collection.

Cohort	Country	Centre(s)	Inclusion and exclusion criteria N (n)	Methods of maternal information collection	Gestational age estimation	Pregnancy (Years)	Air sampling (Pollutants) (Years)
BAMSE 'Barn, Allergi, Miljo, Stockholm, Epidemiologi' 'Child, Allergy, Environment, Stockholm, Epidemiology'	Sweden	Jarfalla Solna Sundbyberg Stockholm	All parents of newborn children during 1994-1996 living in the study area, with no plans of moving within 1 year after birth, sufficient Swedish language skills and no serious family diseases. Included only women with one child. N=4,089. Pregnancy exposure to air pollution is available (n=3,868).	Self-administrated questionnaires starting at 3 months after birth of the child.	US based estimation (89%)	1994-1996	PM + NO _x 2008-2009
DNBC 'Bedre Sundhed for Mor og Barn Undersøgelsen' 'Danish National Birth Cohort'	Denmark	National	All pregnant women who attended general practitioner in week 6-12 of pregnancy, who wanted to carry their pregnancy to term, and had sufficient Danish language skills to complete interviews during 1996-2002. Same women may participate multiple times. N=101,042. Pregnancy exposure to air pollution is available for the greater Copenhagen (n=17,577).	Computerized telephone interviews starting in week 12 of pregnancy.	LMP and US based estimation available.	1996-2002	PM + NO _x 2009-2010
KANC	Lithuania	Kaunas	All pregnant women who attended general practitioner in first trimester of pregnancy during 2007-2008. Women who lived outside Kaunas municipality, had medical records of pregnancy induced hypertension and/or diabetes were excluded. Pregnancy exposure to air pollution is available (n=4,101).	Face-to-face interviews by trained nurse and telephone interviews during pregnancy.	Maternity unit based estimation in which LMP is combined with US.	2007-2008	PM + NO _x 2010-2011
ABCD 'Amsterdam Born Children and Their Development'	The Netherlands	Amsterdam	All pregnant women who lived in Amsterdam and attended prenatal care in early pregnancy during 2003-2004. Excluded multiple, stillbirth. N=7,863. Pregnancy exposure to air pollution is available (n=7,592).	Self-administrated questionnaires starting in early pregnancy.	Maternity unit based estimation relying on US or LMP if US was unavailable (<10%).	2003-2004	PM + NO _x 2009-2010
PIAMA 'Prevention and Incidence of Asthma and Mite Allergy'	The Netherlands	North West Middle	Pregnant women who attended prenatal healthcare in approximately 50 clinics located in different parts of the Netherlands. Atopic (n=1327) and non-atopic women (n=2,819) were included. Pregnancy exposure to air pollution is available (n=3,839).	Self-administrated questionnaires starting at the women's first visit to the prenatal health clinics, which usually takes place during the first trimester.	Maternity unit based estimation in which LMP is combined with US.	1996-1997	PM + NO _x 2009-2010

Table S1. Mother-child cohort data collection – cont.

Cohort	Country	Centre(s)	Inclusion and exclusion criteria N (n)	Methods of maternal information collection	Gestational age estimation	Pregnancy (Years)	Air sampling (Pollutants) (Years)
DUIBURG	Germany	Duisburg	Pregnant women who lived in a predefined area of Duisburg. Healthy, German or Turkish speaking women without serious pregnancy and/or birth complications with birth at term (i.e. 38-42 weeks of gestation) to children without APGAR scores ≤ 8 and without congenital anomalies. N=232. Pregnancy exposure to air pollution is available (n=194).	Face-to-face interviews starting in early pregnancy.	Maternity unit based estimation in which LMP is combined with US.	2000-2002	PM + NO _x 2008-2009
GASPII	Italy	Rome	Women delivering at two hospitals in the area of the local health unit RME in the north of the city, resident in the same area, Italian speaking, aged more than 17 years. Out of the all women contacted, 55% responded, out the eligible women contacted 34% responded. Pregnancy exposure to air pollution is available (n=684).	Face-to-face the day after delivery.	LMP based estimation and maternity unit.	2003-2004	PM + NO _x 2010-2011
INMA 'Infancia y Medio Ambiente' 'Childhood and Environment'	Spain	Sabadell	Pregnant women who attended prenatal care 10-13 week of pregnancy. Included women had delivery and residence in the study areas, at least 16 years old, singleton pregnancies, no assisted reproduction and no communication problems. Enrolment took place in Sabadell (n=657, 2004-2006).	Face-to-face interviews and self-administrated questionnaires starting early pregnancy.	LMP, US and maternity unit based estimation in which LMP is combined with US. US was used when the difference with the LMP and US estimation was ≥ 7 days (12% of the cases).	2004-2006	PM + NO _x 2009-2010

N refers to total number of participation women at birth; n refers to the number of participation women living in the ESCAPE LUR exposure areas with sufficient data to estimate the exposures during pregnancy; NO_x refers to nitrogen oxides; LMP refers to last menstrual period; PM refers to particulate matter and US refers to ultrasound.

Table S2. Land-use regression model's prediction (R^2) by study area.

Study area	PM _{2.5}								PM ₁₀							
	Cu	Fe	K	Ni	S	Si	V	Zn	Cu	Fe	Ni	K	S	Si	V	Zn
Sweden	0.69	0.93	0.68	na	0.34	0.82	0.19	0.35	0.87	0.75	0.88	0.80	0.30	0.72	0.76	0.89
Denmark	0.69	0.94	0.57	0.18	0.65	0.66	0.44	0.18	0.92	0.94	0.59	0.25	0.52	0.25	0.67	0.77
Lithuania	0.25	na	0.13	na	na	0.40	0.34	na	0.62	0.47	0.23	na	na	0.24	0.39	0.25
The Netherlands	0.83	0.78	0.31	0.76	0.32	0.40	0.68	0.66	0.80	0.78	0.78	0.51	0.48	0.46	0.72	0.65
Germany	0.92	0.68	?	0.32	0.56	0.75	0.66	0.74	0.94	0.89	0.22	0.22	0.59	0.49	0.62	0.61
Italy	0.82	0.72	0.46	0.28	0.44	0.67	0.20	0.78	0.89	0.85	0.90	0.64	0.46	0.51	0.72	0.85
Spain	0.77	0.74	0.31	0.79	0.83	0.62	0.83	0.85	0.75	0.72	0.81	0.71	0.81	0.18	0.82	0.78

Na refers to not available.

Table S3. Correlations between elemental concentrations (ng/m³).

	PM _{2.5}							PM ₁₀						
	Cu	Fe	K	Ni	Si	V	Zn	Cu	Fe	K	Ni	Si	V	Zn
Fe	0.77							0.85						
K	0.61	0.33						0.52	0.69					
Ni	0.48	0.39	-0.06					0.54	0.68	0.28				
S	0.50	0.20	0.26	0.82				0.41	0.38	-0.01	0.75			
Si	0.53	0.58	0.34	0.55	-0.07			0.44	0.72	0.84	0.41	-0.07		
V	0.35	0.18	0.00	0.91	0.73	-0.08		0.44	0.46	0.07	0.80	0.77	0.14	
Zn	0.44	0.24	0.33	0.36	0.66	0.17	0.27	0.52	0.65	0.41	0.53	0.60	0.38	0.35

All Pearson correlations had a p-value <0.001.

Table S4. Correlations between elemental (ng/m³) and total mass concentration of PM (g/m³) by cohort.

	BAMSE		DNBC		ABCD		PIAMA		KANC		DUISBURG		GASPII		INMA	
	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀
Cu	0.60	0.28	0.58	0.72	0.34	0.29	0.60	0.44	0.41	0.42	0.44	0.56	0.78	0.83	0.61	0.53
Fe	0.56	0.69	0.55	0.73	0.21	0.48	0.53	0.59	na	0.67	0.44	0.79	0.81	0.86	0.48	0.62
K	0.35	0.92	0.09	0.18	0.13	0.41	0.34	0.50	na	na	na	0.33	0.62	0.67	0.43	0.75
Ni	na	0.09	0.62	0.76	0.02 ^a	0.30	0.43	0.46	na	0.42	0.65	0.78	0.20	0.28	0.40	0.50
S	0.45	0.44	0.62	0.73	0.08	0.19	0.55	0.40	na	na	0.47	0.63	0.69	0.30	0.44	0.44
Si	0.42	0.92	0.66	0.77	0.14	0.46	0.51	0.63	0.05 ^a	0.11	0.70	0.65	0.56	0.54	0.69	0.76
V	0.32	0.68	0.60	0.71	0.02 ^a	0.15	0.41	0.40	-0.02 ^a	-0.03 ^a	0.39	0.39	0.34	0.70	0.35	0.38
Z	0.44	0.60	0.57	0.73	0.13	0.38	0.29	0.30	na	0.26	0.60	0.59	0.70	0.85	0.44	0.22

Na refers to not available.

^aPearson Correlations had a p-value >0.001, all others p-values were<0.001

Table S5. Sensitivity and stratified analyses of sulfur on term low birth weight.

Model	PM _{2.5}				PM ₁₀			
	N ^a	n ^b	OR	(95% CIs)	N	n	OR	(95% CIs)
Women who did not change address ^c	25,765	300	1.35	(1.14, 1.60)	25,765	300	1.28	(1.12, 1.45)
Study areas with highest LUR-model prediction ^d	17,006	192	1.18	(0.90, 1.55)	27,339	351	1.17	(1.01, 1.36)
Excluding DNBC	14,949	223	1.36	(1.11, 1.68)	14,949	233	1.30	(1.10, 1.53)
Women who participated once	29,878	379	1.35	(1.16, 1.57)	29,878	379	1.27	(1.13, 1.43)
Women with information on maternal ethnic origin	29,904	379	1.32	(1.14, 1.55)	29,904	377	1.25	(1.11, 1.41)
Additional adjustment for maternal ethnic origin	29,904	377	1.30	(1.11, 1.53)	29,904	377	1.23	(1.09, 1.40)
Women born in country of cohort	26,714	309	1.27	(1.07, 1.51)	26,714	309	1.24	(1.02, 1.50)
Women born elsewhere	3,190	68	1.60	(0.96, 2.64)	3,190	68	1.45	(0.99, 2.11)
Women with low education	6,029	119	1.25	(0.92, 1.70)	6,029	119	1.18	(0.93, 1.49)
Women with middle education	14,017	158	1.48	(1.18, 1.86)	14,017	158	1.50	(1.12, 2.01)
Women with high education	10,530	104	1.25	(0.95, 1.65)	10,530	104	1.12	(0.90, 1.38)
Women with information on second-hand smoke exposure	27,245	377	1.18	(0.97, 1.45)	27,245	346	1.15	(0.99, 1.33)
Additional adjustment for second-hand smoke exposure	27,245	346	1.18	(0.96, 1.45)	27,245	346	1.14	(0.98, 1.33)
Non-smoking women	26,061	265	1.27	(1.07, 1.51)	26,061	265	1.21	(1.06, 1.39)
Smoking women	4,515	116	1.47	(1.09, 1.98)	4,515	116	1.36	(1.08, 1.71)
Women giving birth to a boy	15,500	148	1.35	(1.06, 1.72)	15,500	148	1.27	(1.05, 1.53)
Women giving birth to a girl	15,076	233	1.36	(1.12, 1.65)	15,076	233	1.28	(1.10, 1.48)
Primiparous women	14,694	116	1.64	(1.24, 2.17)	14,694	116	1.44	(1.16, 1.79)
Multiparous women	15,882	265	1.26	(1.05, 1.50)	15,882	265	1.21	(1.05, 1.39)
Women aged <25 years at time of giving birth	3,180	59	1.27	(0.82, 1.96)	3,180	59	1.07	(0.78, 1.47)
Women aged 25-35 years at time of giving birth	22,325	250	1.30	(1.08, 1.57)	22,325	250	1.23	(1.07, 1.43)
Women aged >35 years at time of giving birth	5,071	72	1.45	(1.03, 2.03)	5,071	72	1.44	(1.10, 1.88)
Conception in January-March	6,622	87	1.36	(1.01, 1.84)	6,622	87	1.39	(1.09, 1.77)
Conception in April-June	6,360	76	1.13	(0.80, 1.58)	6,360	76	1.03	(0.79, 1.34)
Conception in July-September	8,271	97	1.63	(1.19, 2.23)	8,271	97	1.41	(1.12, 1.79)
Conception in October-December	9,323	121	1.35	(1.03, 1.77)	9,323	121	1.28	(1.04, 1.57)

Effect estimates refer to odds ratio (OR) and 95% confidence interval (CIs) for low birth weight (<2,500 g) among term births (> 37 weeks of gestation) from pooled analyses using logistic regression models with random effect of centre. See table 3 for increments and adjustment. ^aN refers number of subjects in each model. ^bn refers number of cases in each model. ^cDuring pregnancy. ^dExcluding BAMSE, ABCD and PIAMA for S PM_{2.5} and BAMSE for S PM₁₀

Figure S1. Distributions of PM_{2.5}, PM₁₀, maternal height, pre-pregnancy weight, birth weight, birth head circumference and gestational age by cohorts and for the pooled study population.

The line in the middle of the box represents the median values, the ends of the box refer to the 25th and 75th percentiles and the ends of the whiskers indicate the variability outside the upper and lower quartiles (i.e., within 1.5 interquartile range of the lower quartile and upper quartile). Outliers are plotted as individual dots.

