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ABSTRACT

Background: Few studies have investigated traffic-related air pollution as a risk factor for respiratory infections during early childhood.

Objectives: To investigate the association between air pollution and pneumonia, croup and otitis media in 10 European birth cohorts - BAMSE (Sweden), GASPII (Italy), GINIplus and LISAplus (Germany), MAAS (UK), PIAMA (The Netherlands), and four INMA cohorts (Spain) - and to derive combined effect estimates using meta-analysis.

Methods: Parent report of physician diagnosed pneumonia, otitis media and croup during early childhood were assessed in relation to annual average pollutant levels [NO_2 , NO_x , $\text{PM}_{2.5}$, $\text{PM}_{2.5}$ absorbance, PM_{10} , $\text{PM}_{2.5-10}$ (coarse PM)] estimated using land use regression models and assigned to children based on their residential address at birth. Identical protocols were used to develop regression models for each study area as part of the ESCAPE project. Logistic regression was used to calculate adjusted effect estimates for each study, and random-effects meta-analysis was used to calculate combined estimates.

Results: For pneumonia, combined adjusted odds ratios (ORs) were elevated and statistically significant for all pollutants except $\text{PM}_{2.5}$ (e.g., OR = 1.30; 95% CI: 1.02, 1.65 per $10\text{-}\mu\text{g}/\text{m}^3$ increase in NO_2 and OR = 1.76; 95% CI: 1.00, 3.09 per $10\text{-}\mu\text{g}/\text{m}^3$ PM_{10}). For otitis media and croup, results were generally null across all analyses except for NO_2 and otitis media (OR = 1.09; 95% CI: 1.02, 1.16 per $10\text{-}\mu\text{g}/\text{m}^3$).

Conclusion: Our meta-analysis of 10 European birth cohorts within the ESCAPE project found consistent evidence for an association between air pollution and pneumonia in early childhood, and some evidence for an association with otitis media.

INTRODUCTION

Respiratory infections are a leading reason for outpatient physician visits and hospitalizations among children (Williams et al. 2002). Most infections resolve with minimal utilization of healthcare resources; however, episodes of severe or recurrent infection may require hospitalization or surgery and the resultant burden is substantial (Black et al. 2010).

Young children are particularly susceptible to respiratory pathogens and are also a susceptible group in terms of air pollution (Bateson and Schwartz 2008; Heinrich and Slama 2007). There is strong evidence for indoor air pollution, such as secondhand smoke and the use of biomass, as a risk factor for respiratory infections in children (da Costa et al. 2004). Evidence is growing to support an association with outdoor air pollution (Brauer et al. 2006; Leonardi et al. 2000; MacIntyre et al. 2011).

The European Study of Cohorts for Air Pollution Effects (ESCAPE; <http://www.escapeproject.eu>) is a project aimed at investigating the impacts of long-term exposure to air pollution through the development of harmonized exposure data assigned to previously established cohorts that collected information on specific health outcomes of interest for air pollution research. We have analyzed data from 10 European birth cohorts and completed a meta-analysis of air pollution and respiratory infection (pneumonia, croup and otitis media) during early childhood.

METHODS

Study population

We included 10 ESCAPE birth cohorts. The inclusion criteria for each birth cohort were that data on at least one outcome of interest were available during early childhood, and that the ESCAPE exposure assignment was complete.

BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiological Survey) is a population-based prospective birth cohort of children born during 1994-1996 in Stockholm county, Sweden (Wickman et al. 2002). GASPII (Gene and Environment: Prospective Study on Infancy in Italy) is a prospective birth cohort of children born during 2003-2004 in Rome, Italy (Porta et al. 2006). GINIplus (German Infant Nutrition Intervention Study Plus Influence of Pollution and Genetics) is a population-based prospective birth cohort, with a nutritional intervention, of children born during 1995-1998 in Wesel and Munich, Germany (Zirngibl et al. 2002). LISApplus (Influence of Life Style Factors on the Development of the Immune System and Allergies in Childhood Plus the Influence of Traffic Emissions and Genetics) is a population-based prospective birth cohort study of children born during 1997-1999 in Wesel, Munich, Leipzig, and Bad Honnef, Germany (Heinrich et al. 2002). INMA (INfancia y Medio Ambiente; Environment and Childhood) is a network of Spanish birth cohorts. The INMA cohorts in the present analysis comprise children born during 2004-2008 in both major cities and rural towns - Asturias, Gipuzkoa, Sabadell, and Valencia (Guxens et al. 2012). MAAS (Manchester Asthma and Allergy Study) is an unselected, prospective population-based birth cohort study (with a small nested allergen control intervention) of children born during 1995-1997 in the Greater Manchester conurbation in the UK (Custovic et al. 2002). Finally, the PIAMA (Prevention and Incidence of

Asthma and Mite Allergy) study is a population based prospective birth cohort, with an intervention component, of children born during 1996-1997 in cities and small towns across The Netherlands (Brunekreef et al. 2002). Each cohort obtained parental consent and protocols were approved by all relevant ethical review boards.

Exposure to outdoor air pollution was estimated using land use regression models, and methods were harmonized across each cohort (Cyrus et al. 2012; Eeftens et al. 2012a, 2012b; Beelen et al. 2013; <http://www.escapeproject.eu/manuals/>). Briefly, sampling sites for particulate matter (N = 20-40) and nitrogen oxides (N = 40-80) were strategically chosen for each study area to represent the spatial distribution of concentrations at the residential address of each child at birth, with some over-representation of locations with heavy traffic where the largest heterogeneity was expected. Three 2-week sampling campaigns were spread out over one year and used to estimate an annual average. Measurement data used to develop the land use regression models were collected during: 2008-2009 (BAMSE, GINIplus/LISAplus, PIAMA), 2009 (INMA), 2009-2010 (MAAS), and 2010-2011 (GASPII). The annual average was temporally adjusted using continuous measurement data from a fixed monitor that was used to capture background levels in each study area. Models based on GIS variables related to traffic, land use, population density, altitude, and regional background pollution were developed using common ESCAPE protocols to predict measured air pollution concentrations.

Separate models were developed for NO₂, NO_x (NO₂+NO), PM_{2.5}, PM_{2.5} absorbance, PM₁₀, and coarse PM (PM₁₀-PM_{2.5}). In addition, two variables were created to describe traffic intensity at the residential address: traffic intensity on the nearest street, and traffic load on all major roads within a 100-meter buffer. Annual average air pollution concentrations and traffic intensity variables were assigned to children for the first year of life based on their residential address

reported at birth. The LISApplus study centers of Leipzig and Bad Honnef were not included in the ESCAPE exposure assessment so children from these cities could not be included in the meta-analysis.

The air pollution data used to derive the ESCAPE exposure models were measured in 2008 – 2011, while children included in the study cohorts were born as early as 1994. Therefore, we conducted sensitivity analyses using routine monitoring data to back-extrapolate exposure estimates based on land-use regression to each child's year of birth. We used two approaches for the back-extrapolation: The first used the ratio of the average concentration measured from the date of birth through the second birthday to the average concentration measured during the ESCAPE monitoring year; the second used the absolute difference between the average concentrations at each time period (http://www.escapeproject.eu/manuals/Procedure_for_extrapolation_back_in_time.pdf). Both methods altered the spatial contrast derived from the current LUR models without affecting the spatial patterns of air pollutants in the study areas.

For each cohort, parents reported (yes/no) physician-diagnosed pneumonia, otitis media, and croup during early childhood (see Supplemental Material for the specific questions used for each cohort). Outcomes were assessed at 6 months (GASPII, LISApplus), 1 year (BAMSE, GINIplus, INMA Valencia, LISApplus, PIAMA), 14 months (INMA Gipuzkoa, INMA Sabadell), 15 months (GASPII), 18 months (LISApplus, INMA Asturias), 2 years (BAMSE, GINIplus, LISApplus, PIAMA), and 3 years (MAAS). It was not possible to evaluate respiratory infections restricted to the first two years of life for the MAAS birth cohort because these outcomes were not assessed in the full cohort until 3 years of age. Pneumonia data were available for all cohorts; otitis media data were available for all except GINIplus and MAAS; and croup data were available for all

except GASPII, INMA and PIAMA. Cumulative incidence was modeled in each analysis, unless otherwise specified.

Logistic binomial regression was used in all individual cohort analyses and statistical significance was defined by *p*-values less than 0.05. Air pollution was entered as a continuous variable and was not transformed. Models were assessed using the Hosmer-Lemeshow goodness-of-fit test and the Pearson's χ^2 test. Potential confounders were identified from previous literature and selected *a priori*. Individual cohort models were adjusted for municipality/city (BAMSE only), gender, older siblings (any/none), partial or exclusive breastfeeding at 6 months, atopy of either parent, daycare attendance reported at any time during follow-up, maternal smoking during pregnancy, secondhand smoke in the home reported at any time during follow-up (not available for INMA), visible mold or dampness in the home, gas stove, birth season (Winter: January-March; Spring: April-June; Summer: July-September; Fall: October-December), parental socio-economic status (highest education attained by either parent (BAMSE, GINIplus, LISApplus, PIAMA, INMA – low, medium, high); highest occupational level by either parent (GASPII – low, medium, high); or household income (MAAS - less than £10,000; £10,000-20,000; £20,000-30,000; more than £30,000)), and intervention (GINIplus, MAAS and PIAMA only). Models for traffic intensity and traffic load were additionally adjusted for background NO₂ concentrations. Children with missing data for any covariate were excluded from individual analyses. Based on the ESCAPE protocol, estimates were calculated for the following increments in exposure: 10 µg/m³ for NO₂, 20 µg/m³ for NO_x, 1 unit for PM_{2.5} absorbance, 5 µg/m³ for PM_{2.5}, 10 µg/m³ for PM₁₀, 5 µg/m³ for coarse PM, 5,000 vehicles/day for traffic intensity on the nearest street; and 4,000,000 vehicle*^{*}m/day for traffic load on major roads within a 100 m buffer. Heterogeneity of effect estimates between studies was assessed

using the I^2 statistic (Huedo-Medina et al. 2006). Random-effects meta-analysis models were used to calculate combined estimates (DerSimonian and Laird 1986).

Sensitivity analyses were used to test the robustness of effect estimates to the inclusion of additional potential confounders: birth weight, maternal age at birth and area-level socio-economic indicators. In addition, we stratified associations for outcomes that were diagnosed during the first year of life and outcomes diagnosed during the second year of life for cohorts that completed follow-ups at one and two years of age (BAMSE, GINIplus, LISApplus, PIAMA). Additional analyses were stratified by gender, parental socio-economic status (low, middle or high), and residential mobility (moved from the birth address at any time during the follow-up period) to examine potential effect modification. As noted above, we also performed sensitivity analyses using exposure estimates that were recalculated for selected pollutants using back-extrapolation techniques to assess the consistency of associations. In addition, we performed a sensitivity analysis of the influence of neighborhood clustering by including an area-level variable (BAMSE: neighborhood; GINIplus: zip-code; LISApplus: zip-code; INMA: rural indicator; PIAMA: neighborhood) as a random effect in adjusted models. Area-level data were not available for GASPII or MAAS. Finally, we used two-pollutant models to estimate the independent effects of NO_2 and PM.

All individual and combined analyses were completed using identical protocols. Individual estimates are presented by cohort except for the German birth cohorts (LISApplus and GINIplus), which had almost identical study designs and parental questionnaires, and are presented as GINI/LISA North (Wesel) and GINI/LISA South (Munich) because separate air pollution models were developed for each area as part of ESCAPE. Statistical analyses were completed using SPSS 20 and SAS 9.1 (SAS Institute, Cary NC, 2002).

RESULTS

There was complete outcome (at least one), exposure (a minimum of NO₂ and NO_x) and potential confounder information for 16,059 children across all 10 cohorts (79.6% of the total recruited population). Children excluded due to missing data were more likely to have parents of lower socioeconomic status (BAMSE, GINI/LISA South, GINI/LISA North, MAAS, PIAMA), mothers who smoked during pregnancy (BAMSE, GASPII, GINI/LISA South, GINI/LISA North, PIAMA); and were less likely to be breastfed for at least six months (GASPII, GINI/LISA South, GINI/LISA North, MAAS, PIAMA) or to have atopic parents (GINI/LISA South, INMA Sabadell). Table 1 shows the cumulative incidence of parent-reported physician-diagnosed respiratory infection, by cohort. The cumulative incidence of pneumonia during early childhood ranged from 1.5% in INMA Sabadell to 7.9% in BAMSE (0.7-3.6% during the first year only). Otitis media ranged from 21.8% in GASPII to 50.0% in BAMSE (6.8-26.6% for the first year), and croup ranged from 10.6% in MAAS to 12.9% in GINI/LISA North (4.2-5.6% for the first year). There were differences in breastfeeding, daycare attendance, parental atopy, and secondhand smoke exposure among the cohorts (Supplemental Material, Table S1). Air pollution concentrations were highest in GASPII and lowest in BAMSE; while GINI/LISA South, GINI/LISA North and PIAMA had similar mean concentrations (Table 1). Additional statistics on air pollutant concentrations by cohort are available in Supplemental Material, Table S2. Air pollutant concentrations were moderately to highly correlated (Supplemental Material, Table S3; e.g., correlation between PM_{2.5} and NO₂ ranged between 0.42 and 0.80, correlations between PM_{2.5} absorbance and NO₂ ranged between 0.40 and 0.93).

Associations between air pollution and respiratory infection during early childhood are presented in Figure 1 for (1) individual and (2) combined effect estimates. Table 2 presents combined

effect estimates for crude (adjusted for sex and municipality) and adjusted (adjusted for all potential confounders) models and p-values for heterogeneity. The heterogeneity between studies varied and the largest I^2 statistics were for models of pneumonia and NO_2 , $\text{PM}_{2.5}$ and PM_{10} . Effect estimates were robust to adjustment for older siblings, breastfeeding, parental atopy, daycare, maternal smoking during pregnancy, environmental tobacco smoke, visible mold or dampness, gas stove, birth season and parental socio-economic status. For pneumonia, elevated odds ratios were found in almost all analyses, and the combined estimates were statistically significant for all measures of air pollution except $\text{PM}_{2.5}$ (OR = 2.58; 95% CI: 0.91, 7.27 for a $5\text{-}\mu\text{g}/\text{m}^3$ increase). For otitis media and croup, results were generally null across all analyses except for NO_2 and otitis media for which the adjusted OR was 1.09 (95% CI: 1.02, 1.16 for a $10\text{-}\mu\text{g}/\text{m}^3$ increase).

Effect estimates in two-pollutant models that included NO_2 plus one of the PM exposures were closer to the null (versus estimates from single pollutant models) and the only statistically significant finding was for NO_2 and otitis media (OR = 1.13; 95% CI: 1.01, 1.26 for a $10\text{-}\mu\text{g}/\text{m}^3$ increase in NO_2) when adjusted for coarse PM (Supplemental Material, Table S4). Confidence intervals increased substantially in two-pollutant models, reflecting the high correlation between pollutants (Supplemental Material, Table S3).

All measures of air pollution were associated with pneumonia (p -value < 0.05) in analyses restricted to the first year of life (e.g., OR = 4.06; 95% CI: 1.93, 8.57 for a $5\text{-}\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$) (Table 3). Further, the combined effect estimate for all associations (pneumonia, otitis media and croup) increased when analyses were restricted to outcomes in the first year of life.

Stratified meta-analyses suggested slightly stronger effects in females and in those from middle socioeconomic groups (Supplemental Material, Tables S5 and S6). In analyses stratified by residential mobility during follow-up the associations between air pollution and respiratory infection were not consistent by strata – pneumonia effects were greater for movers (OR = 1.62; 95% CI: 1.20, 2.18 versus 1.21; 95% CI: 0.88, 1.67 for NO₂); while otitis media effects were greater for non-movers (OR = 1.08; 95% CI: 1.01, 1.16 versus 1.03; 95% CI: 0.71, 1.48 for NO₂; Supplemental Material, Tables S7). Inclusion of additional covariates into the individual cohort models (birth weight, maternal age and area level socio-economic indicators) did not change air pollution effect estimates or improve model fit (data not shown). There was no consistent evidence for spatial clustering when area-level variables were included as a random effect in models (data not shown). Finally, analyses using back-extrapolated monitoring data were generally consistent with the main findings (Supplemental Material, Table S8).

DISCUSSION

As part of the ESCAPE project we had the unprecedented opportunity to examine outdoor air pollution as a risk factor for respiratory infection during early childhood in an analysis combining 10 European birth cohorts ($N_{\text{Total}} = 16,059$) with data on parent-reported physician-diagnosed pneumonia, otitis media, and croup; and individual air pollution exposure estimates based on common ESCAPE protocols. We found consistent evidence for an association between air pollution and pneumonia, and some evidence for otitis media, during the first two years of life.

Urban air pollution has been associated with respiratory tract infections (Jedrychowski, et al. 2013; Lin et al. 2005), pneumonia (Gouveia and Fletcher 2000), croup (Schwartz et al. 1991),

persistent cough (Esplugues et al. 2011), and otitis media (MacIntyre et al. 2011) during childhood. Associations have also been reported for indoor air pollution and pneumonia in developing countries (da Costa et al. 2004; Mahalanabis et al. 2002) where concentrations are considerably higher than in our study areas. Our findings are consistent with previous studies that used similar methods to examine air pollution and otitis media in three of our cohorts: PIAMA (Brauer et al. 2006), LISApplus Munich (Brauer et al. 2006) and INMA (Aguilera et al. 2013); and a recent meta-analysis on long-term PM_{2.5} and acute lower respiratory infection in children, which also included the PIAMA study (Mehta et al. 2013).

Similar to secondhand smoke (Office on Smoking and Health, 2006), air pollution is thought to increase susceptibility to respiratory infections primarily via an inflammatory response (Li et al. 2008). Urban air pollution may impair defense mechanisms (Clarke et al. 2000; Leonardi et al. 2000;) and oxidant pollutants, in particular, may exacerbate virus-induced inflammation of the respiratory system (Spannhake et al. 2002; Lambert et al. 2003).

Analyses were restricted to the first years of life to include the period of greatest age-specific incidence of respiratory infections (Schnabel et al. 2009; Walker et al. 2013). Our findings suggested that air pollution effects may be slightly stronger during the first year (Table 3). This finding could highlight a unique period of susceptibility when children are at increased risk of respiratory infections due to air pollution (Gehring et al. 2002; Gouveia and Fletcher 2000; Heinrich and Slama 2007). It is also possible that the null findings for infections during the second year of life are due to increased exposure misclassification as older children may spend less time at their home address due to increased daycare enrollment.

A unique strength of land-use regression models is their ability to capture small-scale spatial variability in exposure; however, the measurements used to create the ESCAPE exposure models were taken after the birth year (Eeftens et al. 2012; Cyrus et al. 2012) and this may have introduced exposure misclassification. Although it is possible that overall levels of air pollution changed during this period, previous findings suggest that the spatial distribution of air pollutants within each area remained consistent (Cesaroni et al. 2012; Eeftens et al. 2011; Wang et al. 2013). Further, our sensitivity analyses using monitoring data to back-extrapolate exposure estimates to the actual first year of life were consistent with our main findings (Supplementary Material, Table S8).

The wording of parental questionnaires was similar across each cohort and previous research has shown good agreement between maternal recall and medical records during early childhood (D'Souza-Vazirani et al. 2005; Vernacchio et al. 2007). Geographical differences in the prevalence of outcomes across the cohorts were most pronounced for otitis media and may point to potential diagnostic biases or disease misclassification between countries. It was not possible to adjust for epidemics, the impact of vaccinations, or the frequency of infections because data were not available across all cohorts. Furthermore, defining upper respiratory tract infections (otitis media, croup) by physician diagnosis is complicated by the fact that not all infections present with acute symptoms severe enough to warrant a physician visit, in contrast with pneumonia, which routinely presents with a high fever and/or difficulty breathing (Edmond et al. 2012).

CONCLUSION

Our meta-analysis of 10 European birth cohorts found consistent evidence for an association between traffic-related air pollution and pneumonia, and some evidence to suggest an association with otitis media. Policies aimed at reducing air pollution may be successful in reducing the overall burden of pneumonia in early childhood.

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Table 1. The cumulative incidence of respiratory infections and distribution of air pollution for each ESCAPE birth cohort.

	BAMSE	GASPII	GINI/LISA South	GINI/LISA North	INMA Asturias	INMA Gipuzkoa	INMA Sabadell	INMA Valencia	MAAS	PIAMA
Respiratory infections [no. (%)]										
Total included	3821 (100)	678 (100)	3321 (100)	2460 (100)	360 (100)	437 (100)	402 (100)	559 (100)	695 (100)	3475 (100)
Pneumonia, 0-1 yr	137 (3.6)	5 (0.7) ^a	81 (2.4)	80 (3.3)	-	-	-	10 (1.8) ^b	-	84 (2.4)
Pneumonia, 0-2 yr	301 (7.9)	14 (2.1) ^c	198 (6.0)	144(5.9)	8 (2.2) ^d	9 (2.1) ^e	6 (1.5) ^f	-	13 (1.9) ^g	150 (4.3)
Otitis media, 0-1 yr	1017 (26.6) ^h	46 (6.8) ^a	202(16.4) ⁱ	49 (18.2) ⁱ	-	-	-	139 (24.9) ^b	-	603 (18.0)
Otitis media, 0-2 yr	1911 (50.0) ^h	148 (21.8) ^c	422 (34.2) ⁱ	103 (38.3) ⁱ	143 (39.7) ^d	161 (36.8) ^e	144 (35.8) ^f	-	-	1144 (32.9)
Croup, 0-1 yr	201 (5.3)	-	140 (4.2)	135 (5.6)	-	-	-	-	-	-
Croup, 0-2 yr	410 (10.7)	-	362 (10.9)	318 (12.9)	-	-	-	-	74 (10.6) ^g	-
Air pollution (median [IQR])										
NO ₂ (µg/m ³)	12.4 [9.3]	43.2 [10.4]	20.8 [8.3]	23.2 [3.2]	22.2 [14.4]	18.4 [5.7]	41.7 [12.4]	27.9 [18.1]	23.0 [2.4]	23.1 [8.4]
NO _x (µg/m ³)	20.9 [18.2]	65.8 [23.9]	34.6 [12.2]	33.3 [8.4]	44.0 [39.0]	37.2 [11.1]	69.7 [21.2]	44.7 [31.1]	38.7 [5.2]	32.8 [11.0]
PM _{2.5} (µg/m ³)	8.1 [1.9]	18.8 [2.0]	13.3 [1.2]	17.2 [0.9]	-	-	14.6 [1.1]	-	9.4 [0.0]	16.5 [1.2]
PM _{2.5} absorbance (10 ⁻⁵ /m)	0.6 [0.3]	2.5 [0.4]	1.7 [0.2]	1.2 [0.2]	-	-	2.2 [0.5]	-	1.1 [0.2]	1.2 [0.3]
PM ₁₀ (µg/m ³)	15.6 [3.9]	34.9 [6.1]	20.4 [2.9]	25.2 [1.6]	-	-	26.4 [3.4]	-	17.0 [0.2]	24.6 [1.2]
Coarse PM (µg/m ³)	7.7 [3.0]	15.7 [4.3]	6.5 [2.0]	8.4 [0.7]	-	-	11.3 [2.5]	-	6.9 [0.8]	8.1 [0.8]
Traffic intensity on nearest street (vehicles/day)	500 [1450]	-	500 [0]	500 [0]	-	-	-	-	500 [0]	215 [436]
Traffic load on major streets within 100 m buffer (vehicle*m/day)	0 [1621333]	-	15000 [11599]	0 [0]	-	-	-	-	0 [0]	0 [0]

^a Assessed at 6 months; ^b Assessed at 12 months; ^c Assessed at 15 months; ^d Assessed at 18 months; ^e Assessed at 14 months; ^f Assessed at 14 months; ^g Assessed at 3 years; ^h Requiring antibiotic; ⁱ Otitis media was only collected in the LISApplus study (total South = 1242; North = 280) .

Table 2. Combined estimates from random-effects meta-analyses for residential air pollution and respiratory infections during early life (up to 36 months)^a.

	Crude ^b			Adjusted ^c		
	OR (95% CI)	I ²	P-val	OR (95% CI)	I ²	p-val
Pneumonia						
NO ₂	1.25* (1.04, 1.50)	37.1	.112	1.30* (1.02, 1.65)	52.9	.024
NO _x	1.23* (1.06, 1.41)	22.2	.239	1.26* (1.04, 1.52)	44.0	.066
PM _{2.5}	2.13 (0.82, 5.49)	79.7	.000	2.58 (0.91, 7.27)	81.7	.000
PM _{2.5} absorbance	1.78* (1.30, 2.43)	0	.734	1.99* (1.44, 2.75)	0	.663
PM ₁₀	1.55* (1.03, 2.34)	29.2	.205	1.76* (1.00, 3.09)	51.2	.051
Coarse PM	1.23* (1.02, 1.47)	0	.626	1.24* (1.03, 1.50)	0	.579
Traffic, nearest street	1.08* (1.03, 1.14)	0	.997	1.09* (1.03, 1.15)	0	.969
Traffic, major streets	1.19* (1.08, 1.31)	0	.979	1.21* (1.09, 1.34)	0	.843
Otitis Media						
NO ₂	1.08* (1.01, 1.15)	4.8	.395	1.09* (1.02, 1.16)	0	.515
NO _x	1.04 (0.98, 1.10)	0.5	.430	1.05 (0.98, 1.12)	0	.458
PM _{2.5}	1.02 (0.71, 1.45)	55.5	.047	1.06 (0.75, 1.49)	47.9	.088
PM _{2.5} absorbance	1.05 (0.80, 1.37)	46.7	.095	1.08 (0.83, 1.39)	39.9	.139
PM ₁₀	0.98 (0.83, 1.17)	11.6	.341	0.98 (0.84, 1.14)	0	.539
Coarse PM	0.96 (0.87, 1.06)	0	.608	0.97 (0.88, 1.08)	0	.805
Traffic, nearest street	0.98 (0.94, 1.03)	1.4	.385	0.98 (0.93, 1.02)	0	.497
Traffic, major streets	1.00 (0.91, 1.09)	0	.462	0.99 (0.89, 1.10)	18.2	.300
Croup						
NO ₂	0.92 (0.80, 1.07)	0	.884	0.96 (0.83, 1.12)	0	.909
NO _x	0.96 (0.83, 1.10)	0	.895	0.99 (0.86, 1.14)	0	.936
PM _{2.5}	0.83 (0.58, 1.19)	0	.760	0.90 (0.63, 1.30)	0	.703
PM _{2.5} absorbance	0.95 (0.66, 1.37)	5.0	.368	1.03 (0.72, 1.47)	0	.554
PM ₁₀	0.89 (0.70, 1.13)	0	.586	0.92 (0.72, 1.18)	0	.595
Coarse PM	0.95 (0.80, 1.12)	0	.551	0.97 (0.82, 1.15)	0	.787
Traffic, nearest street	0.98 (0.93, 1.04)	0	.926	0.99 (0.93, 1.05)	0	.853
Traffic, major streets	0.97 (0.86, 1.09)	0	.734	0.98 (0.87, 1.11)	0	.901

^a Outcomes assessed up to 12 months (INMA Valencia), 14 months (INMA Gipuzkoa, INMA Sabadell), 15 months (GASPII), 18 months (INMA Asturias), 24 months (BAMSE, GINIplus, LISApplus, PIAMA) and 36 months (MAAS). ^b Crude models were adjusted for gender and municipality (BAMSE). ^c Adjusted models included municipality (BAMSE), sex, older siblings, breastfeeding at 6 months, atopy of either parent, any daycare reported during follow-up, maternal smoking during pregnancy, any environmental tobacco smoke in the child's home reported during follow-up, visible mold or dampness in the home, gas stove, birth season, parental socio-economic status (low, medium, high), and intervention (GINIplus, MAAS, PIAMA). * Statistically significant elevated odds ratios ($p < 0.05$). Associations are presented for the following increments in exposure: 10 $\mu\text{g}/\text{m}^3$ for NO_2 , 20 $\mu\text{g}/\text{m}^3$ for NO_x , 5 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 1 unit for $\text{PM}_{2.5}$ absorbance, 10 $\mu\text{g}/\text{m}^3$ for PM_{10} , 5 $\mu\text{g}/\text{m}^3$ for coarse PM, 5,000 vehicles/day for traffic intensity on the nearest street; and 4,000,000 vehicle·m/day for traffic load on major roads within a 100 m buffer; associations with traffic intensity and traffic load were additionally adjusted for background NO_2 concentrations.

Table 3. Adjusted combined estimates for air pollution exposure at the birth address and respiratory infection by year of life.

	Pneumonia^a (N=12,891) OR (95%CI)	Otitis Media^b (N=8,722) OR (95%CI)	Croup^c (N=9,101) OR (95%CI)
Respiratory infections during the 1st year^d of life			
NO ₂	1.47* (1.15,1.89)	1.19* (1.07,1.33)	1.05 (0.83,1.32)
NO _x	1.45* (1.21,1.75)	1.09 (0.98,1.22)	1.10 (0.90,1.36)
PM _{2.5}	4.06* (1.93,8.57)	1.21 (0.64,2.28)	1.15 (0.67,1.97)
PM _{2.5} absorbance	2.71* (1.68,4.37)	1.32 (0.99,1.75)	1.04 (0.59,1.83)
PM ₁₀	1.77* (1.18,2.67)	1.24 (0.76,2.02)	1.07 (0.75,1.53)
Coarse PM	1.46* (1.11,1.92)	1.16 (0.80,1.70)	1.02 (0.80,1.30)
Traffic, nearest street	1.14* (1.07,1.22)	0.99 (0.94,1.04)	1.03 (0.94,1.13)
Traffic, major streets	1.31* (1.15,1.50)	1.03 (0.93,1.14)	1.00 (0.81,1.24)
Respiratory infections during the 2nd year^e of life			
NO ₂	1.40* (1.04,1.88)	1.07 (0.96, 1.20)	0.92 (0.78, 1.09)
NO _x	1.29* (1.07, 1.55)	1.02 (0.89, 1.17)	0.92 (0.78, 1.08)
PM _{2.5}	2.65 (0.63, 11.2)	1.06 (0.64, 1.74)	0.76 (0.51, 1.15)
PM _{2.5} absorbance	1.90 (0.93, 3.87)	1.20 (0.80, 1.79)	0.89 (0.59, 1.35)
PM ₁₀	1.42 (0.99, 2.03)	1.00 (0.84, 1.19)	0.83 (0.63, 1.09)
Coarse PM	1.24 (0.98, 1.56)	1.00 (0.89, 1.13)	0.89 (0.73, 1.08)
Traffic, nearest street	1.05 (0.98, 1.13)	0.96 (0.90, 1.03)	0.93 (0.81, 1.07)
Traffic, major streets	1.10 (0.90, 1.34)	0.96 (0.83, 1.10)	1.00 (0.88, 1.14)

^a Based on 4 studies: BAMSE, GINI/LISA North, GINI/LISA South, PIAMA; ^b Based on 3 studies:

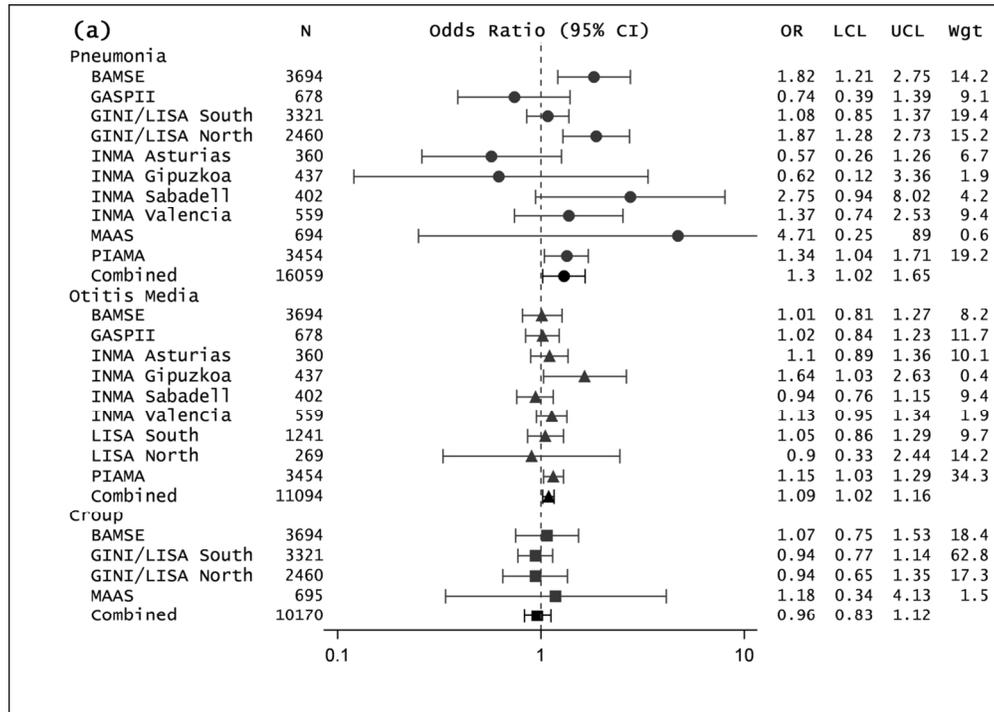
BAMSE, LISApplus North, LISApplus South, PIAMA; ^c Based on 3 studies: BAMSE, GINI/LISA North,

GINI/LISA South; ^d Defined as 0-12 months. ^e Defined as 13-24 months. Models were adjusted for municipality (BAMSE), gender, older siblings, breastfeeding at 6 months, atopy of either parent, any daycare reported during follow-up, maternal smoking during pregnancy, any environmental tobacco smoke in the child's home reported during follow-up, visible mold or dampness in the home, gas stove, birth season, parental socio-economic status (low, medium, high), and intervention (GINIplus, PIAMA).

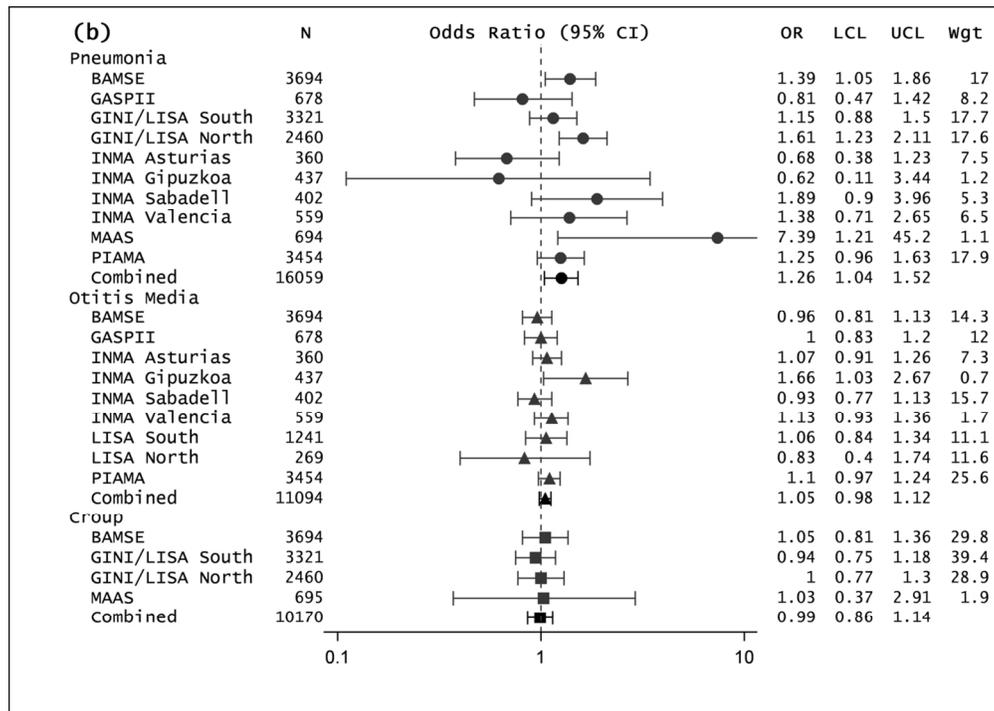
*Statistically significant elevated odds ratios ($p < 0.05$). Associations are presented for the following increments in exposure: 10 $\mu\text{g}/\text{m}^3$ for NO₂, 20 $\mu\text{g}/\text{m}^3$ for NO_x, 5 $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 1 unit for PM_{2.5} absorbance, 10 $\mu\text{g}/\text{m}^3$ for PM₁₀, 5 $\mu\text{g}/\text{m}^3$ for coarse PM, 5,000 vehicles/day for traffic intensity on the nearest street; and 4,000,000 vehicle·m/day for traffic load on major roads within a 100 m buffer; associations with traffic intensity and traffic load were additionally adjusted for background NO₂ concentrations.

Figure Legend

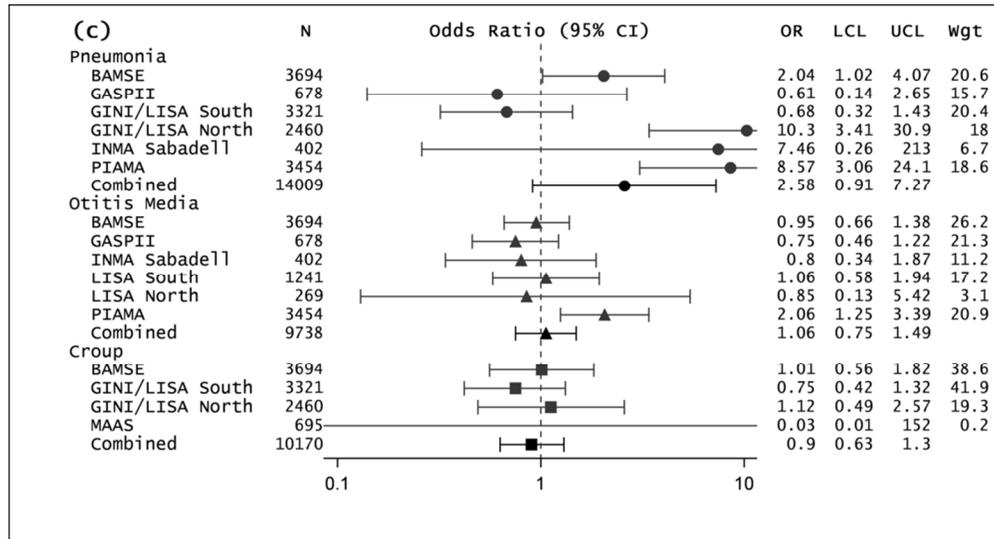
Figure 1. Forest plots of individual cohort and combined effect estimates (odds ratios) by outcome for (a) NO₂, (b) NO_x, (c) PM_{2.5}, (d) PM_{2.5} absorbance, (e) PM₁₀, (f) Coarse PM, (g) traffic intensity on nearest street, and (h) traffic load on all major roads. The lifetime cumulative incidence of respiratory infection (pneumonia [●]; otitis media [▲]; croup [■]) was assessed at 12 months (INMA Valencia), 14 months (INMA Gipuzkoa, INMA Sabadell), 15 months (GASPII), 18 months (INMA Asturias), 24 months (BAMSE, GINI/LISA North, GINI/LISA South, PIAMA) and 36 months (MAAS) of age. Individual cohort models were adjusted for municipality (BAMSE), gender, older siblings, breastfeeding at 6 months, atopy of either parent, any daycare reported during follow-up, maternal smoking during pregnancy, any environmental tobacco smoke in the child's home reported during follow-up, visible mold or dampness in the home, gas stove, birth season, parental socio-economic status (low, medium, high), and intervention (GINIplus, MAAS, PIAMA). Associations are presented for the following increments in exposure: 10 µg/m³ for NO₂, 20 µg/m³ for NO_x, 5 µg/m³ for PM_{2.5}, 1 unit for PM_{2.5} absorbance, 10 µg/m³ for PM₁₀, 5 µg/m³ for coarse PM, 5,000 vehicles/day for traffic intensity on the nearest street; and 4,000,000 vehicle·m/day for traffic load on major roads within a 100 m buffer. N – sample size; CI – confidence interval; OR – odds ratio; LCL – lower 95% confidence limit; UCL – upper 95% confidence limit; Wgt – relative weight (%) assigned using random-effects meta-analysis.



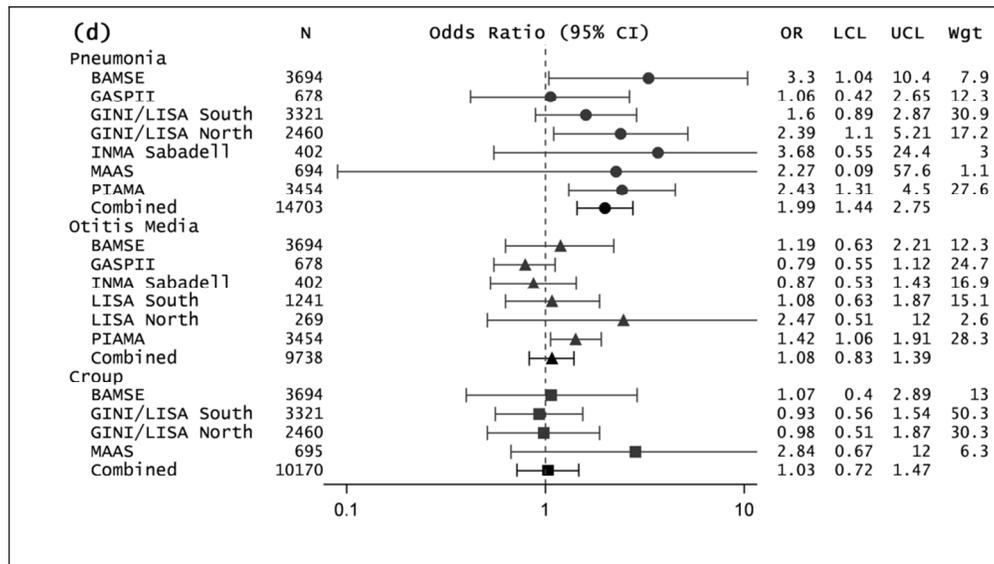
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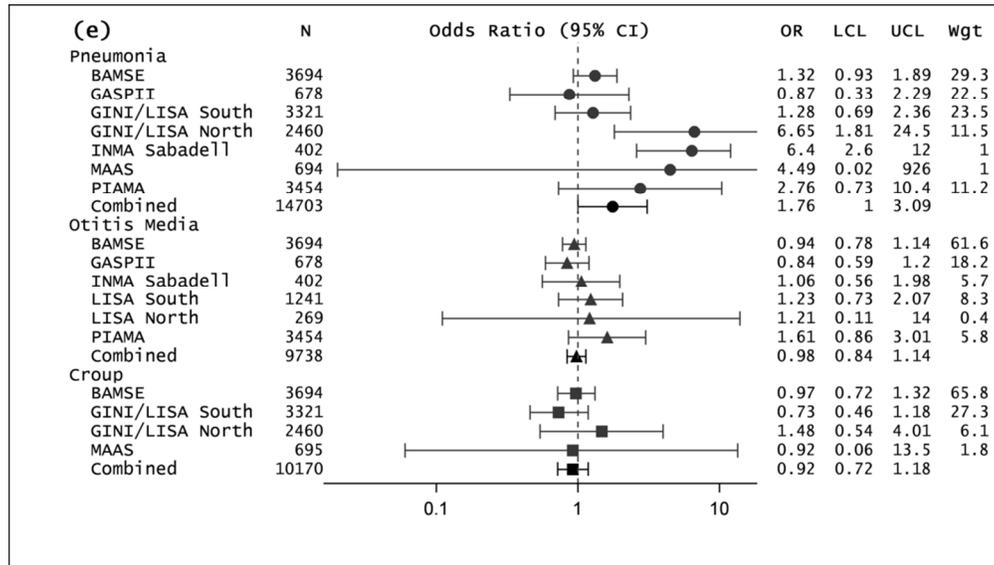
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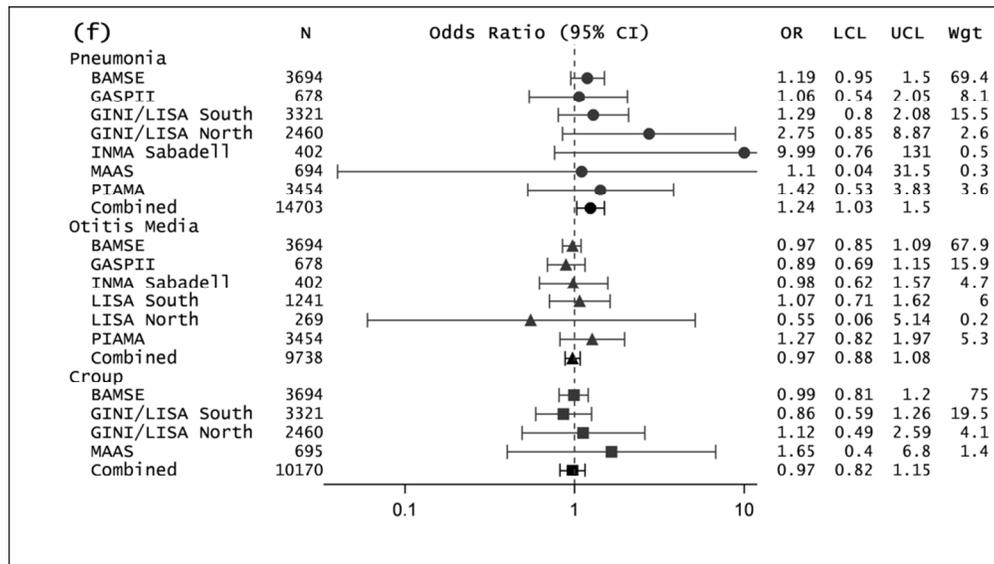
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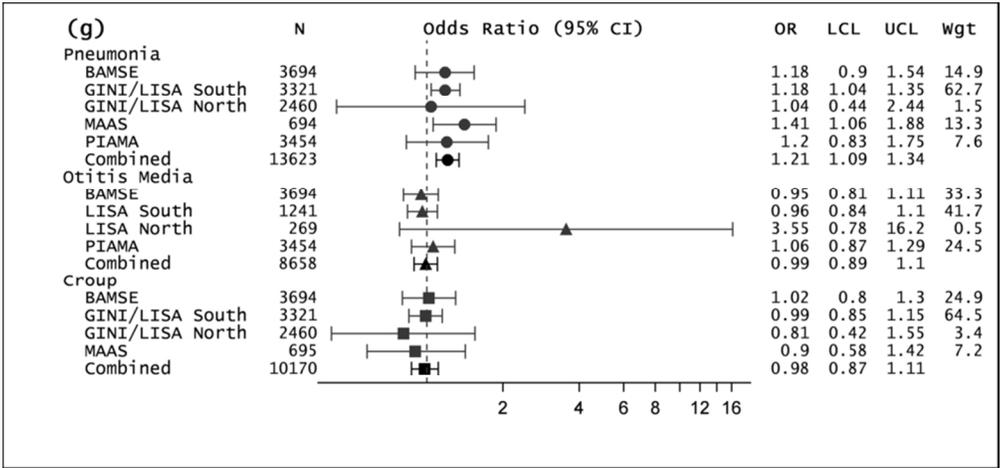
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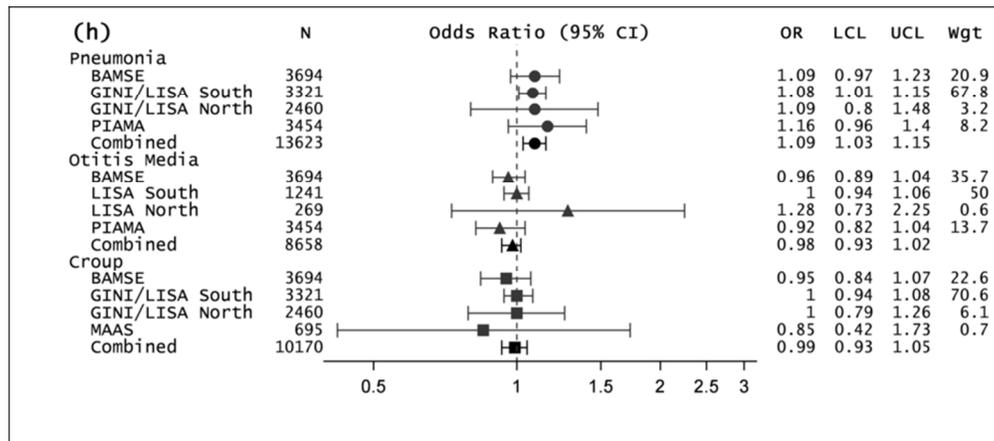
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1f
100x57mm (300 x 300 DPI)



1g
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1h

78x34mm (300 x 300 DPI)