

High prevalence of childhood asthma in Northern Israel is linked to air pollution by particulate matter: evidence from GIS analysis and Bayesian Model Averaging

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The medical records of 3922 school children residing in the Greater Haifa Metropolitan Area in Northern Israel were analyzed. Individual exposure to ambient air pollution (SO₂ and PM₁₀) for each child was estimated using Geographic Information Systems tools. Factors affecting childhood asthma risk were then investigated using logistic regression and the more recently developed Bayesian Model Averaging (BMA) tools. The analysis reveals that childhood asthma in the study area appears to be significantly associated with particulate matter of less than 10 µm in aerodynamic diameter (PM₁₀) (Odds Ratio (OR) = 1.11; $P < 0.001$). However, no significant association with asthma prevalence was found for SO₂ ($P > 0.2$), when PM₁₀ and SO₂ were introduced into the models simultaneously. When considering a change in PM₁₀ between the least and the most polluted parts of the study area (9.4 µg/m³), the corresponding OR, calculated using the BMA analysis, is 2.58 (with 95% posterior probability limits of OR ranging from 1.52 to 4.41), controlled for gender, age, proximity to main roads, the town of a child's residence, and family's socio-economic status. Thus, it is concluded that exposure to airborne particular matter, even at relatively low concentrations (40–50 µg/m³), generally below international air pollution standards (55–70 µg/m³), appears to be a considerable risk factor for childhood asthma in urban areas. This should be a cause of concern for public health authorities and environmental decision-makers.

Keywords: childhood asthma; air pollution; residential communities

Introduction

Asthma is characterized by a variable degree of airflow obstruction, bronchial hyper-responsiveness, and airway inflammation (Busse and Lemanske 2001). Childhood asthma often begins in early life and continues into adulthood, being exacerbated by weather changes, viral infections, and exposure to allergens and airborne pollutants (Johnson et al. 2002; Castro-Rodriguez and Garcia-Marcos 2008). The third phase of the ISAAC study revealed high prevalence of childhood asthma in most developed countries (New Zealand – 22.2%, USA – 22.3%, Canada – 18.2%, UK – 20.9%,

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Germany – 17.5%, Spain – 9.6%, and Israel – 7%) and increased childhood asthma prevalence in many developing nations: Poland – 10.2%, Mexico – 11.6%, Chile – 15.5% (Asher et al. 2006; Romano-Zelekha et al. 2007; Lai et al. 2009). An increase in the prevalence of asthma in the 6–7 age groups has also been reported – from 0.65% in Germany to 0.1% in Japan per annum (Asher et al. 2006).

Several epidemiological studies reported significant health effects of ambient air pollution on children's health, even at relatively low levels of air pollution exposure (van der Zee et al. 1999; Gauderman et al. 2004, 2009; Brauer et al. 2007). In particular, exposure to air pollution was found to exacerbate asthmatic symptoms and impede normal lung functioning among both healthy and asthmatic children (Mortimer et al. 2002; Gauderman et al. 2004, 2005; McConnell et al. 2006; Holguin et al. 2007). Substantial evidence has also been accumulated to date linking the incidence of childhood asthma with traffic related air pollution and early life exposure to ambient air pollution (Brauer et al. 2007; Jerrett et al. 2008; Clark et al. 2010; McConnell et al. 2010). Exposure to nitrogen dioxide (NO₂) and ozone (O₃), resulting from residential proximity to major thoroughfares and interacting with genetic factors, was also found to be associated with childhood asthma incidence in urban areas (Gauderman et al. 2005; Salam et al. 2007; Jerrett et al. 2008; McConnell et al. 2010).

Although these results are consistent with inflammation and oxidative stress theory (Kelly 2003; Lands 2007; Islam et al. 2008; Yang et al. 2008), the interaction between air pollution exposure and childhood asthma incidence was investigated in previous studies mainly on a general population level (i.e. on the aggregate level of townships and small statistical areas), without taking into account differences in individual exposures of children residing in different parts of the same region or a township, which is likely to lead to an exposure misclassification bias (McConnell et al. 2006; Brauer et al. 2007; Portnov et al. 2007).

The recently developed approach of Individual Exposure Estimates (IEE) helps to assign air pollution exposure estimates for each subject in the study cohort based on the residential locations of individuals. This approach is based on advanced Geographic Information Systems (GIS) technology, and can thus help to overcome significant causes of misclassification bias. As indicated by several recent empirical studies (cf. *inter alia* McConnell et al. 2006; Brauer et al. 2007; Dubnov et al. 2007; Portnov et al. 2007; Morgenstern et al. 2008), the IEE approach appears to be more sensitive to intra-area differences in individual exposure than the traditional ecological approach (based on aggregate exposure estimates for statistical areas and townships) for detecting a variety of health outcomes associated with environmental hazards.

Using the IEE approach, we investigated the association between asthma prevalence, and air pollution among a cohort of schoolchildren residing in the Greater Haifa Metropolitan Area (GHMA). The analysis was performed using both traditional logistic regression and Bayesian Model Averaging (BMA) tools (Hoeting et al. 1999; Viallefont 2001; Wang et al. 2004).

Methods

Study population

GHMA, which forms our study area, hosts several major industrial enterprises, including oil refineries, a major power station (with a production capacity of 450 MW), and several smaller petrochemical facilities, and is considered to be highly polluted (Goren et al. 1990). The GHMA has a total population of about 500,000

residents and consists of seven separate municipalities (townships): Haifa (267,000 residents), Qiryat Tivon (13,100 residents), Nesher (21,300 residents), Qiryat Ata (49,600 residents), Qiryat Motzkin (39,600 residents), Qiryat Bialik (36,400 residents) and Qiryat Yam (37,000 residents) (see Figure 1).

The study population consisted of a cohort of 3922 schoolchildren of the first through eighth grade (6–14 year old) residing in different residential communities of the GHMA (see Figure 1).

The children's medical records were retrieved from the "Clalit" Health Services database, which is the largest Health Maintenance Organization (HMO) in Israel that provides health care coverage for more than 54% of the GHMA population (Cohen et al. 2010). All schoolchildren in the 6–14-year-old age group recorded (as of June 2009) in this database, and living within a radius of less than 500 m from one of the 14 air quality monitoring stations (AQMSs) located in the study area, were covered by the analysis. The selection of children residing in the vicinity of the AQMSs was important for minimizing a potential bias associated with

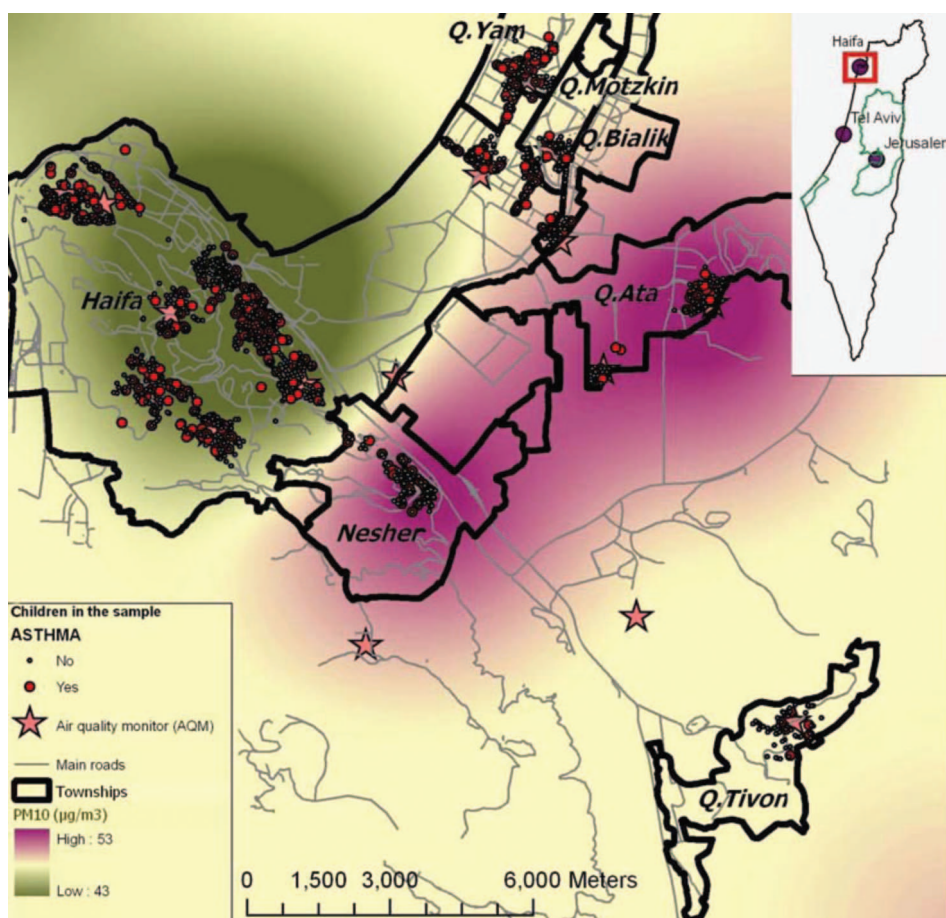


Figure 1. Map of the study area showing the locations of homes of children under study and PM₁₀ pollution estimates. Note: Not-labeled Small Census Areas (SCAs) are non-residential census sub-divisions which have no permanent population.

misclassification of air pollution exposure. The issue of concern is that AQMS records may be less representative for more remote areas, due to differences in the local topography and wind regimes. This may result in exposure classification errors due to “spatial misalignment” (Peng and Bell 2010).

Although medical records of schoolchildren serviced by other, smaller HMOs (such as “Maccabi”, “Meuheded” and “Leumi”) were unavailable for the study, our analysis indicated that the schoolchildren covered by the study are representative of the entire age cohort of children residing in the study area in terms of gender and age ($P > 0.5$) (ICBS 2010). In addition, asthma prevalence was recorded by “Clalit” and other HMOs do not appear to differ significantly (Bibi; unpublished data).

For classification purposes, we used the diagnosis of asthma whenever one of the following two criteria was met: the asthma diagnosis appeared as a chronic disease in the computerized medical chart (i.e. ever diagnosed asthma) (515 cases) or asthma appeared as a diagnosis in the follow up record of a primary health care visit between January 2008 and June 2009 years (32 cases). In addition, we included, as probable asthma cases, 81 children without a recorded asthma diagnosis, who, between January 2008 and June 2009, were prescribed any beta agonist drug in combination with inhaled or oral steroids, i.e. children actually treated for asthma, but not recorded as asthmatics in the computerized database.

Air pollution estimates

Air pollution data for the present study were obtained from 14 air quality-monitoring stations (AQMS) located in the study area. All stations measure half-hour mean concentrations of SO_2 . In addition, seven AQMS also measure half-hour concentrations of PM_{10} .

In the analysis, average concentrations of these air pollutants were estimated for the period of 2006–2008, as arithmetic means of the AQMS half-hour measurements, and compared with the children’s health status in the first half of 2009, in order to allow for a latency period. The use of three-month (or longer) periods between previous exposure to air pollution and asthma prevalence is common in cross-sectional epidemiological studies, especially for the estimation of effects associated with chronic exposure (Akinbami et al. 2010).

The average values of SO_2 and PM_{10} , were interpolated by *kriging*, enabling us to obtain continuous surfaces SO_2 and PM_{10} pollution levels covering the entire study area (see PM_{10} interpolates as the background surface in Figure 1). According to previous studies (cf. e.g. (Wong et al. 2004, Son et al. 2010)), the *kriging* interpolation method appears to provide better results than other interpolation techniques for air pollution smoothing. However, this method works best with multiple sample locations. Therefore, during a preliminary analysis stage, we also used another interpolation technique – Inverse Distance Weighted (IDW), – to ensure that our results were robust (see the Results section). Both calculations (i.e. *kriging* and IDW) were performed using default parameter values of the ArcMap 9.xTM software’s “Spatial Analyst” module (McCoy and Johnston 2009).

GIS mapping of children and Individual Exposure Estimates

An indirect approach to estimate air pollution exposure, known as the IEE, which has become a popular research tool in recent years (see *inter alia* Dubnov et al. 2007;

Portnov et al. 2007; Jerrett et al. 2008; Kim et al. 2009; Zou et al. 2009), was used in the present study. According to this approach, the home addresses of children in the study cohort were geo-coded (i.e. their home addresses were converted into X , Y coordinates), positioned on the map, and then superimposed upon SO_2 and PM_{10} air pollution surfaces (see Figure 1). The raster surfaces were then converted into vector maps (i.e. air pollution contours). Next, the levels of SO_2 and PM_{10} air pollution, to which each child in the study cohort was exposed, were estimated. The task was performed in the ArcGIS 9.xTM software, using its “spatial join” tool, which makes it possible to match between different geographic layers (maps) based on the spatial relationship between them (Minami 2000).

In addition, in order to estimate the children’s exposure to mobile sources of air pollution (i.e. motor vehicles), we defined the proximity of residences to main roads using a dichotomous variable. A residence closer than 50 m (i.e. the first row of buildings) to a main road’s longitudinal axis was conditionally defined as a high exposure area (1); otherwise it was defined as a low exposure area (0). [We chose a 50 m distance band (i.e. the first row of houses adjacent to the road) because, according to a Gaussian dispersion model (English et al. 1999), this distance range is likely to capture about 70% of traffic-generated air pollution].

The estimation of air pollution exposure for adults using the places of residences may be somewhat problematic because adults may live in places with high air pollution and work in places with low pollution and vice versa. Such estimations, using residential addresses, may, however, be less problematic for children, who spend most of their time in close proximity to their homes (Bateson et al. 2008; Setton et al. 2008).

Statistical analysis

The participants’ data were analyzed anonymously and the analysis was performed in several phases. In the first phase of the analysis, we calculated childhood asthma prevalence and several environmental and demographic indicators (viz. air pollution, percent of children from families receiving welfare support, etc.).¹ The analysis was performed separately for individual townships covered by the study (see Figure 1). Next, binary logistic regression was run to identify and measure the relative strength of factors potentially affecting the prevalence of asthma in different loci of GHMA.

The logistic regression model used in the analysis can be written as:

$$\log[p_i/(1 - p_i)] = \beta_0 + \beta_1 x_{i1} + \dots + \beta_p x_{ip} \quad (1)$$

where p_i is the probability that the i th case experiences the event of interest (i.e. asthma diagnosis); x_{ij} is the j th predictor for the i th case, β_j is the j th coefficient, and p is the number of predictors.

Statistical analysis was performed using the SPSS 17.0[©] software. The probability level of less than 0.05 (two-sided) was set as the accepted statistical significance level.

A major emerging issue in epidemiological studies is model selection uncertainty, which is often neglected in “standard frequentist models” (Hoeting et al. 1999; Greenland et al. 2006). Although there are numerous models that could explain childhood asthma, traditional “frequentist” statistical techniques (such as classical logistic regression) do not incorporate the uncertainty over the choice of model.

The chosen model is assumed to be correct and statistical inference (i.e. tests, confidence intervals, etc.) is obtained conditional on the selected model. The uncertainties associated with the model selection can be addressed by the BMA approach that is based on the standard logistic regression model, with the above functional form (1), but takes into consideration the interaction of variable and model uncertainty by analyzing and averaging estimates of dozens of alternative models, weighted by their posterior probabilities (Annest et al. 2009).

In our study, the BMA analysis was implemented in the R (v.2.12) software using the *bic.glm* program for generalized linear models which includes logistic regression (Raftery et al. 2010). A readable description of this package and the basic underlying theory can be found in Raftery et al. (2005). If there are k explanatory variables, *bic.glm* considers all the 2^k possible models, all of which are considered to be a priori equally likely. This preliminary set of models is reduced to a more manageable subset by excluding highly implausible models using methods described in the above cited BMA references. The averaging is carried out on the remaining models weighting by the model posterior probabilities (*ibid.*).

Results

General trends

Table 1 shows personal demographic and health variables including estimated exposure to air pollution, while Table 2 features the differences between seven townships covered by the study.

The prevalence of asthma in the study area appears to be substantially higher than the countrywide average — 16% vs. 7%, respectively (see Table 1) (Romano-Zelekha et al. 2007; Shohat et al. 2000). In addition, as Table 2 shows, the prevalence of childhood asthma appears to vary widely across the townships forming the study area, with the town of Qiryat Yam (see Figure 1) exhibiting especially high asthma prevalence — 21.4% of all children in the sample. A relatively large share of families

Table 1. Characteristics of schoolchildren surveyed in the Haifa Bay area in 2009: Estimated exposure to air pollution, personal demographic and health variables.

Variable	Abs. number or mean value	Min.–max.	Percent (SD)
<i>Gender</i>			
Female	1928	—	49.2
Male	1994		50.8
Age (years)	10.2	6–15	(2.6)
Asthma ever diagnosed	628	—	16.0
Welfare support ^a			
Yes	441	—	11.2
No	3481		88.8
Average estimated exposure dose to PM ₁₀ [$\mu\text{g}/\text{m}^3$]	47.6	43.1–52.5	(2.7)
Average estimated exposure dose to SO ₂ [ppb]	5.4	3.5–8.5	(1.3)
<i>Proximity to main roads</i>			
High exposure ^b	1919	—	48.9
Low exposure	2003		51.1

Note: ^aData of National Insurance Institute of Israel; ^bLiving less than 50 m from a main road.

Table 2. Characteristics of schoolchildren surveyed by cities of residence (see Figure 1).

Variable	Qiryat Tivon	Nesher	Haifa	Qiryat Ata	Qiryat Motzkin	Qiryat Bialik	Qiryat Yam
Number of children	126	349	2687	288	84	93	295
Female gender (%)	54.0	50.1	49.2	45.5	51.2	39.8	51.2
Mean age (years)	10.1	10.2	10.1	10.4	10.0	10.4	10.3
Asthma ever diagnosed (%)	8.7*	13.8	16.6	14.9	11.9	8.6*	21.4*
Low welfare status (%)	4.8*	15.2*	11.3	4.5**	9.5	18.3*	13.9
Proximity to the main road (percent of children)	19.8**	52.1	48.6	40.6*	52.4	38.7	70.8**
Average estimated exposure to PM ₁₀ (μ g/m ³)	49.1	51.6	46.2	52.1	49.4	49.9	49.1
Average estimated exposure to SO ₂ (ppb)	8.5	6.2	5.4	3.6	6.1	6.7	5.0

^Note: * P value < 0.05 (χ^2 test; ref. category: Haifa). ** P value < 0.01 (χ^2 test; ref. category: Haifa).

Table 3. Factors affecting asthma prevalence (method – binary logistic regression; dependent variable – asthma diagnosis; interpolation method used for air pollution estimates – *kriging*)*.

Variable	Model 1			Model 2			Model 3		
	B	P-value	OR (95% CI)	B	P-value	OR (95% CI)	B	P-value	OR (95% CI)
Gender (male)	0.389	<0.001	1.476 (1.241–1.756)	0.388	<0.001	1.475 (1.239–1.754)	0.387	<0.001	1.472 (1.237–1.752)
Age (years)	0.007	0.675	1.007 (0.974–1.041)	0.008	0.649	1.008 (0.975–1.042)	0.008	0.635	1.008 (0.975–1.042)
Family on welfare (yes)	–0.013	0.925	0.987 (0.750–1.298)	–0.007	0.960	0.933 (0.755–1.307)	–0.012	0.932	0.988 (0.751–1.300)
SO ₂	0.099	0.026	1.104 (1.012–1.204)	–	–	–	–0.076	0.287	0.926 (0.805–1.066)
PM ₁₀	–	–	–	0.102	<0.001	1.107 (1.048–1.169)	0.138	0.002	1.149 (1.053–1.253)
Road distance (<50 m)	0.074	0.409	1.077 (0.903–1.283)	0.073	0.415	1.075 (0.903–1.281)	0.063	0.486	1.065 (0.893–1.269)
Townships: ^a	0.001	0.001	–	–	<0.001	–	–	<0.001	–
Qiryat Tivon	–1.029	0.003	0.357 (0.181–0.706)	–1.016	0.002	0.362 (0.189–0.691)	–0.889	0.011	0.411 (0.206–0.819)
Nesher	–0.275	0.098	0.759 (0.548–1.052)	–0.753	0.001	0.471 (0.306–0.723)	–0.902	<0.001	0.406 (0.244–0.674)
Qiryat Ata	0.032	0.869	1.032 (0.708–1.506)	–0.733	0.002	0.480 (0.303–0.761)	–1.086	0.007	0.338 (0.153–0.746)
Qiryat Motzkin	–0.439	0.200	0.645 (0.329–1.262)	–0.685	0.051	0.504 (0.253–1.004)	–0.749	0.035	0.473 (0.235–0.950)
Qiryat Bialik	–0.916	0.015	0.400 (0.190–0.840)	–1.159	0.003	0.314 (0.147–0.670)	–1.195	0.002	0.303 (0.141–0.648)
Qiryat Yam	0.365	0.018	1.440 (1.065–1.948)	0.061	0.716	1.063 (0.764–1.480)	–0.062	0.761	0.940 (0.630–1.402)
Intercept	–2.472	<0.001	0.084	–6.648	<0.001	0.001	–7.939	<0.001	0.000
<i>Hosmer–Lemeshow test of the goodness of fit:</i>									
Chi-square	4.419			5.658			4.597		
Sig.	0.817			0.686			0.800		
–2 Log likelihood	3406.162			3398.163			3396.552		

Notes: Model 1: PM₁₀ excluded; Model 2: SO₂ excluded; Model 3: Both PM₁₀ and SO₂ are included. *Total number of cases (of them with asthma) = 3922 (628); ^areference category – Haifa.

supported by public welfare institutions characterizes this town as do a large number of residences (70.8%) located in close proximity to main traffic routes.

Conversely, in the town of Qiryat Tivon (see Figure 1), which enjoys a relatively high socio-economic status, asthma prevalence was found to be the lowest (8.7%), albeit PM₁₀ air pollution estimates there are higher than the study area average (see Table 2).

Using the cross-validation tool of the ArcGIS9.xTM “Geostatistical Analyst,” we also investigated estimation errors resulting from *kriging* interpolation. The estimation errors, resulting from the interpolation of PM₁₀ observations, are reported in the “Supplementary materials” section and implications of these errors for the study results are discussed in the Conclusions section.

Multivariate analysis

Table 3 reports results of standard logistic regression for asthma relative risks. The models are estimated first for the SO₂ and PM₁₀ variables separately, and then for both of them introduced simultaneously.

As Table 3 shows, gender is a strong factor for asthma with boys being more prone to developing asthmatic symptoms than girls (OR = 1.475–1.476; $P < 0.001$). This conclusion is consistent with results of several studies primarily carried out in Europe (cf. e.g. (Bjornson and Mitchell 2000; Gehring et al. 2002)), but is not consistent with findings of studies carried out elsewhere (see *inter alia* (McConnell et al. 2006; Clark et al. 2010)). Air pollution, measured by both SO₂ and PM₁₀, (represented by *kriging* interpolates) also emerged as statistically significant (SO₂ : OR = 1.104, CI (95%) = 1.012–1.204, $P < 0.05$; and PM₁₀: OR = 1.107, CI

Table 4. Factors affecting asthma prevalence (Method – binary logistic regression; dependent variable – asthma diagnosis; interpolation technique used for air pollution estimates – IDW method).

Variable	Model 4 (IDW)		
	B	P-value	OR (95% CI)
Gender (male)	0.387	<0.001	1.473 (1.238–1.752)
Age (years)	0.009	0.615	1.009 (0.976–1.043)
Family on welfare (yes)	–0.015	0.912	0.985 (0.748–1.296)
SO ₂	–0.012	0.834	0.988 (0.880–1.109)
PM ₁₀	0.085	0.003	1.089 (1.029–1.152)
Road distance (< 50 m)	0.081	0.366	1.084 (0.910–1.293)
Townships:		<0.001	
Qiryat Tivon	–1.144	0.001	0.318 (0.160–0.634)
Nesher	–0.901	0.001	0.406 (0.241–0.686)
Qiryat Ata	–0.882	0.015	0.414 (0.203–0.844)
Qiryat Motzkin	–0.735	0.039	0.479 (0.238–0.964)
Qiryat Bialik	–1.189	0.002	0.305 (0.142–0.653)
Qiryat Yam	–0.009	0.964	0.991 (0.672–1.461)
Intercept	–5.725	<0.001	0.003
<i>Hosmer-Lemeshow test of the goodness of fit:</i>			
Chi-square	4.777		
Sig.	0.781		
–2 Log likelihood	3397.452		

Table 5. Factors affecting childhood asthma prevalence (Method – BMA); GLM family – binominal; dependent variable – asthma diagnosis)*.

Variable	$P(\beta \neq 0)^a$	B (wa ^c)	SD (wa ^c)	OR (wa ^c)	B-Model 1	B-Model 2	B-Model 3	B-Model 4	B-Model 5
Gender (male)	99.70	0.388	0.091	1.473	0.389	0.387	0.388	0.389	0.389
Age (years)	1.60	0.000	0.002	1.000	–	–	0.008	–	–
Family on welfare (yes)	1.50	0.000	0.017	1.000	–	–	–	–	0.005
PM ₁₀	100.00	0.101	0.029	1.106	0.100	0.139	0.102	0.100	0.100
SO ₂	2.80	–0.002	0.018	0.998	–	–0.081	–	–	–
Road_dist (<50 m)	0.10	0.001	0.016	1.001	–	–	0.073	–	–
Townships: ^d	100.00			1.000					
Qiryat Tivon	–	–0.988	0.330	0.372	–0.991	–0.859	–1.016	–0.991	–0.991
Nesher	–	–0.751	0.221	0.472	–0.746	–0.905	–0.753	–0.747	–0.746
Qiryat Ata	–	–0.726	0.248	0.484	–0.715	–1.090	–0.730	–0.718	–0.715
Qiryat Motzkin	–	–0.685	0.351	0.504	–0.683	–0.751	–0.686	–0.682	–0.683
Qiryat Bialik	–	–1.144	0.386	0.319	–1.143	–1.184	–1.157	–1.145	–1.142
Qiryat Yam	–	0.048	0.170	1.049	0.051	–0.078	0.063	0.050	0.052
Intercept	100.00	–6.105	1.322	0.002	–6.064	–7.448	–6.108	–6.144	–6.066
PostProb ^b					0.917	0.028	0.020	0.016	0.015

Note: *Total number of cases (of them with asthma) = 3922 (628); ^aposterior probability that the variable effect is non-zero (percent); ^bposterior probabilities of the models selected (larger values indicate better models); ^cposterior probability weighted average; ^dreference category – Haifa. B-Model 1 ... B-Model 5: Five best models selected by the BMA procedure.

(95%) = 1.048–1.169, $P < 0.001$, respectively). Several city indicators, especially for Qiryat Yam, a city with increased asthma prevalence, and for Qiryat Tivon, a city with relatively low asthma prevalence, also emerged as statistically significant ($P < 0.01$). Concurrently, other variables (i.e. age, welfare status, and road proximity) were found to be insignificant ($P > 0.1$).

The results of modeling using IDW to obtain PM_{10} and SO_2 interpolated values are reported in Table 4. As a comparison between modeling results based on *kriging* (Table 3, Model 3) and the IDW method (Table 4, Model 4) indicates, the outcomes of the analyses appear to be essentially similar, with *kriging* interpolates providing marginally better results, as indicated by the Hosmer–Lemeshow's goodness-of-fit test (Chi-square = 4.597; $P = 0.8$, Model 3 vs. Chi-square = 4.777; $P = 0.781$; Table 4, Model 4).

All three of the models presented in Table 3 (SO_2 and PM_{10} variables, separately, and both together) have similar goodness of fit statistics. The first two models exhibit positive estimated coefficients for the air pollution measures indicating that the probability of asthma increases with increased pollution however, in the third model, for which both SO_2 and PM_{10} are included, the SO_2 coefficient is negative (albeit non-significant) indicating an unreasonable protective effect. Apparently, this is due to the strong correlation between these two explanatory variables ($r = 0.322$; $P < 0.001$), suggesting that SO_2 should not be added to the model when PM_{10} is included.

The results of the BMA are reported separately in Table 5. We considered $k = 7$ possible explanatory variables (Gender, Age, Family on welfare, Road distance, Townships, SO_2 , PM_{10}) leading to $2^7 = 128$ initially considered models. However, Table 5 presents only the five best models based on the posterior model probabilities. The cumulative posterior probability of these five models is 0.996. In contrast to the standard logistic models reported in Table 3, the BMA results take into account the possible alternative models, with the estimates and standard errors being averaged, weighted by the model posterior probabilities, over the alternative models. The column labeled P ($\beta \neq 0$) (Table 5) represents the posterior probability that the corresponding explanatory variable has an effect on the occurrence of asthma (i.e. the effect is not zero). These posterior probabilities can be interpreted as follows: less than 50% – there is some evidence against the effect; 50–75% – weak evidence for the effect; 75–95% – positive evidence for the effect; 95–99% – strong evidence for the effect; greater than 99% – very strong evidence for the effect (Kass and Raftery 1995; Wang et al. 2004). However, as discussed below, the limitations of this study do not allow us to interpret these effects in a causal manner.

As Table 5 shows, the BMA procedure singles out three explanatory variables as exhibiting very strong evidence of affecting childhood asthma risks – gender (OR = 1.473), PM_{10} (OR = 1.106) and the town of residence. For all the others, the evidence points to them as not having an effect. Our previous conclusion based on the standard logistic regression analysis (see Table 3), that SO_2 should not be added to the model when PM_{10} is included, is thus strengthened by the BMA approach which estimates the posterior probability for an SO_2 effect to be only 2.8% (Table 5).

The 95% CI for PM_{10} in the classical logistic model is between 1.048 and 1.169 (see Table 3), which is nearly identical to the 95% posterior probability limits for PM_{10} Odds Ratio (OR) in the BMA model calculated as 1.045, 1.171. We need to emphasize that these OR estimates reflect a change of only one PM_{10} unit (i.e. $1 \mu g/m^3$). A change of $9.4 \mu g/m^3$, which reflects the difference in the PM_{10} pollution between the least and most polluted parts of the study area (see Table 1), results in

OR = 2.584 with 95% posterior limits (1.515, 4.409), according to the BMA model (Table 5), and in OR = 2.609 (CI = 1.554, 4.340), according to the traditional logistic model (Table 3). The fact that different modeling approaches lead to very similar estimates of the PM₁₀ effect indicates that our results appear to be robust.

Figure 2 illustrates the estimated increases in the probability of childhood asthma calculated as a function of PM₁₀ using the BMA model reported in Table 5. As this figure shows, the increase of PM₁₀ from its minimal level observed in the study area (43.1 $\mu\text{g}/\text{m}^3$) to its maximum level of 52.5 $\mu\text{g}/\text{m}^3$, is associated with an increase in the posterior probability of childhood asthma by about 0.07–0.20 for boys and 0.05–0.13

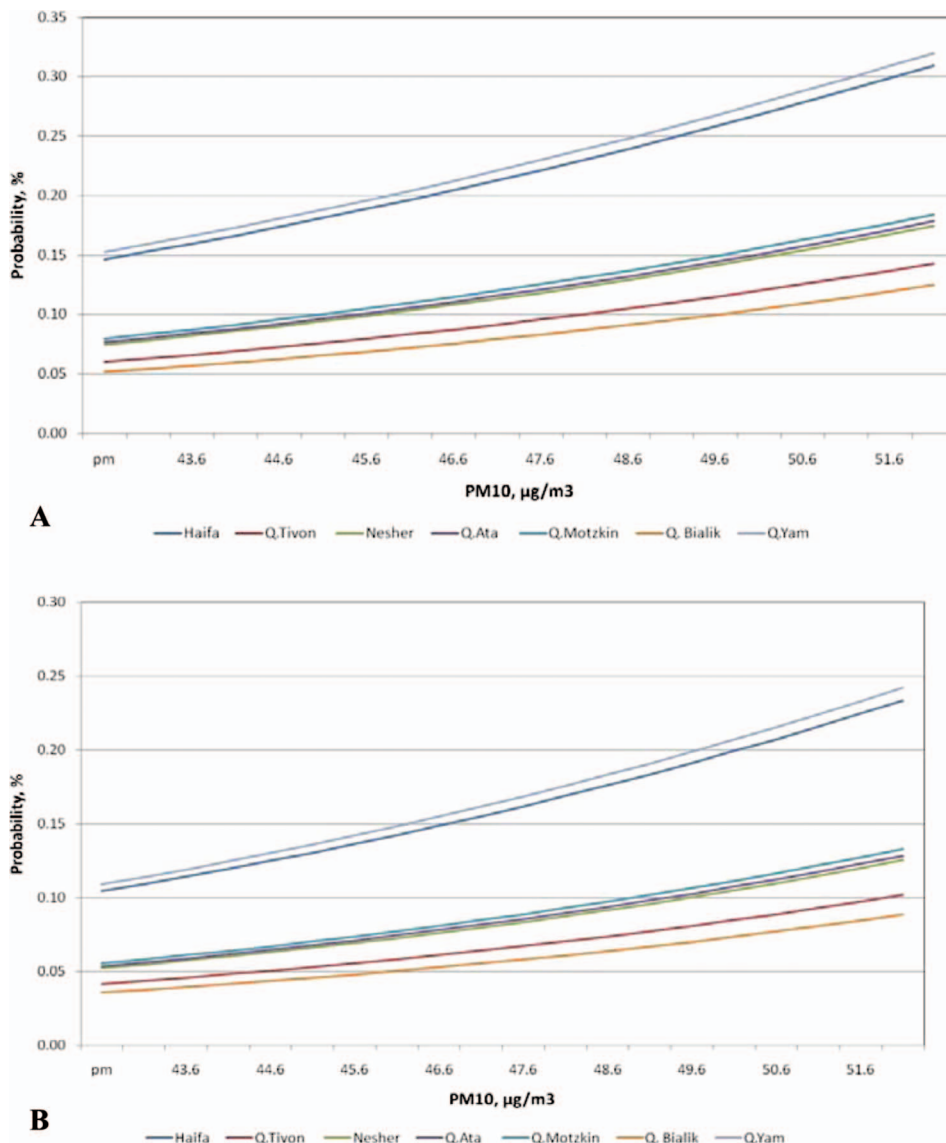


Figure 2. Probability change in asthma morbidity as a function of plausible changes in PM₁₀ levels (model sensitivity test) A – Males; B – Females. Note: Based on the BMA model reported in Table 5.

for girls, with children residing in Haifa and Qiryat Yam exhibiting the highest probabilities of asthma morbidity.

Discussion

The prevalence of asthma in the GHMA was found to be substantially higher than average asthma prevalence countrywide (16% in GHMA vs. 7% in the country as a whole; $P < 0.001$). Our asthma rate estimates appear to be also higher than asthma prevalence (10%) reported by the Clalit Health Services or revealed in a previous study by Goren et al. (1990). These large differences cannot solely be attributed to differences in asthma definition, since our study did not include self-reported symptoms of wheezing or whistling as a definable criterion of asthma, but only the diagnosis of asthma recorded by a physician, or defined according to the medical treatment a child received. These criteria are comparable with asthma definitions used in previous studies in Israel and abroad, and are usually lower than self-reported asthma symptoms by individuals (Castro-Rodriguez and Lemanske 2001; Raftery et al. 2005; Romano-Zelekha et al. 2007; Patel et al. 2008). A more likely explanation is an increase in the number of asthmatic children the study area in recent years, that is, between the late 1980s (Goren et al. 1990) and 2009, when the present study was carried out.

In addition, the study revealed considerable differences in asthma prevalence between the residential communities forming the study area: 8.7% in Qiryat Tivon vs. 21.4% in Qiryat Yam ($P < 0.05$). These differences cannot be attributed to unequal access to health services, since all the survey participants are members of the same HMO (the Clalit Health Services), with the same health insurance plan offered according to the 1995 National Health Insurance Law.

In recent years, the hypotheses that air pollution (in interaction with other environmental and genetic factors) may contribute not only to the exacerbation of existing asthma symptoms, but also to the onset of asthma, gained strong support (Gauderman et al. 2005; Brauer et al. 2007; Clark et al. 2010; McConnell et al. 2010). Early studies of air pollution and respiratory morbidity (including asthma) concentrated on field measured air pollutants such as sulfur dioxide (SO_2), nitrogen dioxide (NO_x), ozone (O_3) and coarse particles (Patel and Miller 2009). According to the findings of several multi-city studies, there appears to be a short term-effect of SO_2 events on hospital admissions and exacerbation of asthma symptoms (Anderson et al. 1997; Barnett 2005). In particular, in several studies, in which SO_2 pollution was analyzed in two-pollutant model (jointly with PM_{10}), the inclusion of SO_2 as an additional explanatory variable reduced the strength of association between PM_{10} and hospital admissions with asthma symptoms (Atkinson et al. 2001; Sunyer et al. 2003). However, studies carried out elsewhere did not reveal any conclusive evidence about SO_2 association with asthma prevalence (Hwang et al. 2005; Akinbami et al. 2010; Penard-Morand et al. 2010), whereas a strong association between traffic-related pollution by NO_x , PM_{10} , and $\text{PM}_{2.5}$ and asthma prevalence (and more recently asthma incidence) was detected by several studies (Gauderman et al. 2005; McConnell et al. 2005; Brauer et al. 2007; Jerrett et al. 2008; Morgenstern et al. 2008; Clark et al. 2010; McConnell et al. 2010).

Although several air pollutants may simultaneously be present in the air, the associations between some of them and the observed health effect may, in fact, be spurious, as the present study demonstrates. Thus, for instance, when the SO_2 and

PM₁₀ variables were introduced in the multivariate models separately, both of them emerged as statistically significant (see Table 3). However, only the latter variable (i.e. PM₁₀) exhibited a high posterior probability of affecting childhood asthma in the BMA analysis (Table 5). A similar conclusion could also be reached from the traditional logistic model, in which these two air pollutants were introduced simultaneously (see Table 3; Model 3). The weak statistical significance and unexpected sign of the SO₂ variable in this model clearly indicated that this variable should not be included in the model if PM₁₀ is included. Thus, presuming that only the former variable (i.e. SO₂) was available for the study, the analysis would have flagged it as significantly associated with childhood asthma, a clearly spurious outcome. This result thus emphasizes the importance of jointly looking at various air pollutants in multi-pollutant models.

Another conclusion which can be drawn from the results of the present study relates to the importance of local variations in childhood asthma prevalence. As our analysis indicates, several township indices emerged as highly statistically significant, despite the fact that individual-level confounders (such as families on welfare and road proximities in the townships) were controlled. The emergence of these local indicators as significant predictors of asthma morbidity may be explained by the presence of missing confounders, such as, background smoking, parental stress or local variations in housing densities (Shankardass et al. 2009; Northridge et al. 2010).

However, there is another possibility. The introduction of these local effects may have compensated for the lack of variation of some factors' values within local areas. For instance, in any of our models, the proximity to the main road variable did not emerge as statistically significant. Concurrently, the town of Qiryat Yam, in which nearly 71% of all children surveyed live in close proximity to main roads, was singled out as deviating significantly from the rest of the sample. The use of this township's dummy might thus have compensated for the lack of local variation of the values of the road proximity variable in this township, by separating it from the rest of the sample.

Although previous studies carried out in Israel did not find exceeded asthma morbidity linked to air pollution (Goren and Hellmann 1997; Peled et al. 2001), our analysis revealed that childhood asthma morbidity in the study area is significantly related to the local variations in the levels of air pollution by particular matter (PM₁₀; $P < 0.001$). These differences in findings may have several possible explanations.

Designed as a large-scale cross-sectional study, our study was based on a large sample of about 4000 schoolchildren with available health records, thus resulting in a good statistical power. Second, most previous studies carried out in Israel and abroad were based on zonal approaches to the estimation of exposure, according to which the same exposure levels are assigned to all residents of relatively large statistical areas or townships (Goren et al. 1990; Goren and Hellmann 1997; Peled et al. 2001; Elliott et al. 2004). Conversely, in our analysis, we used the recently developed IEE approach. According to several previous studies, this approach helps to provide more sensitive "air pollution–health outcome" estimates and minimizes misclassification of exposure (Portnov et al. 2007; Patel and Miller 2009).² Lastly, we used in our analysis the recently developed BMA approach, which takes into account an uncertainty associated with model selection process, which may have also contributed to the robustness of the study's results.

A somewhat surprising result of the present study is that childhood asthma morbidity appears to vary considerably across townships located a few kilometers apart from each other. Thus, the highest prevalence of asthma (21.4%) was found in the town of Qiryat Yam, while relatively low rates of asthma were detected in the town of Qiryat Tivon (8.7%). These local differences may be attributed to different residential conditions of families (crowded multi-story buildings in Qiryat Yam vs. spacious villas and single family houses in Qiryat Tivon) and parental smoking habits, often associated with family welfare (Sanders et al. 2009; Centers for Disease Control and Prevention 2010). These differences should become a challenge for public health and welfare policy, by guiding it towards a reduction in local income disparities.

The influence of air pollution on asthma morbidity has been supported by empirical evidence accumulated during past years (Gauderman et al. 2005; Brauer et al. 2007; Clark et al. 2010; McConnell et al. 2010; Penard-Morand et al. 2010). According to several recent studies, high-income neighborhoods tend to exhibit low asthma prevalence, while ambulatory visits to the physician for asthma were found to be associated with air pollution and disproportionately increased among low-income socio-economic groups (Burra et al. 2009; Gupta et al. 2009; Subramanian et al. 2009). The results of the present analysis provide additional evidence for the presence of such general linkages.

The large differences in asthma prevalence between regions or countries are well documented (Asher et al. 2006; Lai et al. 2009). However, such differences are rather unusual for small geographic areas (e.g. townships), such as those detected by the present study. Possible explanations include social-economic disparities between communities, with low socio-economic strata suffering more from air pollution, reflecting the phenomenon known as “environmental injustice” (Neidell 2001; Wheeler and Ben-Shlomo 2005; Subramanian and Kennedy 2009).

The present study has several limitations which should be mentioned. First, as we previously noted, medical records of schoolchildren were obtained from the “Clalit” HMO, while medical records of children serviced by other, smaller HMOs (such as “Maccabi”, “Meuheded” and “Leumi”) were unavailable for the study. However, as our analysis indicated, the schoolchildren covered by the study are representative of the entire age cohort of children residing in the study area in terms of gender and age ($P > 0.5$). In addition, asthma prevalence recorded by “Clalit” and other HMOs do not appear to differ significantly (Bibi, unpublished data). It should also be noted that in our analysis, SO_2 and PM_{10} air pollution estimates were controlled for several individual-level confounders, such as gender, age, family’s welfare status (i.e. receiving welfare support), and proximity to main roads. In addition, individual townships were represented in the analysis by dichotomous (indicator) variables, aimed at capturing local differences in housing conditions, building density and other localized factors, not directly covered by the analysis.

Parental smoking is missing from our study, due to data unavailability in the HMO children records. However, we partially controlled for this confounder by including the socio-economic status variable (families on welfare). As found in several studies, low welfare levels are strongly associated with smoking in western countries, including Israel (Richter et al. 2009; Baron-Epel et al. 2010; Doku et al. 2010).

Limitations of a cross sectional design (i.e., the unknown time of exposure, smoking habits and other confounding factors) are also well known. These limitations did not allow us to formulate causal associations. Such inferences may

be obtained by a follow up analysis of the same children cohort in the future, thus helping to determine causal relationships between asthma morbidity, air pollution and community influence.

Lastly, we should note that our findings may be applicable to other urban areas of the country with similar demographic and socio-economic characteristics of residents and comparable levels of air pollution. However, follow-up studies are needed to verify this assumption.

Conclusions

According to the results of the present analysis, the prevalence of asthma in our study area surpasses the rates of childhood asthma in the country as a whole by more than twofold: 16% vs. 7% ($P < 0.001$). In addition, the rates of childhood asthma are found to differ across communities forming the study area, ranging from 8.7% in a wealthy town of Qiryat Tivon to 21.4% in the densely populated suburban town of Qiryat Yam. The study also revealed that asthma morbidity is related to air pollution by Particulate Matter (PM₁₀) at the places of the children's residences.

Our analysis of childhood asthma risk factors using traditional logistic regression and the more recently developed BMA tools lead us to a conclusion that the patterns of PM₁₀, air pollution are a significant factor affecting the local variation of childhood asthma morbidity. Thus, when using multivariate analysis tools and considering a change in PM₁₀, between the least and most polluted areas in our study (9.4 $\mu\text{g}/\text{m}^3$) the corresponding OR, calculated using the BMA analysis, is OR = 2.584 (with 95% posterior probability limits of 1.515–4.409), controlled for gender, age, proximity to main roads, the town of a child's residence, and family's socio-economic status. This indicates that the relative risk of childhood asthma tends to increase, *ceteris paribus*, by an average of about 11% per 1 $\mu\text{g}/\text{m}^3$ of increase in the level of PM₁₀, air pollution, which is comparable to those previously reported in epidemiological literature (cf. e.g. McConnell et al. 2010).

Characteristically, the above linkages between childhood asthma morbidity and air pollution are detected for relatively low levels of PM₁₀ pollution – 47.6 $\mu\text{g}/\text{m}^3$ (see Table 1) vs. the average value of 60 $\mu\text{g}/\text{m}^3$, stipulated, as permitted annual maximum, by air pollution standards in Israel (ImEP 2011) and 55–70 $\mu\text{g}/\text{m}^3$ in several other developed countries (see *inter alia* (EPD 2010)). This result should thus be a cause for concern for public health and environmental policy-makers, urging them to revisit the efficiency of the local air pollution regulations.

We should emphasize, however, that, as mentioned previously, there are estimation errors, resulting from the interpolation of PM₁₀ values, which may influence our results. In particular, as Figure S1 shows (see the Supplementary materials section), the standard errors (SEs) of the estimate appear to be higher in peripheral parts of the study area that have no PM₁₀ monitors and where PM₁₀ values were obtained by extrapolation (e.g. in the town of Qiryat Tivon), than in Haifa and its immediate suburbs, where PM₁₀ monitors are installed. For example, as Figure S1 shows, the SEs in Qiryat Tivon are estimated at about 5.4 $\mu\text{g}/\text{m}^3$. The resulting 95%CI of PM₁₀ estimates for this location thus ranges between 38.6 and 58.6 $\mu\text{g}/\text{m}^3$ ($X \pm \text{SE} \times 1.96$). Although the SEs are smaller in Haifa, where most of the children covered by our survey (about 70%), reside, the error range for this location is also relatively large (95%CI = 46.2 $\pm$ 8.2 $\mu\text{g}/\text{m}^3$). It should be kept in mind, however, that these errors are non-differential errors, that is, errors not

necessarily leading to the overestimation of PM_{10} effects on asthma prevalence. In other words, although our study suggests that there is a significant PM_{10} -attributed effect on asthma prevalence, the strength of this effect does have some assessment errors associated with it. A possible way to minimize such errors would be to install more air quality monitors in the study area in the future. This should, in our view, become an object of public policy intervention.

Lastly, it should be noted that the elevated prevalence of childhood asthma, we observed in relatively poor townships, should alarm public welfare authorities, justifying possible intervention, especially among the weakest socio-economic groups.

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Notes

1. Recent publications documented overweight and obesity as risk factors for childhood asthma [see *inter alia* Camargo et al. 1999; Redd et al. 2002; King et al. 2004]. The analysis was therefore also run independently for 2024 children ($\sim 52\%$) with available body mass index (BMI) data. However, this index did not emerge as statistically significant ($P > 0.3$) and the BMI – based models were found to be essentially similar to the non-BMI models. Two models, in which BMI is included as an additional explanatory variable, can be found in the Supplementary material section.
2. It should be acknowledged that the IEE approach performs best when the number of air quality monitors is large. However, as previously mentioned, in our study area, we had only 14 monitors for SO_2 and seven monitors for PM_{10} . Yet, using this (albeit restricted) number of air pollution observations may, nevertheless, be preferable to aggregating them into zonal averages, considering that some of our townships (i.e. Haifa) have several monitors while others (e.g. Qiryat Motzkin) have none.

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