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THE USE OF CHAINED TWO-POINT CLUSTERS FOR THE EXAMINATION OF ASSOCIATIONS OF AIR POLLUTION WITH HEALTH CONDITIONS

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Abstract
Objectives: There are a few accepted and intensively applied statistical methods used to study associations of ambient air pollution with health conditions. Among the most popular methods applied to assess short term air health effects are case-crossover (using events) and time-series methodologies (using counts). A few other techniques for studying counts of events have been proposed, including the Generalized Linear Mixed Models (GLMM). One suggested GLMM technique uses cluster structures based on natural embedded hierarchies: days are nested in the days of a week (dow), which, in turn, are nested in months and months in years (< dow, month, years >). **Material and Methods:** In this study the authors considered clusters with hierarchical structures in a form of < dow, 14-days, year >, where the 14-days hierarchy determines 7 clusters composed of 2 days (the same days) of a week (2 Mondays, 2 Tuesdays, etc.), in 1 year. In this work the authors proposed hierarchical chained clusters in which 2 days of a week are grouped as follows: (first, second), (second, third), (third, fourth) and so on. Such an approach allows determination of an additional series of the slopes on the clusters (second, third), (fourth, fifth), etc., i.e., estimation of the coefficients for other configurations of air pollutant levels. The authors considered a series of 2 point chained clusters covering a year. In such a construction each cluster has one common data point (day) with another one. **Results:** The authors estimated coefficients (slopes) related to the ambient ozone exposure (mortality) and to 3 selected air pollutants (particulate matter, nitrogen dioxide and ozone) combined into index and considered as health risk exposure (emergency department (ED) visits). The generated results were compared to the estimations obtained from the time-series method and the time-stratified case-crossover method applied to the same data. **Conclusions:** The proposed statistical method, based on the chained hierarchical clusters (< dow, 14-days, year >), generated results with shorter confidence intervals than the other methods.

Key words:
Ambient air pollution, Mortality, Case-crossover, Cluster, Relative risk, Odds ratio

INTRODUCTION

In studies of environmental epidemiology, there are a number of accepted statistical techniques used to estimate associations between ambient air pollution and health conditions, including the Generalized Additive Model (GAM) time series methods [1,2], Generalized Linear Mixed Models (GLMM) [3] and the commonly used, and widely accepted, case-crossover (CC) method [4,5].

The CC method uses individual events and is based on the case-control methodology. This design is useful when the risk exposure is both transient and has transitory occurrences. For each case, a period of time (case window) during which the individual was considered a case is defined.

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Most frequently this window is just a single day: the day on which an event occurred. In a similar way, a period of time (the control window) in which the person was not a case is determined. Risk exposure during the case time-window is compared to the risk exposure during the control time-window. In the CC design for individual cases, matched controls are also included, usually with a few days defined as controls for one case day.

The most popular technique for matching the controls is a time-stratified approach: for a given event day, the other days of the same day-of-week for a given month are considered as the control days [5]. In the case of such an approach we have 3 or 4 control days, depending on the particular calendar month, with the number depending on the particular day-of-week and length of a month for the considered calendar year (28–31 days). Thanks to such a design, modeling the effects of week days which must be accounted for in the time series methods may be avoided. In this paper we used the CC method as a baseline for comparison with the new proposed approach.

One of the possible methods for studying the count of events is the methodology based on the GLMMs [3]. This methodology was proposed to be used on naturally occurring hierarchical clusters defined by a 12-month annual calendar. The following embedded structures were considered: days were grouped by days of a week (dow), then days of a week were grouped by month and the months were grouped by years, defining the structure < dow, month, year >, which organized the days of the study into hierarchical clusters. Such grouping is very similar to that used in the CC method: in both methods we would consider the same days of a week in one month.

In general, in the domain of air pollution and health, we have 2 main (important and antagonistic) axis-factors: time and exposure. Both considered methods (the CC technique and GLMM based on hierarchical clusters) "cut" time into monthly segments. In the case of each such a chunk of time (one month), the regression is performed only with respect to one factor, which is air pollution level, thus, eliminating the time variable. The time is managed by clusters or, in the case of the CC method, by the time-window (one month or others).

We know that 2 data points are necessary to uniquely determine a line. Consequently, we may consider the minimal hierarchical structure of the form < dow, 14-days, year >, which has only 2 points in the second level, rather than the hierarchy based on one month, which uses 3 or 4 points. When applying the < dow, 14-days, year > approach we have a series of 2 point (day) clusters defined by year in the study period, as in the study of Szyszkowicz [3], with the years being considered independent of one another.

In this work we proposed a chained structure for such 2 point hierarchical clusters, so that 2 neighboring clusters, i.e., the 2 closest pair by time, always have one common day. For example: the first and second Monday in January and the second and third Monday in January are 2 separate clusters but with one common day, which in this case is the second Monday of January. Defining such a series of clusters for a given year, each particular day-of-week is a member of 2 clusters – one in which it is the first temporal point (with a point following it), and one in which it is the second temporal point (with a point preceding it).

This is the same philosophy as that used by any clustering algorithm, except for the fact that we have deliberately used every possible temporal pairing of days-of-week, rather than offsetting by one as in the previous two-week (non-chained) cluster approach. By applying the mixed-model regression to these two-point chained clusters, we expected to obtain more stable results than the motivating technique by Szyszkowicz [3], as our sample size is two times larger. The proposed technique doubles the number of the constructed clusters.

MATERIAL AND METHODS

To compare the proposed method (chained clusters within a GLMM framework) with previously published approaches, we used 2 different health databases, with one set of data related to mortality, and the other set of data containing daily emergency department (ED) visits for certain conditions originating in the perinatal period. Both data are real.

The mortality data have been used in a number of other studies under the banner of the Air Health Indicator project [6,7] and constitute a robust and well-understood data set. The data for ED visits were used as example data for an illustrative purpose only, with no claims as to biological viability, and are an extension of the data considered in the study of Zemek et al. [8].

We considered the daily counts of health events (number of deaths, number of ED visits) as health outcome measurements. For the CC method we used individual events (deaths, visits) rather than their daily counts. Environmental data, ambient air pollution and weather factors were also considered on a daily basis.

Mortality and ED data

Daily mortality counts recorded in Toronto, Ontario, Canada reported over the years 1984–2007 (24 year, or 8766 days), with primary cause of death related to cardio-pulmonary conditions were considered as epidemiological health data. Mortality data were classified with an underlying cause of death encoded using the International Classification of Diseases, 9th revision (ICD-9, World Health Organization (WHO) 1977), for deaths before 2000 and using ICD-10 (WHO 1992) for deaths registered from 2000 onward [9,10].

Under ICD-9, cardio-pulmonary mortality was considered to be a combination of circulatory and respiratory conditions, with ICD codes 390–520. Under ICD-10, cardio-pulmonary is considered to be all codes beginning with I or J, as well as a small number of G, M and R codes, on the basis of expert physician advice.

On average, Toronto experienced almost 20 deaths per day, with observed maximum deaths of 48 and minimum of 4. For this mortality set, the size of the database was dictated by availability, with this set consisting of all time periods released by the Statistics Canada for the city of Toronto.

As a second set of health data set we used ED visits for problems starting during perinatal periods. The data were obtained from 5 hospitals in Edmonton, Alberta, Canada, and due to restriction dictated by availability of air pollution data and consistency of ICD coding, they were considered for the period between 17 April 1998 and 31 March 2002 (1379 days). We used ICD-9 codes 760–779 to identify cases in the database diagnosed as "certain conditions originating in the perinatal period," including: birth trauma, hypoxia, infection and many others [9]. In total, we identified 2521 cases with the highest frequency occurring for ICD-9 code 774 (jaundice) with 1079 observed number of cases (43% of total). Note that the transition to ICD-10 occurred after the end of the period of interest, so we did not require 2 sets of codes.

The results included in this work are not meant to represent scientific findings on ED visits, but are presented as an illustrative example for the use of the presented statistical method: if other accepted methods provide similar results for associations between pollution and health, this strengthens the viability of the chained cluster approach. In addition, the considered in the study data set has been used in a previous study [8] and was found to be robust and interesting.

Air pollution data

For acute air pollution exposure and its association with mortality in Toronto, ambient ozone was considered. It has previously been observed to have strong associations [11–14] with both all-cause and cardio-pulmonary mortality. The levels of exposure were calculated as the maximum of each day's set of 8-h average concentrations. For these daily maximums, the mean level was 30.4 ppb, with standard deviation (SD) = 15.7 ppb, minimum = 0.7 ppb, and maximum = 111.4 ppb. In our study of mortality we used the same day exposure (lag 0) for ozone, as this lag was found to have a high association in previous studies.

In Edmonton (perinatal ED visits) we considered 3 ambient air pollutants (see [8] for a full description of air pollutants in Edmonton), i.e., ozone, nitrogen dioxide (NO_2) and particulate matter ($PM_{2.5}$, no greater than 2.5 microns in diameter). These 3 pollutants have been shown by Zemek et al. [8] to have a significant association with otitis media, so considering their association with perinatal conditions is reasonable, and additionally have been combined to define a risk index known as the Air Quality Health Index (AQHI) [15].

This AQHI index is based on weighted values of the mentioned above air pollutant levels and was calculated hourly (24 values per day) based on a rolling three-hour pollutant concentration. In the estimation of an association with ED visits, the risk index was represented as its daily mean, similar to the representation for the mortality data above. Previous research has shown that daily means are associated more strongly with childhood morbidity data [8,14], as compared to daily minimums or maximums, which led us to choose the daily mean as our input in this model.

Our main goal in this paper was to present a new methodology, thus, we used this risk index only as a proxy for exposure to a mixture of air pollutants. We considered a series of exposures to the risk index lagged 0–20 days. The risk index (RI) was calculated according to the following formula (obtained from the standard AQHI formulation, see [15] for details):

$$RI = \frac{1000}{10.4}\left(e^{0.000871 \times NO_2} + e^{0.000537 \times O_3} + e^{0.000487 \times PM_{2.5}} - 3\right) \quad (1)$$

where:

NO_2 – nitrogen dioxide,

O_3 – ozone,

$PM_{2.5}$ – particulate matter no greater than 2.5 μm in diameter.

Statistical method

The GLMM technique of Szyszkowicz [3] was applied to hierarchical clusters. Random intercept and fixed slope GLMMs were assumed in the constructed models, with the fixed slope assumed to be an underlying (shared) risk, and the random intercepts included to account for seasonal and other variations in the mean levels of the counts.

We generated clusters using a natural embedded structure of days in the calendar with the following 3-level hierarchies. In the first level of the hierarchy days are grouped by day of a week (dow). As the second level we considered 3 different cases:

– 1 month grouping – thus, 3 or 4 days,

– 2 weeks (14 days) – 2 days,

– 3 weeks (21 days) – 3 days.

These approaches were compared with the case, which is the main proposition of this paper:

– 2 weeks with a chained structure of the days.

In the chained structures, for each created cluster there exists another cluster paired to it, paired by one common day. In practice, we created 2 copies of our data (composed of calendar days, health outcomes and air pollutants) and in one copy we numbered each cluster by odd numbers (first 14 days get 1, next 14 days get 3, etc.). In the second copy we skipped the first 7 days (removed) and started to number the clusters by even numbers (the second and third week get 2, next 14 days get 4, etc.). We merged 2 files and the resulted file contains clusters labeled 1 and 2 with common second week, clusters labeled 2 and 3 have third common week, etc.

The CC method was implemented using the Cox proportional hazard regression (PHREQ) procedure in the Statistical Analysis System (SAS) software environment, version 9.3 [16]. The GLMMs were fit using the GLMM-penalized quasi-likelihood (glmmPQL) function from the Modern Applied Statistics with S (MASS) [17] package for the R [18] environment for statistical computing, version 3.0.1.

We used temperature and relative humidity as weather factors, included via natural cubic spline links with 3 degrees of freedom (df). Statistical significance was assumed at the level of p-values < 0.05. The results for ED visits, produced using the CC models, were reported as odds ratios (OR) and their corresponding 95% confidence intervals (CI). The estimated values were presented for an increase of the risk index by one unit [14,15]. The results from the glmmPQL function were reported as the coefficient (slope) related to the air pollutant of interest. Also for mortality data, the results from the CC models were presented in the same form. The 95% confidence intervals were calculated for the estimated slopes.

In addition, for comparison purposes only, we estimated the annual risk due to ozone via a traditional generalized additive model (GAM) framework, in the style of the studies by Dominici et al. [1,2]. This approach (GAM) was considered for the purpose of comparing our new methodology with a different statistical methodology, which accounts for time in a different fashion (via the smooth function of time inclusion). Formally, the model is (with temperature included in the model):

$$\log(y_t) = \beta_0 + \beta x_t + S_1(\text{temp}, \text{df} = 3) + S_2(\text{time}, \text{df} = 7/\text{year}) \quad (2)$$

where:

$\log(y_t)$ – Poisson distribution with $E[Y_t] = y_t$, where Y_t are the daily number of counts,

β_0 – an intercept,

βx_t – the association between air pollution, a slope,

$S_1(\ )$ – a natural cubic spline link with 3 df, and terms for day-of-week,

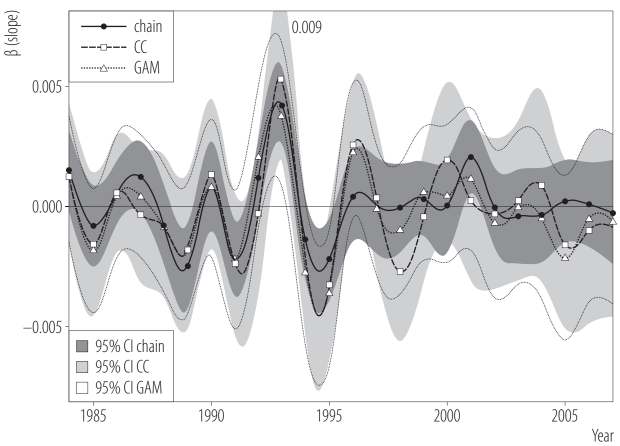
$S_2(\ )$ – a smooth function of time (again a natural cubic regression spline with 7 df/year) also included, as is the standard approach. A Poisson family link was used.

The proposed method was also tested on 4 sets of simulated data, created as in the study by Burr et al. [19] and compared with 8 different time-series methods.

RESULTS

Mortality data

The results are presented in a form of 2 figures. Figure 1 and Table 1 show the results from the CC method and the GLMM method on chained hierarchical structures applied to mortality in Toronto, with the GAM annual risks also plotted. The values were calculated for each year separately and Figure 1 represents corresponding 24 years, each with a slope and 95% CI. Figure 2 shows more details concerning the years: 1984, 1993, 1996, 1998, and 2001. For these years, we present the results obtained using 5 methods (GLMMs on 2 week clusters (W12), 3 week clusters (W123), chained 2 week clusters (W1223), month clusters, and the case-crossover method). Figures 1 and 2 lead to 2 conclusions. The first (from Figure 1) is that the CC and W1223 (chained two-week clusters) approaches are similar and track the GAM method from 1984 to the mid-to-late 1990s. After this point, all three methods start to diverge. This divergence has been observed before, and is a current topic of research, with no explanation for this phenomenon. As the GAM and CC methods are the two most common approaches for estimation of acute risk due to air pollution, the close



CC – case-crossover; GAM – generalized additive model;
CI – confidence interval.

Fig. 1. Mortality in Toronto between 1984–2007

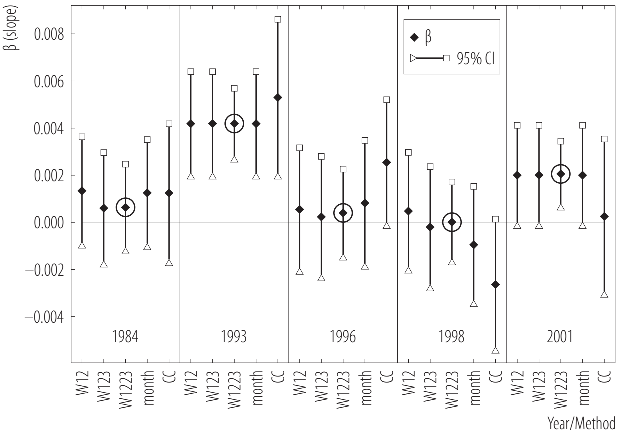
Table 1. Estimated risks (slopes) and standard errors (SE) for the 3 methods (CC, chained clustering GLMM, and GAM), for Toronto, Ontario, 1984–2007*

Year	Method					
	CC		chained clustering GLMM		GAM	
	slope	SE	slope	SE	slope	SE
1984	1.245×10^{-4}	1.510×10^{-3}	1.448×10^{-3}	8.337×10^{-4}	1.128×10^{-3}	1.381×10^{-3}
1985	-1.565×10^{-3}	1.486×10^{-3}	-7.893×10^{-4}	8.441×10^{-4}	-1.822×10^{-3}	1.281×10^{-3}
1986	5.292×10^{-4}	1.225×10^{-3}	5.678×10^{-4}	6.695×10^{-4}	4.181×10^{-4}	1.172×10^{-3}
1987	-3.501×10^{-4}	1.397×10^{-3}	1.235×10^{-3}	7.410×10^{-4}	4.124×10^{-4}	1.240×10^{-3}
1988	-8.374×10^{-4}	1.483×10^{-3}	-7.666×10^{-4}	8.370×10^{-4}	-8.690×10^{-4}	1.305×10^{-3}
1989	-1.832×10^{-3}	1.622×10^{-3}	-2.473×10^{-3}	8.953×10^{-4}	-1.761×10^{-3}	1.426×10^{-3}
1990	1.324×10^{-3}	1.555×10^{-3}	8.277×10^{-4}	9.281×10^{-4}	7.969×10^{-4}	1.428×10^{-3}
1991	-2.368×10^{-3}	1.481×10^{-3}	-2.132×10^{-3}	7.848×10^{-4}	-2.206×10^{-3}	1.345×10^{-3}
1992	-2.886×10^{-4}	1.678×10^{-3}	1.196×10^{-3}	8.461×10^{-4}	2.030×10^{-3}	1.533×10^{-3}
1993	5.337×10^{-3}	1.719×10^{-3}	4.189×10^{-3}	8.190×10^{-4}	3.739×10^{-3}	1.578×10^{-3}
1994	-2.717×10^{-3}	1.503×10^{-3}	-1.370×10^{-3}	8.946×10^{-4}	-2.736×10^{-3}	1.385×10^{-3}
1995	-3.233×10^{-3}	1.581×10^{-3}	-2.174×10^{-3}	8.742×10^{-4}	-3.608×10^{-3}	1.510×10^{-3}
1996	2.544×10^{-3}	1.360×10^{-3}	4.093×10^{-4}	9.412×10^{-4}	2.254×10^{-3}	1.294×10^{-3}
1997	3.599×10^{-4}	1.564×10^{-3}	4.810×10^{-5}	1.003×10^{-3}	-9.474×10^{-5}	1.453×10^{-3}
1998	-2.709×10^{-3}	1.434×10^{-3}	-5.300×10^{-5}	9.288×10^{-4}	-9.020×10^{-4}	1.340×10^{-3}
1999	-4.289×10^{-4}	1.390×10^{-3}	3.250×10^{-4}	7.749×10^{-4}	5.477×10^{-4}	1.252×10^{-3}
2000	1.936×10^{-3}	1.615×10^{-3}	3.900×10^{-5}	9.852×10^{-4}	5.196×10^{-4}	1.461×10^{-3}
2001	2.574×10^{-4}	1.697×10^{-3}	2.053×10^{-3}	7.674×10^{-4}	1.141×10^{-3}	1.531×10^{-3}
2002	-2.775×10^{-4}	1.561×10^{-3}	-4.760×10^{-5}	8.396×10^{-4}	-6.944×10^{-4}	1.457×10^{-3}
2003	2.546×10^{-4}	1.657×10^{-3}	-3.947×10^{-4}	9.770×10^{-4}	-5.265×10^{-5}	1.582×10^{-3}
2004	8.436×10^{-4}	1.988×10^{-3}	-3.522×10^{-4}	9.778×10^{-4}	-5.078×10^{-4}	1.776×10^{-3}
2005	-1.569×10^{-3}	1.746×10^{-3}	2.174×10^{-4}	8.659×10^{-4}	-2.130×10^{-3}	1.618×10^{-3}
2006	-9.851×10^{-4}	1.933×10^{-3}	9.460×10^{-5}	8.844×10^{-4}	-5.334×10^{-4}	1.792×10^{-3}
2007	-7.453×10^{-4}	1.911×10^{-3}	-2.085×10^{-4}	1.079×10^{-3}	-5.345×10^{-4}	1.718×10^{-3}

GLMM – the generalized linear mixed model.
Other abbreviations as in Figure 1.
* Models use ozone and cardio-pulmonary mortality as common elements.

agreement during the stable portion of time (1984–1995) is encouraging, and indicates that the new chained clustering method is viable with respect to the mean risk.

The second conclusion (from Figure 2) is that the W1223 method compares well with all the other clustered GLMM approaches. As the clustering approach is a simple alternative to the CC approach, developed to compensate for some of the variability issues of the CC approach (see [3] for details), and the W1223 chained cluster GLMM appears to estimate the mean risk centered in the distribution of varying control group sizes (W12, W123, month), this promotes the result that the chain clustering approach can replace hierarchical clustering methods, which have the issue of choosing the size



W12 – 2 point clusters (14 days); W123 – 3 point clusters; W1223 – chained 2 point clusters; month – clusters with monthly grouping in the structure < days of week (dow), month, year >.
Other abbreviations as in Figure 1.

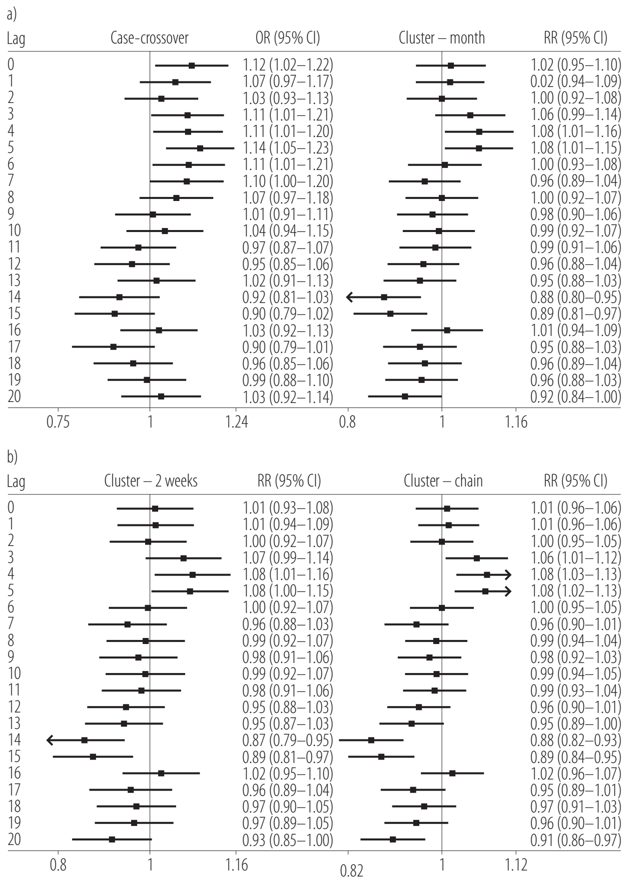
Fig. 2. Mortality in Toronto in the years 1984, 1993, 1996, 1998, and 2001

of the second level. In other words, rather than estimating W12, W123, W1234 (or W-monthly), etc., and rather than examining the results year-by-year to determine their overlap, we can simply estimate W1223 (chained clusters) and have a reasonable estimate of their mean effect – that is, their mean risk. As the risk is the goal of this estimation procedure, this result is appealing.

Emergency department data

The results for perinatal ED visits in Edmonton are summarized in Figure 3. The figure shows the results obtained using 4 different methods (the CC method and the GLMMs based on three types of clusters: one-month, two-week, and chained two-week) for a large range of lagged exposures 0–20 days, presented as relative risks (RR) for one unit increase in the risk index. In general, the results agree quite well, with lags 3, 4 and 5 days being positive and significant (or nearly so) for all the 4 approaches. Similarly, lags 14 and 15 are negative and significant for the three GLMM methods, and negative (but not significant) for the CC approach. In other words, the lag-trend of all the 4 methods agree: positive risks in early lags, leading up to a significant association at and around 3–5 day-lags, mostly zero association through lags 6–12, and then, a negative (possibly significant) association at and around lags 14–15. In addition, all three GLMM methods show a decreasing trend at lag 20, although we assign no interpretation to this. Finally, while the CC method indicates a positive and significant risk at lag 0, none of the GLMM methods agree, including the new chained cluster approach.

For lag 5 we included Table 2. It contains more detailed results from the GLMM used on chained two-week,



OR – odds ratio.
Other abbreviations as in Figure 1, Table 1 and 2.

Fig. 3. Emergency department visits in Edmonton:
a) the CC method and GLMM on 1 month,
b) GLMM on 2-week and chained 2-week

Table 2. Detailed estimations for perinatal emergency department (ED) visits (lag 5 days)

Method	Slope	SE	RR	95% CI	Variance		
					var-dow (SE)	var-week (SE)	var-year (SE)
W1223	0.074	0.027	1.077	1.021–1.135	0.052 (0.026)	0.026 (0.013)	0.003 (0.004)
W12	0.076	0.038	1.079	1.002–1.162	0.054 (0.037)	0.030 (0.018)	0.001 (0.004)
Month	0.078	0.038	1.081	1.004–1.165	0.051 (0.028)	0.015 (0.014)	0.001 (0.004)

SE – standard error of the slope; RR – relative risk (= exp(slope)); var – variance estimated (random effects) for the 3 levels of the clusters.
Other abbreviations as in Figure 1 and 2.

two-week, and one-month clusters. The table presents estimated variances for the 3 levels of the hierarchical clusters (e.g., dow, week, year). In parentheses with the variances their standard errors are included.

Simulated data

In addition, we tested our method using 4 sets of simulated data as originally developed in a recent paper of the second author [19]. Estimating slopes (effectively, risks) for these 4 sets of realizations we obtained the results contained in Table 3, with arithmetic average slopes and their standard deviation given, computed across 250 realizations for each simulation. In all the 4 cases the true slope was set to be $\beta = 1.0$. Our method out-performed the most commonly used time-series method (natural cubic spline time smoothers with 6 degrees-of-freedom per year) due to the lack of robustness of that method to seasonality. In fact, the two-point chained cluster method was comparable to the 12 df/year time-series method, while being comparable in complexity.

DISCUSSION AND CONCLUSIONS

The main goal of this work was to present a new statistical method for estimation of air pollution effects on health, here measured as mortality and perinatal ED visits. The proposed technique is inspired by a previously developed statistical methodology based on the GLMMs [3]. The main objective of this paper was to propose the possibility of using two-point chained clusters in the hierarchical cluster structures < dow, 2-week, year >. Fixed slope and random intercept GLMMs on the considered clusters were constructed and estimated.

Table 3. Simulations (see [19]) for 3 models (NS(6), NS(12), and chains)*

Simulation	NS(6)		NS(12)		Chains	
	M	SD	M	SD	M	SD
Sim1	2.84×10^{-2}	7.87×10^{-3}	9.32×10^{-1}	2.66×10^{-3}	8.32×10^{-1}	3.44×10^{-3}
Sim2	6.42×10^{-2}	4.82×10^{-5}	8.37×10^{-1}	4.35×10^{-5}	7.60×10^{-1}	4.00×10^{-5}
Sim3	1.40×10^{-1}	1.28×10^{-2}	8.59×10^{-1}	6.82×10^{-3}	7.91×10^{-1}	5.05×10^{-3}
Sim4	-1.78×10^{-1}	1.80×10^{-2}	8.06×10^{-1}	9.56×10^{-3}	7.16×10^{-1}	7.06×10^{-3}

Sim – simulation; NS(6) – natural cubic regression splines with 6 degrees-of-freedom (df) per year; NS(12) – NS with 12 df/year.
M – mean; SD – standard deviation.
* For all 4 simulations the true slope is $\beta = 1$, and the presented mean and standard deviation are across 250 random realizations. The simulations are ranked in order of most seasonality; we clearly see that the NS time-series model with 6 df/year is not robust to this. By contrast, the chained CC method, while biased for all 4 simulations, is quite resistant to the contamination from seasonal effects, and is thus comparable to the NS time-series model with 12 df/year.

The results are generally comparable with previous methods, and are especially representative of the GLMM hierarchical clustering methods. In particular, they solve the problem of choosing the period for the GLMM approach, as the results indicate that two-point chained clusters well represent the average across common choices of period.

We conclude that the proposed method, i.e., the GLMMs on two-point chained clusters, may be used as an additional technique for estimating associations between air pollution and health outcomes, and in particular, is a sufficient replacement for the GLMM clustering methods, as it avoids the issue of period choice. The method may be applied to confirm results obtained using other methodologies such as the case-crossover or GAM time series approach, which is especially useful when considering changes in the risk over time, as many of those changes appear to act spuriously in one method only to be stable in another, the causes for which are an open topic of research.

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