Detecting Graded Exposure Effects: A Report on an East Boston Pregnancy Cohort

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Abstract

Introduction: The effects of tobacco exposure are typically examined by comparing groups based on a cut-score of self-reported number of cigarettes or bioassays collected in cross-sectional studies. This study introduces a new fuzzy clustering method that facilitates detection of subtle exposure effects by objectively deriving subgroups from modeling multidimensional exposure measures. We test the new method on a known exposure effect (fetal growth) and report on the graded exposure effect detected in a pregnancy cohort.

Methods: A total of 978 pregnant women were enrolled from 1986 to 1992 in the Maternal Infant Smoking Study of East Boston (MISSEB). Four kinds of exposure data were used to generate exposure groups: self-reported smoking, cotinine levels, nicotine levels, and nicotine dependence scores. Subgroups were identified via a comprehensive validation procedure. The results from MISSEB (number of exposure clusters, exposure effects on birth weight, body length, and head circumference) were compared with those obtained in a separate cohort.

Results: Using our new method in MISSEB, the same number of clusters was generated as previously, and graded exposure effects were again detected. Neonates with heavier exposure weighed less at birth relative to nonexposed neonates, with no difference between lighter-exposed and nonexposed neonates.

Conclusions: The same graded prenatal exposure effect emerges for known exposure-related outcomes across 2 different studies, about 2 decades apart. Our new method characterizes the degree of prenatal exposure, with the potential to help detect subtler effects on developmental outcomes, such as deficits in growth or development, neonatal temperament and behavior, and psychological functioning.

Introduction

Maternal self-reported number of cigarettes and bioassays are commonly used proxies to reflect the degree of prenatal tobacco exposure. Typically, the amount of exposure is quantified by comparing groups defined by a predetermined cut-score of the number of cigarettes or level of cotinine, for example, collected at a certain time in cross-sectional studies. However, smoking has varying and complex patterns across pregnancy, as many women underreport smoking, and smoking behavior across pregnancy varies substantially (e.g., Espy et al., 2011; Pickett, Rathouz, Kasza, Wakschlag, & Wright, 2005). Characterizing the degree of prenatal tobacco exposure is thus a significant challenge but an important step if researchers are to detect more nuanced exposure effects on offspring.

Dukic, Niessner, Benowitz, Hans, & Wakschlag (2007) developed a calibration method that adjusts self-reported smoking by cotinine values to address both underreporting and enhance measurement precision by capturing variation in smoking behavior across pregnancy. This integrated method resulted in improved prediction of outcome and also can be expanded to accommodate variations in maternal metabolism (Dukic, Niessner, Pickett, Benowitz, & Wakschlag, 2009). Fang, Johnson, Stopp, & Espy (2011) presented a new method that objectively derives subgroups of women with common patterns of smoking behavior across pregnancy by modeling multidimensional exposure measures. This new approach, called the “specially-designed multiple imputation-based fuzzy clustering method” (s-FCM), can be used even when there are missing values.

Using this method, Fang et al. (2011) detected a graded exposure effect on neonatal birth weight and neurobehavioral outcome in a sample of 361 women in the Midwest Infant Development Study (MIDS, R01 DA014661; Espy, PI). The

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MIDS dataset has four types of exposure data (22 exposure variables, where 9 had missing value rates ranging from 0.6% to 18.3%): self-reported smoking, maternal urine cotinine levels, nicotine by cigarette brand, and nicotine dependence scores. Using the s-FCM, three subgroups with distinct smoking behavior patterns across pregnancy resulted, which were labeled: nonexposed (NE, $N = 172$), lighter tobacco-exposed (ITE, $N = 140$), and heavier tobacco-exposed (hTE, $N = 40$).

Differences in birth weight were observed between the hTE ($M = 3,277.7$ g) and NE ($M = 3,431.6$ g) groups but not between the ITE ($M = 3,400.3$ g) and NE groups. Furthermore, on a standardized neonatal behavioral assessment (Riese, 1982) administered at birth, 2-, and 4 weeks of age, the s-FCM identified differences in the pattern of developmental change in irritable reactivity, again, with significant differences between hTE and NE but not between ITE and NE. The predictive power increased by at least 13% over the nonsignificant comparisons of exposure groups defined by traditional binary cut-score groupings (Espy et al., 2011).

These findings suggest that s-FCM may facilitate the detection of subtle exposure effects on a variety of smoking-related outcomes. To understand whether s-FCM has this utility, we need to test it further on known exposure-related outcomes (e.g., birth weight). Thus, the purpose of the present study is to examine if a similar number of exposure subgroups and a graded exposure effect can again be detected on perinatal growth outcomes by applying the s-FCM method to a study cohort, the Maternal Infant Smoking Study of East Boston (MISSEB, now followed as the East Boston Family Study; Pickett, Kasza, Biesecker, Wright, & Wakschlag, 2009; Wakschlag et al., 2011), with different exposure variables and participant characteristics (Pickett et al., 2008). Specifically, we hypothesize that as in MIDS, three subgroups will be identified: (a) heavier, (b) lighter, and (c) nonexposed and that these groups, particularly the heavier versus nonexposed groups, will differ in fetal growth outcomes. Since mixed results exist in the literature as to the significance of exposure effects on neonatal body length and head circumference (e.g., Conter, Cortinovis, Rogari, & Riva, 1995; Espy et al., 2011; Hardy & Mellits, 1972; Nelson, Jodscheit, & Guo, 1999), these effects may differ in MISSEB and MIDS.

Methods

Participants

MISSEB was a prospective cohort ($N = 978$ women) enrolled from 1986 to 1992, with the primary purpose of investigating the adverse impact of smoking during pregnancy on offspring respiratory function. Detailed recruitment and eligibility criteria are discussed in Pickett et al. (2005) and Wakschlag et al. (2009, 2011). Pickett et al. (2005) found considerable variation in patterns of maternal smoking across pregnancy in this sample.

Self-reported Measures, Biospecimen, and Perinatal Outcomes

At each prenatal visit, women reported current smoking, preferred cigarette brands, and nicotine dependence scores on the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Blood and urine samples were obtained for cotinine assays at each visit, and biospecimen analyses were conducted by radioimmunoassay (Wang, Van Vunakis, Sperizer, & Hanrahan, 1997). For the s-FCM, the

following variables were utilized: three trimester-specific averages of (a) nicotine levels in preferred cigarette brands, (b) self-reported cigarettes per day, (c) cotinine levels from maternal urine samples, and (d) cotinine levels from maternal serum samples, yielding 12 variables (four variables measured every trimester). In addition, we used the following two variables (total 14 variables): the average scores of two items for nicotine dependence over pregnancy (i.e., “How many cigarettes per day do you smoke?” and “How soon after you wake up do you smoke your first cigarette?”). We also evaluated for inclusion the effect of environmental tobacco smoke exposure to the mother during pregnancy, as indexed by the self-reported number of smokers in the home during pregnancy and daily partner smoking amount in the presence of the maternal participant. Consistent with Wakschlag et al. (2009), inclusion of environmental tobacco smoke exposure did not substantially influence classification and did not change the accuracy rates, and thus these variables were not included in the final s-FCM. Missing value rates for 14 exposure variables ranged from 1.0% to 42.5%.

Neonatal body weight (g), length (cm), and head circumference (cm), taken from the neonate’s hospital chart, were used as the three outcome measures.

s-FCM Procedures

The s-FCM was designed specifically for use in prenatal exposure studies with longitudinal designs, using all available data to provide a more comprehensive characterization of exposure that accounts for variation between and within individuals across pregnancy. s-FCM allows a pregnant smoker to be a member of multiple groups to varying degrees (hence the label “fuzzy”) related to changes in her smoking during pregnancy. In addition to this typical fuzzy clustering feature, s-FCM accommodates missing data that routinely occur in clinically oriented patient studies.

As discussed in Fang et al. (2011), the s-FCM procedure, developed and implemented in MatLab (2007), involves three major steps: variable selection (here using all 14 relevant exposure measures), s-FCM clustering, and cluster (i.e., latent class) validation. Unlike simple imputation methods such as M , regression, and hot deck that can cause bias and loss of precision (Fang et al., 2009; Little & Rubin, 2002), the s-FCM algorithm accounts for uncertainties generated by imputation. (Due to the arbitrary missing patterns, five imputed datasets [Rubin, 1996] were generated using the Markov Chain Monte Carlo method with multiple chains, noninformative Jeffreys prior of the Bayesian approach, and 500 burn-in iterations [Schafer, 1997]. For each imputed dataset, we then minimized this fuzzy objective function [e.g., we minimized the intracluster variance; Bezdek, 1981; Bezdek, Keller, Krisnapuram, & Pal, 2005; Fang et al., 2011].) Given a termination clustering number (C_t) of 22 [$C_t = (N/2)^{1/2}$], where N is the sample size (Bezdek et al., 2005), the s-FCM algorithm searched for the optimal number of latent classes through a comprehensive validation procedure, including (a) evaluation of exposure inconsistency rate (ratio of the number of mothers who have inconsistent labels to the total sample size [the larger the value, the less stable the algorithm]); (b) accuracy rate (average rate calculated based on misclassified smokers and nonsmokers across imputed datasets, where we know who are smokers and nonsmokers but not subgroups within smokers). (Compared with typical clustering techniques such as hierarchical and K-means, s-FCM was demonstrated to have the best accuracy and consistency rates across imputed

datasets [Fang et al., 2011].) (c) validation indices (to identify the optimal number of latent classes [groups with like patterns of smoking behavior across pregnancy], s-FCM calculates a set of fuzzy cluster validation indices based on multiple imputed datasets. These validation indices were modified and computed as the average scores across imputed datasets. The Xie-Beni Index [XB_{mi}], widely used for fuzzy clustering, quantifies the ratio of the total variation within and between latent classes, with smaller being better [Xie & Beni, 1991]. The other two indices used were partition coefficient [PC_{mi}] with decreasing monotonicity [the smaller the better] and partition entropy [PE_{mi}] with increasing monotonicity [the larger the better; Bezdek et al., 2005; Fang et al., 2011]); (d) graphs (Sammon [1969] mapping was incorporated into the algorithm to visualize the latent classes in two-dimensional space from multidimensional data, while the functional curves for repeatedly measured smoking variables reflect the intensity of variation over time for each latent exposure class); and (e) statistical testing (the differences between exposure variables [used to characterize smoking during pregnancy] then were examined among identified latent classes to provide quantitative information on tobacco exposure across latent classes over time; Fang et al., 2011). Attribute redundancy test was performed to find a minimal number of attributes to characterize the exposure and reduce model complexity (to examine the attribute redundancy, we removed one category of smoking variables at a time, reran the clustering, calculated the exposure clustering accuracy

rate, and then replaced the variables back into the model and iteratively repeated the process for each category of variables. If the exposure clustering accuracy rates decreased, the original variables were retained. If not, the subset was removed from the model. This strategy maximized the information used to characterize exposure and minimized model complexity). Finally, we tested whether the graded exposure effect was evident on the three fetal growth outcomes using s-FCM–derived exposure groups.

Results

Consistent with Fang et al. (2011) using the MIDS dataset, three exposure groups were identified, with an exposure accuracy rate of 94% and an inconsistency rate of 0%. Validation indices and graphs further supported three optimal number of latent classes (XB_{mi} clearly revealed three optimal latent classes. The other two indices also favored three classes, as their constantly increasing or decreasing properties showed only a minimal difference or trivial advantage at larger number of latent classes in comparison to three classes (see Supplementary Figure 1). Sammon mapping further supported three classes (see Supplementary Figure 2), where asterisks represent the projected centroids and dots represent subjects within the identified classes. The values on the two axes are the projected normalized scores for these subjects). Figure 1 shows the variation in self-reported smoking,

Figure 1. Functional curves of self-reported smoking (upper panel, x-axis: Trimester 1, 2, and 3), cotinine level in maternal urine samples (middle panel, x-axis: Trimester 1, 2, and 3) and in maternal serum (lower panel, x-axis: Trimester 1, 2, and 3) for the tobacco exposure latent classes.

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urinary cotinine levels, and serum cotinine levels during pregnancy among the nonexposed (NE, $N = 536$), lighter-exposed (ITE, $N = 229$), and heavier-exposed (hTE, $N = 213$) groups. Similar to results with the MIDS dataset, the hTE group had the most intensive variation, followed by ITE and NE.

Table 1 shows differences in exposure attributes between lighter- and heavier-exposed groups. For self-reported smoking (number of cigarettes per day, nicotine levels, and nicotine dependence items), the values reported for the s-FCM identified groups with MISSEB and MIDS were comparable but not for urinary cotinine levels.

Also consistent with results with the MIDS dataset (Fang et al., 2011), the offspring of the hTE group weighed less at birth than those in the NE group, the estimated M difference was -205.39 g ($SE = 48.01$, $p < .001$), and the ITE and NE groups

were comparable in offspring birth weight (M difference = -3.64 g, $SE = 44.84$, $p = .94$). Although in the MIDS dataset there were no s-FCM group differences in body length or head circumference, in the MISSEB dataset, there were. The offspring of the hTE group was shorter on average in body length (-0.99 cm, $SE = 0.26$, $p < .001$) and had a smaller M head circumference than those in the NE group (-0.63 cm, $SE = 0.15$, $p < .001$). Again, there were no differences in these outcomes between the ITE and NE groups ($M_{bl_difference} = 0.11$ cm, $SE = 0.24$, $p = .67$; $M_{hc_difference} = -0.20$ cm, $SE = 0.14$, $p = .14$).

Discussion

A graded prenatal tobacco exposure effect was again detected in established exposure-related fetal growth outcomes, in applying the s-FCM method in a second pregnancy cohort. The findings

Table 1. Differences in Tobacco Exposure Attributes Between NE, ITE, and hTE neonates

Four components of exposure data with 14 variables	hTE ($n=213$)		ITE ($n=229$)		NE ($n=536$) ^a	
	M^b (MISSEB/MIDS)	SE^b	M^b (MISSEB/MIDS)	SE^b	M^b (MISSEB/MIDS)	SE^b
Self-reported typical smoking (cigarettes/day)						
Trimester 1***	15.1/13.1	6.52/5.58	1.9/2.8	3.44/3.05	0.0/0.0	0.16 ^a /0.00
Trimester 2***	14.6/12.7	6.96/6.71	1.5/1.3	3.03/2.12	0.0/0.0	0.03 ^a /0.00
Trimester 3***	14.4/12.5	6.68/6.72	1.3/0.9	2.85/1.68	0.0/0.0	0.22 ^a /0.00
Cotinine levels						
Urine trimester 1***	7254.14/1165.17	2021.34/844.89	708.12/120.67	2107.72/225.18	32.21/5.70	38.82 ^a /13.48
Urine trimester 2***	4521.13/1063.05	3085.44/686.30	709.00/134.61	1699.67/25.64	30.77/10.75	52.34 ^a /18.61
Urine trimester 3***	4571.41/279.16	3432.33/308.68	640.03/22.01	1207.90/46.66	32.78/11.69	88.11 ^a /18.81
Serum trimester 1***	179.39	113.71	28.66	41.39	1.60	4.15 ^a
Serum trimester 2***	226.11	193.74	30.19	69.69	1.23	4.99 ^a
Serum trimester 3***	174.44	133.03	20.59	61.70	1.20	4.61 ^a
Nicotine dependence						
Item 1*** ^c	4.57/0.98	2.49/0.58	0.48/0.24	0.98/0.51	0.00/0.00	0.05 ^a /0.00
Item 2*** ^d	1.98/2.03	1.99/0.97	0.47/0.61	0.47/1.06	0.00/0.00	0.58 ^a /0.00
Nicotine level						
Trimester 1***	0.90/1.02	0.30/0.27	0.42/0.94	0.45/0.27	0.00/0.00	0.08 ^a /0.00
Trimester 2	0.90/1.03	0.26/0.27	0.95/0.94	0.20/0.27	0.00/0.00	0.17 ^a /0.00
Trimester 3	0.90/1.03	0.27/0.27	0.92/0.94	0.26/0.27	0.00/0.00	0.74 ^a /0.00

Notes. FTND = Fagerström Test for Nicotine Dependence; hTE = heavier Tobacco-Exposed; ITE = lighter Tobacco-Exposed; MIDS = Midwest Infant Development Study; MISSEB = Maternal Infant Smoking Study of East Boston; NE = Non-Exposed.

^aFor MISSEB, recall the exposure accuracy rate is 94%. The 6% of 978 neonates whose mothers reported ever smoking at the first visit were classified as NE. These smokers had a very small average number of cigarettes smoked per day across trimesters (<0.06 cigarettes/day). Thus, SE s are not zero. Excluding those smokers, the SE s are zero for all variables, except the category of cotinine levels. The M s and SE s for this category have slight changes (urine Trimester 1: $M = 31.94$, $SE = 37.63$; urine Trimester 2: $M = 29.37$, $SE = 50.74$; urine Trimester 3: $M = 28.54$, $SE = 70.86$; serum Trimester 1: $M = 1.37$, $SE = 3.74$; serum Trimester 2: $M = 1.03$, $SE = 2.99$; serum Trimester 3: $M = 0.89$, $SE = 3.71$). These smokers may be categorized into the group of lighter smokers; however, the results showed that they did not change the significance level of the graded exposure effect on all three perinatal outcomes already detected.

^bFor multiple imputation, the M s and SE s were computed based on five imputed datasets (Rubin, 1996; Schafer, 1997); see results from MIDS in Fang et al. (2011).

^cItem 1: "How many cigarettes per day do you smoke?" The unit of Item 1 is kept as number of cigarettes per day and was not mapped to FTND Item 5 ("How many cigarettes per day do you smoke?" where 0 = 10 or less; 1 = 11–20; 2 = 21–30; 3 = 31 or more). The results of Item 1 are similar to those of MIDS, where the unit of Item 5 is based on FTND categorical scores.

^dItem 2: "How soon after you wake up do you smoke your first cigarette?" Item 2 was mapped to Item 6 ("How soon after you wake up do you smoke your first cigarette?" where 0 = after 60 min; 1 = 31–60 min; 2 = 6–30 min; 3 = within 5 min) and recoded to be consistent with all other item scores, where higher scores reflect greater nicotine dependence. All item scores were averaged across visits.

* $p < .05$. ** $p < .01$. *** $p < .001$.

demonstrate the utility of this approach for characterizing fetal tobacco exposure. As we expected, s-FCM identified three exposure groups (using 14 exposure measures), although these variables differed somewhat from the MIDS study (Fang et al., 2011). For example, self-reported smoking was measured somewhat differently (monthly in MIDS; by trimester in MISSEB), and different methods were used to determine cotinine levels (radioimmunoassay in MISSEB; GC/MS in MIDS) at trimester intervals. The nicotine in preferred brands and nicotine dependence scores were measured similarly in both datasets.

The clustering results obtained with the MISSEB dataset were largely consistent with those from Fang et al. (2011) using the MIDS dataset. Importantly, three groups resulted when s-FCM was applied to both datasets. Furthermore, there was coherence in the amounts of self-reported smoking in the s-FCM groups identified in MIDS and MISSEB. Heavier smokers reported *Ms* of about 13–15 cigarettes per day across three trimesters for both datasets, and the *Ms* for lighter smokers ranged between 1 and 2 cigarettes per day across trimesters. The consistency of these findings across the two datasets suggests that the s-FCM method may be reliable and robust to differences in study design and sampling characteristics and thus should be tested in other studies with different measures of exposure.

Furthermore, the pattern of exposure group differences in birth outcomes was consistent across the MIDS and MISSEB datasets. As birth weight is one of the most established outcomes affected by prenatal tobacco exposure (e.g., Difranza & Lew, 1995), the validation of the pattern of cluster group differences across datasets is substantive. In both datasets, the birth weight difference between heavier tobacco-exposed (about 3,200 g) and nonexposed groups (about 3,400 g) was estimated to be around 200 g on average, in two studies that were conducted differently and almost two decades apart. In neither dataset did lighter-exposed and nonexposed groups differ, likely reflecting the higher prevalence in the ITE group of women who quit smoking or smoked very few cigarettes in the latter half of pregnancy when the fetus puts on substantial body mass. In contrast, the s-FCM method yielded different results for body length and head circumference for the two datasets, but this difference reflects the mixed findings more broadly in the literature (e.g., Conter et al., 1995; Espy et al., 2011; Nelson et al., 1999).

In conclusion, a finer graded prenatal exposure effect emerges by integrating and modeling multidimensional data to reflect complex smoking behavioral changes across pregnancy. Grouping women with similar smoking behavior across pregnancy, the s-FCM seems to fit and is fairly robust to missing values below 42%. In future, simulation studies could be conducted to evaluate this method more comprehensively. Compared with traditional cut-score methods, the s-FCM method seems to better capture varying smoking behaviors across pregnancy, quantify the intensity of tobacco exposure, and identify latent classes of women consistently across different datasets, thus having promise as a useful technique to objectively characterize the degree of prenatal exposure and possessing the power to detect subtle exposure effects on outcomes. The s-FCM method could also be combined with the method of Dukic et al. (2007, 2009), which enhances measurement precision by calibrating the self-reported number of smoked cigarettes with adjustments based on bioassay results to derive calibrated smoking exposure trajectory patterns. More generally, these findings, across two different datasets from our

separate studies and especially those from the known exposure-related birth weight outcome test, demonstrate the potential utility of applying advanced measurement models to understand multidimensional variation in smoking behavior. This work can potentially improve our understanding of prenatal tobacco exposure mechanisms by detecting subtler effects on important developmental outcomes, such as deficits in growth or development, neonatal temperament and behavior, and psychological functioning.

Supplementary Material

Supplementary Figures 1 and 2 can be found online at <http://www.ntr.oxfordjournals.org>

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Declaration of Interests

The authors have no competing interests related to this research and had access to all relevant data.

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