Title

A family of partial-linear single-index models for analyzing complex environmental exposures with continuous, categorical, time-to-event, and longitudinal health outcomes

Author names and affiliations

Yuyan Wang[1], Yinxiang Wu[1], Melanie Jacobson[3], Myeonggyun Lee[1], Peng Jin[1], Leonardo Trasande[1,2,3], Mengling Liu[1,2,*]

[1] Department of Population Health, NYU Langone Health, New York, NY, USA

[2] Department of Environmental Medicine, NYU Langone Health, New York, NY, USA

[3] Department of Pediatrics, Divisions of Nephrology and Environmental Pediatrics, NYU Langone Health, New York, NY, USA

Yuyan Wang: yuyan.wang@nyulanong.org;

Yinxiang Wu: yinxiang.wu@nyulangone.org;

Melanie Jacobson: melanie.jacobson2@nyulangone.org;

Myeonggyun Lee: myeonggyun.lee@nyulangone.org;

Peng Jin: peng.jin@nyulangone.org;

Leonardo Trasande: leonardo.trasande@nyulangone.org;

[*]Corresponding author

Mengling Liu, PhD

Email address: mengling.liu@nyulangone.org

Postal address: 180 Madison Avenue, New York, NY, 10016

Tel: 646-501-3652

Abstract

Background: Statistical methods to study the joint effects of environmental factors are of great importance to understand the impact of correlated exposures that may act synergistically or antagonistically on health outcomes. This study proposes a family of statistical models under a unified partial-linear single-index (PLSI) modeling framework, to assess the joint effects of environmental factors for continuous, categorical, time-to-event, and longitudinal outcomes. All PLSI models consist of a linear combination of exposure factors into a single index for practical interpretability of relative direction and importance, and a nonparametric link function for modeling flexibility.

Methods: We presented PLSI linear regression and PLSI quantile regression for continuous outcome, PLSI generalized linear regression for categorical outcome, PLSI proportional hazards model for time-to-event outcome, and PLSI mixed-effects model for longitudinal outcome. These models were demonstrated using a dataset of 800 subjects from NHANES 2003-2004 survey including 8 environmental factors. Serum triglyceride concentration was analyzed as a continuous outcome and then dichotomized as a binary outcome. Simulations were conducted to demonstrate the PLSI proportional hazards model and PLSI mixed-effects model. The performance of PLSI models was compared with their counterpart parametric models.

Results: PLSI linear, quantile, and logistic regressions showed similar results that the 8 environmental factors had both positive and negative associations with triglycerides, with a-Tocopherol having the most positive and trans-b-carotene the most negative association. For the time-to-event and longitudinal settings, simulations showed that PLSI models could correctly identify directions and relative importance for the 8 environmental factors. Compared with parametric models, PLSI models got similar results when the link function was close to linear, but clearly outperformed in simulations with nonlinear effects.

Conclusions: We presented a unified family of PLSI models to assess the joint effects of exposures on four commonly-used types of outcomes in environmental research, and demonstrated their modeling flexibility and effectiveness, especially for studying environmental factors with mixed directional effects and/or nonlinear effects. Our study has expanded the analytical toolbox for investigating the complex effects of environmental factors. A practical contribution also included a coherent algorithm for all proposed PLSI models with R codes available.

Keywords: Environmental mixtures, NHANES, Semiparametric model, Triglyceride

Background

Humans are constantly exposed to a mixture of environmental factors that have the potential to affect health adversely or beneficially, such as chemical contaminants, air pollutants, dietary factors, and behavioral and socioeconomic characteristics. The *exposome*, which is defined as the totality of environmental (non-genetic) exposures from conception onwards (i.e., environmental factors), has been proposed to address the complexities related to studying multiple exposures (1). It is well acknowledged that single-exposure-outcome approaches do not allow for the disentangling of effects of multiple exposures, and miss the interplay among them (2). Therefore, quantifying the complex effects of multiple and simultaneous environmental exposures on health outcomes has become a focus of environmental health research (3, 4). The National Institute of Environmental Health Sciences (NIEHS) has been supporting and conducting combined exposure research, and highlighted this direction as a priority in its 2012–2017 Strategic Plan (5).

Statistical approaches have been proposed to assess the effects of multiple exposures on health outcomes from different perspectives, each focusing on distinct scientific questions (2, 6). However, several challenges for statistical modeling are apparent in these investigations (2).

First, multiple environmental exposures occur simultaneously, often with complex correlation structures among them. Second, they may exhibit synergistic or antagonistic effects on the health outcome, and their associations with health outcomes can be positive, negative, or null, which reflect the complex web of physiological relationships and/or "reverse causality" (7, 8). Third, the relationships between environmental factors and health outcomes can be non-linear, which pose challenges to standard parametric regression-based methods (9). Fourth, it is well recognized that statistical methods have different strengths in addressing various aspects of scientific investigations. For example, from the methodology perspective, Stafoggia et al (2) classified the statistical methods for analysis of environmental mixtures into dimension reduction, variable selection, or grouping or clustering. From the view of scientific questions, Gibson et al (4) distinguished different study objectives as: identifying the important components in the mixtures, studying synergistic effects, or characterizing the overall effect of the mixtures.

Specifically, in studying the joint effects of environmental exposures, weighted quantile sum regression (WQS) (9, 10) and Bayesian kernel machine regression (BKMR) (11, 12) are two popular modeling approaches. In each run of analysis, the WQS method assumes that all exposures are associated with the outcome in one direction, and then derives a one-dimensional weighted sum score of the exposures under the assumed direction for the estimation of overall effect. BKMR estimates the posterior inclusion probability (PIP) as the measure of importance for environmental exposures using a flexible nonparametric Bayesian framework. However, the estimated PIPs sometimes can be close to 1 for exposures that have strong effects on the outcome, and thus do not directly provide useful information on effect direction and relative importance. In addition, WQS and BKRM have been generalized to study environmental mixtures with several types of outcomes, such as WQS for longitudinal outcomes (13) and

BKMR for time-to-event outcomes (14). However, a general modeling framework that can alleviate the above limitations in environmental health research is still desired (15).

Partial-linear single-index (PLSI) models are a family of semiparametric models that reside between the completely unstructured nonparametric models and restrictive parametric regression models (16-18). By reducing multiple exposures into the single index, the PLSI models can reduce the "curse of dimensionality" issue and improve modeling efficiency. The application and performance of single-index linear regression for analysis of environmental exposures with continuous outcomes has been evaluated previously (pending publication). Specifically, the PLSI modeling framework allows the associations between exposures and outcomes to be in the positive or negative direction, provides explicit and interpretable quantification on the relative direction and importance of the exposures, and models these effects with flexibility. In recent years, research on PLSI models has attracted increasing attention and extended to different types of outcomes, such as categorical (19-21), time-to-event (22-25) and longitudinal (26-29) outcomes. Table 1 summarizes the outcome types of interest and corresponding PLSI models with key references and their corresponding counterpart parametric models.

Table 1 Summary of outcome types and corresponding PLSI models and parametric models

Outcome type	PLSI models	Counterpart models	Key references	Equation
Continuous	PLSI linear regression	Linear regression	(16), (19), (20), (30),(31), (32), (33), (34), (35), (36)	(1)
	PLSI quantile regression	Quantile regression	(37), (38), (39), (40), (41), (42)	(2)
Categorical (binary)	PLSI generalized linear (logistic) regression	Generalized linear (logistic) regression	(16), (20), (34), (36)	(3)
Time-to-event	PLSI PH model	Cox PH model	(22), (23), (24), (25)	(4)
Longitudinal	PLSI mixed-effects model	Linear mixed-effects model	(26), (27), (43), (44), (45)	(5)

The main goal of this study was to unify the resource advantages of PLSI models into one general framework for analyzing environmental factors, and to demonstrate their values in environmental research for different types of health outcomes. We exemplified the use of PLSI

models in assessing the associations between correlated environmental factors with health outcomes using real and simulated datasets based on National Health and Nutrition Examination Survey (NHANES) 2003-2004 cycle. Another aim was to develop effective computation algorithms for the PLSI models and to consolidate these models using R packages.

Methods

NHANES dataset

To demonstrate the PLSI models, we used the data from the NHANES 2003-2004 cycle based on the original paper by Patel et al (46), which systematically evaluated the associations of environmental factors with serum lipid levels. We used serum triglyceride concentrations as the primary outcome for demonstration and also considered three demographic variables, age, sex, and race/ethnicity as potential confounders. Participants with data on serum triglycerides, environmental factors and confounders were included in this study (n=800). Details on data pre-processing are provided in Additional file 1: Figure S1. Subjects provided written informed consent, and the Institutional Review Board of the National Center for Health Statistics approved the survey (47). Table 2 summarizes the final variables included in analyses, and Figure 1 shows the correlation matrix of the final 8 environmental factors and triglycerides. The dataset is provided as Additional file 2, and the R codes conducting data cleaning is included in the R markdown file (Additional file 3).

Table 2 List of analyzed variables from NHANES 2002-2003 dataset

Type	Variable name	Abbreviations	Symbol
Outcome			
	Triglycerides (mg/dL)	TG	Y
Environmental factors			
	a-Tocopherol (ug/dL)	a-Tocopherol	X1
	g-tocopherol (ug/dL)	g-tocopherol	X2
	Retinyl palmitate (ug/dL)	Retinyl-palmitate	X3

	Retinol (ug/dL)	Retinol	X4
	3,3',4,4',5-Pentachlorobiphenyl (pncb) Lipid Adj (pg/g)	3,3,4,4,5-pncb	X5
	Polychlorinated Biphenyl (PCB) 194 Lipid Adj (ng/g)	PCB156	X6
	2,3,4,6,7,8-hxcdf Lipid Adj (pg/g)	2,3,4,6,7,8-hxcdf	X7
	trans-b-carotene (ug/dL)	trans-b-carotene	X8
Confounders			
	Age (years)	Age	Z1
	Sex (1: male; 2: female)	Sex	Z2
	Race/Ethnicity (1: Non-Hispanic white; 2: Non-Hispanic black; 3: Mexican American; 4: Other race - Including multi-racial; 5: Other Hispanic)	Race	Z3

For notational convention throughout this article, we let Y denote the outcome, $X = (X_1, \ldots, X_8)$ denote the 8 exposure variables to be modeled into the "single index" term, and vector Z represent the confounders (age, sex, and race/ethnicity). The outcome, continuous triglycerides, and all exposure variables, except for retinol, were log-transformed, and all exposure variables were standardized to have mean of zero and standard deviations of 1 before model fitting. We use $\beta's$ to denote the single index coefficients that characterize the relative direction and importance of each exposure X_i, and γ for the corresponding linear coefficient vector for confounder vector Z. To ensure model identifiability, the L_2 norm of β's (i.e.$\sqrt{\beta_1^2 + \ldots + \beta_8^2}$) is set to be 1 with the first component $\beta_1 > 0$, which are the standard parametrization constraints for all PLSI models.

Continuous outcome: mean regression

The PLSI linear regression model is considered as a generalization of both standard linear regression and missing-link function problem in linear modeling (48), and specified as

$$Y = g\left(\sum_{j=1}^{8} \beta_j X_j\right) + \gamma'\mathrm{Z} + \varepsilon \qquad (1)$$

The semiparametric PLSI linear regression has the parametric component $\sum_{j=1}^{8} \beta_j X_j$ and $\gamma'\mathrm{Z}$ for easy linear representation and interpretation, and the nonparametric components $g(\cdot)$ is totally

unspecified and represents the overall effect of single index. When the estimated $g(\cdot)$ is monotone, the effect of X_j can be interpreted qualitatively using the sign of β_j. If $g(\cdot)$ is monotone increasing, then a positive sign for β_j suggests increased conditional expectation of Y at larger value of X_j, and vice versa for a negative sign. As the overall scale of β is set, $|\beta_j|$ can be explained as the relative importance of X_j affecting the mean of outcome Y as X_j is perturbed while $g(\cdot)$ and other variables are held fixed. We can also intuitively interpret β_j^2 as the proportion of contribution to the single index by variable X_j because, when $(X_1, X_2, \ldots, X_8)$ are independent, β_j^2 simply represents X_j's variance contribution.

Continuous outcome: quantile regression

Beyond the commonly-considered effects of environmental factors on the mean of a continuous outcome, sometimes we are interested in the specific relations cross multiple points of the outcome's distribution, such as higher quantiles of triglycerides (49), higher quantiles of blood pressure (50), low quantiles of birth weight (51), or lower quantiles of intelligence quotient scores (52). Moreover, when the distribution of continuous outcome deviates from Gaussian, modeling the median can be more robust than evaluating the mean by conventional linear regression (53). For this purpose, quantile regression (QR), which was originally proposed by Koenker and Bassett (54) and used as a useful technique in econometrics (55) and growth curve analysis (56), enables us to study the associations of environmental factors with continuous health outcomes as various quantiles across its distribution. PLSI quantile regression is a combination of the PLSI technique and QR (40, 41), and thus we consider it for the analysis of joint effects of multiple environmental factors on the quantile(s) of continuous outcome variable.

Given a specific $\tau \in (0,1)$, the PLSI quantile regression for the τth conditional quantile θ_τ of continuous outcome Y given environmental factors X and covariates Z can be specified as

$$\theta_\tau(Y|X,Z) = g_\tau\left(\sum_{j=1}^{8}\beta_{\tau j}X_j\right) + \gamma_\tau'\mathrm{Z} \quad (2)$$

Interpretation of coefficients $\beta_\tau{}'$s in the PLSI quantile regression is similar to that of PLSI linear regression, with the difference being that the associations are now with the conditional quantiles of outcome variable $\theta_\tau(Y|X,Z)$ instead of the mean.

Categorical outcome: generalized linear regression

PLSI generalized linear regression can be employed for categorical outcomes, such as binary, multinomial, or count variables. Here we considered the binary outcome of high triglycerides (> 150 milligrams per deciliter) (57), which accounted for 30.75% of the 800 subjects. The PLSI logistic model is specified as

$$logit\big(P(Y=1|X,Z)\big) = g\left(\sum_{j=1}^{8}\beta_j X_j\right) + \gamma'\mathrm{Z} \quad (3)$$

The interpretation of coefficients is based on the log odds that response value is '1' conditioning on the predictors, and β_j represents the relative direction and importance of X_j associated with the log odds of high triglycerides when scale of β is set and $g(\cdot)$ and other variables are held fixed. The logit function can be adapted accordingly to the type of categorical outcome.

Time-to-event outcome: proportional hazards model

The Cox proportional hazards (PH) regression has been the pivotal model in time-to-event analysis since Sir Cox proposed it in 1972 (58, 59). The Cox PH regression models the hazard function and assumes that covariates have linear effects on the log hazard function. Combining PLSI modeling technique and Cox PH regression, the PLSI PH model is specified as

$$\lambda(t|X,Z) = \lambda_0(t)\exp\left\{g\left(\sum_{j=1}^{8}\beta_j X_j\right) + \gamma'\mathrm{Z}\right\}, \quad (4)$$

where β_j can be explained as the relative effect direction and importance of X_j on the log hazard function and $g(\cdot)$ characterizes the overall effect of the index.

Longitudinal outcome: mixed-effects model

Longitudinal studies arise frequently in environmental research, in which outcomes are measured repeatedly over a period of time with either baseline or time-dependent environmental factors. As measurements from the same subject are often correlated, subject-specific random effects are used to accommodate within-subject dependence and to explain across-subject heterogeneity. Mixed-effects models provide a general and flexible framework for modeling longitudinal data, consisting of two modeling components: fixed effects and random effects, characterizing the population mean and individual variation, respectively (60, 61). Mixed-effects models in general are amenable to missing data and can accommodate missing completely at random or missing at random (60, 62). Without loss of generality, we consider a longitudinal study with N subjects and the ith subject has n_i observations over time. Repeated measures of the outcome are denoted by Y_{ij}, exposure vector X_{ij}, covariate vector Z_{ij} and observation time T_{ij}, and then the observed full dataset is $\{(Y_{ij}, X_{ij}, Z_{ij}, T_{ij}), i = 1, \dots, N, j = 1, \dots, n_i\}$.

Specifically, the PLSI mixed-effects model with a random intercept is specified as

$$Y_{ij} = g\left(\sum_{l=1}^{8}\beta_l X_{ijl}\right) + Z_{ij}'\gamma + b_i + \omega T_{ij} + \varepsilon_{ij}, \quad (5)$$

where b_i represents the subject-specific random intercept and ω represents the time effect on the outcome. Note that PLSI mixed-effects model can accommodate additional random effects and other model specifications of fixed effects and interactions. The index coefficient β_l can be

explained as the relative direction and importance of X_{ijl} as X_{ijl} is perturbed when scale of β is set and $g(\cdot)$ and other variables are held fixed, and $g(\cdot)$ represents the overall effect of the single index with the mean of longitudinal outcome.

Simulation settings

Since the NHANES survey dataset does not have time-to-event outcome nor longitudinal outcome, we conducted simulations to demonstrate the PLSI PH model and PLSI mixed-effects model. The coefficients for the 8 environmental factors and three confounding variables were set based on the results from the PLSI linear regression for continuous triglycerides. We kept the original direction of these associations and the absolute rank for each environment factor, and set the effect sizes in a wider range to be more distinguishable (see details in Table 3 and Table 4). Moreover, we considered the link function $g(.)$ to be either $g(x) = x$ to facilitate the direct comparison with the parametric models, or as a quadratic function $g(x) = x^2$ to mimic the scenario with nonlinear effects and pair-wise interactions between the exposures as $g\left(\sum_{j=1}^{8} \beta_j X_j\right) = \beta_1^2 X_1^2 + \cdots + \beta_8^2 X_8^2 + 2\beta_1\beta_2 X_1 X_2 + \cdots + 2\beta_7\beta_8 X_7 X_8$.

Time-to-event outcomes were generated using model (4) with $\lambda_0 = 1$ in identity link function scenario and $\lambda_0 = 1/\exp(2)$ in quadratic link function scenario, and censoring rate as 20%. Longitudinal outcomes were generated using model (5) with t_{ij} ranged [1, 6] and $\omega = 1$. The number of possible observations for each subject was assumed to vary randomly between 2 and 6. The errors followed a first order autoregressive process (i.e. AR(1)), with the autocorrelation as 0.4 and standard deviation as 1.5 to mimic decreasing dependence with time. All details of data generation used in these simulations are included in the R markdown file (Additional file 3).

Performance evaluation

In all analyses, the estimated coefficients for the 8 environmental factors and confounders were reported. Ranks based on the absolute values of estimated coefficients were presented to evaluate the relative importance of each environmental factor, and squares of estimated coefficients were shown to represent the respective proportion of contribution to the single index. For all models, the standard errors of coefficient estimates and of the estimated link function were estimated using 500 runs of bootstrapping samples and used to construct the 95% confidence intervals (CIs). We compared the performance of each PLSI model with its counterpart parametric model. The estimated coefficients of 8 environmental factors from the parametric counterpart models were reported in both original values and scaled values to have L_2 norm of 1 for comparison.

Statistical software

All statistical analyses were performed using statistical software R 3.5.0. R codes for the PLSI models for different types of outcomes were developed using 'gam', 'qgam' or 'gamm' function call from 'mgcv' or 'qgam' package. Linear regression and logistic regression were fit using 'glm' function, and quantile regressions using 'rq' function in the 'quantreg' package. Cox PH model was fitted using 'coxph' function from 'survival' package, and linear mixed-effects model using 'lme' function from 'nlme' package. All descriptive and analytical codes were provided as an R Markdown document in Additional file 3.

Results

Continuous triglycerides: PLSI mean regression

We applied the PLSI linear regression and multivariable linear regression to study the associations of the 8 environmental factors with continuous triglycerides, and summarized the estimates in Figure 2 (numerical results in Additional file 1: Table S1). The ranks, estimated coefficients, and directions were similar between these two models, and the estimated link

function was close to be linear (Additional file 1: Figure S3). As the estimated link function was monotone and increasing, the positive estimates indicated a positive association with triglycerides. Specifically, a-Tocopherol had a $\hat{\beta}_1 = 0.612$ and 95% CI of (0.517, 0.707), indicating that a-Tocopherol had the strongest positive association with triglycerides among the 8 factors, and made about 37.4% contribution to the single index; trans-b-carotene had the most negative association of $\hat{\beta}_8 = -0.383$. These results were consistent with original results from Patel's study, which also observed a-Tocopherol with the strongest positive and trans-b-carotene with the strongest negative association with triglycerides (46). As the 8 environmental factors showed both positive and negative associations with triglycerides, this application highlighted the need of statistical methods to accommodate both directional effects for studying multiple environmental exposures.

Continuous triglycerides: PLSI quantile regression

We applied the PLSI quantile regression to study the associations between 8 exposures and three quartiles (25^{th}, 50^{th}, and 75^{th} percentiles) of triglycerides and summarized the main results in Figure 3 (numerical results in Additional file 1: Table S2). We observed that the estimated link functions for all three quartiles were increasing and close to linear (Additional file 1: Figure S4), which explained the similarities between the results of the PLSI quantile regressions and regular quantile regressions. In addition, the 8 environmental factors showed fairly consistent associations across the three quartiles of triglycerides. For example, a-Tocopherol was the factor having the strongest positive association with triglycerides and trans-b-carotene was the factor having the strongest negative association with triglycerides at all three quartiles.

Binary triglycerides: PLSI logistic regression

For dichotomized triglycerides, the ranks and estimates from PLSI logistic regression and multivariable logistic regression are shown in Figure 4 (numerical results in Additional file 1: Table S3), which demonstrated similar results from these two models. The estimated link function by PLSI logistic regression was monotone increasing and close to be linear (Additional file 1: Figure S5). Thus, the estimated directions can be interpreted qualitatively and the estimated coefficients represented the relative importance of each exposure on the log odds of high triglycerides. For example, the estimated coefficient of a-Tocopherol was $\hat{\beta}_1 = 0.584$ (95% CI: 0.433-0.735), which represented that a-Tocopherol had the strongest positive association with the odds of high triglycerides among the 8 factors.

Simulated time-to-event outcome: PLSI PH model

We summarize the simulation results from both PLSI PH model and Cox PH model in Table 3. Under the identity link function setting, results from the PLSI PH model and the conventional Cox PH model were very similar as expected, and both close to the true values. The PLSI PH model estimated the link function to be close to the true linear function (Additional file 1: Figure S6 (a)). Under the quadratic link function setting, results from the PLSI PH model were still consistent to true coefficients, but the conventional Cox PH model failed for most of the environmental factors because the linear model assumption was insufficient. The PLSI PH model also captured the U-shape and estimated the link function close to the true quadratic function (Additional file 1: Figure S6 (b)).

(Table 3 should appear here)

Simulated longitudinal outcome: PLSI mixed-effects model

The results from PLSI mixed-effects model and linear mixed-effects model under identify or quadratic link function are presented in Table 4. Under the identity link function setting, the

PLSI mixed-effects model estimated all coefficients close to the true coefficients with correct directions, and conventional linear mixed-effects model also had similar estimations. The estimated link function by PLSI mixed-effects model was close to the true linear function (Additional file 1: Figure S7 (a)). Under the quadratic link function setting, the results from PLSI mixed-effects model were still consistent; however, the conventional linear mixed-effects model clearly showed biased results for some factors like PCB194. The estimated link function by PLSI mixed-effects model had a U-shape and was close to the true quadratic function (Additional file 1: Figure S7 (b)).

(Table 4 should appear here)

Discussion

We presented five PLSI models aiming to provide a unified family of statistical models to assess the joint effects of environmental exposures on four types of health outcomes: continuous, categorical, time-to-event, and longitudinal outcomes. We demonstrated the flexibility and effectiveness of this PLSI family for modeling various types of outcomes using NHANES data supplemented with simulations. One contribution of this work is that the novel modeling options under the PLSI framework complement existing methods and address some common statistical challenges in the analysis of multiple environmental exposures, such as mixed directions, interactions, and non-linear effects. Another contribution is that coherent computation algorithms are developed for all the PLSI models and implemented using the existing R packages, which can facilitate direct applications in practice and reproducible research.

In our analyses of the cross-sectional NHANES studies for continuous and binary triglycerides by PLSI models, we found that the 8 environmental factors exhibited mixed directional associations with the outcome, with a-Tocopherol having the strongest positive

association and trans-b-carotene having the strongest negative association with triglycerides. A-Tocopherol and carotenes are transported in serum with HDL and LDL, and the level of serum a-Tocopherol depends on serum lipids (63, 64). The strong positive association between a-Tocopherol and triglycerides is expected (46), and the negative association between b-carotene and triglycerides is supported by previous studies (65, 66). Our results were consistent with the results of previously known and validated environmental chemical factors correlated with triglycerides (46), clearly demonstrating the value of PLSI models as a flexible and useful tool for analyzing complex exposures. Using additional simulations for time-to-event and longitudinal outcomes, we showed that the PLSI models could correctly identify the directions and magnitudes of associations for these environmental factors in scenarios with different types of outcomes.

In our NHANES applications of studying triglycerides continuously and categorically, we estimated that the link functions of PLSI models were very close to be linear, which were also reflected by the similar results with their counterpart parametric models. In general, standard errors from the PLSI models were larger than those from their counterpart parametric models, which was expected as the former are semiparametric models.

Moreover, our results remained consistent when we conducted several sensitivity analyses. First, we conducted a sensitivity analysis including all 22 environmental factors to investigate the performance of PLSI linear regression to handle highly correlated exposures. Results showed that the key observations on the important environmental factors were similar (Additional file 1: Table S4). When there are many highly correlated exposure factors ($r > 0.9$, Additional file 1: Figure S2), we also recommend to use p-values to rank the importance of variables because the value of estimates can be affected by collinearity. As shown in Table S4, the 8 selected environmental factors still showed top ranks among the 22 factors, except for PCB194 which

was highly correlated with other PCBs. In addition, we conducted another sensitivity weighted analysis incorporating the laboratory subsample C weights from NHANES 2003-2004 cycle (following general guideline to use the weights from "least common denominator") (67), and the weighted results (Additional file 1: Table S5) were similar with the results from unweighted models. Note that most of the PLSI models are readily incorporate weights in R function codes (Additional file 3).

Interaction among multiple correlated environmental factors is very common, and it has been long appreciated that the co-exposures may have synergistic (additive or multiplicative) or antagonistic effects on health outcomes (69). For parametric models, it's difficult to directly model the interaction effects among co-exposures if we don't know the 'degree of interaction'. However, PLSI models can handle the interaction easily through the unknown link function as we evaluated using the simulations. Specifically, in our simulated time-to-event and longitudinal analyses with quadratic link function, which reflected both the pairwise interactions and non-linear quadratic effects, both PLSI PH model and PLSI mixed-effects were able to capture the U-shape link function and correct direction and importance of the environmental factors, while parametric models failed in most factors because the parametric assumptions were no longer satisfied. Therefore, PLSI models readily accommodate the factors showing non-linear or interactive effect on the health outcome.

There are other ways and models using various definitions of weighted sums to model the joint effect for multiple environmental components. For example, molar sums were used to show relationships between prenatal phenol and phthalate exposures and birth outcome (70), and a potency-weighted sum was used to calculate phthalates exposures among reproductive-aged women (71). The weights for environmental factors can be calculated from their expected potency relative to a reference factor, like the common cases in toxicology (72), or based on their

373 percent contribution to the total mixture effect, like WQS (9). PLSI models can be considered as
374 one of these weighting approaches, and their advantages from the semiparametric structure are
375 evident compared with existing methods, especially for the scenarios when the environmental
376 exposures have mixed-directional associations and/or a potential high-degree interaction.
377 Meanwhile, due to the flexibility of the nonparametric link function, PLSI models can represent
378 complex joint effects more than additive structures (73), which is commonly encountered since
379 environmental exposures may act together in a biological sense via a shared mechanistic
380 pathway (4). The ability of handling various types of outcomes is another important advantage of
381 the proposed PLSI framework. This is important because, with the accumulation of
382 environmental exposure measurements and development of data collection methods, time-to-
383 event or longitudinal studies are desired to explore the associations over time.
384 In this study, the coherent algorithms for PLSI models are based on the 'gam' and 'gamm'
385 functions from 'mgcv' package and 'qgam' function from 'qgam' package in R, which includes
386 many of the generalized additive model (GAM) fitting techniques developed by Simon Wood et
387 al (74). The rationale behind this algorithms is to use 'gam', 'qgam' or 'gamm' call (usually
388 using penalized regression splines or similar smoothers) to profile out the smooth model
389 coefficients and smoothing parameters for estimation of the link function contained in PLSI
390 model, leaving only a finite parameter vector to be estimated by a general purpose optimizer.
391 Based on this algorithm, it is easy to adapt the models to include multiple single index terms,
392 parametric terms, and further smoothing. We have compared the estimates for single index
393 models among different iterative procedures using existing packages (e.g., projection pursuit
394 regression with one term using 'ppr' function; 'sim.est' function from 'simest' package) in
395 various simulations, and they have similar estimation performance. We finally chose 'gam' call
396 series because of its flexibility for covariate adjustment and ability of modeling various types of

outcomes. This 'gam', 'qgam', 'gamm' call approach has demonstrated efficient and robust performance in our numerical studies, and we believe this coherent algorithm strategy wrapped as a toolbox is beneficial for practical application.

The PLSI models considered here may not be directly applicable to extreme high-dimensional settings, for which we could consider using extensions with adaptive LASSO (75), smoothly clipped absolute deviation penalty (76), and smooth-threshold estimating equations (77). Another future research direction is to extend from the single index to multiple-index models, such as the projection pursuit regression (78), so that more complex data structures and exposure effect patterns can be captured and modeled.

Conclusions

A family of PLSI models exemplified great value of identifying important components among environmental exposures when they demonstrate associations in various directions and complex non-linear relationships between the exposures and outcome.

Additional files

Addition file 1: Figure S1. Data flow diagram for deriving 800 subjects and 8 environmental factors. Figure S2. Correlation matrix of Pearson correlation coefficient of 22 factors and triglycerides in NHANES 2002-2003 (N=800). Table S1. Results from PLSI linear regression and multivariable linear regression in NHANES 2002-2003. Figure S3. Estimated link function by PLSI linear regression in NHANES 2002-2003. Tables S2.1-S2.3. Results from PLSI quantile regressions and multivariable quantile regression at three quantiles (25th, 50th, and 75th percentiles) of triglycerides in NHANES 2002-2003. Figure S4. Estimated link functions by PLSI quantile regressions at three quartiles in NHANES 2002-2003. (a) 25th percentile; (b) 50th percentile; (c)

75th percentile. **Table S3.** Results from PLSI logistic regression and multivariable logistic regression in NHANES 2002. **Figure S5.** Estimated link function by PLSI logistic regression in NHANES 2002-2003. **Figure S6.** Estimated link functions by PLSI PH model in simulated time-to-event study. (a) identity link function; (b) quadratic link function. **Figure S7.** Estimated link functions by PLSI mixed-effects model in simulated longitudinal study. (a) identity link function; (b) quadratic link function. **Table S4.** Sensitivity analysis results from PLSI linear regression and multivariable linear regression in NHANES 2002-2003 with 22 environmental factors. **Table S5.** Sensitivity analysis results from weighted PLSI linear regression and weighted linear regression in NHANES 2002-2003 using NHANES laboratory subsample C weights.

Addition file 2: cleaning dataset of 800 subjects from NHANES 2003-2004 cycle. Variables include respondent sequence number of subject, outcome triglyceride, 22 environmental factors, 3 demographic confounding variables, and laboratory subsample C weight.

Addition file 3: R markdown document demonstrating all descriptive and analytical process of this article.

Abbreviations

AR: autoregressive process; BKMR: Bayesian kernel machine regression; NHANES: National Health and Nutrition Examination Survey; NIEHS: National Institute of Environmental Health Sciences; PH: proportional hazards; PLSI: partial-linear single-index; PIP: posterior inclusion probability; QR: quantile regression; WQS: weighted quantile sum regression

Declarations

Ethics approval and consent to participate

Subjects provided the written informed consent, and the institutional review board of the National Center for Health Statistics approved the survey for NHANES study.

Consent for publications

Not applicable.

Availability of data and materials

The dataset used and/or analyzed during the current study supporting the conclusions of this article is included within the additional file.

Competing interests

The authors declare that they have no competing interests.

Funding

This work is partially supported by UG3/UH3OD023305 and 4P30ES000260-52 from the National Institutes of Health.

Authors' contributions

YWang and MLiu: Performed data curation, conducted statistical analyses and prepared original manuscript draft. YWang, YWu, MLee, and PJ: Designed the algorithm and performed simulations. MJ, LT and MLiu: Directed the data set collection and quality control, acquired funding to support this analysis, contributed to literature review and reviewed the manuscript. All authors read and approve the final manuscript.

Acknowledgements

The contributions of the subjects in the NHANES study are gratefully acknowledged.

References

1. Wild CP. Complementing the genome with an "exposome": The outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiology Biomarkers & Prevention. 2005;14(8):1847-50.
2. Stafoggia M, Breitner S, Hampel R, Basagana X. Statistical Approaches to Address Multi-Pollutant Mixtures and Multiple Exposures: the State of the Science. Curr Environ Health Rep. 2017;4(4):481-90.
3. Sanders AP, Claus Henn B, Wright RO. Perinatal and Childhood Exposure to Cadmium, Manganese, and Metal Mixtures and Effects on Cognition and Behavior: A Review of Recent Literature. Curr Environ Health Rep. 2015;2(3):284-94.
4. Hamra GB, Buckley JP. Environmental exposure mixtures: questions and methods to address them. Curr Epidemiol Rep. 2018;5(2):160-5.
5. Carlin DJ, Rider CV, Woychik R, Birnbaum LS. Unraveling the health effects of environmental mixtures: an NIEHS priority. Environ Health Perspect. 2013;121(1):A6-8.
6. Billionnet C, Sherrill D, Annesi-Maesano I, Study G. Estimating the Health Effects of Exposure to Multi-Pollutant Mixture. Annals of Epidemiology. 2012;22(2):126-41.
7. Mann RM, Hyne RV, Choung CB, Wilson SP. Amphibians and agricultural chemicals: review of the risks in a complex environment. Environ Pollut. 2009;157(11):2903-27.
8. Chaumont A, Nickmilder M, Dumont X, Lundh T, Skerfving S, Bernard A. Associations between proteins and heavy metals in urine at low environmental exposures: Evidence of reverse causality. Toxicology Letters. 2012;210(3):345-52.
9. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. Journal of Agricultural Biological and Environmental Statistics. 2015;20(1):100-20.

10. Czarnota J, Gennings C, Colt JS, De Roos AJ, Cerhan JR, Severson RK, et al. Analysis of Environmental Chemical Mixtures and Non-Hodgkin Lymphoma Risk in the NCI-SEER NHL Study. Environmental Health Perspectives. 2015;123(10):965-70.
11. Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M, et al. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics. 2015;16(3):493-508.
12. Valeri L, Mazumdar MM, Bobb JF, Henn BC, Rodrigues E, Sharif OIA, et al. The Joint Effect of Prenatal Exposure to Metal Mixtures on Neurodevelopmental Outcomes at 20-40 Months of Age: Evidence from Rural Bangladesh. Environmental Health Perspectives. 2017;125(6).
13. Levin-Schwartz Y, Gennings C, Schnaas L, Del Carmen Hernandez Chavez M, Bellinger DC, Tellez-Rojo MM, et al. Time-varying associations between prenatal metal mixtures and rapid visual processing in children. Environ Health. 2019;18(1):92.
14. Zhang L, Kim I. Semiparametric Bayesian kernel survival model for evaluating pathway effects. Statistical Methods in Medical Research. 2019;28(10-11):3301-17.
15. Gibson EA, Nunez Y, Abuawad A, Zota AR, Renzetti S, Devick KL, et al. An overview of methods to address distinct research questions on environmental mixtures: an application to persistent organic pollutants and leukocyte telomere length. Environmental Health. 2019;18(1).
16. Ichimura H. Semiparametric Least-Squares (Sls) and Weighted Sls Estimation of Single-Index Models. Journal of Econometrics. 1993;58(1-2):71-120.
17. Horowitz JL, Hardle W. Direct semiparametric estimation of single-index models with discrete covariates. Journal of the American Statistical Association. 1996;91(436):1632-40.

18. Wang JL, Xue LG, Zhu LX, Chong YS. Estimation for a Partial-Linear Single-Index Model. Annals of Statistics. 2010;38(1):246-74.
19. Hardle W, Hall P, Ichimura H. Optimal Smoothing in Single-Index Models. Annals of Statistics. 1993;21(1):157-78.
20. Carroll RJ, Fan JQ, Gijbels I, Wand MP. Generalized partially linear single-index models. Journal of the American Statistical Association. 1997;92(438):477-89.
21. Yi GY, He WQ, Liang H. Analysis of correlated binary data under partially linear single-index logistic models. Journal of Multivariate Analysis. 2009;100(2):278-90.
22. Wang W. Proportional hazards regression models with unknown link function and time-dependent covariates. Statistica Sinica. 2004;14(3):885-905.
23. Huang JHZ, Liu LX. Polynomial spline estimation and inference of proportional hazards regression models with flexible relative risk form. Biometrics. 2006;62(3):793-802.
24. Sun J, Kopciuk KA, Lu XW. Polynomial spline estimation of partially linear single-index proportional hazards regression models. Computational Statistics & Data Analysis. 2008;53(1):176-88.
25. Li JB, Zhang RQ. Partially varying coefficient single index proportional hazards regression models. Computational Statistics & Data Analysis. 2011;55(1):389-400.
26. Bai Y, Fung WK, Zhu ZY. Penalized quadratic inference functions for single-index models with longitudinal data. J Multivariate Anal. 2009;100(1):152-61.
27. Li GR, Zhu LX, Xue LG, Feng SY. Empirical likelihood inference in partially linear single-index models for longitudinal data. J Multivariate Anal. 2010;101(3):718-32.
28. Xu PR, Zhu LX. Estimation for a marginal generalized single-index longitudinal model. Journal of Multivariate Analysis. 2012;105(1):285-99.

29. Zhao WH, Lian H, Liang H. GEE analysis for longitudinal single-index quantile regression. J Stat Plan Infer. 2017;187:78-102.
30. Stoker TM. Consistent Estimation of Scaled Coefficients. Econometrica. 1986;54(6):1461-81.
31. Hardle W, Stoker TM. Investigating Smooth Multiple-Regression by the Method of Average Derivatives. Journal of the American Statistical Association. 1989;84(408):986-95.
32. Hardle W, Tsybakov AB. How Sensitive Are Average Derivatives. Journal of Econometrics. 1993;58(1-2):31-48.
33. Hristache M, Juditsky A, Spokoiny V. Direct estimation of the index coefficient in a single-index model. Annals of Statistics. 2001;29(3):595-623.
34. Yu Y, Ruppert D. Penalized spline estimation for partially linear single-index models. Journal of the American Statistical Association. 2002;97(460):1042-54.
35. Xia YC, Hardle W. Semi-parametric estimation of partially linear single-index models. Journal of Multivariate Analysis. 2006;97(5):1162-84.
36. Liang H, Liu X, Li RZ, Tsai CL. Estimation and Testing for Partially Linear Single-Index Models. Annals of Statistics. 2010;38(6):3811-36.
37. Chaudhuri P. Global Nonparametric-Estimation of Conditional Quantile Functions and Their Derivatives. Journal of Multivariate Analysis. 1991;39(2):246-69.
38. Chaudhuri P, Doksum K, Samarov A. On average derivative quantile regression. Annals of Statistics. 1997;25(2):715-44.
39. Wu TZ, Yu KM, Yu Y. Single-index quantile regression. Journal of Multivariate Analysis. 2010;101(7):1607-21.
40. Kong EF, Xia YC. A Single-Index Quantile Regression Model and Its Estimation. Econometric Theory. 2012;28(4):730-68.

555 41. Lv YZ, Zhang RQ, Zhao WH, Liu JC. Quantile regression and variable selection of partial
556 linear single-index model. Annals of the Institute of Statistical Mathematics. 2015;67(2):375-
557 409.
558 42. Ma SJ, He XM. Inference for Single-Index Quantile Regression Models with Profile
559 Optimization. Annals of Statistics. 2016;44(3):1234-68.
560 43. Lai P, Li GR, Lian H. Quadratic inference functions for partially linear single-index models
561 with longitudinal data. Journal of Multivariate Analysis. 2013;118:115-27.
562 44. Li GR, Lai P, Lian H. Variable selection and estimation for partially linear single-index
563 models with longitudinal data. Statistics and Computing. 2015;25(3):579-93.
564 45. Li JB, Lian H, Jiang XJ, Song XY. Estimation and testing for time-varying quantile single-
565 index models with longitudinal data. Computational Statistics & Data Analysis. 2018;118:66-
566 83.
567 46. Patel CJ, Cullen MR, Ioannidis JPA, Butte AJ. Systematic evaluation of environmental
568 factors: persistent pollutants and nutrients correlated with serum lipid levels. International
569 Journal of Epidemiology. 2012;41(3):828-43.
570 47. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National health and
571 nutrition examination survey: plan and operations, 1999-2010. Vital Health Stat 1.
572 2013(56):1-37.
573 48. Weisberg S, Welsh AH. Adapting for the Missing Link. Annals of Statistics.
574 1994;22(4):1674-700.
575 49. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major
576 Lipids, Apolipoproteins, and Risk of Vascular Disease. Jama-Journal of the American
577 Medical Association. 2009;302(18):1993-2000.

578 50. Bind MA, Peters A, Koutrakis P, Coull B, Vokonas P, Schwartz J. Quantile Regression
579 Analysis of the Distributional Effects of Air Pollution on Blood Pressure, Heart Rate
580 Variability, Blood Lipids, and Biomarkers of Inflammation in Elderly American Men: The
581 Normative Aging Study. Environmental Health Perspectives. 2016;124(8):1189-98.
582 51. Burgette LF, Reiter JP, Miranda ML. Exploratory Quantile Regression With Many
583 Covariates An Application to Adverse Birth Outcomes. Epidemiology. 2011;22(6):859-66.
584 52. Ratcliff R, Thapar A, McKoon G. Individual differences, aging, and IQ in two-choice tasks.
585 Cognitive Psychology. 2010;60(3):127-57.
586 53. Jung SH. Quasi-likelihood for median regression models. Journal of the American Statistical
587 Association. 1996;91(433):251-7.
588 54. Koenker R, Bassett G. Regression Quantiles. Econometrica. 1978;46(1):33-50.
589 55. Koenker R, Hallock KF. Quantile regression. Journal of Economic Perspectives.
590 2001;15(4):143-56.
591 56. Wei Y, Pere A, Koenker R, He XM. Quantile regression methods for reference growth
592 charts. Statistics in Medicine. 2006;25(8):1369-82.
593 57. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive
594 Summary of The Third Report of The National Cholesterol Education Program (NCEP)
595 Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults
596 (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
597 58. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society Series
598 B-Statistical Methodology. 1972;34(2):187-+.
599 59. Cox DR. Partial Likelihood. Biometrika. 1975;62(2):269-76.

60. Dempster AP, Laird NM, Rubin DB. Maximum Likelihood from Incomplete Data Via Em Algorithm. Journal of the Royal Statistical Society Series B-Methodological. 1977;39(1):1-38.
61. Laird NM, Ware JH. Random-Effects Models for Longitudinal Data. Biometrics. 1982;38(4):963-74.
62. Rubin DB. Inference and Missing Data. Biometrika. 1976;63(3):581-90.
63. Ogihara T, Miki M, Kitagawa M, Mino M. Distribution of Tocopherol among Human-Plasma Lipoproteins. Clinica Chimica Acta. 1988;174(3):299-305.
64. Winbauer AN, Pingree SS, Nuttall KL. Evaluating serum alpha-tocopherol (vitamin E) in terms of a lipid ratio. Ann Clin Lab Sci. 1999;29(3):185-91.
65. Vanvliet T, Schreurs WHP, Vandenberg H. Intestinal Beta-Carotene Absorption and Cleavage in Men - Response of Beta-Carotene and Retinyl Esters in the Triglyceride-Rich Lipoprotein Fraction after a Single Oral Dose of Beta-Carotene. American Journal of Clinical Nutrition. 1995;62(1):110-6.
66. Redlich CA, Chung JS, Cullen MR, Blaner WS, Van Bennekum AM, Berglund L. Effect of long-term beta-carotene and vitamin A on serum cholesterol and triglyceride levels among participants in the Carotene and Retinol Efficacy trial (CARET) (vol 143, pg 427, 1999). Atherosclerosis. 1999;145(2):423-+.
67. Johnson CL, Paulose-Ram R, Ogden CL, Carroll MD, Kruszon-Moran D, Dohrmann SM, et al. National health and nutrition examination survey: analytic guidelines, 1999-2010. Vital Health Stat 2. 2013(161):1-24.
68. Ioannidis JP, Loy EY, Poulton R, Chia KS. Researching genetic versus nongenetic determinants of disease: a comparison and proposed unification. Sci Transl Med. 2009;1(7):7ps8.

69. Walter SD, Holford TR. Additive, Multiplicative, and Other Models for Disease Risks. American Journal of Epidemiology. 1978;108(5):341-6.
70. Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, et al. Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect. 2008;116(8):1092-7.
71. Varshavsky JR, Zota AR, Woodruff TJ. A Novel Method for Calculating Potency-Weighted Cumulative Phthalates Exposure with Implications for Identifying Racial/Ethnic Disparities among U.S. Reproductive-Aged Women in NHANES 2001-2012. Environ Sci Technol. 2016;50(19):10616-24.
72. Howard GJ, Webster TF. Contrasting theories of interaction in epidemiology and toxicology. Environ Health Perspect. 2013;121(1):1-6.
73. VanderWeele TJ. On the Distinction Between Interaction and Effect Modification. Epidemiology. 2009;20(6):863-71.
74. Pedersen EJ, Miller DL, Simpson GL, Ross N. Hierarchical generalized additive models in ecology: an introduction with mgcv. PeerJ. 2019;7:e6876.
75. Foster JC, Taylor JMG, Nan B. Variable selection in monotone single-index models via the adaptive LASSO. Stat Med. 2013;32(22):3944-54.
76. Yang H, Yang J. A robust and efficient estimation and variable selection method for partially linear single-index models. J Multivariate Anal. 2014;129:227-42.
77. Lai P, Wang QH, Lian H. Bias-corrected GEE estimation and smooth-threshold GEE variable selection for single-index models with clustered data. J Multivariate Anal. 2012;105(1):422-32.
78. Friedman JH, Stuetzle W. Projection Pursuit Regression. Journal of the American Statistical Association. 1981;76(376):817-23.

Table 3 Simulation results from PLSI PH model and Cox PH model

Variable	True rank	True coefficient	PLSI PH rank	PLSI PH estimate	PLSI PH 95% CI	PLSI PH Proportion of contribution (%)	Cox PH rank	Cox PH original estimate	Cox PH original 95% CI	Cox PH normed estimate	Cox PH normed 95% CI
Identity link function											
Environmental factors											
a-Tocopherol	1	0.560	1	0.546	(0.437, 0.656)	29.9	1	0.558	(0.428, 0.688)	0.546	(0.446, 0.646)
g-tocopherol	2	0.490	2	0.500	(0.427, 0.572)	25.0	2	0.511	(0.417, 0.605)	0.500	(0.428, 0.571)
Retinyl-palmitate	3	0.420	3	0.408	(0.297, 0.520)	16.7	3	0.418	(0.310, 0.526)	0.409	(0.301, 0.516)
Retinol	7	0.140	7	0.122	(0.029, 0.216)	1.5	7	0.125	(0.029, 0.221)	0.122	(0.034, 0.210)
3,3,4,4,5-pncb	8	0.070	8	0.059	(-0.039, 0.158)	0.4	8	0.061	(-0.040, 0.161)	0.059	(-0.033, 0.151)
PCB194	6	-0.210	6	-0.207	(-0.346, -0.068)	4.3	6	-0.212	(-0.351, -0.074)	-0.208	(-0.329, -0.087)
2.3.4.6.7.8.hxcdf	5	-0.280	5	-0.270	(-0.356, -0.183)	7.3	5	-0.275	(-0.367, -0.183)	-0.269	(-0.354, -0.185)
trans.b.carotene	4	-0.350	4	-0.388	(-0.467, -0.310)	15.1	4	-0.397	(-0.493, -0.302)	-0.389	(-0.465, -0.313)
Covariates											
Age		0.005		0.009	(0.001, 0.017)			0.009	(0.002, 0.016)		
Sex (female)		-0.076		-0.039	(-0.216, 0.138)			-0.039	(-0.217, 0.138)		
Ethnicity											
Non-Hispanic white		Ref		Ref				Ref			
Non-Hispanic black		-0.138		-0.135	(-0.367, 0.097)			-0.135	(-0.361, 0.091)		
Mexican American		0.175		0.114	(-0.116, 0.344)			0.114	(-0.107, 0.335)		
Other race		0.409		0.528	(0.118, 0.937)			0.528	(0.077, 0.978)		
Other Hispanic		0.355		0.477	(-0.021, 0.975)			0.477	(0.018, 0.936)		
Quadratic link function											
Environmental factors											
a-Tocopherol	1	0.560	1	0.526	(0.403, 0.648)	27.6	1	0.289	(0.124, 0.455)	0.861	(0.621, 1.101)
g-tocopherol	2	0.490	2	0.513	(0.296, 0.730)	26.3	3	0.098	(-0.011, 0.207)	0.292	(-0.024, 0.607)
Retinyl-palmitate	3	0.420	3	0.445	(0.231, 0.659)	19.8	6	0.037	(-0.088, 0.161)	0.109	(-0.253, 0.470)
Retinol	7	0.140	7	0.161	(0.041, 0.281)	2.6	4	-0.041	(-0.154, 0.072)	-0.122	(-0.465, 0.222)
3,3,4,4,5-pncb	8	0.070	8	0.061	(-0.023, 0.146)	0.4	8	0.013	(-0.102, 0.128)	0.040	(-0.305, 0.384)
PCB194	6	-0.210	6	-0.208	(-0.322, -0.093)	4.3	7	0.020	(-0.132, 0.172)	0.059	(-0.338, 0.457)
2.3.4.6.7.8.hxcdf	5	-0.280	5	-0.252	(-0.392, -0.113)	6.4	5	-0.039	(-0.138, 0.061)	-0.115	(-0.445, 0.215)
trans.b.carotene	4	-0.350	4	-0.355	(-0.477, -0.234)	12.6	2	-0.120	(-0.228, -0.012)	-0.358	(-0.637, -0.079)
Covariates											
Age		0.005		0.003	(-0.002, 0.008)			-0.005	(-0.012, 0.003)		
Sex (female)		-0.076		-0.081	(-0.269, 0.108)			-0.103	(-0.297, 0.092)		
Ethnicity											
Non-Hispanic white		Ref		Ref				Ref			
Non-Hispanic black		-0.138		0.044	(-0.211, 0.299)			0.083	(-0.154, 0.320)		
Mexican American		0.175		0.100	(-0.152, 0.352)			0.125	(-0.118, 0.369)		
Other race		0.409		0.186	(-0.438, 0.811)			-0.189	(-0.722, 0.345)		
Other Hispanic		0.355		0.096	(-0.567, 0.759)			-0.096	(-0.634, 0.442)		

657 **Table 4** Simulation results from PLSI mixed-effects model and linear mixed-effects model

Variable	True rank	True coefficient	PLSI ME rank	PLSI ME estimate	PLSI ME 95% CI	PLSI ME Proportion of contribution (%)	Linear ME rank	Linear ME original estimate	Linear ME original 95% CI	Linear ME normed estimate	Linear ME normed 95% CI
Identity link function											
Environmental factors											
a-Tocopherol	1	0.560	1	0.584	(0.469, 0.698)	34.1	1	0.590	(0.456, 0.723)	0.580	(0.519, 0.642)
g-tocopherol	2	0.490	2	0.481	(0.396, 0.566)	23.1	2	0.490	(0.401, 0.579)	0.482	(0.439, 0.525)
Retinyl-palmitate	3	0.420	3	0.402	(0.284, 0.520)	16.2	3	0.408	(0.302, 0.513)	0.401	(0.336, 0.467)
Retinol	7	0.140	7	0.091	(-0.025, 0.206)	0.8	7	0.088	(-0.011, 0.186)	0.086	(0.027, 0.145)
3,3,4,4,5-pncb	8	0.070	8	0.054	(-0.067, 0.175)	0.3	8	0.058	(-0.047, 0.164)	0.057	(0.000, 0.114)
PCB194	6	-0.210	6	-0.225	(-0.378, -0.072)	5.1	6	-0.236	(-0.372, -0.099)	-0.232	(-0.303, -0.160)
2.3.4.6.7.8.hxcdf	5	-0.280	5	-0.236	(-0.344, -0.128)	5.6	5	-0.241	(-0.331, -0.151)	-0.237	(-0.295, -0.179)
trans.b.carotene	4	-0.350	4	-0.386	(-0.475, -0.297)	14.9	4	-0.392	(-0.486, -0.298)	-0.386	(-0.433, -0.339)
Covariates											
Intercept		0.000		-0.069	(-0.426, 0.287)			-0.074	(-0.486, 0.339)		
Age		0.005		0.011	(0.004, 0.019)			0.011	(0.005, 0.018)		
Sex (female)		-0.076		-0.121	(-0.245, 0.003)			-0.125	(-0.302, 0.051)		
Ethnicity											
Non-Hispanic white		Ref		Ref				Ref			
Non-Hispanic black		-0.138		-0.225	(-0.368, -0.082)			-0.231	(-0.450, -0.012)		
Mexican American		0.175		0.030	(-0.123, 0.184)			0.027	(-0.195, 0.249)		
Other race		0.409		0.086	(-0.231, 0.403)			0.081	(-0.395, 0.557)		
Other Hispanic		0.355		0.811	(0.463, 1.158)			0.811	(0.322, 1.300)		
Time effect		1.000		0.978	(0.951, 1.005)			0.978	(0.947, 1.008)		
Quadratic link function											
Environmental factors											
a-Tocopherol	1	0.560	1	0.558	(0.500, 0.617)	31.2	1	0.526	(0.288, 0.764)	0.614	(0.565, 0.664)
g-tocopherol	2	0.490	2	0.499	(0.453, 0.544)	24.9	3	0.333	(0.176, 0.489)	0.389	(0.324, 0.454)
Retinyl-palmitate	3	0.420	3	0.422	(0.363, 0.482)	17.8	4	0.279	(0.090, 0.467)	0.325	(0.242, 0.409)
Retinol	7	0.140	7	0.167	(0.108, 0.227)	2.8	8	-0.006	(-0.181, 0.169)	-0.007	(-0.078, 0.064)
3,3,4,4,5-pncb	8	0.070	8	0.073	(0.024, 0.122)	0.5	6	0.216	(0.027, 0.405)	0.252	(0.164, 0.341)
PCB194	6	-0.210	6	-0.209	(-0.269, -0.149)	4.4	2	0.378	(0.137, 0.619)	0.441	(0.352, 0.531)
2.3.4.6.7.8.hxcdf	5	-0.280	5	-0.268	(-0.327, -0.209)	7.2	7	-0.061	(-0.221, 0.100)	-0.071	(-0.141, -0.001)
trans.b.carotene	4	-0.350	4	-0.335	(-0.388, -0.283)	11.3	5	-0.273	(-0.44, -0.106)	-0.319	(-0.381, -0.257)
Covariates											
Intercept		0.000		0.877	(0.653, 1.100)			2.202	(1.478, 2.925)		
Age		0.005		0.007	(0.004, 0.009)			-0.023	(-0.035, -0.011)		
Sex (female)		-0.076		-0.061	(-0.158, 0.036)			-0.150	(-0.465, 0.165)		
Ethnicity											
Non-Hispanic white		Ref		Ref				Ref			
Non-Hispanic black		-0.138		-0.078	(-0.206, 0.050)			-0.004	(-0.395, 0.387)		
Mexican American		0.175		0.219	(0.081, 0.358)			0.323	(-0.070, 0.717)		
Other race		0.409		0.642	(0.372, 0.911)			0.095	(-0.763, 0.953)		
Other Hispanic		0.355		0.152	(-0.093, 0.397)			-0.125	(-0.976, 0.726)		
Time effect		1.000		1.014	(0.987, 1.041)			1.013	(0.983, 1.044)		

658

659

660

661

662

663

664

Figure titles and legends

Fig. 1 Correlation matrix of Pearson correlation coefficients of 8 factors and triglycerides in NHANES 2002-2003 (N=800).

Fig. 2 Results from PLSI linear regression and multivariable linear regression in NHANES 2002-2003 (d=8, N=800). Bars show the estimated relative importance (absolute value of estimated coefficient) of 8 environmental factors on continuous triglycerides. Red/green color represents positive/negative effect. Error bars indicate 95% CIs.

Fig. 3 Results from PLSI quantile regression and multivariable quantile regression in NHANES 2002-2003 (d=8, N=800). Bars show the estimated relative importance (absolute value of estimated coefficient) of 8 environmental factors on three quartiles (25th, 50th, and 75th percentiles) of triglycerides. Red/green color represents positive/negative effect. Error bars indicate 95% CIs.

Fig. 4 Results from PLSI logistic regression and multivariable logistic regression in NHANES 2002-2003 (N=800). Bars show the estimated relative importance (absolute value of estimated coefficient) of 8 environmental factors on dichotomized triglycerides. Red/green color represents positive/negative effect. Error bars indicate 95% CIs.