# Supplementary Materials

## 1 Models for the Trend-in-Trend Design

### 1.1 Notation

The trend-in-trend design requires longitudinal data on individuals. We assume that there are $N$ individuals and $T$ time periods. Let $\mathrm{X}_i$ denote the vector of covariates associated with individual $i$, which represents intrinsic characteristics that might influence a particular exposure and/or outcome. $X_i$ can be either observed, unobserved, or partially observed. $X_i$ is assumed to follow a distribution $F$ across the population. $Z_i^t$ and $Y_i^t$ are exposure and outcome,respectively, for individual $i$ at time $t$. $G$ is the index for the subject's CEP group.

#### 1.1.1 Subject-Specific Model

The outcomes for individual $i$ are assumed to satisfy:

$$\mu_i^t = E[Y_i^t | Z_i^t, G, X_i] \tag{1}$$

$$h(\mu_i^t) = \beta_0 + \beta_1 Z_i^t + \beta_2 t + \gamma^T X_i \tag{2}$$

where h is referred to as the "link" function that transforms the expected outcome into a linear form of exposure, time, and covariates.

### 1.2 Population-Averaged Model

We derived an alternative model that has similar interpretations to that of the subject-specific model when $X_i$ is not fully observed. We started with the population-averaged model, in which the marginal expectation $\nu_i^t = E(Y_i^t | Z_i^t, G)$ is the focus. We assume the marginal expectation to satisfy:

$$\nu_i^t = E(Y_i^t | Z_i^t, G) \tag{3}$$

$$h^*(\nu_i^t) = \beta_0^* + \beta_1^* Z_i^t + \beta_2^* t + c(Z_i^t, G) \tag{4}$$

where $h^*$ is the link function and $c$ is a constant that depends on exposure and group.

It is worth noting that the vector $(\beta_0^*, \beta_1^*, \beta_2^*)$ describes how the population-averaged response rather than any individual's response depends on the fixed effects. This model is used when the difference in the population-averaged response among different groups with different risk factors (i.e., the marginal effect, the one estimated by randomized trials) is the focus rather than the change in an individual's response (i.e., the conditional effect). For example, if $Z_i^t$ indicates whether individual $i$ takes a drug at time $t$, and $Y_i^t$ is the presence/absence of an outcome, the population-averaged model estimates the difference in outcome rates between the treated and the untreated while the subject-specific model estimates the expected change in an individual's probability of the outcome given a change in treatment status. Coefficients of the population-averaged model are directly estimable from the aggregated data on treatment and outcome as the marginal expectation does not require knowledge of covariates or assumptions of the heterogeneity across individuals.

## 1.3 Connection between the Subject-Specific Model and the Population-Averaged Model

The subject-specific model and the population-averaged model have different uses and interpretations. However, if the two sets of coefficients $(\beta_0, \beta_1, \beta_2)$ and $(\beta_0^*, \beta_1^*, \beta_2^*)$ could be mathematically related, making inference on either one would be equivalent to making inference on the other. In particular, if the population-averaged model was re-parameterized using $(\beta_0, \beta_1, \beta_2)$, conclusions drawn from the group-level data could imply parameters for the subject-specific causal effect model*(15)*. In general:

$$\nu_i^t = E(Y_i^t | Z_i^t, G) = E(E(Y_i^t | Z_i^t, G, X_i^t)) = E(\mu_i^t) \tag{5}$$

$$h^{*-1}(\beta_0^* + \beta_1^* Z_i^t + \beta_2^* t + c(Z_i^t, G)) = \int h^{-1}(\beta_0 + \beta_1 Z_i^t + \beta_2 t + \gamma^T X_i) dF(X_i | Z_i^t, G) \tag{6}$$

Because of non-linearity, the link function $h$ that transforms $\mu_i^t$ into a linear form of the fixed and random effects does not necessarily do the same for $\nu_i^t$. In Zeger et al. *(6)*, cases of identity, log, probit, and logit link functions are discussed and the corresponding mathematical relations between $(\beta_0, \beta_1, \beta_2)$ and $(\beta_0^*, \beta_1^*, \beta_2^*)$ are listed.

### 1.3.1 Estimation of the causal effect

We now show how the TT method helps to make causal inference when $h$ and $h^*$ are both logit functions. We first stratify the entire population into five strata according to the quintiles of the estimated CEP, which is estimated based on the observed covariates via the logistic regression. For each subgroup $G$ and each time point t, we aggregate the individual-level

data to obtain quantities in the following $2 \times 2$ table

| | outcome $Y_i^t = 1$ | outcome $Y_i^t = 0$ | Total |
|---|---|---|---|
| Exposure $Z_i^t = 1$ | $n_{11}^t$ | $n_{10}^t$ | $n_1^t$ |
| Exposure $Z_i^t = 0$ | $n_{01}^t$ | $n_{00}^t$ | $n_0^t$ |

Because $h$ is the logit function, we have:

$$\begin{aligned} E(Y_i^t|Z_i^t, G) &= E(E(Y_i^t|Z_i^t, G, X_i)) \\ &= \int \frac{exp(\beta_0 + \beta_1 Z_i^t + \beta_2 t + \gamma^T X_i)}{1 + exp(\beta_0 + \beta_1 Z_i^t + \beta_2 t + \gamma^T X_i)} dF(X_i|Z_i^t, G) \end{aligned} \tag{7}$$

In general, there is no closed-form for the marginal mean as a function of the fixed effects and $\beta_1$ cannot be identified. However, an approximate form is available when we impose the following assumptions:
(1) Covariates and time have multiplicative effects on being exposed. i.e. $P(Z_i^t|X_i) = h_1(X_i)h_2(t)$.
(2) Covariates for all individuals in any subgroup G are random variables from an unknown distribution. i.e., $p(X_i|G) = f_G$.
(3) The outcome is a rare event, and therefore we can omit the denominator of the integrand in equation (7).

With these assumptions, we have:

$$\begin{aligned} E(Y_i^t|Z_i^t, G) &\approx \int exp(\beta_0 + \beta_1 Z_i^T + \beta_2 t + \gamma^T X_i) dF(X_i|Z_i^t, G) \\ &= exp(\beta_0 + \beta_1 Z_i^T + \beta_2 t) E(\gamma^T X_i|Z_i^t, G) \end{aligned} \tag{8}$$

In order to expand $E(\gamma^T X_i|Z_i^t, G)$, we compute the conditional distribution of covariates $X_i$ given $Z_i^T$ and $G$ using the Bayes rule:

$$\begin{aligned} p(X_i|Z_i^t = 1, G) &= \frac{p(Z_i^t = 1, X_i|G)}{p(Z_i^t = 1|G)} = \frac{p(Z_i^t = 1|X_i, G)p(X_i|G)}{p(Z_i^t = 1|G)} \\ &= \frac{p(Z_i^t = 1|X_i)p(X_i|G)}{p(Z_i^t = 1|G)} = \frac{h_1(X_i)h_2(t)f_G}{p(Z_i^t = 1|G)} \end{aligned} \tag{9}$$

$$\begin{aligned} p(X_i|Z_i^t = 0, G) &= \frac{p(Z_i^t = 0, X_i|G)}{p(Z_i^t = 0|G)} = \frac{p(Z_i^t = 0|X_i, G)p(X_i|G)}{p(Z_i^t = 0|G)} \\ &= \frac{p(Z_i^t = 0|X_i)p(X_i|G)}{p(Z_i^t = 0|G)} = \frac{f_G - h_1(X_i)h_2(t)f_G}{p(Z_i^t = 0|G)} \end{aligned} \tag{10}$$

Therefore,

$$p(X_i|Z_i^t = 1, G) = \frac{h_1(X_i)h_2(t)f_G}{p(Z_i^t = 1|G)} \tag{11}$$

$$p(X_i|Z_i^t = 0, G) = \frac{f_G - h_1(X_i)h_2(t)f_G}{p(Z_i^t = 0|G)} \tag{12}$$

Define the following constants which only depend on $G$

$$C_{1G} := \int exp(\gamma^T X_i) h_1(X_i) f_G dX_i \tag{13}$$

$$C_{2G} := \int exp(\gamma^T X_i) f_G dX_i \tag{14}$$

$$C_{3G} := \int h_1(X_i) f_G dX_i \tag{15}$$

The marginal expectation $E(Y_i^t | Z_i^t, G)$ now becomes:

$$E(Y_i^t | Z_i^t = 1, G) = exp(\beta_0 + \beta_1 + \beta_2 t) \frac{C_{1G}}{C_{3G}} \tag{16}$$

$$E(Y_i^t | Z_i^t = 0, G) = exp(\beta_0 + \beta_2 t) \frac{C_{2G} - C_{1G} h_2(t)}{1 - C_{3G} h_2(t)} \tag{17}$$

Equations (18) and (19) are covariates-free. In other words, the marginal expectation of outcome is the same across treated/control individuals within the same subgroup.
Because each $Y_i^t$ is a binary variable, aggregating outcomes for the treated and the control yield two binomial distributions. Consequently, we can write down the parametric likelihood for $(n_{11}^t, n_{01}^t, n_{10}^t, n_{00}^t)$:

$$n_{11} \sim Binomial(n_{11} + n_{10}, e^{\beta_0 + \beta_1 + \beta_2 t} \frac{C_{1G}}{C_{3G}}) \tag{18}$$

$$n_{01} \sim Binomial(n_{01} + n_{00}, e^{\beta_0 + \beta_2 t} \frac{C_{2G} - h_2(t) C_{1G}}{1 - h_2(t) C_{3G}}) \tag{19}$$

where $C_{1G}, C_{2G}, C_{3G}$ are unknown constants that depend on group.

$(\beta_0, \beta_1, \beta_2, C_{1G}, C_{2G}, C_{3G})$ are unknown parameters and can be estimated by maximizing the above likelihood using an optimization algorithm. In particular, $e^{\beta_1}$is the odds ratio of interest.

## 2 Simulation

We present a simulation study with population size $N$=250,000 and calendar periods $T = 20$.

The covariate vector $X_i^t = (X1_i^t, X2_i^t, X3_i^t, X4_i^t, X5_i^t)$, where $X1_i^t \sim N(2,1), X2_i^t \sim N(2,1), X3_i^t \sim Bernoulli(0.8), X4_i^t \sim Bernoulli(0.2), X5_i^t \sim Bernoulli(0.1)$. Three different scenarios are considered: 1) For each unit $i$, $X_i^t$ is sampled only once and fixed over time 2) $X_i^t$ is sampled independently for each calendar period 3) $X_i^t$ is sampled repeatedly for each calendar period with autocorrelation coefficient of 0.5, i.e., $corr(X_i^t, X_i^{t+1}) = 0.5$.

We choose $a_0 = -13, a_1 = c(1, 0.5, 0.1, 0.1, 0.1), a_2 = 0.9, a_3 = 0.03125$. We assign $Z_i^t$ to 1 with the probability of $e^{a_0 + a_1 X_i^t + a_2 t - a_3 t^2}$ for $t$ from 1 to

15 and the probability of $e^{a_0+a_1X_i^t+a_2t-(0.007+a_3)t^2}$ for $t$ from 16 to 20. The simulated simulated exposure has the "up-and-down" shape shown in Fig. 1, which mimics the exposure trend of a drug that becomes widely used after introduction, and is then withdrawn (e.g., rofecoxib).

We choose $\beta_0 = -4, \beta_1 = log(2.5), \beta_2 = 0.001, \beta_3 = c(0.1, 0.05, 0.01, 0.01, 0.01)$. We assign $Y_i^t$ to 1 with the probability of $\frac{exp(\beta_0+\beta_1Z_i^t+\beta_2t+\beta_3X_i^t)}{1+exp(\beta_0+\beta_1Z_i^t+\beta_2t+\beta_3X_i^t)}$. We then stratify the population into quintiles based on the CPEs estimated via logistic regression. As shown in Fig. 2, each quintile of cumulative probability of exposure exhibits a different trend of exposure prevalence over time.

We considere the following scenarios : (1), the OR takes values of 2.5, 2.0, 1.5, 1.0, i.e., $\beta_1 = log(2.5), log(2), log(1.5), 0$; (2) the strength of the CPE model has three levels quantified by 0, 2, and 4 omitted confounders out of 5 confounders in total, and a c-statistic is calculated for each level to gauge unobserved heterogeneity in factors affecting outcome; (3) the number of CPE strata is fixed to be 5. We compare the estimated OR with those calculated using the cohort method. The results, which are the average values of 1000 simulations, are summarized in Tables 1-3, corresponding three different scenarios of covariates sampling as described above.

# 3 Application to the Optum Clinformatics Database

## 3.1 Identification of Study Sample

Our study population was sampled using data extracted from the Optum Clinformatics database from April 1, 2000 through Dec 30, 2004. The University of Pennsylvania's institutional review board (IRB) has determined that research using OptumInsight data is exempt from IRB review. The sampling procedure is as follows:

(1) We identified all persons age 18 years or older in Optum who received one or more prescriptions for rofecoxib during the study period. For each rofecoxib-exposed person episode, we ascertained the first month and the last month of their continuous enrollment episode (or episodes, for persons with multiple enrollment episodes) during the study period. Thus, the unit of observation was the enrollment episode, defined as a period of continuous enrollment for a person. A person could contribute multiple episodes.

(2) For each rofecoxib-exposed episode, we randomly sampled, without replacement, nine rofecoxib-unexposed enrollment episodes with an enrollment start date on or before the rofecoxib-exposed subject's enrollment start date, and with an enrollment end date on or after the rofecoxib-exposed subject's enrollment end date. The rationale for this criterion was to ensure that

follow-up calendar time for untreated subjects includes all of the time of follow-up for exposed subjects. Thus, the study population contained ten times as many total episodes as there were rofecoxib-exposed enrollment episodes.

### 3.2 Definition of Outcomes (AMI, Hypoglycemia, Non-spine Bone Fracture)

We defined acute myocardial infarction (AMI) as the first occurrence of an any-position inpatient International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) code for 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, or 410.91 *(12)*.

We defined acute severe hypoglycemia as the first occurrence of an any-position emergency department or principal inpatient ICD-9-CM code for: a) 251.0, 251.1, or 251.2; or b) 250.8, 250.80, 250.81, 250.82, or 250.83—only if not co-occurring with 259.8, 272.7, 681, 681.0, 681.00, 681.01, 681.02, 681.1, 681.10, 681.11, 681.9, 682, 682.0, 682.1, 682.2, 682.3, 682.4, 682.5, 682.6, 682.7, 682.8, 682.9, 686.9, 707.1, 707.10, 707.11, 707.12, 707.13, 707.14, 707.15, 707.19, 707.2, 707.20, 707.21, 707.22, 707.23, 707.24, 707.25, 707.8, 707.9, 709.3, 730.0, 730.00, 730.01, 730.02, 730.03, 730.04, 730.05, 730.06, 730.07, 730.08, 730.09, 730.10, 730.11, 730.12, 730.13, 730.14, 730.15, 730.16, 730.17, 730.18, 730.19, 730.20, 730.21, 730.22, 730.23, 730.24, 730.25, 730.26, 730.27, 730.28, 730.29, or 731.8 *(13,14)*.

We defined non-spine bone fracture as the first occurrence of an any-position emergency department or inpatient ICD-9-CM code for 800.x–829.x. Of note, we did not include vertebral column fractures in our outcome definition based on findings from Vestergaard et al *(17)*.

### 3.3 Definition of Explanatory Variables (Rheumatoid Arthritis, Osteoarthritis)

We defined rheumatoid arthritis as the first occurrence of an any-position inpatient International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) code in range 714.0 - 714.4.

We defined osteoarthritis as the first occurrence of an any-position inpatient International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) code 715.9.

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