Causal inference based lifestyle coaching system for thyroid disease patients

[1]Youngin Kwon†, [1]Minhyun Kang†, [3]Kyubo Shin†, [3]Juhui Lee†, [1]Joonhyung Kim, [1]Yeongho Lee, [1,2]Gi-Soo Kim*,[3,4]Jae Hoon Moon*,

[1]Artificial Intelligence Graduate School, Ulsan National Institute of Science and Technology,

[2]Department of Industrial Engineering, Ulsan National Institute of Science and Technology,

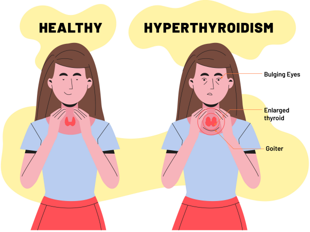
[3]R&D division, THYROSCOPE INC.,

[4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul National University Bundang Hospital

Contents

Introduction
Research Background

Symptoms of thyroid dysfunction including hypo- and hyperthyroidism are caused by low/high serum concentration of thyroid hormone.



Thyroid gland vector created by freepik - www.freepik.com

- 1.4 million(0.02%) Korean with thyroid disease in 2020.
- Monitored by blood test.
- Difficulty in early diagnosis and self-management.
- Medical expense from frequent hospital visits.

Introduction

Objective

- Daily habits may affect hormones and cause the symptoms.
- A lifestyle coaching system can help patients control their symptoms.
- Our approach: We provide coaching based on **causal inference**.

Example

Drinking $\xrightarrow[\text{Causal Effect}]{\text{Found}}$ Nervousness

Daily Survey:
Drinking 1
Smoking 0
Overwork 1
...

$\Longrightarrow$ Recommend to reduce drinking

Method

Causal Inference

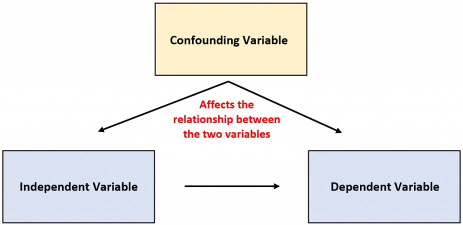
We aim to estimate population average treatment effect(ATE),

$$\tau = \mathbb{E}[Y_i(1) - Y_i(0)].$$

$Y_i(t)$: Potential outcome under treatment t of i-th patient.

T: Assigned Treatment $\in \{0(\text{control}), 1(\text{treated})\}$.

Correlation $\neq$ Causation. Confounding variables should be adjusted for causal inference.



Confounding variable created by statology - www.statology.org

Method
Assumptions

- Stable Unit Treatment Value Assumption(SUTVA)

  The outcome of one unit should be unaffected by the particular assignment of treatments to the other units.

Patient ID \ Treatment	P1 = T, P2 = C	P1 = T, P2 = T	P1 = C, P2 = T	P1 = C, P2 = C
1	140	130	125	120

- Strongly Ignorable

$$(Y(0), Y(1)) \perp T|X.$$

- Overlap

$$0 < P(T = 1|X) < 1.$$

Method

Causal Inference

There are two representative methods to estimate ATE: Regression Adjustment and Propensity Score Weighting.

Regression Adjustment

Patient ID	T	Y(1)	Y(0)
1	1	9.0	E(Y(0)|X=1)
2	1	9.0	E(Y(0)|X=1)
3	0	E(Y(1)|X=0)	1.0
4	0	E(Y(1)|X=1)	9.0
5	1	1.0	E(Y(0)|X=1)
6	0	E(Y(1)|X=0)	1.0
7	1	9.0	E(Y(0)|X=1)
8	0	E(Y(1)|X=0)	1.0
9	1	1.0	E(Y(0)|X=0)
10	0	E(Y(1)|X=0)	9.0

: X = 1, : X = 0

$$\hat{\tau} = \frac{1}{N}\sum_{i=1}^{N}[T_i\{Y_i - \mathbb{E}(Y_i(0)|X_i)\} + (1 - T_i)\{\mathbb{E}(Y_i(1)|X_i) - Y_i\}]$$

Propensity Score Weighting

Patient ID	T	Y(1)	Y(0)
1	1	9.0	?
2	1	9.0	?
3	0	?	1.0
4	0	?	9.0 **X 4**
5	1	1.0	?
6	0	?	1.0
7	1	9.0	?
8	0	?	1.0
9	1	1.0 **X 4**	?
10	0	?	9.0

: X = 1, : X = 0

$$\hat{\tau} = \frac{1}{N}\sum_{i=1}^{N}\left[\frac{T_i}{P(T_i = 1|X_i)}Y_i - \frac{(1 - T_i)}{P(T_i = 0|X_i)}Y_i\right]$$

Population Average Treatment Effect

Regression Adjustment

We assume linear models for conditional expectation of potential outcome ,

$$\mathbb{E}[Y(1)|X = x] = \beta_{10} + \beta'_{11}x$$
$$\mathbb{E}[Y(0)|X = x] = \beta_{00} + \beta'_{01}x.$$

Then the causal effect τ is given by

$$\begin{aligned}
\tau &= \mathbb{E}_x[\mathbb{E}[Y(1)|X = x] - \mathbb{E}[Y(0)|X = x]] \\
&= \mathbb{E}_x[(\beta_{10} - \beta_{00}) + (\beta'_{11} - \beta'_{01})x] \\
&= (\beta_{10} - \beta_{00}) + (\beta'_{11} - \beta'_{01})\mathbb{E}[x].
\end{aligned}$$

Population Average Treatment Effect

Regression Adjustment

The i-th outcome variable Y_i is given by

$$
\begin{aligned}
Y_i =& T_i Y_i(1) + (1 - T_i) Y_i(0) \\
=& T_i(\beta_{10} + \beta_{11}' x_i + \epsilon_1) + (1 - T_i)(\beta_{00} + \beta_{01}' x_i + \epsilon_2) \\
=& \alpha_0 + \tau T_i + \alpha_1' X_i + \alpha_2' \left(X_i - \bar{x} \right) T_i + \epsilon_i .
\end{aligned}
$$

Population Average Treatment Effect

Propensity Score Weighting

We can use the propensity score e(x) as a balancing score.

$$Y_i(1), Y_i(0) \perp T \mid e(x).$$

We assume the logistic model for the propensity score,

$$e(x) := \mathbb{P}\left(T = 1 | X = x\right) = \frac{\exp(x'\gamma)}{1 + \exp(x'\gamma)}.$$

We use the above value for the weight of the model.
Assume there are N number of patients each with N_i number of data. Then a weight of j-th data of the i-th patient is given by

$$\hat{\omega}_{i,j}(T_{i,j}, X_{i,j}) = \frac{1}{N_i}\left(\frac{T_{i,j}}{e(X_{i,j})} + \frac{1 - T_{i,j}}{1 - e(X_{i,j})}\right).$$

Population Average Treatment Effect

Weighted Least Square

Combining the two models, we use the weighted least square model,

$$v^* = \arg\min_{v} \frac{1}{N} \sum_{i=1}^{N} \sum_{j=1}^{N_i} \hat{\omega}_{i,j} \left(y_{i,j} - w'_{i,j} v \right)^2 ,$$

where $w_{ij} = [1, T_{ij}, x'_{ij}]'$ is a covariates vector of i-th patient's j-th data and $v = [\alpha_0, \tau, \alpha']'$ is a vector of coefficient.

The given method has doubly robust property:
the model is valid if at least one of two model assumption is valid.

Population Average Treatment Effect

Doubly Robustness

- Suppose

$$Y_{ij} \neq \alpha_0 + \tau T_{ij} + \alpha_1' X_{ij} + \alpha_2' (X_{ij} - \bar{x}) T_{ij} + \epsilon_{ij}$$

  but $e(X_{ij}) = \frac{\exp(X_{ij}'\gamma)}{1+\exp(X_{ij}'\gamma)}$.
- Weighting by $\hat{\omega}_i(T_{i,j}, X_{i,j})$ achieves balance between $T = 1$ group and $T = 0$ group $\Rightarrow$ T and X are **independent** after weighting.
- Even if the outcome model is wrong,

$$\hat{\tau} \to \mathbb{E}[Y_{i,j}(1)] - \mathbb{E}[Y_{i,j}(0)].$$

Variance estimation

Linearization Method

Let $f_1(\theta)$ and $f_2(\theta)$ be the estimation function for propensity score model and WLSE model, respectively, where $\theta = (\gamma, v)$.
We have

$$f(\hat{\theta}) = \begin{pmatrix} f_1(\hat{\theta}) \\ f_2(\hat{\theta}) \end{pmatrix} = 0.$$

We can estimate a variance of a θ with the linearization method.
By Taylor approximation,

$$\begin{aligned} 0 = \sqrt{N} f(\hat{\theta}) &\approx \sqrt{N} f(\theta^*) + \sqrt{N}(\hat{\theta} - \theta^*) \frac{d}{d\theta} f(\theta^*) \\ \Rightarrow \sqrt{N}(\hat{\theta} - \theta^*) &\approx \left(\frac{d}{d\theta} f(\theta^*) \right)^{-1} \sqrt{N} f(\theta^*). \end{aligned}$$

Variance estimation

Linearization Method

By the central limit theorem, our estimator has an asymptotic normality,

$$\sqrt{n}(\hat{\theta} - \theta^*) \xrightarrow{d} N(0, (D'\phi^{-1}D)^{-1}),$$

where $\phi = \mathbb{E}\left[f(\theta^*)f(\theta^*)'\right]$ and $D = \mathbb{E}\left[\frac{\partial f}{\partial \theta'}\right]$.

Individual Treatment Effect

Random Effect Model

We assume,

$$\begin{aligned} Y_{i,j} =& \alpha_0 + \tau T_{i,j} + \alpha_1^{'} X_{i,j} + \alpha_2^{'} \left(X_{i,j} - \bar{X}_i \right) T_{i,j} + b_{0i} + b_{1i} T_{i,j} + \epsilon_{i,j} \\ =& \alpha_0 + \alpha_1^{'} X_{i,j} + \alpha_2^{'} \left(X_{i,j} - \bar{X}_i \right) T_{i,j} + b_{0i} + (\tau + b_{1i}) T_{i,j} + \epsilon_{i,j} \end{aligned}$$

b_{0i}, b_{1i} are patient-specific effects. We assume $b_{0i}, b_{1i} \sim N(0, \sigma^2)$. The causal effect for the i-th patient is now

$$\tau + b_{1i}.$$

Because of normal distribution constraint on coefficients b_{0i} and b_{1i}, we use the value τ calculated from the previous model.

Experiment

Data Description

Data was gathered by Glandy™App of THYROSCOPE INC. from 150 hyperthyroidism patients for 15 months.

- X: covariate vector averaged over 28-day window
- Y: change in hyperthyroid symptom (average of 4th week−1st week)
- T: daily feature averaged over 28-day window and converted to binary value (whether larger or smaller than a criterion)

  (We moved the window with 7 days - stride.)
- There are 99 combinations of T and Y.

Type	Name of Feature	Basis	Description
Static Feature	birth		The year of the birth
	gender		Male or Female
	height		Height
	weight		Weight
Daily Feature	iodine_avg	$[0, 1]$	The averaged intensity of intaking iodine
	drinking_avg	$[0.235]$	The averaged intensity of drinking alcohol
	smoking_avg	$[0]$	The averaged intensity of smoking cigarette
	st_training_avg	$[0]$	The averaged duration of strength exercise (min.)
	cd_training_avg	$[10]$	The averaged duration of aerobic exercise (min.)
	over_work_avg	$[0]$	The averaged status of doing overwork or not
	shift_work_avg	$[0]$	The averaged status of doing shift work or not
	sleep_time_avg	$[300, 420]$	The averaged duration of sleep (min.)
	taken_avg	$[0.98]$	The averaged ratio of drug compliance
Hyperthyroidism Symptom	sense_of_weakness_delta		The changes for intensity of sense of weakness
	nervousness_delta		The changes for intensity of nervousness
	sweating_delta		The changes for intensity of sweating
	heat_intolerance_delta		The changes for intensity of sensitivity feeling heat
	hyperactivity_delta		The changes for intensity of hyperactivity
	tremor_delta		The changes for intensity of tremor
	diarrhea_delta		The changes for intensity of diarrhea
	appetite_delta		The changes for intensity of appetite
	daily_function_delta		The changes for intensity of function for daily life

Experiment

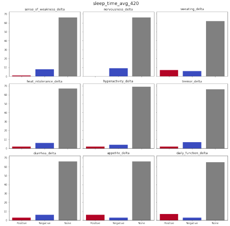
Result

We constructed a confidence interval of $\tau + b_{1i}$ for each patient. We provided coaching when the ITE showed that the habit significantly affects the symptoms.

- Positive: $0 <$ low CI $<$ high CI - Symptom is increased by treatment
- Negative: $0 >$ high CI $>$ low CI - Symptom is decreased by treatment
- None: low CI $< 0 <$ high CI

t	y	causal effect	sigma (std)	low_CI	high_CI	result
sleep_time_avg_420.0	hyperthyroidism_sense_of_weakness_delta	-0.178516578	0.040352691	-0.239045615	-0.117987542	Negative
sleep_time_avg_420.0	hyperthyroidism_nervousness_delta	-0.279891622	0.061166855	-0.371641905	-0.18814134	Negative
sleep_time_avg_420.0	hyperthyroidism_sweating_delta	0.031530062	0.063630302	-0.063915392	0.126975515	None
sleep_time_avg_420.0	hyperthyroidism_heat_intolerance_delta	-0.076458116	0.068044275	-0.178524528	0.025608296	None
sleep_time_avg_420.0	hyperthyroidism_hyperactivity_delta	-0.054736833	0.061734756	-0.147338967	0.0378653	None
sleep_time_avg_420.0	hyperthyroidism_tremor_delta	-0.113547796	0.030035607	-0.158601206	-0.068494386	Negative
sleep_time_avg_420.0	hyperthyroidism_diarrhea_delta	-0.164259532	0.124505974	-0.351018494	0.022499429	None
sleep_time_avg_420.0	hyperthyroidism_appetite_delta	0.040659106	0.060499201	-0.050089696	0.131407908	None
sleep_time_avg_420.0	hyperthyroidism_daily_function_delta	-0.006636931	0.045769904	-0.075291786	0.062017924	None

ATE for averaged sleep time with basis as 420min



ITE for averaged sleep time with basis as 420min

Experiment

Recommendation Example

요오드 섭취량의 갑상선 관련 증상에 영향을 주지 않는 것으로 분석됩니다.

흡연은 갑상선 관련 증상에 영향을 주지 않는 것으로 분석됩니다.

음주는 갑상선 관련 증상에 영향을 주는것으로 분석됩니다.

당신의 최근 1주일의 음주량은 하루 평균 소주 기준 0.2 잔(기준: 0.235 잔)입니다.

음주량을 유지하세요.

무산소운동은 갑상선 관련 증상에 영향을 주지 않는 것으로 분석됩니다.

유산소운동은 갑상선 관련 증상에 영향을 주지 않는 것으로 분석됩니다.

야간근무는 갑상선 관련 증상에 영향을 주지 않는 것으로 분석됩니다.

초과근무는 갑상선 관련 증상에 영향을 주지 않는 것으로 분석됩니다.

수면은 갑상선 관련 증상에 영향을 주는것으로 분석됩니다.

인과효과가 있는 증상 중, 최근 1주일 간 가장 큰 값을 가진 증상은 열불내성으로 더위를 많이 타는 증상입니다.

당신의 최근 1주일 수면량은 251 분(기준: 300 분)입니다.

평균 300분 이상의 수면을 권장해드려요.

현재 약제 복용이 증상에 큰 영향을 주지 않고 있습니다. 주치의와 상의하십시오.

Conclusion

- Our method analyzes causality between thyroid-associated symptoms and lifestyle of patients.
- It also provides estimates of heterogeneous, individual causal effect for each patients.
- It also correctly assesses the significance of causal effects.