Web appendix for "The application of target trials with longitudinal targeted maximum likelihood estimation to assess the effect of alcohol consumption in adolescence on depressive symptoms in adulthood"

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A. Covariates

Baseline covariates and time-invariant covariates

- Sex (female vs. male)
- Mothers' education (less university vs. some university)
- Whether the participant lives in a single-parent home (no vs. yes)
- Whether the participant speaks French at home (no vs. yes)
- Country of birth (outside Canada vs. Canada)
- Self-esteem
  The time-invariant variable was measured in the cycle 12 using Rosenberg's Self-Esteem Scale (1). Adolescents rated nine items over the past three months on a 3-point scale (*not at all true* to *very true*). Higher values indicate higher self-esteem (2).
- Impulsivity
  This time-invariant variable was assessed in the cycle 12 with an abbreviated version of the Eysenck Impulsivity Scale (3), which was previously validated among adolescents (4). Adolescents rated seven items on a 5-point scale (*not at all true* to *very true*) with higher scores indicating greater impulsivity (2).
- Novelty-seeking
  This time-invariate variable was assessed in the cycle 12 using nine items based on Cloninger's Tridimensional Personality Questionnaire (5) rated on a 5-point scale (*not at all true* to *very true*) with high scores indicating greater novelty-seeking (2).

Time-varying covariates

- Current depressive symptoms
  This variable is different from the outcome (i.e., the Major Depression Inventory). It was

measured with a validated six-item symptoms scale (6, 7). Items include: 1) felt too tired to do things; 2) had trouble going to sleep or staying asleep; 3) felt unhappy, sad or depressed; 4) felt hopeless about the future; 5) felt nervous or tense; 6) worried too much about things. Adolescents rated each item over the past three months using a 4-point response (*never* to *often*). The score was calculated as the mean value of the six items. Higher scores indicated higher levels of depressive symptoms.

- Participation in team sports (no vs. yes)
- Family stress
  Stress perception about family was measured using a validated scale over the past three months on a 4-point scale (*not at all* to *a whole lot*) with higher values indicating higher levels of stress (2).
- Other stress
  Types of stress other than family related the past three months on a 4-point scale (*not at all* to *a whole lot*) (2) with higher values indicating higher levels of stress.
- Worry about weight (no vs. yes)
- Ever smoked (no vs. yes)

Handling covariate missingness in the analysis

We imputed missing values of the covariates that were not due to censoring. (Missing values due to censoring were handled using LTMLE with censoring weights.) Last observation carried forward was used to impute information for no more than one full academic year of follow-up. Baseline and remaining time-varying covariate missingness were handled using multiple imputations by chained equations (MICE), mice `R` package (8), maintaining time-ordering of the follow-up variables. We imputed ten databases, ran the analyses, and combined estimates using Rubin's rules (9).

B. Major Depression Inventory scale items and depression severity

Depression severity was measured with the self-report Major Depression Inventory (MDI) (10, 11) in cycle 21. Participants asked how much time in the past two weeks they had: 1) felt low in spirit; 2) lost interest in or could no longer enjoy their daily activities; 3) felt a lack of energy and strength; 4) felt less confident; 5) had a bad conscience or feelings of guilt; 6) felt life was not worth living; 7) had difficulty concentrating; 8) felt very restless; 9) felt subdued or slowed down; 10) had trouble sleeping at night or waking up too early; 11) suffered from reduced appetite; and, 12) suffered from increased appetite. A score of four or more for items 1) and 2), and a score of three or more for the other items indicated a diagnostic demarcation for the depression symptom. For items 8) and 9), the highest score was retained for scoring, similarly for items 11) and 12). Based on a 6-point scale ranging from 0 (*no time*) to 5 (*all the time*) for each item, responses were summed to generate a continuous score from 0 to 50 with higher scores indicating more severe symptoms (6).

Depression severity is typically stratified based on the following cut-off points (6, 11): no or doubtful depression 0-20; mild depression 21-25; moderate depression 26-30; severe depression 31-50. Thombs et al. thought that one should be cautious when using cut-offs with self-reported questionnaires because cut-off thresholds are set to cast a wide net and identify substantially more participants who may have depression than those who actually meet diagnostic criteria (12).

C. Loss function

We have the observed data structure

$$O = \{\boldsymbol{W}, \boldsymbol{L}_1, A_1, \boldsymbol{L}_2, C_2, A_2 \cdots, \boldsymbol{L}_{19}, C_{19}, A_{19}, \boldsymbol{L}_{20}, C_{20}, Y\}.$$

By design, $C_1 = 0$ for all participants. Recall that we use the notation $\bar{\boldsymbol{L}}_t$ to denote the history of time-dependent covariates up to time t and likewise $\bar{A}_t$ represents the history of the exposure $A_1, \cdots, A_t$. We rescale the bounded continuous outcome Y to be contained in $(0, 1)$. Starting with $\bar{Q}_{21}(\bar{\boldsymbol{a}}^d) = Y$, we recursively define

$$\bar{Q}_t(\bar{\boldsymbol{a}}^d) = \mathbb{E}[\bar{Q}^d_{t+1} | \boldsymbol{W}, \bar{\boldsymbol{L}}_t, C_t = 0, \bar{\boldsymbol{A}}_t = \bar{\boldsymbol{a}}^d_t], \quad t = 20, \cdots, 1.$$

Note that these functions are produced depending on the realizations of $(\boldsymbol{W}, \bar{\boldsymbol{L}}_t)$ in the observed data and here we suppressed the notations for brevity. In words, $\bar{Q}_t(\bar{\boldsymbol{a}}^d)$ represents the counterfactual mean outcome at time t had past exposures been set to the pattern $\bar{\boldsymbol{a}}^d_{t-1}$ given the covariate history $(\boldsymbol{W}, \bar{\boldsymbol{L}}_t)$ under some specific treatment pattern $\bar{\boldsymbol{a}}^d \in \mathcal{D}$. We denote the logistic log-likelihood loss function $\mathcal{L}_{d,t}$ for $\bar{Q}_t(\bar{\boldsymbol{a}}^d)$ as

$$-\mathcal{L}_{d,t} = \mathbb{1}(\bar{\boldsymbol{A}}_t = \bar{\boldsymbol{a}}^d_t, C_t = 0) \times \left\{ \bar{Q}_{t+1}(\bar{\boldsymbol{a}}^d) \log[\bar{Q}_t(\bar{\boldsymbol{a}}^d)] + [1 - \bar{Q}_{t+1}(\bar{\boldsymbol{a}}^d)] \log[1 - \log \bar{Q}_t(\bar{\boldsymbol{a}}^d)] \right\}$$

where $\mathbb{1}(\cdot)$ is an indicator function. The true parameter values are computed by minimizing the risk under a squared error loss function where $\bar{Q}_1(\bar{\boldsymbol{a}}^d)$ should be transformed to the original scale. Then, the total loss is computed as follows,

$$\mathcal{L} = \sum_{t=1}^{20} \sum_{\bar{\boldsymbol{a}}^d \in \mathcal{D}} \mathcal{L}_{d,t} + \sum_{\bar{\boldsymbol{a}}^d \in \mathcal{D}} \left\{ \bar{Q}_1(\bar{\boldsymbol{a}}^d) - m(\text{sex}, \bar{\boldsymbol{a}}^d; \boldsymbol{\beta}^d) \right\}^2.$$

D. Identification of the parameter of interest

Under the assumptions discussed in manuscript, we can identify the parameter of interest using Iterated Conditional Expectations (ICE) (13).

$$
\begin{aligned}
&\mathbb{E}[Y(\bar{\boldsymbol{a}}^d)|\text{sex}] \\
=&\mathbb{E}[\mathbb{E}[Y(\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d)|\boldsymbol{W},\bar{\boldsymbol{L}}_{20},C_{20}=0]|\text{sex}] \\
=&\mathbb{E}[\mathbb{E}[Y(\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d)|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{20},C_{20}=0]|\text{sex}] && \text{(by randomization assumption)} \\
=&\mathbb{E}[\mathbb{E}[Y|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{20},C_{20}=0]|\text{sex}] && \text{(by consistency assumption)} \\
=&\mathbb{E}[\mathbb{E}[\mathbb{E}[Y|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{20},C_{20}=0]|\boldsymbol{W},\bar{\boldsymbol{L}}_{19},C_{19}=0]|\text{sex}] && \text{(by double expectation)} \\
=&\mathbb{E}[\mathbb{E}[\mathbb{E}[Y|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{20},C_{20}=0]|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{19},C_{19}=0]|\text{sex}] \\
&\vdots \\
=&\mathbb{E}[\mathbb{E}[\ldots\mathbb{E}[\mathbb{E}[Y|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{20},C_{20}=0]|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{19},C_{19}=0]\ldots|\boldsymbol{W},\boldsymbol{L}_1,A_1=a_1^d]|\text{sex}] \\
=&\mathbb{E}[\mathbb{E}[\ldots\mathbb{E}[\bar{Q}_{20}(\bar{\boldsymbol{a}}^d)|\bar{\boldsymbol{A}}_{19}=\bar{\boldsymbol{a}}_{19}^d,\boldsymbol{W},\bar{\boldsymbol{L}}_{19},C_{19}=0]\ldots|\boldsymbol{W},\boldsymbol{L}_1,A_1=a_1^d]|\text{sex}] \\
=&\mathbb{E}[\mathbb{E}[\ldots\bar{Q}_{19}(\bar{\boldsymbol{a}}^d)\ldots|\boldsymbol{W},\boldsymbol{L}_1,A_1=a_1^d]|\text{sex}] \\
&\vdots \\
=&\mathbb{E}[\bar{Q}_1(\bar{\boldsymbol{a}}^d)|\text{sex}]
\end{aligned}
$$

Therefore if we sequentially estimate the quantities $\bar{Q}_{t,n}(\bar{\boldsymbol{a}}^d)$ where the subscript n is used to denote an estimate of a quantity, we can ultimately obtain a plug-in estimator for $\mathbb{E}[Y(\bar{\boldsymbol{a}}^d) \mid \text{sex}]$.

E. Model specification

In the AT analysis, in the outcome models we included the main terms of the baseline and time varying covariates, three exposure terms and the first-order interactions of sex and three exposure terms (current and lagged) for uncensored participants. When specified as a GLM, we used the following for $t = 1, \cdots, 20$:

$$
\begin{aligned}
logit\{\bar{Q}_{t,n}(\bar{\boldsymbol{a}})\} \sim &\boldsymbol{W} + \boldsymbol{L}_{t-1} + \boldsymbol{L}_{t-2} + A_{t-1} + A_{t-2} + \mathbb{1}\left\{\left(\sum_{k=1}^{t-3} A_k\right) > 0\right\} + \\
&\text{sex} \times A_{t-1} + \text{sex} \times A_{t-2} + \text{sex} \times \mathbb{1}\left\{\left(\sum_{k=1}^{t-3} A_k\right) > 0\right\}
\end{aligned}
$$

where $\mathbb{1}(\cdot)$ is the indicator function and the variables with negative subscripts are to be disregarded. The treatment model was fit separately for each time $t = 1, \cdots, 19$. GLMs were specified as :

$$
logit\{P(A_t|\boldsymbol{W},\bar{\boldsymbol{A}}_{t-1},\bar{\boldsymbol{L}}_t,C_t=0)\} \sim \boldsymbol{W} + \boldsymbol{L}_t + \boldsymbol{L}_{t-1} + A_{t-1} + \mathbb{1}\left\{\left(\sum_{k=1}^{t-2} A_k\right) > 0\right\}
$$

The censoring model was also fit separately by time points $t = 1, \cdots, 20$ and where the GLM was specified as:

$$logit\{P(C_t = 0|\boldsymbol{W}, \bar{\boldsymbol{A}}_{t-1}, \bar{\boldsymbol{L}}_t, C_{t-1} = 0)\} \sim \boldsymbol{W} + \boldsymbol{L}_t + \boldsymbol{L}_{t-1} + \ A_{t-1} + A_{t-2} + \mathbb{1}\left\{\left(\sum_{k=1}^{t-3} A_k\right) > 0\right\}.$$

In the ITT analysis, the outcome models involved the two lagged exposure terms A_{t-1}, A_{t-2} and the corresponding interaction terms with sex in addition to the baseline and time varying covariates. Both the treatment model and censoring model were stratified by time point. The treatment model was fit using those who have not yet initiated and are uncensored. The model covariates were $\boldsymbol{W}, \boldsymbol{L}_t$, and $\boldsymbol{L}_{t-1}$. The censoring model was fit using those who were not yet censored and conditioned on $\boldsymbol{W}, \boldsymbol{L}_t, \boldsymbol{L}_{t-1}, A_{t-1}, A_{t-2}$.

F. Stabilized weight

Recall that the notation w_t^d represents the cumulative weight which is the cumulative product of the inverse of treatment and censoring probabilities from time one to t under specific treatment pattern $\bar{\boldsymbol{a}}^d$. In NDIT analysis, we used stabilized weights to adjust for the variable sex to update the initial outcome estimates in pooled LTMLE algorithm.

$$w_t^d = \prod_{k=1}^{t}\left\{\frac{P(A_k = a_k^d|C_k = 0, \text{sex})}{P(A_k = a_k^d|\bar{\boldsymbol{A}}_{k-1} = \bar{\boldsymbol{a}}_{k-1}^d, \boldsymbol{W}, \bar{\boldsymbol{L}}_k, C_k = 0)} \times \frac{P(C_k = 0|C_{k-1} = 0, \text{sex})}{P(C_k = 0|\bar{\boldsymbol{A}}_{k-1} = \bar{\boldsymbol{a}}_{k-1}^d, \boldsymbol{W}, \bar{\boldsymbol{L}}_k, C_{k-1} = 0)}\right\}.$$

G. Sequential G-computation algorithm

The sequential G-computation algorithm follows the steps in the identifiability argument, estimating each of the $\bar{Q}_t(\bar{\boldsymbol{a}}^d)$s for each pattern $\bar{\boldsymbol{a}}^d$ (or for each initiation time for the ITT analysis). Then these quantities are stacked. We also create a stacked vector corresponding to the treatment patterns ($\bar{\boldsymbol{a}}^d \in \mathcal{D}$). The stacked vector of the $\bar{Q}_t(\bar{\boldsymbol{a}}^d)$s is regressed on functions of the stacked baseline covariates and stacked treatment patterns corresponding to the marginal structural model of interest. The detailed steps are described in Table S1.

H. Simulation

We verified our hand-coded pooled LTMLE algorithm using two simulations with two-time points and estimated ITT and AT parameters. We simulated 500 datasets where we drew 100 participants from each of 50 clusters, resulting in a sample size of $5,000$. The simulation consists of n $i.i.d$ observations with data structure

$$O = \{S, W1, W2, L_0, A_1, L_1, C_1, A_2, L_2, C_2, Y\}$$

for the clustered setting (14). S is denoted as a continuous cluster level covariate, and $W1, W2, L_0$ are individual level baseline covariates. A_t is binary treatment assigned at time t for $t = 0, 1, 2$.

Table S1: Sequential G-computation algorithm

Algorithm: sequential G-computation

1. Scale the outcome Y to $(0,1)$ and define $\bar{Q}^d_{21,n} = Y$.
2. For $t = 20, \cdots, 1$.
   - 2.1 Fit logistic regression of the outcome $\bar{Q}_{t+1,n}$ on the history of all baseline covariates and time-varying covariates among those uncensored participants until time t with observed treatment patterns $(\bar{\boldsymbol{A}}_t, \bar{\boldsymbol{L}}_t, \boldsymbol{W})$.
   - 2.2 Generate $\bar{Q}_{t,n}$ for all participants by making predictions setting $\bar{\boldsymbol{A}}_t = \bar{\boldsymbol{a}}^d_t$ based on the given pattern $\bar{\boldsymbol{a}}^d$.
3. Rescale $\bar{Q}^d_{1,n}$ to the original scaling of Y.
4. Fit a pooled linear regression of $\bar{Q}^d_{1,n}$ on the stacked covariates and all treatment patterns $\mathcal{D}$ corresponding to the MSM model of equation (2) in manuscript.

Table S2: The simulation data generating mechanism for $J = 50$ studies and $n_j = 100$ ($for\ j = 1, 2, \cdots, J$) participants in each study.

Variable	Generating Mechanism
S	$S_j \sim N(mean = 0.5, sd = 1, n = J)$ Set $S_{ij} = S_j$ for all $i = 1, ..., n_j$.
$W1$	$W1_{ij} \sim N(mean = 0.5S_j, sd = 0.7, n = n_j)$
$W2$	$W2_{ij} \sim Bin(logit(p) = 0.5 + 0.8S_j, n = n_j)$
L_0	$L_{0,ij} \sim N(mean = 0.2 + 0.2W1_{ij} + 0.3W2_{ij}, sd = 0.7, n = n_j)$
A_1	$A_{1,ij} \sim Bin(logit(p) = 0.7W1_{ij} + 0.8W2_{ij} + 0.9L_{0,ij}, n = n_j)$
L_1	$L_{1,ij} \sim N(mean = 0.2W1_{ij} + 0.3W2_{ij} + 0.5L_{0,ij} + 0.5A_{1,ij}, sd = 1, n = n_j)$
C_1	$C_{1,ij} \sim Bin(logit(p) = -2.5 + 0.2W1_{ij} + 0.4W2_{ij} + 0.3L_{1,ij} + 0.2A_{1,ij}, n = n_j)$
A_2	Intention to treat $A_{2,ij} \begin{cases} = 1 & if\ A_{1,ij} = 1\ and\ C_{1,ij} = 0 \\ \sim Bin(logit(p) = 0.5W1_{ij} + 0.3W2_{ij} + 0.7L_{1,ij}, n = n_j) & if\ A_{1,ij} = 0\ and\ C_{1,ij} = 0 \\ NA & otherwise \end{cases}$ As treated $A_{2,ij} \begin{cases} \sim Bin(logit(p) = 0.5W1_{ij} + 0.3W2_{ij} + 0.7L_{1,ij}, n = n_j) & if\ C_{1,ij} = 0 \\ NA & otherwise \end{cases}$
L_2	$L_{2,ij} \begin{cases} \sim N(mean = 0.2W1_{ij} + 0.3W2_{ij} + 0.7L_{0,ij} + 0.4A_{1,ij}, sd = 0.8, n = n_j) & if\ C_{1,ij} = 0 \\ NA & otherwise \end{cases}$
C_2	$C_{2,ij} \begin{cases} \sim Bin(logit(p) = -3 + 0.2W1_{ij} + 0.4W2_{ij} + 0.3L_{2,ij} + 0.4A_{2,ij}, n = n_j) & if\ C_{1,ij} = 0 \\ NA & otherwise \end{cases}$
Y	$Y_{ij} \begin{cases} \sim [2S_{ij} + 0.6W1_{ij} + W2_{ij} + 0.4L_{1,ij} + 0.5L_{2,ij} + 0.3(A_{1,ij} + A_{2,ij}) + \\ \quad 0.2W2_{ij}(A_{1,ij} + A_{2,ij}) + \epsilon, n = n_j] \quad \text{where } \epsilon \sim N(mean = 0, sd = 1) & if\ C_{2,ij} = 0 \\ NA & otherwise \end{cases}$

L_1, L_2 are time-varying covariates. C_t is the censoring indicator with value 1 indicating being censored. The outcome Y is a continuous variable. The data generating mechanism is detailed described in Table S2.

We used the working marginal structural model:

$$m(W2, \bar{\boldsymbol{a}}^d; \boldsymbol{\beta}) = \beta_0 + \beta_1 W2 + \beta_2 cum(\bar{\boldsymbol{a}}^d) + \beta_3 \{cum(\bar{\boldsymbol{a}}^d) \times W2\}$$

where $cum(\cdot)$ is the cumulative function. As discussed previously, $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3)$ under the given loss function are our target parameters. We designed treatment strategies with respect to ITT analysis and AT analysis. Under ITT, there were three potential treatment patterns, $\bar{\boldsymbol{a}}^1 = (1, 1)$, $\bar{\boldsymbol{a}}^2 = (0, 1)$ and $\bar{\boldsymbol{a}}^3 = (0, 0)$. In the AT analysis there were four treatment patterns, with the additional $\bar{\boldsymbol{a}}^4 = (1, 0)$. We drew 500 samples; each sample involved 50 studies with 100 participants each, leading to a total sample size of $n = 5,000$.

The results of ITT and AT analyses are presented in Table S3. The true values of the target parameters of interest are displayed in the first row. The point estimates are unbiased for both ITT and AT. In addition, compared to the non clustered standard errors, clustered influence function based standard errors were closer to the Monte Carlo standard errors for the intercepts (β_0). A variance estimator that accommodates clustering would be expected to work better for β_0 specifically since we used random intercept terms but not random treatment effects in the outcome model.

Table S3: True values, mean estimates, and Monto Carlo standard error (MC-SD), non clustered standard error (SD) and clustered standard error (clu-SD) and the corresponding coverage rates in 500 samples for ITT and AT analysis

Results	ITT				AT			
	β_0	β_1	β_2	β_3	β_0	β_1	β_2	β_3
True value	0.06	1.95	0.59	0.20	0.09	1.95	0.59	0.20
Estimate	0.07	1.95	0.59	0.20	0.09	1.95	0.59	0.20
MC-SD	0.17	0.26	0.08	0.16	0.16	0.24	0.10	0.16
SD	0.14	0.30	0.08	0.18	0.13	0.27	0.10	0.18
clu-SD	0.17	0.31	0.08	0.17	0.16	0.28	0.09	0.18
Coverage	0.87	0.98	0.96	0.98	0.85	0.97	0.97	0.97
clu-Coverage	0.96	0.98	0.96	0.98	0.94	0.98	0.96	0.97

I.Extended NDIT analysis results

Table S4: Number of treatment patterns follow-up to each time t in AT analysis

t	19	18	17	16	15	14	13	12	11	10
$\lvert\mathcal{D}_t\rvert$	227	494	936	1,688	3,008	5,728	10,304	17,920	29,952	56,320
t	9	8	7	6	5	4	3	2	1	0
$\lvert\mathcal{D}_t\rvert$	86,016	124,928	180,224	294,912	393,216	491,520	524,288	524,288	524,288	524,288

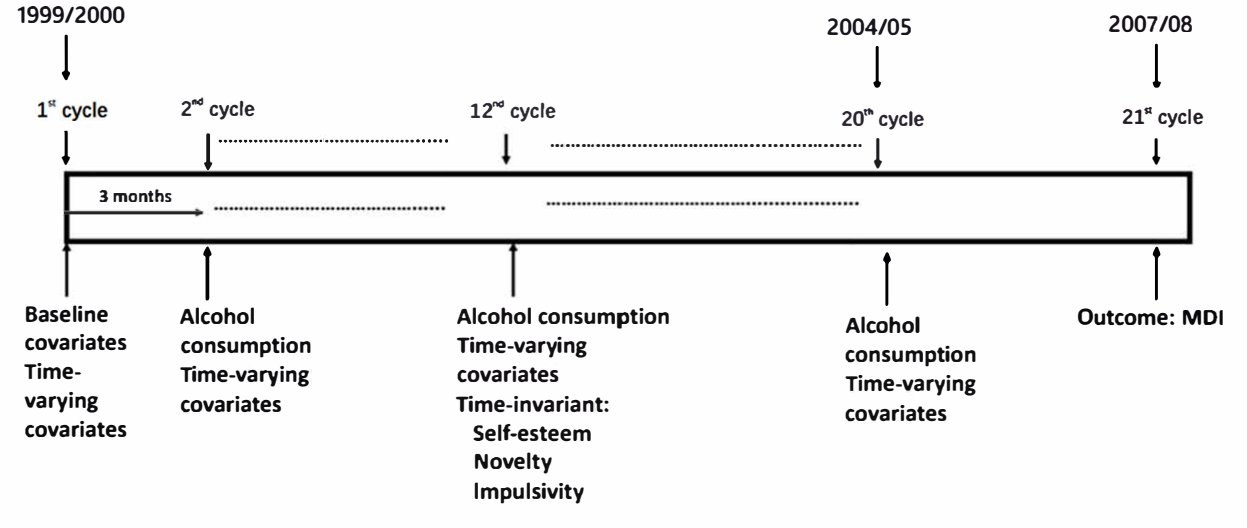

Figure S1: Follow-up in the NDIT study

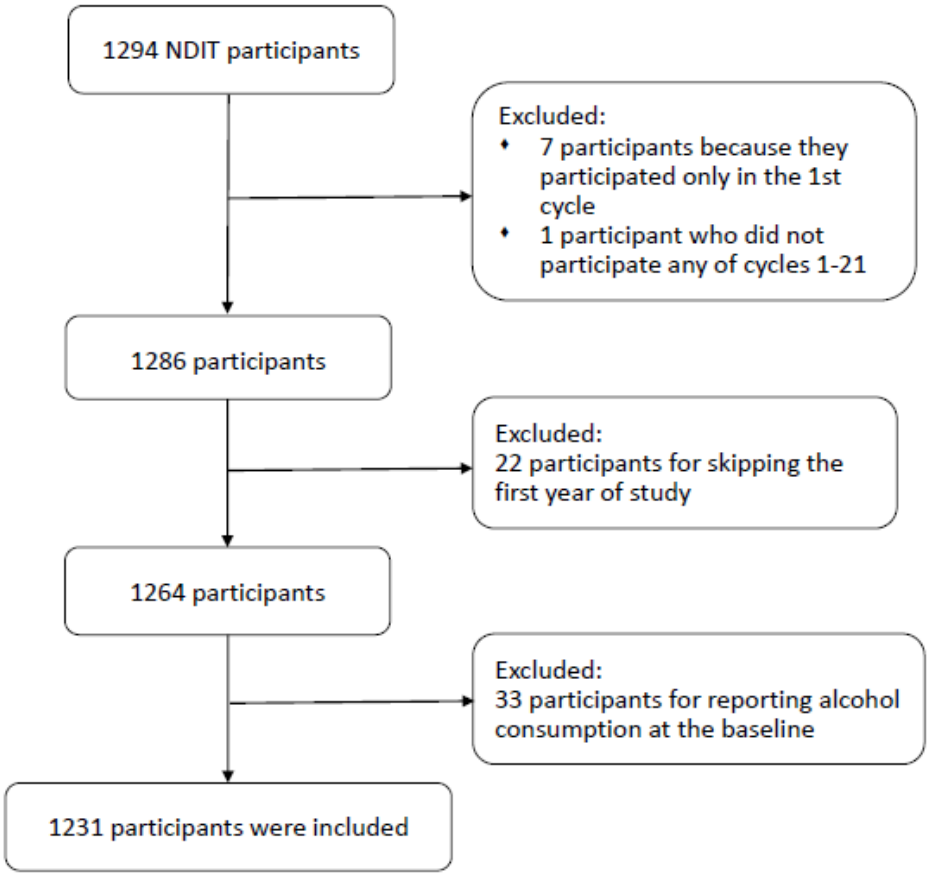

Figure S2: Flowchart of enrolled NDIT participants

Table S5: Results of ITT analysis: estimated coefficients, clustered standard errors and 95% confidence intervals.

Variables	**LTMLE-GLM**			**LTMLE-SL**			**G-comp**		
	$\hat{\beta}$	SE	CI	$\hat{\beta}$	SE	CI	$\hat{\beta}$	SE	CI
Intercept	8.19	0.21	[7.77, 8.61]	8.11	0.21	[7.71, 8.52]	7.82	0.42	[7.01, 8.64]
Sex	4.54	0.59	[3.37, 5.70]	4.77	0.60	[3.60, 5.94]	3.51	0.69	[2.16, 4.85]
cumA	0.05	0.02	[0.02, 0.08]	0.06	0.01	[0.04, 0.09]	0.03	0.02	[-0.00, 0.07]
Sex×cumA	-0.19	0.04	[-0.28, -0.11]	-0.22	0.04	[-0.30, -0.14]	-0.04	0.03	[-0.09, 0.02]

Table S6: LTMLE results of AT analysis involving 227, 494, 936 and 1,688 patterns under 1,000, 5,000 and 10,000 bounds of cumulative stabilized weights and sequential G-computation results of AT analysis involving 227 and 936 patterns: average estimate, clustered standard errors and 95% confidence intervals.

Method	**Bound**	**Variable**	**227 patterns**			**494 patterns**			**936 patterns**			**1,688 patterns**		
			$\hat{\beta}$	SE	CI	$\hat{\beta}$	SE	CI	$\hat{\beta}$	SE	CI	$\hat{\beta}$	SE	CI
G-Comp		Intercept	8.02	0.63	[6.79, 9.25]				8.00	0.54	[6.93, 9.07]			
		Sex	3.78	1.01	[1.81, 5.75]				3.46	0.88	[1.73, 5.19]			
		cumA	0.04	0.08	[-0.12, 0.19]				0.03	0.04	[-0.05, 0.11]			
		I(Sex_cumA)	-0.16	0.12	[-0.39, 0.07]				-0.10	0.07	[-0.23, 0.03]			
LTMLE	**1,000**	Intercept	4.21	1.23	[1.80, 6.62]	4.18	1.15	[1.93, 6.43]]	4.21	1.20	[1.86, 6.57]	4.50	1.18	[2.19, 6.81]
		Sex	4.70	1.54	[1.68, 7.72]	5.25	1.35	[2.61, 7.88]	4.95	1.39	[2.23, 7.68]	4.92	1.49	[1.99, 7.84]
		cumA	1.03	0.29	[0.47, 1.59]	0.95	0.26	[0.44, 1.46]	0.93	0.26	[0.41, 1.45]	0.82	0.25	[0.32, 1.32]
		I(Sex_cumA)	-0.32	0.35	[-1.00, 0.36]	-0.46	0.30	[-1.06, 0.13]	-0.40	0.30	[-0.98, 0.19]	-0.38	0.30	[-0.97, 0.22]
	5,000	Intercept	3.40	2.23	[-0.96, 7.77]	3.75	1.73	[0.36, 7.14]	3.89	1.43	[1.08, 6.70]	4.48	1.26	[2.02, 6.94]
		Sex	5.36	2.96	[-0.43, 11.16]	4.91	2.45	[0.11, 9.72]	4.65	2.04	[0.65, 8.65]	4.40	1.80	[0.88, 7.92]
		cumA	1.19	0.38	[0.44, 1.94]	1.00	0.33	[0.36, 1.64]	0.95	0.29	[0.37, 1.53]	0.77	0.27	[0.25, 1.29]
		I(Sex_cumA)	-0.00	0.58	[-1.15, 1.14]	0.04	0.52	[-0.98, 1.07]	0.10	0.46	[-0.80, 1.00]	0.16	0.40	[-0.63, 0.96]
	10,000	Intercept	4.26	3.59	[-2.77, 11.29]	4.72	2.67	[-0.50, 9.95]	4.82	2.00	[0.91, 8.73]	5.32	1.61	[2.16, 8.47]
		Sex	5.23	4.64	[-3.86, 14.31]	4.27	3.84	[-3.25, 11.80]	3.96	3.05	[-2.02, 9.94]	3.85	2.36	[-0.78, 8.49]
		cumA	1.00	0.49	[0.04, 1.96]	0.79	0.42	[-0.02, 1.61]	0.75	0.35	[0.07, 1.44]	0.60	0.29	[0.03, 1.17]
		I(Sex_cumA)	0.13	0.72	[-1.29, 1.56]	0.29	0.65	[-0.97, 1.56]	0.36	0.55	[-0.71, 1.43]	0.39	0.45	[-0.49, 1.26]

Table S7: LTMLE and sequential G-computation results of AT analysis including 936 patterns: average estimate, clustered standard errors and 95% confidence intervals.

Method	Bound	Variable	GLM			SL		
			$\hat{\beta}$	SE	CI	$\hat{\beta}$	SE	CI
G-comp		Intercept	8.00	0.54	[6.93, 9.07]			
		Sex	3.46	0.88	[1.73, 5.19]			
		cumA	0.03	0.04	[-0.05, 0.11]			
		I(Sex_cumA)	-0.10	0.07	[-0.23, 0.03]			
LTMLE	1,000	Intercept	4.21	1.20	[1.86, 6.57]	4.36	0.81	[2.77, 5.95]
		Sex	4.95	1.39	[2.23, 7.68]	4.35	0.93	[2.53, 6.17]
		cumA	0.93	0.26	[0.41, 1.45]	0.71	0.18	[0.36, 1.05]
		I(Sex_cumA)	-0.40	0.30	[-0.98, 0.19]	0.05	0.25	[-0.43, 0.53]
	5,000	Intercept	3.89	1.43	[1.08, 6.70]	3.68	2.07	[-0.39, 7.74]
		Sex	4.65	2.04	[0.65, 8.65]	2.34	2.81	[-3.17, 7.85]
		cumA	0.95	0.29	[0.37, 1.53]	0.81	0.49	[-0.15, 1.78]
		I(Sex_cumA)	0.10	0.46	[-0.80, 1.00]	0.92	0.78	[-0.62, 2.46]
	10,000	Intercept	4.82	2.00	[0.91, 8.73]	4.09	2.36	[-0.54, 8.71]
		Sex	3.96	3.05	[-2.02, 9.94]	1.60	2.91	[-4.09, 7.30]
		cumA	0.75	0.35	[0.07, 1.44]	0.71	0.57	[-0.40, 1.82]
		I(Sex_cumA)	0.36	0.55	[-0.71, 1.43]	1.21	0.68	[-0.13, 2.55]

J. Longitudinal modified treatment policies (LMTP)

Inspired by the hypothetical interventions where a subject's treatment is assigned based on the natural value of treatment first discussed by Robins et al (15) then formalized by other researchers (16, 17), Díaz et al (18) proposed longitudinal modified treatment policies (LMTP). LMTP involves a hypothetical intervention at each time point which can be expressed as a deterministic or random function of the observed treatment and the unit's covariate history. Specifically, the hypothetical intervention is characterized by a user-defined time-dependent function $\mathrm{d}_t(a_t, \boldsymbol{h}_t, \varepsilon_t)$ where ε_t is an independent random variable across units. Therefore, the function $\mathrm{d}_t(a_t, \boldsymbol{h}_t, \varepsilon_t)$ maps the observed exposed value a_t and the history $\boldsymbol{h}_t$ to generate a new exposure value A_t^{d}. The causal effects are then defined in terms of this intervention under typical assumptions including positivity and sequential randomization assumptions (18).

As an example of intervention function for binary exposures, the incremental propensity score intervention (19–21) shifts the propensity score at each time point. Here, we use a risk ratio incremental propensity score intervention where the observational treatment process is replaced by the hypothetical treatment policy based on a risk ratio to quantify the likelihood of exposure under the intervention. This can weaken the positivity assumptions required in the identification. We can express this intervention policy as an LMTP as follows.

Define $\boldsymbol{H}_t = (\boldsymbol{W}, \bar{\boldsymbol{A}}_{t-1}, \bar{\boldsymbol{L}}_t, C_t = 0)$. The propensity scores are denoted as $g_t(1|\boldsymbol{h}_t) = P(A_t = 1|\boldsymbol{h}_t)$. Let ε_t be a random variable following the uniform distribution (0,1). Then we can define the intervention function as (21):

$$\mathrm{d}_t(a_t, \boldsymbol{h}_t, \varepsilon_t) = \begin{cases} a_t & \text{for } \varepsilon_t < \kappa \\ 0 & \text{otherwise} \end{cases}$$

where κ is the user-defined increment parameter. Then the post-intervention propensity score $g_t^{\mathrm{d}}(1|\boldsymbol{h}_t)$ is equal to $\kappa g_t(1|\boldsymbol{h}_t)$, in other words, κ is indeed the risk ratio of exposure under LMTP and natural exposure (21). Then we define $A_t^{\mathrm{d}} = \mathrm{d}_t(A_t(\bar{A}_t^{\mathrm{d}}), \boldsymbol{H}_t, \varepsilon_t)$. The LMTP effect can be defined in terms of the hypothetical intervention as $\mathbb{E}[Y(\bar{\boldsymbol{A}} = \bar{\boldsymbol{a}}^{\mathrm{d}})]$, which is the expectation of counterfactual outcome had the patient received the hypothetical treatment at each time t.

The `lmtp` R package (available on https://github.com/nt-williams/lmtp and CRAN) can implement LTMLE to estimate the LMTP effects under specified treatment policies (18). Under LMTP, LTMLE requires a preliminary estimator of the density ratio as the nuisance parameter for the treatment mechanism in addition to the estimator for the outcome mechanism. The density ratio is the ratio of densities of A_t^{d} and A_t conditional on the covariate history $\boldsymbol{H}_t$(18), i.e. $r_t(a_t, \boldsymbol{h}_t) = g_t^{\mathrm{d}}(a_t|\boldsymbol{h}_t)/g_t(a_t|\boldsymbol{h}_t)$ which measures the extent to which the intervention d_t differs from the observed treatment.

In this paper we are interested in shifting the propensity score to discourage alcohol use in adolescents. Thus, we chose five values for $\kappa \in (0.1, 0.3, 0.5, 0.7, 0.9)$. We use `lmtp_tmle` function to estimate the LMTP effects under the five specified treatment policies and under no intervention and stratified by sex. The SuperLearner library we used to estimate these effects contained same functions as the pooled LTMLE algorithm described in the manuscript: generalized additive models (`gam` function), generalized linear models (`glm` function), and generalized linear models with penalized maximum likelihood (`glmnet` function). We customized the `glm` and `gam` functions by using the mean outcome as the prediction when any regression coefficient is not estimable due to data sparsity.

Estimated mean MDI and the 95% confidence intervals in males and females under LMTP and no intervention are presented in the Table S8. As in the results for the marginal structural model parameters in main manuscript, female is associated with greater depression under different LMTP policies (eg. 7.96 in male and 11.57 in female under no intervention). The contrasts of LMTP effects using three levels of risk ratios vs no intervention are shown in the Table S9. We can find that if we remove some participants' alcohol use under the five LMTPs, for both males and females, there was no obvious trend in the effects over different levels of drinking discouragement vs no intervention.

Table S8: Estimated mean MDI and 95% confidence intervals under LMTP. 'NA' in κ represents there was no intervention in the estimation (this was the reference for all comparisons).

κ	Female		Male	
	Estimates	CI	Estimates	CI
0.1	11.973	[11.054, 12.893]	8.173	[7.438, 8.908]
0.3	11.976	[11.208, 12.743]	7.943	[7.068, 8.818]
0.5	11.860	[10.969, 12.751]	8.026	[7.304, 8.747]
0.7	11.718	[10.761, 12.675]	8.076	[7.483, 8.668]
0.9	11.587	[10.804, 12.369]	8.049	[7.445, 8.652]
NA	11.568	[10.927, 12.209]	7.957	[7.450, 8.464]

Table S9: Estimated contrasts of LMTP effects with κ equals to $0.1, 0.5$ and 0.9. 'NA' in κ represents there was no intervention in the estimation.

κ	Population	Estimates	Contrasts	CI
NA	Male	7.957		
	Female	11.568		
0.1	Male	8.173	0.216	[-0.443, 0.876]
	Female	11.973	0.405	[-0.334, 1.145]
0.5	Male	8.026	0.069	[-0.435, 0.572]
	Female	11.860	0.292	[-0.519, 1.103]
0.9	Male	8.049	0.092	[-0.333, 0.517]
	Female	11.587	0.019	[-0.446, 0.483]

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