An Introduction to Inverse Probability of Treatment Weighting in Observational Research

Clinical Kidney Journal, 2022, vol. 15, no. 1, 14-20

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CEB

Scheme of presentation

- Introduction
- Case study on propensity score and IPTW
- Casual assumptions
- IPTW accounting for time-dependent confounding
- Inverse probability of censoring weighting to account for informative censoring
- Description of study using IPTW with time-varying covariates
- Advantages and limitations of IPTW

Introduction

- RCTs are considered the gold standard for evaluating the efficacy of an intervention
- Many research questions can not be studied in RCTs (Expensive, time-consuming, limited generalizability and ethical reasons)
- Observational studies suffer less from those limitations
- Lack of randomisation, comparison between exposed and unexposed groups is not straightforward

Introduction

- Various statistical methods are developed to control the confounders under strict assumptions
- Traditional approaches – stratification, multivariable regression
- Advanced approaches – propensity score-based analysis
- Apply weighting in longitudinal studies to deal with time-dependent confounding in the setting of treatment-confounder feedback and informative censoring

Case study (Background)

European Renal Association-European Dialysis and transplant Registry

EHD (> 6 hrs of HD)

Conventional HD (CHD)

Difference in characteristics

- Younger
- Less no. DM and Cardiovascular comorbidities
- Shorter time in dialysis
- Likely to receive a kidney transplant

Better Survival EHD

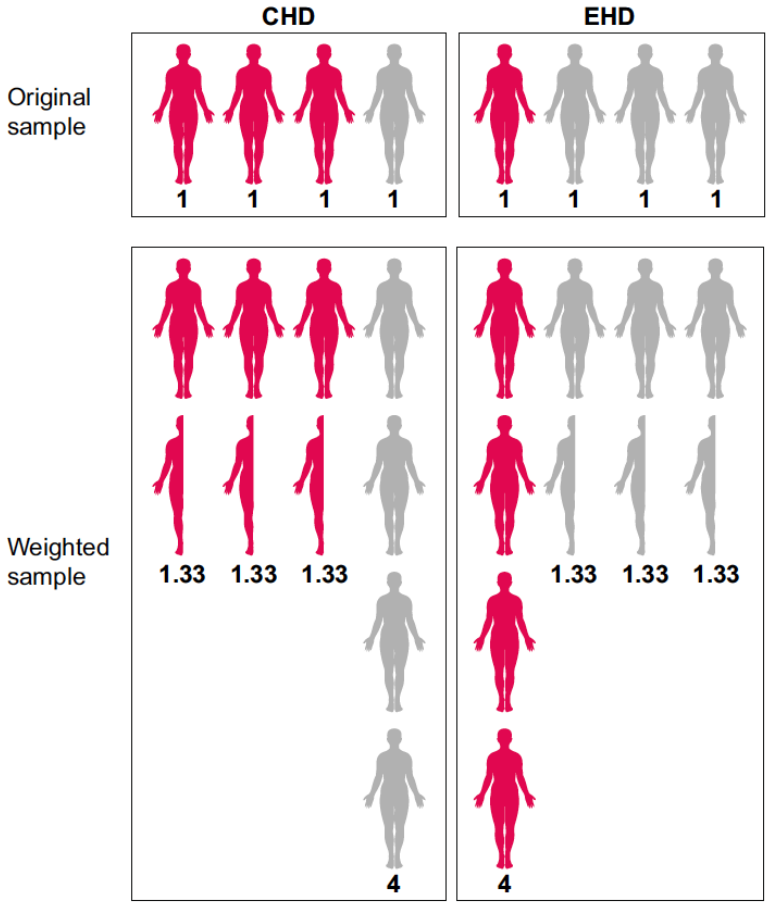
*EHD; extended hours of hemodialysis

Case study – propensity scores

- Calculated using logistic regression
- Probability of being treated with EHD versus CHD
- Baseline confounders as covariates- gender, age, dialysis vintage, received a transplant in the past and other various existing comorbidities
- Cubic spline for age- non-linearity of age and probability of EHD
- Included interaction term between sex and diabetes

Case study - IPTW

- IPTW estimators use propensity scores to balance characteristics between two groups
- Weight calculated as 1/ PS for exposed and (1/1-PS) for unexposed group
- Exposed individuals with a lower probability or vice versa received higher weights
- Example shown for diabetes in EHD and CHD group
- Weight represents not only the patients but also three additional patients
- Good practice is to check SMD



Things to do when SMD is large

- Propensity model should be revisited
  - Include interaction terms
  - Transformation
  - Splines
  - For continuous variables, check for distribution and variance between groups by using box plots and or Kolmogorov _Smirnov test
- Extreme weights- weight stabilization and or weight truncation

Thangs to do when SMD is large

- Weight stabilization can be achieved by replacing the numerator with a crude probability of exposure
- This can be calculated for each individual as
  - Proportion exposed /propensity score of exposed group
  - Proportion unexposed/ 1- propensity score
- Extreme weights can be addressed through truncation (trimming)
  - Typically truncated at the 1st and 99th percentiles

Case study - IPTW

- Once the weight is calculated, it can be incorporated into the outcome model
  - Weighted linear regression – continuous outcome
  - Weighted Cox regression – time to event outcomes
- Estimates the average treatment effects in the entire study population

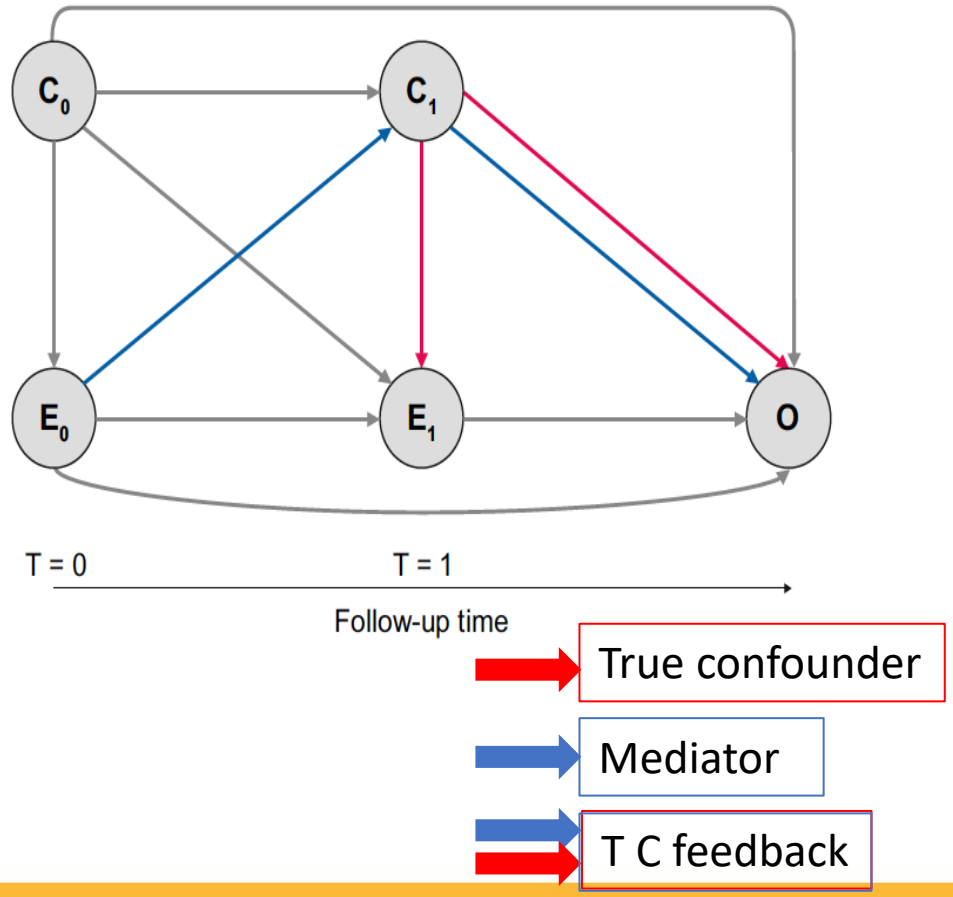
Causal assumptions

- IPTW is interpreted as causal under the following assumption
  - Conditional exchangeability
  - Positivity
  - Consistency or SUTVA

IPTW for time-depending confounding

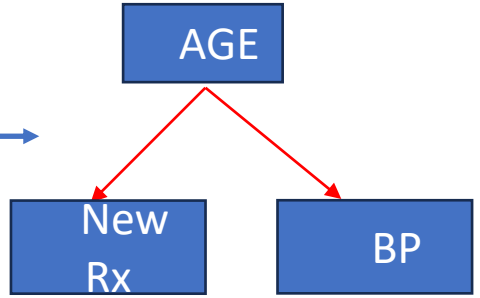
- In longitudinal studies, exposures, confounders and outcomes are measured repeatedly
- Requires additional adjustment for time-dependent confounders when estimating the effect of time-updated exposure on an Outcome
- Time-dependent confounders can also take the dual role of both confounder and mediator

T; treatment, C; confounder



Issues with example

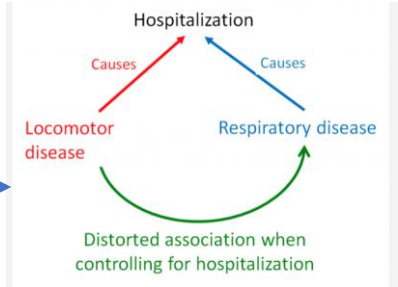
Treatment confounder feedback



Over adjustment bias

Physical activity > Cholesterol > risk of heart disease

Collider stratification bias



IPTW for a time depending confounders

- Estimate parameters of a marginal structural model and adjust for confounding measures over time
- Unlike procedures followed to calculate single weight for baseline confounders
- Separate weight is calculated for each measurement at each time point as the inverse probability of being exposed
  - Given the previous exposure status
  - The previous value of the time-dependent confounder
  - The baseline confounders

IPTW for a time depending confounders

- Creates a pseudo-population where covariate balance between groups is achieved over time
- Ensures that the exposure status is no longer affected by previous exposure nor confounders
- Extreme weights are dealt with in a similar way
- Once the covariate balance is achieved over time, effect estimates can be estimated
  - Using appropriate model
  - Treating each measurement, together with its respective weight as a separate observation

Inverse probability of censoring weighting to account for informative censoring

- Administrative censoring for time-to-event analysis
- Based on the assumption that the reason for censoring is unrelated to the event of interest
- Sometimes the censoring is directly related to certain patient characteristics
  - Poorer health status is likely to drop prematurely biasing the result toward health survivors
  - Censored patients are no longer able to encounter the event
  - Leading to fewer events and thus an overestimated survival probability

Inverse probability of censoring weighting (IPCW) to account for informative censoring

- Issues can be solved by up-weighting those remaining in the study who have similar characteristics to those who were censored – informative censoring
- IPCW calculated for each time point as
  - Up to the current time point
  - Given previous exposure and
  - Patient characteristics related to censoring
- Weight can be incorporated into the MSM model to estimate outcome

Statins were not associated with hepatocellular carcinoma after controlling for time-varying confounders in patients with diabetes

Journal of Clinical Epidemiology 150 (2022) 98-105

Background

- Hepatocellular carcinoma is one of the most common primary malignancies of the liver
- Ranked 6th in cancer incidence and 4th in the mortality
- SRMAs have shown diabetes has 2 to 3-fold higher risks of HCC incidence
- Hyperglycemia, insulin resistance, hyperinsulinemia and activation of insulin-like growth factor signaling pathway are the potential mechanism

Rationale

- Statin induces growth inhibition and apoptosis of HCC cell lines
- Observational studies have also reported a lower risk of HCC in statin users than in non-users
- Only two nested case-control studies have evaluated patients with diabetes
- Treatment decisions in an observational study using real-world data are complex and dynamic
- Liver disease may act as a time-varying confounder and also a mediator in the association between statin use and HCC

PICO

P: T2DM
I/E: Statin initiators
C: Non-initiators
O: Hepatocellular Carcinoma

Materials and methods

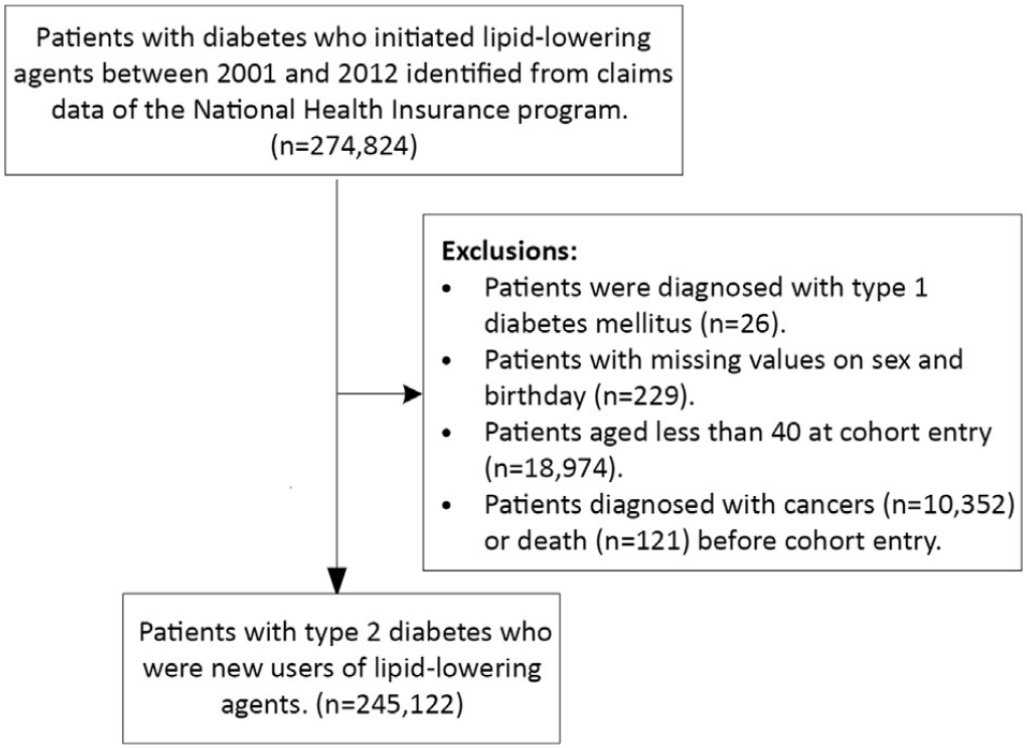


Fig. 1. Flow chart of the study.

Exposure measurements

- Cohorts – T2DM who were new users of lipid-lowering drugs
- Classified into two groups
  - Statin use- receipt of at minimum a cumulative 28 days prescription for statins within 180 days before cohort entry
  - No statin use- did not initiate
- At each 3-month time point categorised into mutually exclusive groups (statin users and non-users)
- Statin users- continue with the use of statin or requested prescription refills within 14 days

Outcomes

- HCC- newly diagnosed during the follow-up period (ICD-9-CM code 155.0) recorded by the Registry for Catastrophic Illness patients
- Verified by reviewing diagnosis certificates and pathological reports
- End date
  - Date of earliest occurrence of HCC
  - Any cause of cancer excluding HCC
  - Withdrawal from NHI
  - Death or study completion (December 31, 2013)

Baseline and time-varying covariates

- Baseline covariates
  - **Demographic variables-** age at the cohort entry, sex, geographic region of NHI registration, calendar year of cohort entry (2001-2003, 2004-2006, 2007-2009, and 2010 – 2012), utilisation of health services
  - **Comorbidities** – cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B and C
  - **Medications**- metformin, sulfonylurea, thiazolidinediones, other oral antidiabetic agents, insulin and aspirin
  - All covariates were evaluated in the year preceding cohort entry

Time-varying covariates

- **Comorbidities** – cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B and C
- Update every three months
- **Continuous variables** – follow-up time, age, duration from diagnosis to cohort entry, and number of outpatient visits were modelled as restricted cubic spline with three knots (5^{th}, 50^{th} and 95^{th} percentiles)

Statistical analysis

- Four models were constructed
- **Model 1**- a crude model that included time-varying statin exposure
- **Model 2**- additionally adjusted for all baseline covariates
- **Model 3**- Model 1 plus Model 2 and time-varying confounders
- **Model 4**- MSM with IPW (weighted model controlling for the potential confounding effects of baseline covariates and time-varying covariates)

Equation used for IPTW

- Estimation of inverse probability of treatment weights

$$sw_i^A(t) = \prod_{k=0}^{t} \frac{pr[A(k) = a_i(k) | \bar{A}(k-1) = \bar{a}_i(k-1), V = v_i]}{pr[A(k) = a_i(k) | \bar{A}(k-1) = \bar{a}_i(k-1), \bar{L}(k) = \tau_i(k)]}$$

- t= follow-up time treating 3 –months since cohort entry
- A(k)= status of receiving statin treatment at time k
- $sw_i^A(t)$ = the probability that individual *i* received statin therapy at time *k*, given his/her previous statin use (A (k-1) and time fixed baseline measured before follow-up started

Equation used for IPCW

- Estimation of inverse probability of censoring weights
- Patients were censored if they were diagnosed with other sites of cancers or died before the study

$$sw_i^C(t) = \prod_{k=0}^{t} \frac{pr[C(k) = 0 | \bar{C}(k-1) = 0, \bar{A}(k-1) = \bar{a}_i(k-1), V = v_i]}{pr[C(k) = 0 | \bar{C}(k-1) = 0, \bar{A}(k-1) = \bar{a}_i(k-1), \bar{L}(k) = \tau_i(k)]}$$

- $C(k)$ was the censoring indicator and defined $C(k)$=1 if patients were censored due to the above events by time *k* and $C(k)$=0 otherwise

To calculate final weights

- $swi(t)$ was calculated by $swiA(t) \times swiC(t)$
- To adjust for both confounding by indication and selection bias due to loss to follow-up

Best-fit Model selection of weight estimation

Supplemental Table 2 The distribution of stabilized weights produced by models with different specifications of continuous variables and the estimated hazard ratios for risk of hepatocellular carcinoma associated with statin use

Specification	Forms of continuous variables specified in the weight estimation	Mean	SD	Max	95th	Med	5th	Min	HR	95% CI
1	The continuous variables, months after cohort entry, age, duration from diabetes to cohort entry, and number of clinic visits in the previous year were included in both numerator and denominator and specified as linear terms.	1.002	0.262	247.962	1.020	1.000	0.975	0.093	1.14	0.97, 1.35
2	All the continuous variables in specification 1 were included in the numerator and denominator, but the linear terms were replaced with step functions (i.e., categories*).	1.002	0.309	309.922	1.020	1.000	0.974	0.087	1.13	0.94, 1.37
3	All the continuous variables in specification 1 were included in the numerator and denominator, but the linear terms were replaced with three-knot splines.	1.002	0.225	112.222	1.015	1.000	0.976	0.082	1.11	0.94, 1.31
4	Specification of continues variables was the same as those in the specification 3, plus a product term of months and statin use in the denominator.	0.982	1.372	1030.070	1.546	0.950	0.397	0.022	1.04	0.88, 1.23

* Continuous variables were categorized as follows: age: 40-54, 55-64, ≥65 years; duration from diabetes to cohort entry: <24, 24-47, 48-71, ≥ 72 months; number of outpatients visit in the previous year: <12, 12-23, 24-35, >35 visits.

Results

Table 1. Baseline characteristics of study participants

Characteristic	All participants (*n* = 245,122)		Noninitiators[a] (*n* = 56,248)		Statin initiators[a] (*n* = 188,874)	
	n	%	*n*	%	*n*	%
Women	117,022	47.7	21,993	39.1	95,029	50.3
Age, years						
40–54	91,845	37.5	25,140	44.7	66,705	35.3
55–64	78,240	31.9	16,140	28.7	62,100	32.9
≥65	75,037	30.6	14,968	26.6	60,069	31.8
Mean and SD	59.7	10.8	58.1	11.0	60.1	10.6
Duration from diabetes to cohort entry[b], month						
<24 mo	104,474	42.6	24,378	43.3	80,096	42.4
24–47 mo	60,641	24.7	15,048	26.8	45,593	24.1
48–71 mo	36,848	15.0	8,320	14.8	28,528	15.1
≥72 mo	43,159	17.6	8,502	15.1	34,657	18.4
Mean and SD	40.2	33.5	38.2	31.3	40.8	34.0
Calendar year of cohort entry[b]						
2001–2003	27,773	11.3	9,184	16.3	18,589	9.8
2004–2006	60,017	24.5	14,220	25.3	45,797	24.3
2007–2009	73,499	30.0	16,314	29.0	57,185	30.3
2010–2012	83,833	34.2	16,530	29.4	67,303	35.6
Geographic region of registration to the health insurance program						
Northern	99,518	40.6	21,272	37.8	78,246	41.4
Central	57,554	23.5	15,157	27.0	42,397	22.5
Southern	74,013	30.2	16,691	29.7	57,322	30.4
Eastern/offshore islands	14,037	5.7	3,128	5.6	10,909	5.8
Number of clinic visits in the year before cohort entry[b]	29.0	18.6	28.3	18.9	29.2	18.5
<12	21,226	8.7	5,638	10.0	15,588	8.3
12–23	96,233	39.3	22,829	40.6	73,404	38.9
24–35	64,853	26.5	14,111	25.1	50,742	26.9
≥35	62,810	25.6	13,670	24.3	49,140	26.0
Hospital admission in the year before cohort entry[b]	53,117	21.7	11,396	20.3	41,721	22.1
Proportion of days covered for lipid-lowering drugs[c]						
≥50%	186,561	76.1	41,097	73.1	145,464	77.0
≥80%	91,628	37.4	19,394	34.5	72,234	38.2
Comorbidities before cohort entry[b]						
Cirrhosis	4,129	1.7	1,302	2.3	2,827	1.5
Alcoholic liver damage	3,388	1.4	1,355	2.4	2,033	1.1
Nonalcoholic fatty liver disease	10,226	4.2	2,682	4.8	7,544	4.0
Hepatitis B and/or C infection	11,932	4.9	2,803	5.0	9,129	4.8
Prescriptions in the year before cohort entry[b]						
Metformin	172,672	70.4	39,300	69.9	133,372	70.6
Sulfonylurea	171,126	69.8	41,178	73.2	129,948	68.8
Thiazolidinediones	27,526	11.2	4,764	8.5	22,762	12.1
Other oral antidiabetic agents	51,828	21.1	10,052	17.9	41,776	22.1
Insulin	10,986	4.5	2,148	3.8	8,838	4.7
Aspirin	61,755	25.2	11,960	21.3	49,795	26.4

[a] Patients who initiated lipid-lowering drugs with statin and received at minimum a cumulative 28-day prescription for statins within 180 days prior to cohort entry were defined as statin initiators; other patients were defined as non-initiators.
[b] The date of 6 months after the first prescription for lipid-lowering drugs was defined as the date of cohort entry.
[c] Proportion of days covered for lipid-lowering drugs was assessed during the enrollment period.

Results comparing different models

Table 2. Hazard ratios for the association between statin use and risk of developing hepatocellular carcinoma

Model	Follow-up person years	Number of cases	Hazard ratio	95% CI
Model 1: Unadjusted model				
No use	722,826	1,054	1.00	
Statin use	567,378	640	0.74	0.67, 0.82
Model 2: Baseline (time-fixed) covariates[a]				
No use	722,826	1,054	1.00	
Statin use	567,378	640	0.88	0.79, 0.97
Model 3: Baseline and time-varying covariates[b]				
No use	722,826	1,054	1.00	
Statin use	567,378	640	0.97	0.87, 1.08
Model 4: MSM of IPW[a,c]				
No use	722,826	1,054	1.00	
Statin use	567,378	640	1.11	0.94, 1.31

Results

Table 3. Sensitivity analyses for the association between statin use and risk of developing hepatocellular carcinoma estimated using MSM with inverse probability weight

Sensitivity analysis	Follow-up person-years	Number of cases	Hazard ratio[a]	95% CI
MSM with IPTW				
No use	722,826	1,054	1.00	
Statin use	567,378	640	1.08	0.93, 1.24
SW of IPCW accounting for statin switch [b]				
No use	625,561	960	1.00	
Statin use	50,620	577	1.09	0.92, 1.30
Exposure did not lag				
No use	790,222	1,290	1.00	
Statin use	622,380	578	0.95	0.76, 1.17
Exposure lagged for 1 y				
No use	658,229	976	1.00	
Statin use	510,233	561	1.01	0.87, 1.18
Proportion of days covered ≥50%[c]				
No use	537,796	771	1.00	
Statin use	452,537	493	1.09	0.92, 1.30
Proportion of days covered ≥80%[c]				
No use	252,334	382	1.00	
Statin use	241,612	257	0.93	0.78, 1.10
Extreme SW was replaced by the 0.01th and 99.99th percentiles				
No use	722,826	1,054	1.00	
Statin use	567,378	640	1.03	0.92, 1.16
Trimmed SW between the 0.01th and 99.99th percentiles				
No use	722,683	1,051	1.00	
Statin use	567,250	635	0.98	0.88, 1.09

Abbreviations: IPCW, inverse probability of censoring weight; IPTW, inverse probability of treatment weight; MSM, marginal structural model; SW, stabilized weight.

Conclusion

- Chronic liver disease may be time dependent confounders
- Diagnosis of liver disease may affect physician decisions on initiating and dicontinuing at baseline or follow up
- Statin is not associated with the risk of developing HCC in patients with diabetes

Advantages of IPTW

- Summarize all patient characteristics into a single covariate (PS)
- Like other propensity-based methods, IPTW retain the most individual in the analysis increasing the effective sample size
- Estimate hazard ratio with less bias compared to PS stratification or adjustment
- Ability to appropriately correct the time-dependent confounders in the setting of treatment confounder feedback

Limitations of IPTW

- Caution to use with sample size < 150 due to the underestimation of variance (SE, CI and p values)
- Sensitive to misspecifications of PS model

Information sharing

- Do not blindly accept the findings from the study
- Look for the confounders, mediators and time-varying covariates in the study
- Look for whether an appropriate statistical technique has been applied


THANK
YOU !