Vitamin D and Acute Respiratory Viral Infections
A Large-scale Pharmacoepidemiologic Study

PSMG Presentation - January 26, 2021

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This material is the result of work supported with resources from the Center of Excellence for Suicide Prevention, Department of Veterans Affairs, Canandaigua, NY.

Support also was provided by the Department of Health Management and Policy of the University of Michigan.

Support was also provided by the Division of Hospital Medicine and Center for Health Statistics at the University of Chicago

The contents do not represent the views of the Department of Veterans Affairs or the United States Government.

None of the authors report conflicts of interest.

Overview

- Martineau et.al. BMJ (2017) meta-analysis of 25 RCTs of vitamin D (vD)
  - Acute respiratory infections
  - Overall: OR=.88 overall,
  - Vitamin D deficient (vDD): OR=0.3 in vDD deficient
  - Do these results generalize to the population?
- We studied Medicare, MarketScan, and VA Medical Claims Databases (44 million+150 million+18 million)
- Examine the association between vD prescriptions and acute viral respiratory infection (AVRI), influenza, and COVID-19
- AVRI - Within-subject design, with propensity-score matched control sample (difference in difference).
- COVID – Between-subject design, propensity score matched, time to event

Statistical Methods

- AVRI and influenza - Within-subject design.
- Compare rate of AVRI before and after index vD prescription in treated and controls
  - GEE Poisson model – population averaged (marginal) estimator
  - GEE and Mixed-effects logistic regression model for monthly analyses
    - Unit-specific (SAS, Stata, R)
    - Population averaged (SuperMix) see Hedeker et.al. 2018 *Biometrics*
  - D2 vs D3 monotherapy as separate analyses
  - DIF in DIF with monthly time trends pre and post exposure
    - Models with and without parallel time trend assumption
  - Time frame – AVRI and Influenza
    - +/- 12 months around index prescription fill

Statistical Methods

- Primary Analysis – Compare AVRI rate before and after 1st prescription fill in vD users and propensity matched controls (DID) using +/- 12-month interval
- Sensitivity analyses
  - Treat vD as a time-varying exposure in treated only
  - Restrict sample to patients with vitamin D deficiency (vDD) diagnoses
  - Compare counts pre and post averaging over time
- Model monthly time trends before and after treatment initiation
  - Code time as 0-11 pre and 0-12 post where post=0 is index script fill
  - Logit(AVRI) = b0 + b1*tx + b2*month + b3*period + b4*tx*month
    + b5*tx*period + b6*month*period + b7*tx*month*period

Statistical Methods

- COVID-19
  - Primary Analysis
    - Define cohort as anyone with a vitamin D prescription fill from 1/1/19-2/28/20, who never had a prior vitamin D prescription fill.
    - Matched controls with no vitamin D prescription history
    - Analysis time, March 2020 through December 2020
    - Compare treated and controls in terms of time to laboratory confirmed COVID-19 separately for D2 and D3
      - Discrete-time survival model
      - Kaplan Meier
      - Cox regression

Acute Respiratory Viral Infections

1. J00 - Acute nasopharyngitis [common cold]
2. J06 - Acute upper respiratory infections of multiple and unspecified sites
3. J09 - Influenza due to certain identified influenza viruses
4. J10 - Influenza due to other identified influenza virus
5. J11 - Influenza due to unidentified influenza virus
6. J12 - Viral pneumonia, not elsewhere classified
7. J18 - Pneumonia, unspecified organism
8. J20.4 - Acute bronchitis due to parainfluenza virus
9. J20.5 - Acute bronchitis due to respiratory syncytial virus
10. J20.6 - Acute bronchitis due to rhinovirus
11. J20.7 - Acute bronchitis due to echovirus
12. J21.0 - Acute bronchiolitis due to respiratory syncytial virus
13. J21.1 - Acute bronchiolitis due to human metapneumovirus
14. B34.0 - Adenovirus
15. B34.2 - Coronavirus infection, unspecified
16. B34.8 - Rhinovirus
17. B97.2 - Coronavirus as the cause of diseases classified elsewhere
    a. B97.21 - SARS-associated coronavirus as the cause of diseases classified elsewhere
    b. B97.29 - Other coronavirus as the cause of diseases classified elsewhere
18. B97.4 - Respiratory syncytial virus as the cause of diseases classified elsewhere

Top 15 Conditions for Cholecalciferol D3

Code	Description	Unique Patients	Proportion of Total Patients
4019	Unspecified essential hypertension	2,585	20.04%
2724	Hyperlipidemia	2,585	20.04%
25000	Diabetes mellitus	2,079	16.12%
53081	Esophageal Reflux	1,479	11.47%
2859	Anemia	1,347	10.44%
4011	Benign Essential Hypertension	1,341	10.40%
5990	Urinary Tract Infection	1,339	10.38%
2449	Hypothyroidism	1,237	9.59%
I10	Essential Hypertension (Primary)	1,206	9.35%
311	Depressive disorder, not elsewhere cl	1,196	9.27%
V5869	Long Term Use of Medications	1,179	9.14%
7295	Limb Pain	1,174	9.10%
2689	Vitamin D Deficiency	1,134	8.79%
V0481	Need for prophylactic vaccination and inoculation against influenza	1,127	8.74%
4280	Congestive Heart Failure	1,071	8.30%

Medicare Dosage Data - 2016

	Generic Name - Short Version	Drug Strength Description	scripts
1	ERGOCALCIFEROL (VITAMIN D2)	50000 UNIT	47792
2	CHOLECALCIFEROL (VITAMIN D3)	1000 UNIT	15824
3	CHOLECALCIFEROL (VITAMIN D3)	2000 UNIT	13708
4	CALCIUM CARBONATE/VITAMIN D3	600 MG-400	10338
5	CALCIUM CARBONATE/VITAMIN D3	500 MG-200	4504
6	CHOLECALCIFEROL (VITAMIN D3)	50000 UNIT	3722
7	CHOLECALCIFEROL (VITAMIN D3)	5000 UNIT	2882
8	CHOLECALCIFEROL (VITAMIN D3)	10000 UNIT	1864
9	CHOLECALCIFEROL (VITAMIN D3)	400 UNIT	1614
10	CALCIUM CARBONATE/VITAMIN D3	500 MG-400	1351
11	CALCIUM CARBONATE/VITAMIN D3	600 MG-200	1252
12	DOXERCALCIFEROL	0.5 MCG	1177
13	ALENDRONATE SODIUM/VITAMIN D3	70 MG-2800	1096
14	CALCIUM CARBONATE/VITAMIN D3	600 MG-800	1092
15	DOXERCALCIFEROL	1 MCG	975
16	CALCIUM CITRATE/VITAMIN D3	315 MG-250	822
17	DOXERCALCIFEROL	2.5 MCG	502
18	CALCIUM CITRATE/VITAMIN D3	200 MG-250	395
19	ALENDRONATE SODIUM/VITAMIN D3	70 MG-5600	337
20	CALCIUM CARBONATE/VITAMIN D3	250 MG-125	75
21	CHOLECALCIFEROL (VITAMIN D3)	400/ML	70
22	CALCIUM CARBONATE/VITAMIN D3	500 MG-100	53

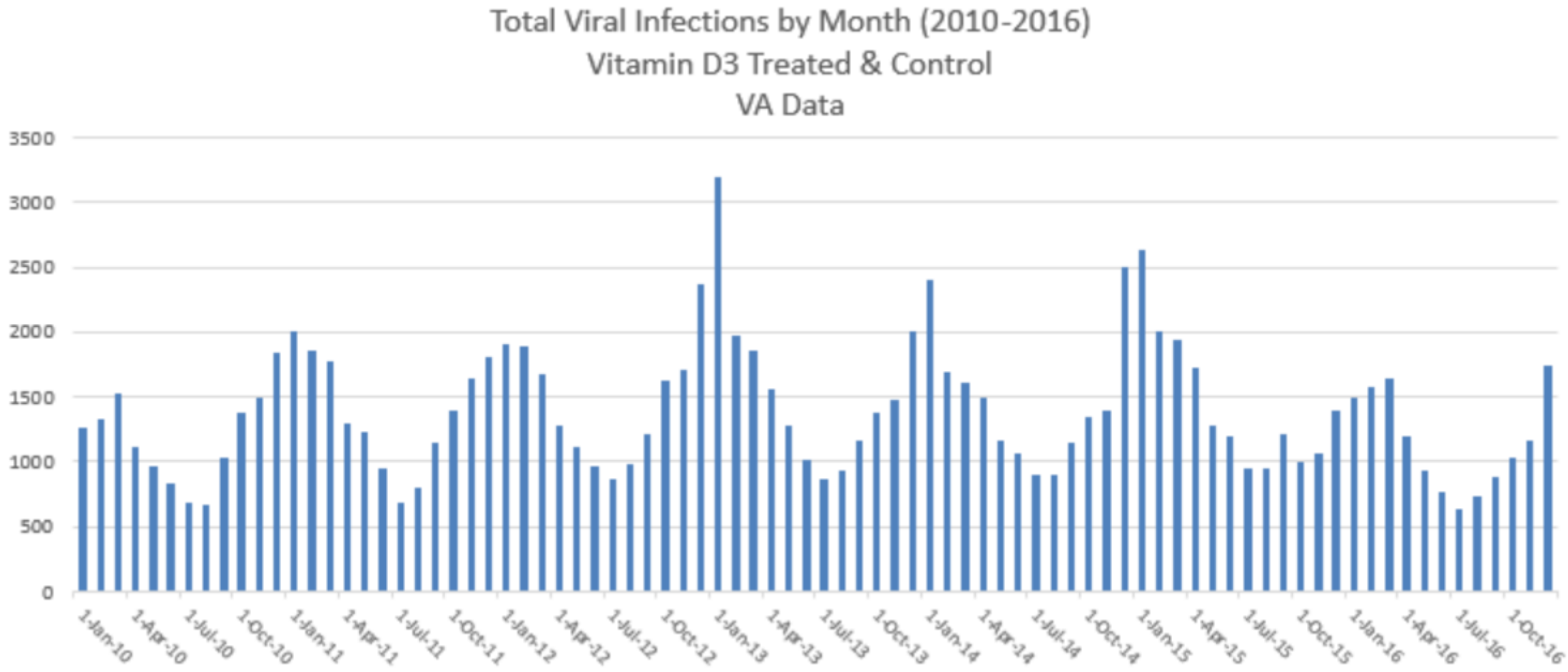
Matching Variables

- Hypertension
- Hyperlipidemia
- Diabetes
- In need of immunization (e.g., flu)
- Reflux
- Anemia
- Hypothyroidism
- Long Term Use Medications
- Limb Pain
- Fatigue
- Hypercholesterolemia
- Depression
- Congestive Heart Failure
- Age
- Sex
- Race
- Control index date set to treated Vitamin D index date

Available Data (All Ages)

- **Medicare** – 2010-2016
  - D2 N = 59,216
  - D3 N = 140,805
- **MarketScan** – 2010-2016
  - D2 N = 2,530,703
  - D3 N = 30,262
- **VA** – 2010-2020
  - D2 N = 815,455
  - D3 N = 1,355,889

VA Results


Total Viral Infections by Month (2010-2016)
Vitamin D3 Treated & Control
VA Data
3500
3000
2500
2000
1500
1000
500
0
1-Jan-10
1-Apr-10
1-Jul-10
1-Oct-10
1-Jan-11
1-Apr-11
1-Jul-11
1-Oct-11
1-Jan-12
1-Apr-12
1-Jul-12
1-Oct-12
1-Jan-13
1-Apr-13
1-Jul-13
1-Oct-13
1-Jan-14
1-Apr-14
1-Jul-14
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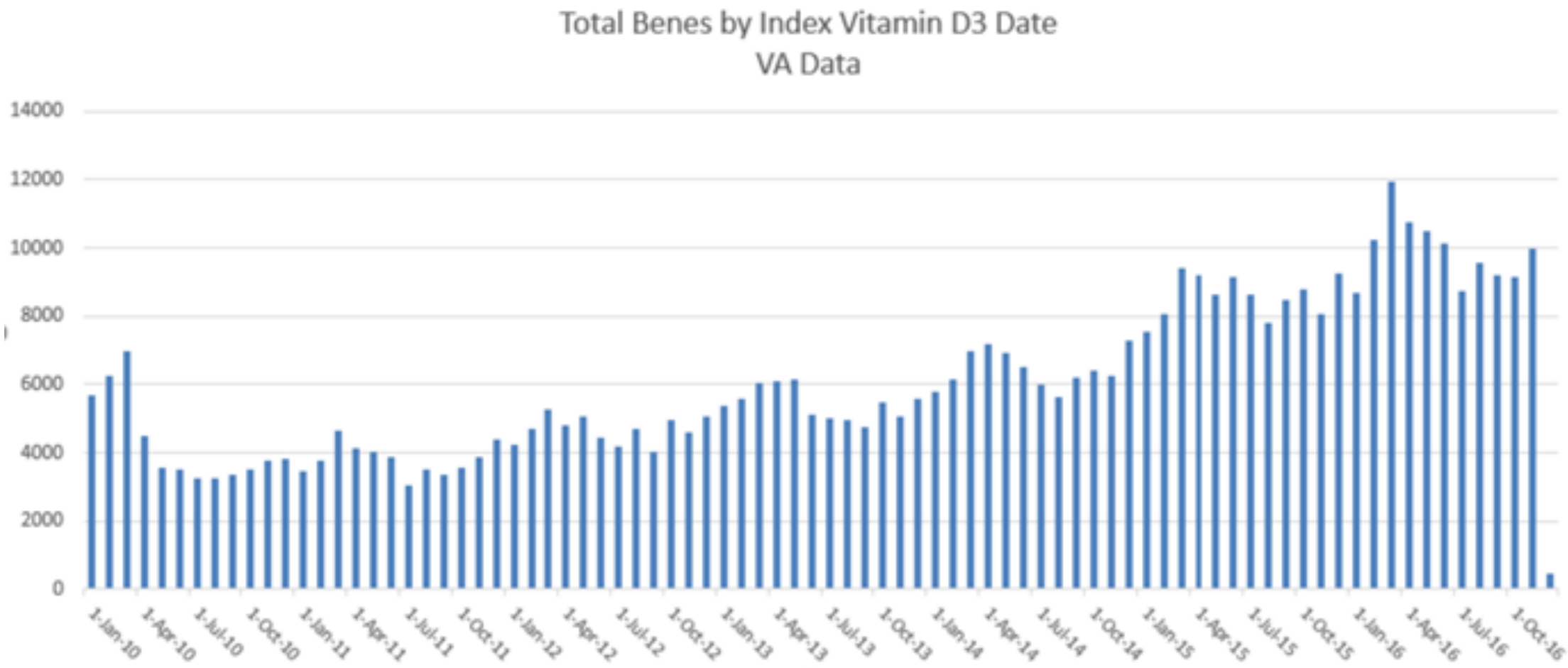
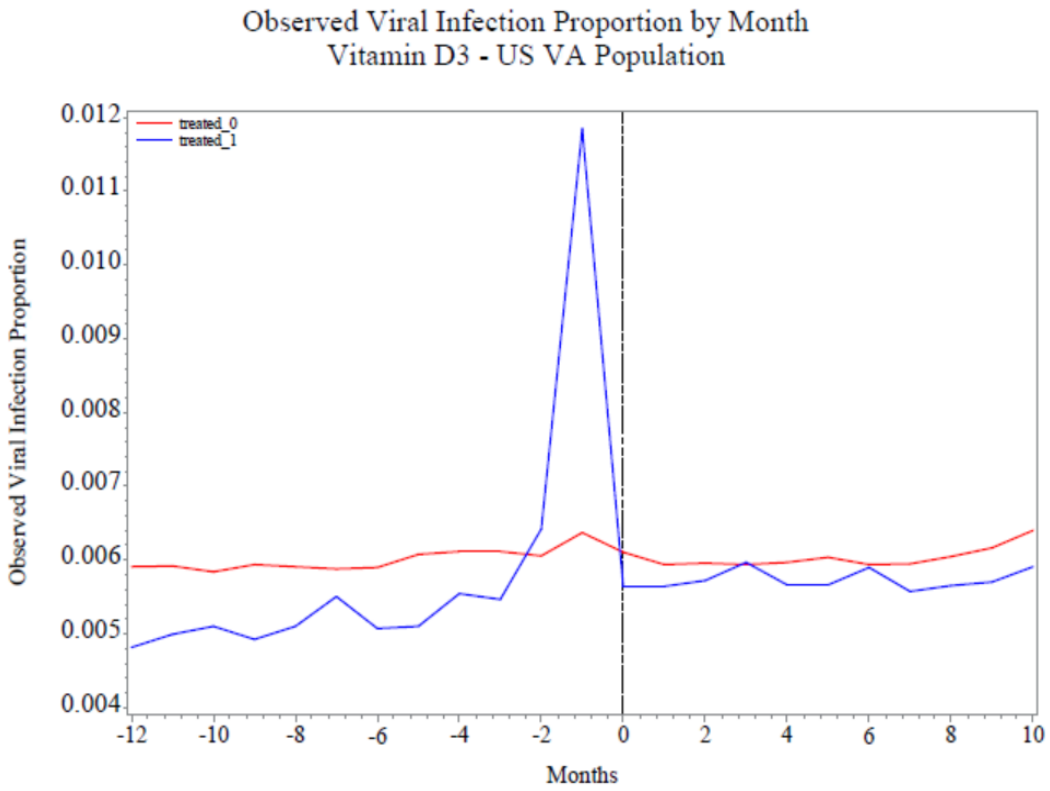
1-Jan-16
1-Apr-16
1-Jul-16
1-Oct-16

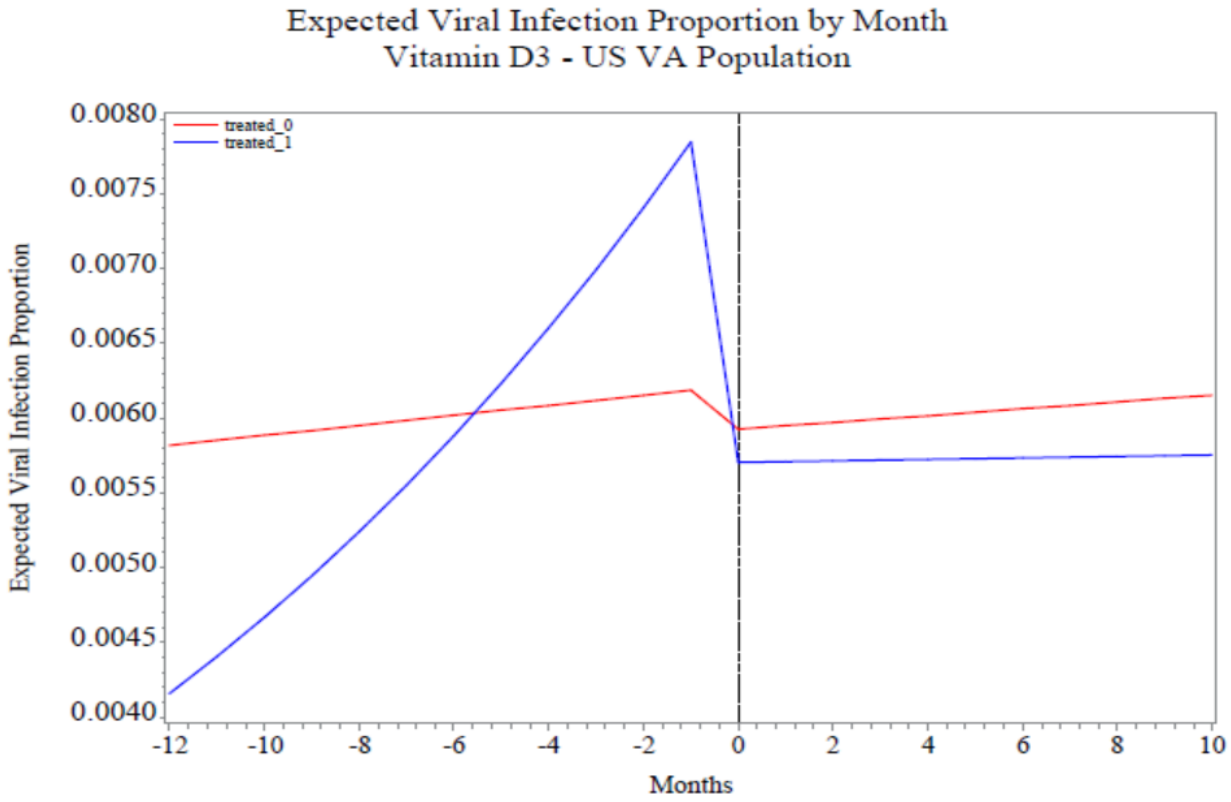

Total Benes by Index Vitamin D3 Date
VA Data
14000
12000
10000
8000
6000
4000
2000
0
1-Jan-10
1-Apr-10
1-Jul-10
1-Oct-10
1-Jan-11
1-Apr-11
1-Jul-11
1-Oct-11
1-Jan-12
1-Apr-12
1-Jul-12
1-Oct-12
1-Jan-13
1-Apr-13
1-Jul-13
1-Oct-13
1-Jan-14
1-Apr-14
1-Jul-14
1-Oct-14
1-Jan-15
1-Apr-15
1-Jul-15
1-Oct-15
1-Jan-16
1-Apr-16
1-Jul-16
1-Oct-16

VA Data: D3 vs AVRI

Observed



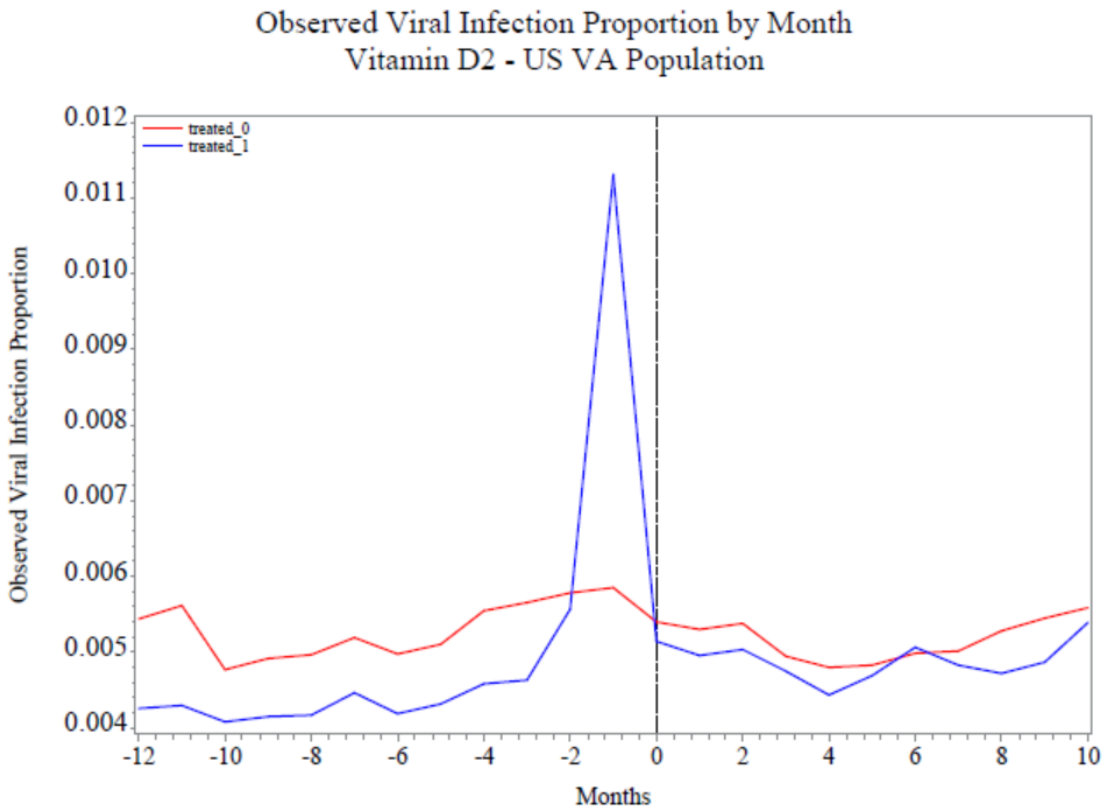
Expected



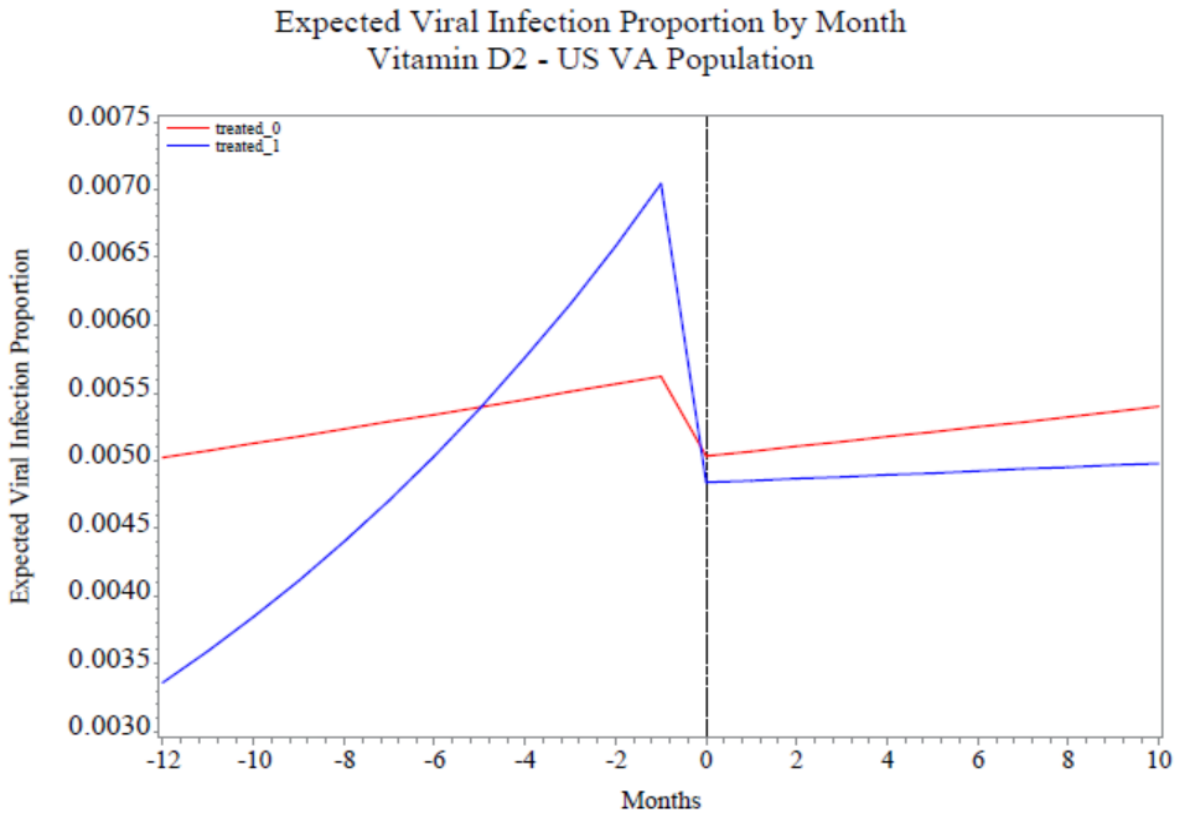
Tx by period by time (at 12 months post) OR = 0.51, 95% CI (0.48, 0.55), p=0.0001 (5.4% reduction in rate per month)
N=34,718,568 months (1,388,744 patients) and 158,643 AVRI claims – All patients have 25 months of observation

VA Data: D2 vs AVRI

Observed



Expected



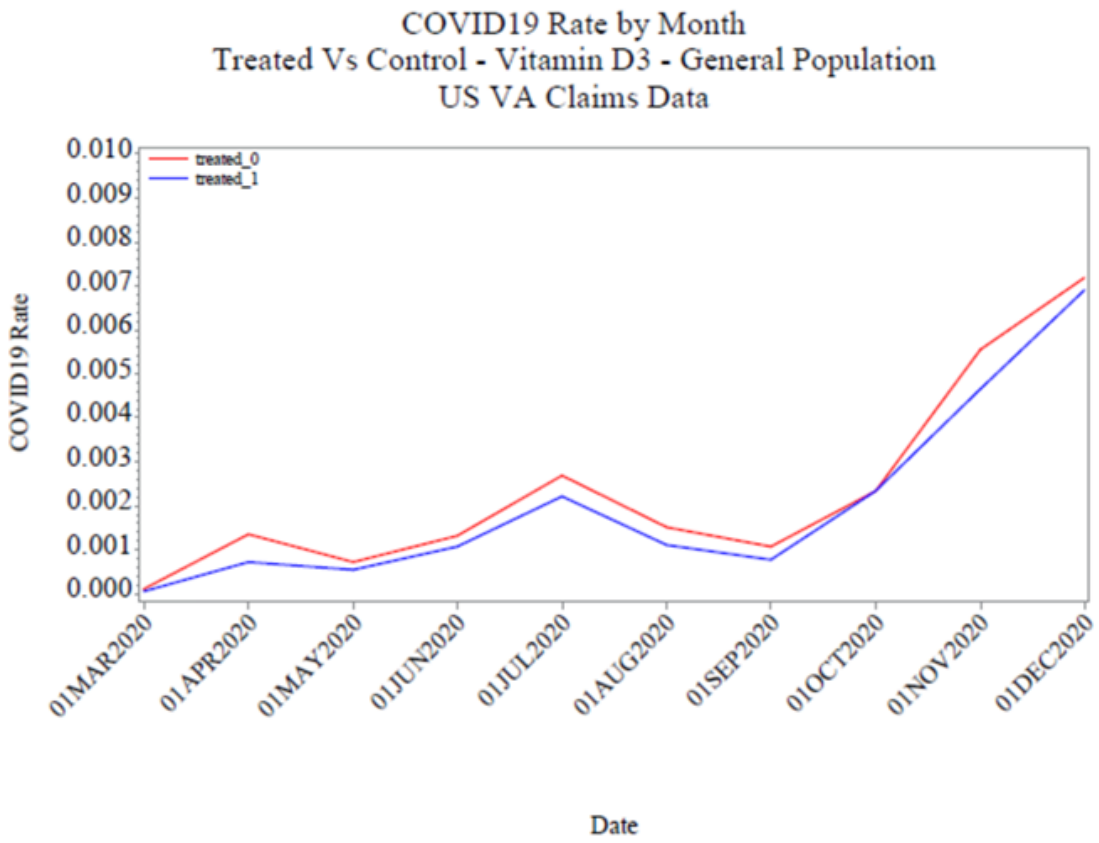
Tx by period by time (at 12 months post) OR = 0.48, 95% CI (0.43, 0.54), p=0.0001 (6.0% reduction in rate per month)
N=10,362,024 months (414,480 patients) and 53,045 AVRI claims – All patients have 25 months of observation

VA COVID Results

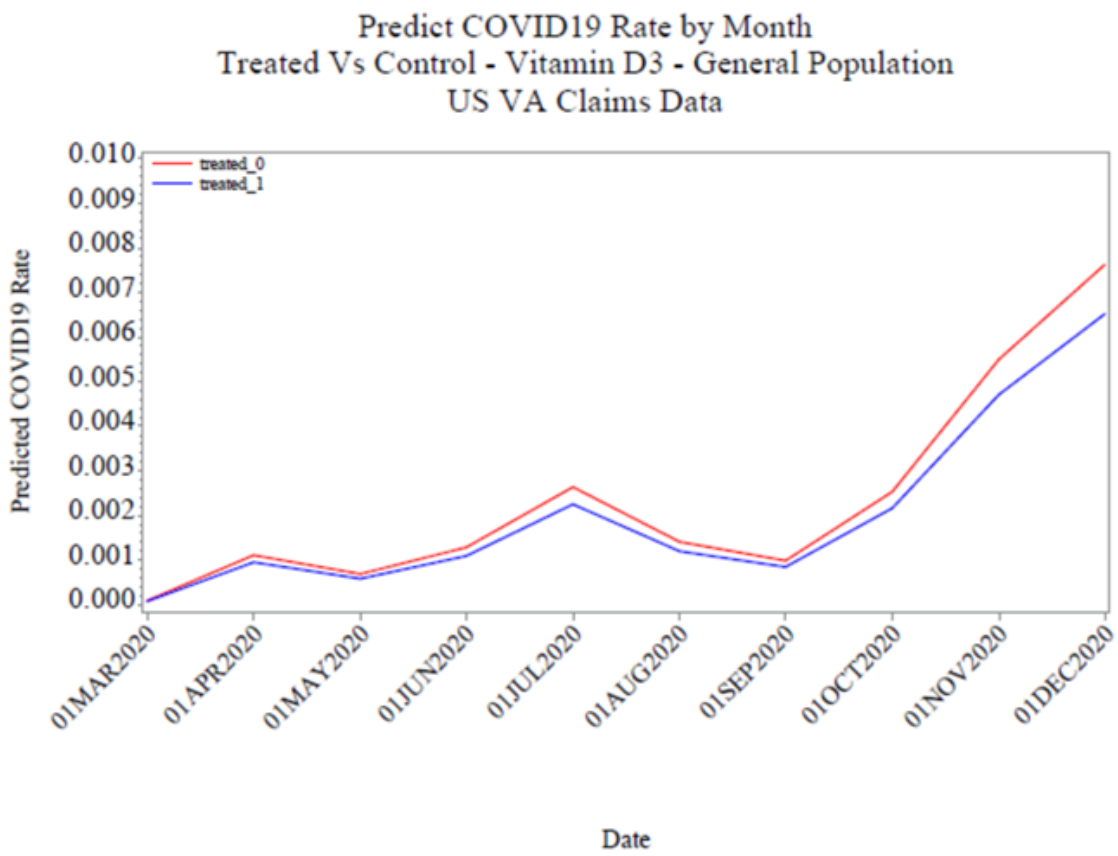
- 41,103 treated with an index vitamin D2 date 1/1/19 - 2/28/20
- 134,459 treated with an index vitamin D3 date 1/1/19 - 2/28/20
- Same numbers of matching controls for D2 and D3
- Month 0 = March 2020
- Month 9 = December 2020
- Months of observations D2 = 786,342, D3 = 2,571,103
- D2 - 1,361 COVID-19 cases (1.7% lab confirmed U07.1)
- D3 – 4,983 COVID-19 cases (1.9% lab confirmed U07.1)
- CDC case counts and death counts include both confirmed and probable cases and deaths U07.1 and U07.2
- Average number of prescriptions filled = 1.79

Discrete Time Survival Model

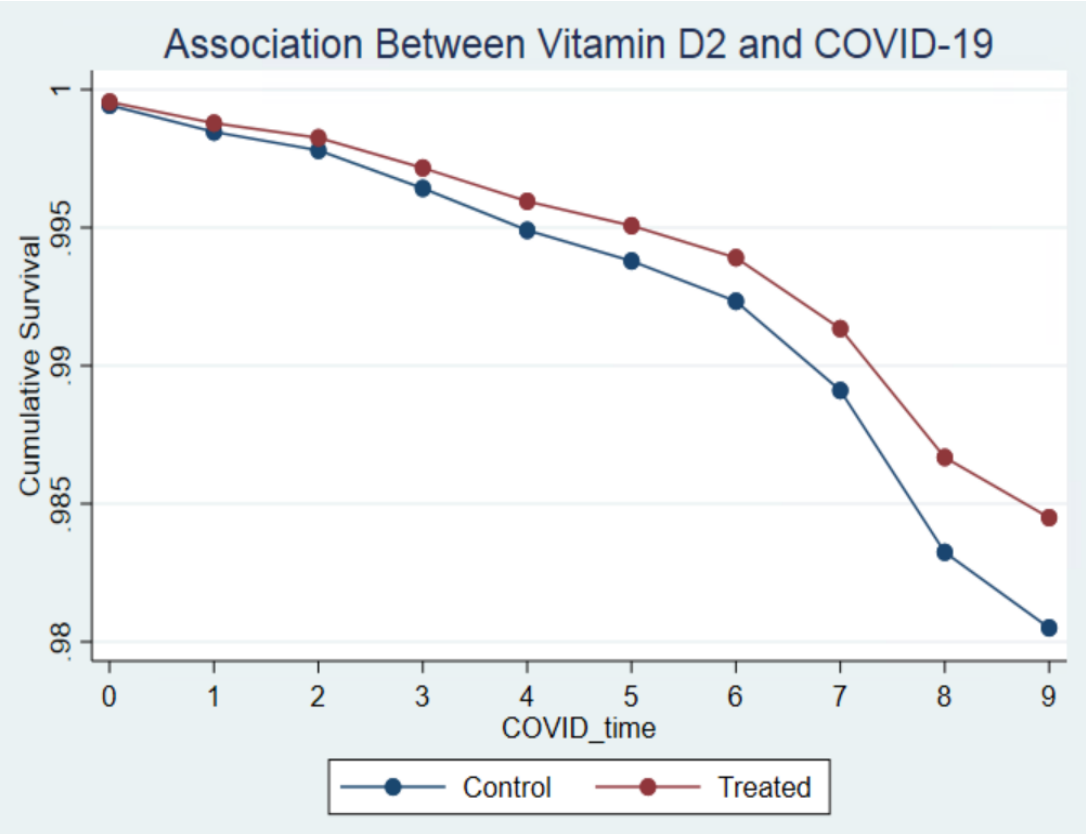
Observed

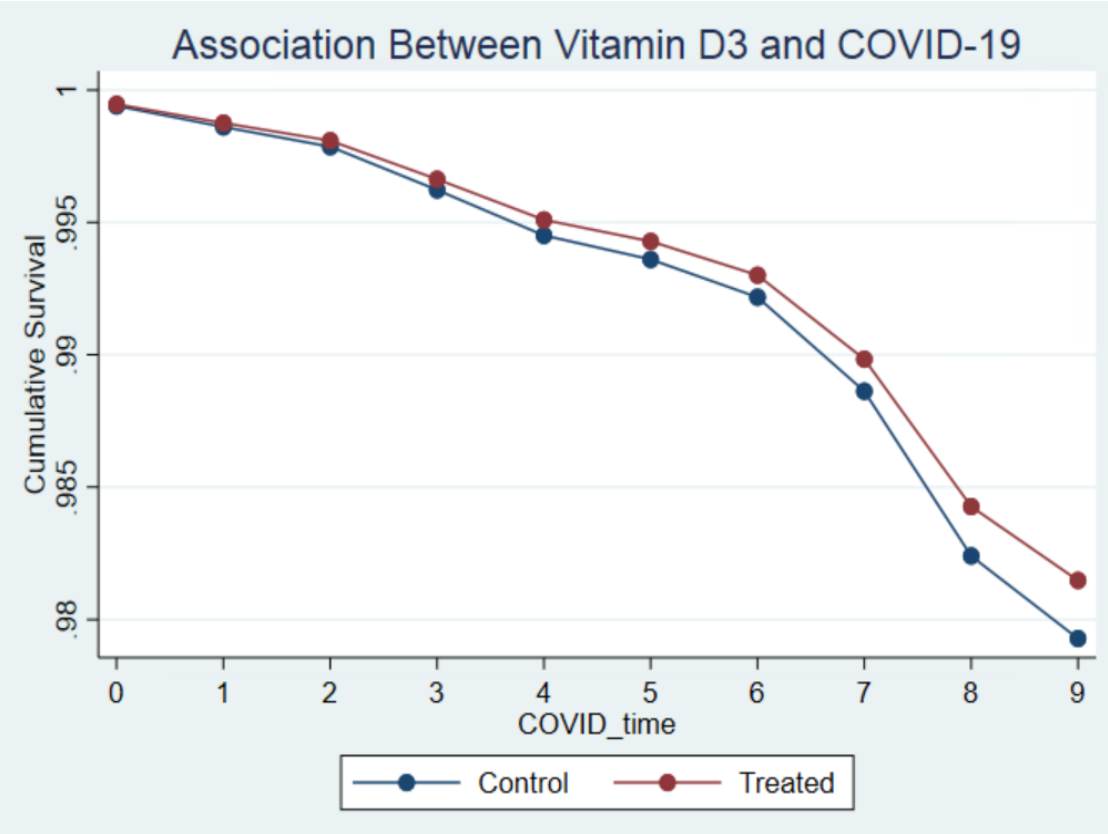


Estimated Hazard Rates



Cumulative Survival Functions





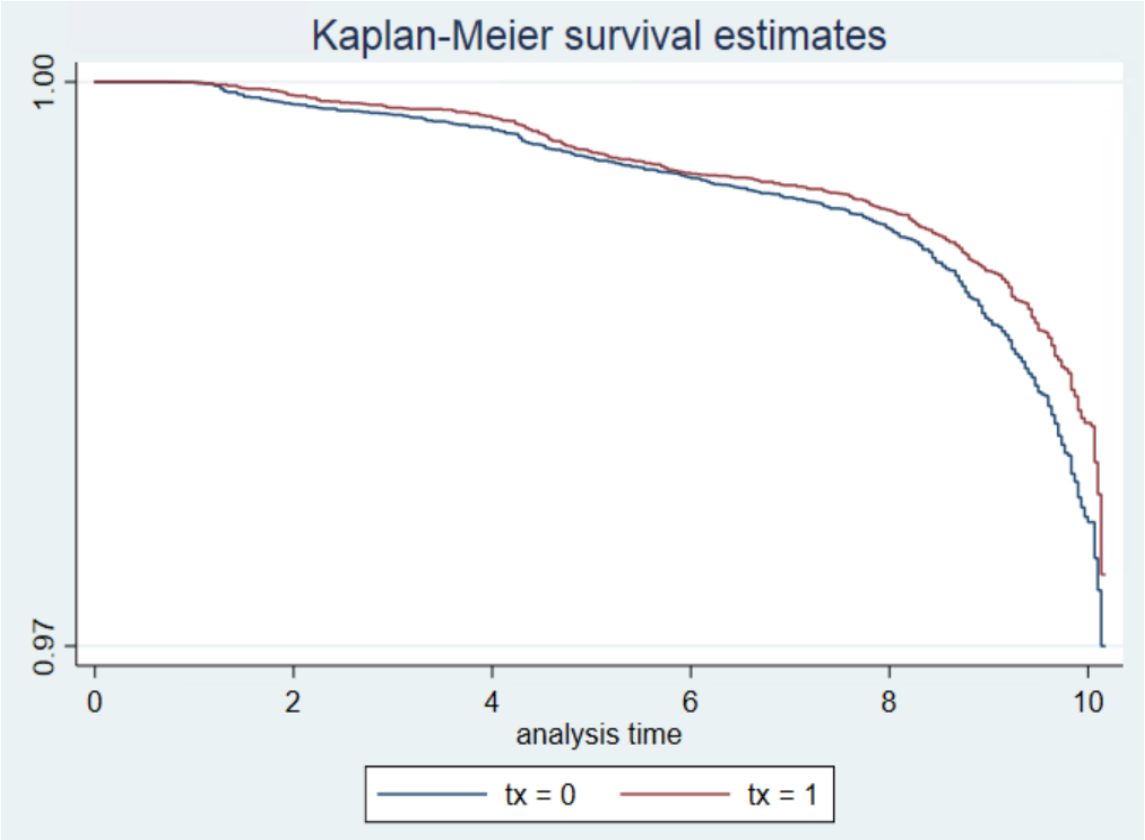
HR = 0.794, 95% CI=(0.714, 0.883), p<0.0001

HR = 0.893, 95% CI=(0.845, 0.943), p<0.0001

Cumulative probability of COVID-19 in D2 treated as of 12/31/2020 = 1.55%, control = 1.95% RR=0.795

Kaplan Meier Curves

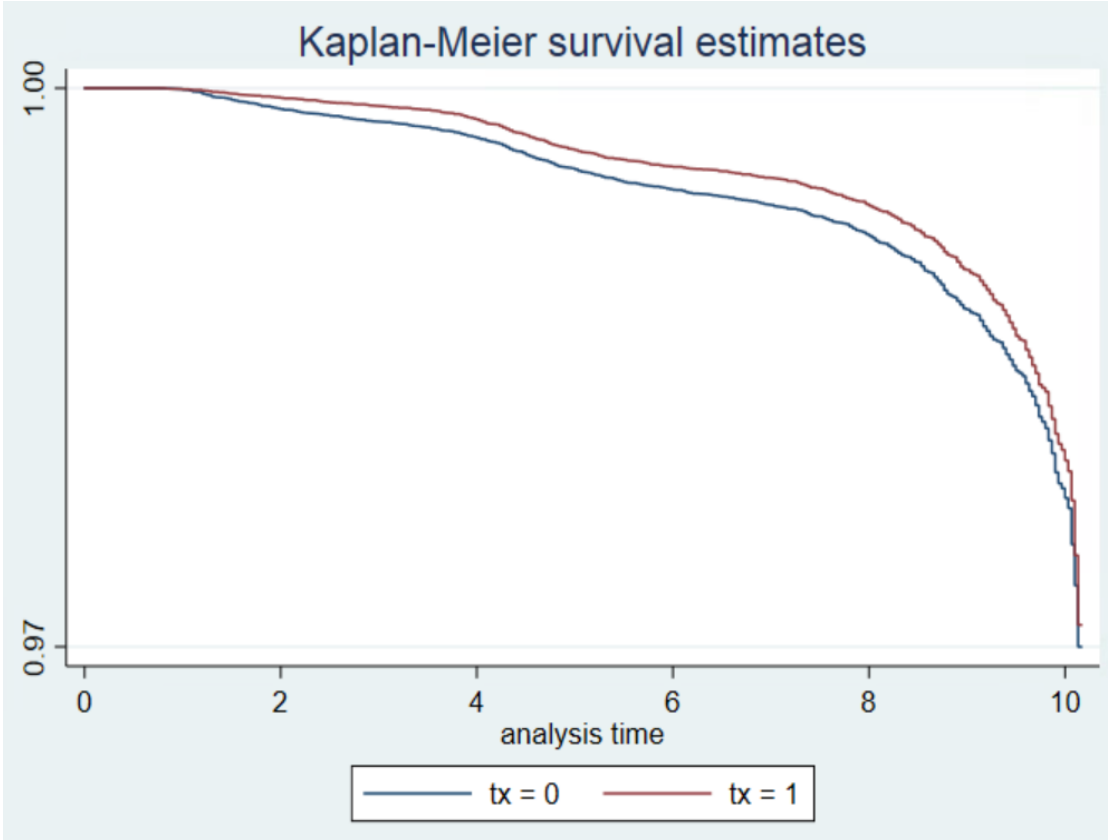
D2



Log Rank test – chi-square = 17.46, df=1, p<0.0001

Cox Model HR = 0.797 (0.716, 0.887), p<0.0001

D3



Log Rank test – chi-square = 7.02, df=1, p=0.008

Cox Model HR = 0.891 (0.843, 0.942), p<0.0001

COVID-19 - Next Steps

- Combine ICD-10 Codes U07.1 (confirmed) and U07.2 (unconfirmed)

- Augment outcomes for COVID-19 related events.
  - COVID-19 with pneumonia (U07 + J12.89)
  - COVID-19 with acute bronchitis (U07 + J20.8)
  - COVID-19 with lower respiratory infection (U07 + J40)
  - COVID-19 with acute respiratory distress syndrome (U07 +J80)
  - COVID-19 resulting in death

- Non-proportional hazards Model

- Are all formulations/dosages equivalent?

Conclusions

- Vitamin D is associated with decreases in rate of acute viral respiratory infections and COVID-19.
- For AVRI effect is largest following vitamin D initiation and decreases over time.
- D2 appears to be equal to or better than D3
- In 2020 D2 was associated with a 20% reduction in COVID-19
- In 2020 D3 was associated with a 11% reduction in COVID-19
- These effects are lower bounds because they ignore OTC vD
- Extrapolation, as of 12/2020, D2 would have reduced the total number of COVID-19 cases by 4,202,938 in the US.