PCOR Data Infrastructure Limitations and Opportunities: COVID-19 as Use Case

Can Vitamin D Reduce the Burden of COVID-19?

NASEM Building Capacity for PCOR: An Agenda for 2021-2030
Virtual Workshop 1: Looking Ahead at Data Needs

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How I got started on this

From: AllMedx™ <allmedx@mail.allmedx.com>
Date: March 10, 2020 at 2:01:32 PM CDT
To: "Meltzer, David [MED]" <dmeltzer@medicine.bsd.uchicago.edu>
Subject: Vitamin D & Respiratory Issues
Reply-To: allmedx@mail.allmedx.com

- Individual-level meta-analysis of RCTs studying effects of daily vitamin D supplementation on viral respiratory tract infection

Population	Trials	Proportion with ≥1 ARTI, control group (%)	Proportion with ≥1 ARTI, intervention group (%)	Adjusted* odds ratio (95% CI)	p
Overall	15	1210/2439 (49.6)	1206/2694 (44.8)	0.81 (0.72 to 0.91)	0.001
Baseline 25(OH)D :					
<10 ng/ml	6	64/107 (59.8)	40/127 (31.5)	0.30 (0.17 to 0.53)	0.001
≥10 ng/ml	11	477/729 (65.4)	516/874 (59.0)	0.75 (0.60 to 0.95)	0.02

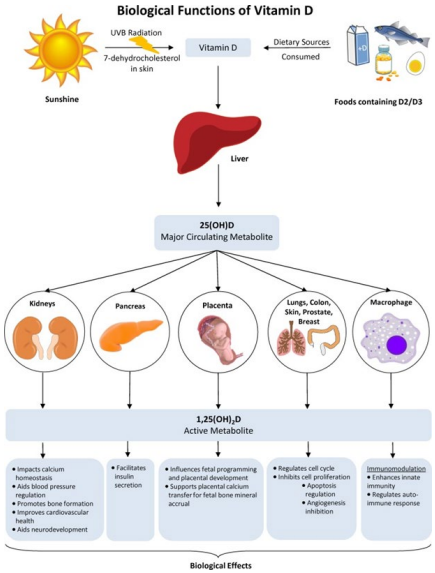
Martineau et al BMJ, 2017

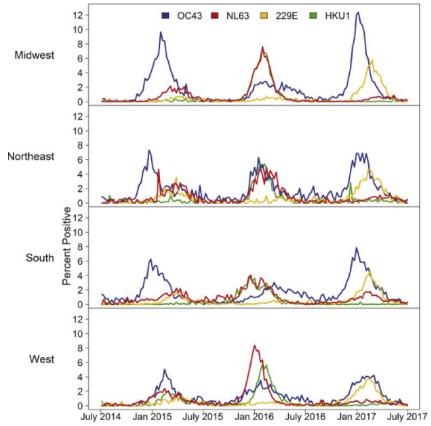
Vitamin D and COVID-19?

- Vitamin D
  - Hormone, produced in response to sunlight
  - Important for many functions, including innate and adaptive immunity, immunomodulation
  - Deficiency common(~50% US adults, >80% non-whites)
  - Supplementation often needed

- Coronaviruses common seasonal cause of lower respiratory tract infections in adults (~7% of LRTIs, 25% viral LRTIs)

- Epidemiologic associations of vitamin D deficiency and COVID-19
  - African-American/Black, Hispanic/LatinX
  - Older adults, nursing home residents, obese persons
  - Winter, UV exposure, Orthodox Jews



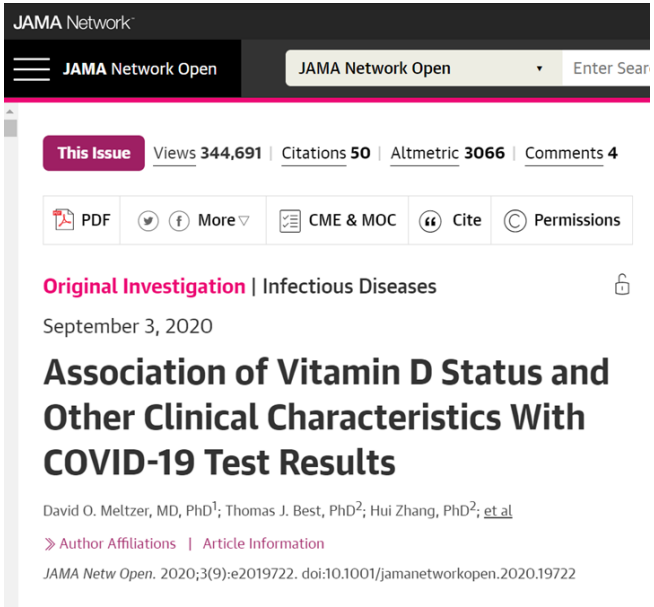


Observational Analysis at University of Chicago Medicine

- Sample: 489 patients with vitamin D level 14-365 days before COVID-19 test (March 3 – April 10, 2020)

- Defined likely deficient vs. likely sufficient 25(OH)D level
  - Likely deficient: level <20 ng/ml, treatment not increased after that level (25%)
  - Likely sufficient: level ≥20 ng/ml, treatment not decreased after that level (59%)
  - Control for demographic variables, comorbidities

- Estimated generalized linear models to predict testing positive for COVID-19
  - Relative risk of testing positive
  - Predicted COVID-19 positive rates



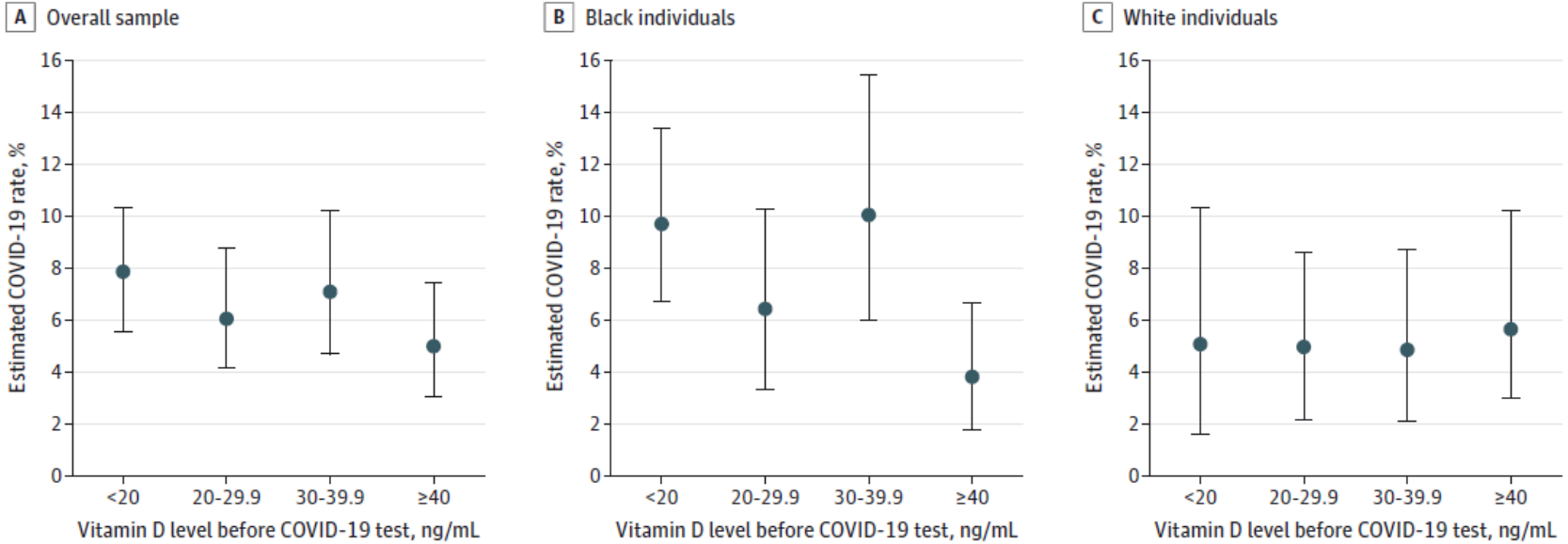
Findings

- Estimated generalized linear models to predict testing positive for COVID-19
  - Relative risk of testing positive:
    - 1.77, 95% CI(1.12-2.81), p<0.02 for likely deficient vs. likely sufficient
  - Predicted COVID-19 positive rates:
    - 21.6% for likely deficient vs. 12.2% for likely sufficient
  - Results in other than Whites (African-Americans) similar to full sample but wide confidence intervals for Whites; low rates and samples size in other than Whites

Table 4. Multivariable Association of Vitamin D Deficiency and Treatment With Testing Positive for COVID-19 in 489 Patients

Characteristic	No. (%)	Relative risk (95% CI)	*P* value
Age (linear spline)[a]			
<50	260 (53)	1.05 (1.01-1.09)	.02
≥50	229 (47)	1.02 (1.00-1.05)	.06
Sex			
Male	123 (25)	1 [Reference]	
Female	366 (75)	0.87 (0.52-1.44)	.58
Race			
White	158 (32)	1 [Reference]	
Other than White	331 (68)	2.54 (1.26-5.12)	.009
Ethnicity			
Non-Hispanic	448 (92)	1 [Reference]	
Hispanic	41 (8)	0.29 (0.04-2.01)	.21
Employee status, UCM employee			
No	328 (67)	1 [Reference]	
Yes	161 (33)	0.93 (0.52-1.64)	.79
Most recent vitamin D <20 ng/mL			
Likely deficient[b]	124 (25)	1.77 (1.12-2.81)	.02
Uncertain deficiency[c]	48 (10)	1.10 (0.49-2.43)	.82
Uncertain deficiency[d]	30 (5)	1.09 (0.43-2.82)	.85
Likely sufficient[e]	287 (59)	1 [Reference]	
Comorbidity indicators			
Hypertension	261 (53)	1.08 (0.60-1.97)	.79
Diabetes	137 (28)	0.78 (0.49-1.26)	.31
Chronic pulmonary disease	117 (24)	0.91 (0.55-1.52)	.73
Pulmonary circulation disorders	20 (4)	0.64 (0.23-1.79)	.40
Depression	119 (24)	1.22 (0.74-2.02)	.44
Chronic kidney disease	116 (24)	0.80 (0.49-1.32)	.39
Liver disease	56 (11)	0.99 (0.47-2.08)	.98
Comorbidities with immunosuppression	105 (21)	0.39 (0.20-0.76)	.005
BMI, mean	29.8	1.02 (0.996-1.048)	.10
Goodness-of-link test of squared predicted value[31]	NA	NA	.87
Hosmer-Lemeshow goodness-of-fit decile test[32]	NA	NA	.89

Figure. Estimated COVID-19 Rates by Most Recent Vitamin D Level



Meltzer et al Association of Vitamin D Levels, Race/Ethnicity, and Clinical Characteristics With COVID-19 Test Results, JAMA Network Open, March 19, 2021

Table 4. COVID-19 Positivity Rate by Most Recent Vitamin D Level and by Treatment

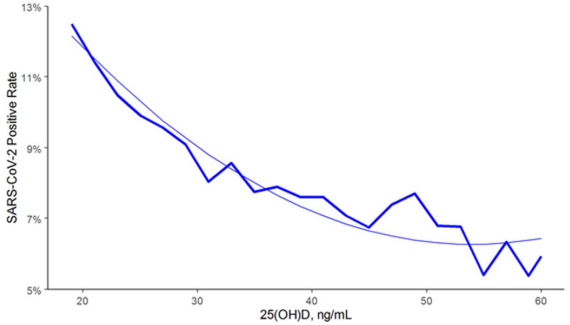
Active treatment 14 d before first COVID-19 test order date	Individuals with positive COVID-19 test result/total tested, No. (%)				
		Most recent vitamin D level from 14 to 365 d before first COVID-19 test order, ng/mL			
	Total	<20	20-29	30-39	≥40
Total	299/4258 (7.0)	100/1076 (9.3)	70/1175 (6.0)	72/961 (7.5)	57/1046 (5.4)
None	239/3338 (7.2)	81/900 (9.0)	53/917 (5.8)	59/733 (8.0)	46/788 (5.8)
1-1000 IU/d D_3 or multivitamin	45/616 (7.3)	13/116 (11.2)	13/171 (7.6)	12/167 (7.2)	7/162 (4.3)
1001-2000 IU/d D_3	9/173 (5.2)	2/36 (5.6)	4/57 (7.0)	0/39	3/41 (7.3)
≥2001 IU/d D_3	6/131 (4.6)	4/24 (16.7)	0/30	1/22 (4.5)	1/55 (1.8)

- Among persons taking ≥2001 IU/day
  - Vitamin D≥20 ng/ml: 2/107 (2%)
  - Vitamin D<20 ng/ml: 4/24 (17%) (p=0.01)

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2777682

Peer-reviewed Person-level Analysis w COVID-19 Infection as Outcome

- Merzon et al.
  - N=7807, Israeli health system cohort
  - OR=1.45 (p<.001) of COVID-19 infection if 25(OH)D < 30 ng/ml
- Kaufman et al.
  - N=190,000 US cases tested by Quest Diagnostics
  - Race imputed by zipcode



- Hastie et al.
  - N=348,958, UK Biobank study cohort
  - 25(OH)D and COVID not associated, but 25(OH)D > 10 yrs before COVID testing
- Ma et al.
  - N=8,297, UK Biobank study cohort
  - OR=0.66 (p=0.034) if habitual use of vitamin D supplements, not associated with baseline or genetically predicted levels

RCTs of Vitamin D and COVID-19 Severity

- Castillo et al RCT of calcifediol vs. usual care
  - ICU transfer: 1/50 (2%) calcifediol vs. 13/26 (50%) usual care ($p<0.001$)
- Murai et al. RCT D3 200,000 IU vitamin D x 1 vs. placebo
  - 240 patients: LOS, mortality, ICU N.S., mech ventilation 7% vs. 14% ($p=0.09$)
  - 25(OH)D$\leq$20 ng/ml: ICU, mech ventilation N.S.
  - 25(OH)D>20 ng/ml re-analysis (Meltzer et al.):
    - ICU: 8/62 (13%) vitamin D vs. 16/60 (27%) placebo, RR=0.48, p(chi-square) = 0.055
    - Mech Vent: 5/62 (8%) ICU vs. 12/60 (20%) placebo, RR=0.40, p(chi-square) = 0.057
    - May reflect benefits for whites; patients of African descent may need daily dosing (Gc1F VDBP, 24-dehydroxylase) to optimize free vitamin D levels
- Rastogi et al. RCT D3 60,000 IU/d x 7d vs. placebo
  - 10/16 (63%) vitD vs. 5/24 (21%) placebo RNA-neg at 14d ($p<0.02$), lower fibrinogen ($p<0.01$)

Castillo et al. J Steroid Biochem Mol Biol. 2020; Murai et al., JAMA, 2021; Ratogi et al., Postgraduate Medical Journal, 2020

Additional Observational Analyses in Progress

- National COVID Cohort Collaborative (N3C)
  - Funded by NCATS, ~ 50 sites, >1 million COVID patients plus controls
  - Data continuously added; some paring of controls vs. COVID cases
  - Secure computing environment, collaborative ecosystem
  - Sample size/coverage to allow analysis of levels, seasonality, location, racial subgroups
- Epic Cosmos
  - Several times larger than N3C
  - Only Epic personnel can access data
- VA data (with Robert Gibbons and others)
  - Includes Rx of vitamin D
  - Examine hazard of COVID diagnosis after new vitamin D prescription
- PCORNet/CAPriCORN
  - Multicenter EHR data with deep Chicago-area coverage and ability to extend nationally
  - Linked contextual data, little PRO data, biomarkers only via routine care
  - Greater neighborhood disorder associated with lower 25(OH)D in pregnant Chicago women (Woo, 2020)

Observations Related to PCOR Infrastructure in Vitamin D/COVID Research

- PCOR data provided important insights, sometimes rapidly
  - Ease of access, including administrative and technical barriers, cost affected use
- Relevant data infrastructure diverse and overlapping
  - Multiple public and private sources provided opportunities
  - International data sources also advanced the field
- Data completeness and quality questions evident
- Contextual and patient-reported variables relevant
- Biomarker data valuable, additional biomarker data important (e.g., All of Us)
- Initiating RCTs important and complementary with observational studies

Thank you!

For more information:

https://chess.uchicago.edu/vitaminD