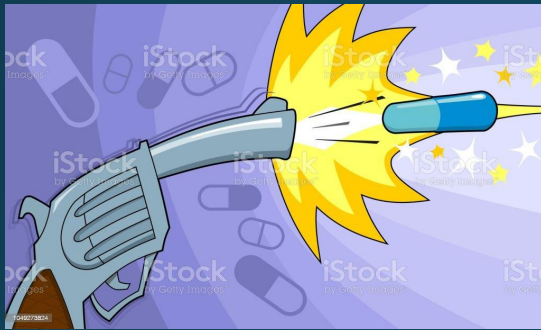


Vitamin D is not a Magic Bullet, but Vitamin D Deficiency is a Poison Arrow



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Note: No conflicts of interest related to vitamin D.

[Note: Not an MD. This is a science presentation with implications for public health policy,
but this is not prescriptive medical advice.]

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VitaminDforAll.org

Outline

1. **Vitamin D: Basics** (4 slides)
2. **Vitamin D Controversy** (5 slides)
3. **Vitamin D & Aging** (4 slides)
4. **(optional) Vitamin D & Covid-19** (5 slides)
5. **Summary & Take-Homes** (3 slides)

Q&A

Vitamin D basics

(Part 1.)

Vitamin D deficiency (VDD): by far the most common deficiency of an essential molecule

Global deficiency ≈ 50% (<20ng/ml, the nearly universal government rec min serum level)

~ 3/4 globally “insufficient” (<30ng/ml, the min rec of the Endocrine Society)

Food is not an adequate source.

Most comes from the sun (UVB). [So it’s not technically a vitamin.]

Outside the tropics hardly any can be made from sun in winter.

Supplements needed for:

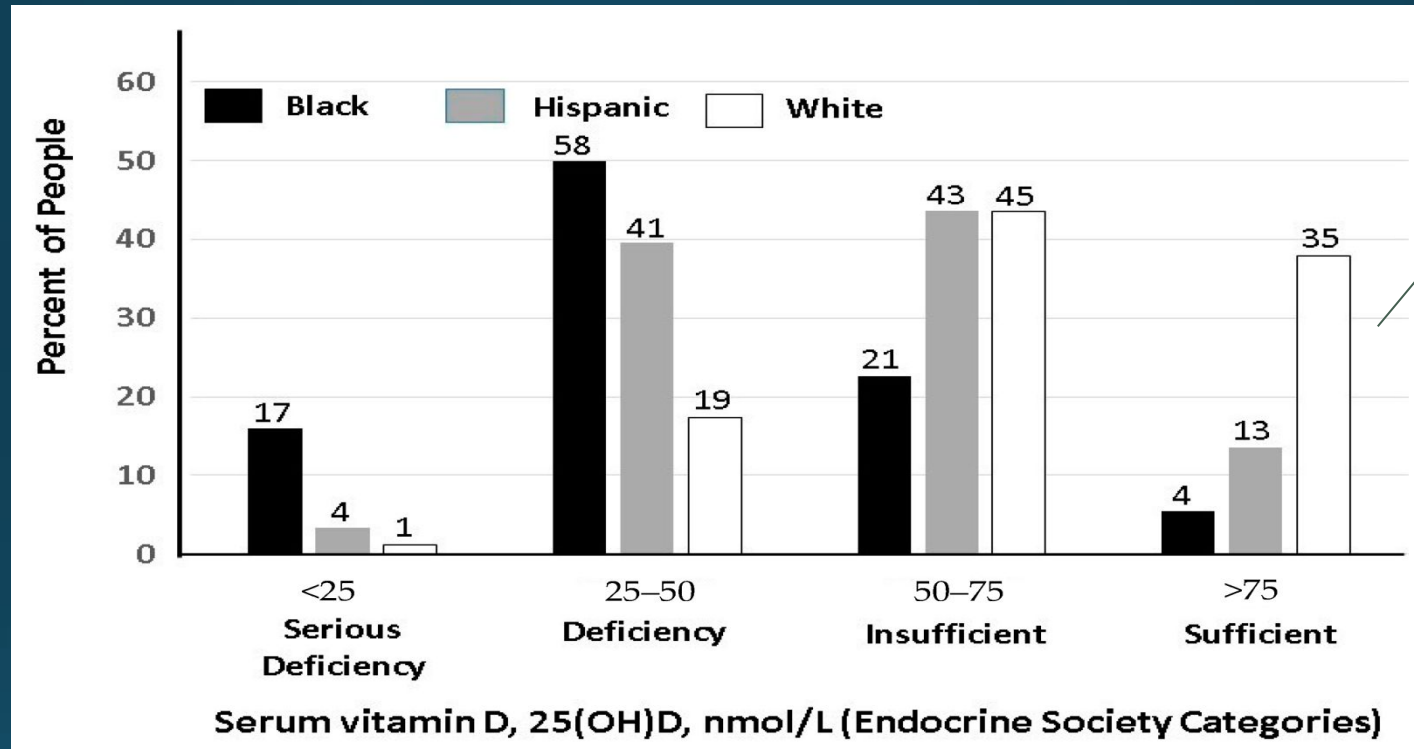
- latitude / skin-tone mismatches, potentially all year
- for almost everyone in winter outside the tropics

Even nearer the equator than most of US & Europe, many deficient:

- 97% of adults in India insufficient. 91% of seniors deficient.
- 51% of young, non-obese adults insufficient even w/ >4hr/day in sun at latitude 21 deg in Hawaii

country/region	D< 50nmol/L (20ng/ml)	D< 75nmol/L (30ng/ml)	2020 est pop (M)
China (w/o HK; see columns to the right)	61%		1432
India	66%	97%	1380
Europe	40%		748
USA	36%		331
Pakistan	58%	84%	221
Brazil	77%		213

Dark skinned minorities particularly at risk & VDD is partially responsible for racial health disparities



So 96%, 87%, & 65% have low vitamin D.

(Divide by 2.5 to obtain ng/mL)

Of the several causes of racial health disparities, VDD is by far the most easily correctable cause.

Ames, Grant, & Willett "Does the High Prevalence of Vitamin D Deficiency in African Americans Contribute to Health Disparities?" *Nutrients* (2021).

Willett is the 2nd most cited author in all of clinical medicine per Wikipedia.

Vitamin D is essential to many aspects of health, especially immune health

Vitamin D family of molecules (inc. metabolites) regulate the expression of thousands of genes, including many for innate immunity & many for adaptive immunity.

Examples:

Vitamin D kills viruses by inducing antimicrobial peptides (eg cathelicidin).

Inhibits inflammatory cytokines (regulates CD4+ T-cell responses eg inhibiting Th1).

Maintains cell tight junctions.

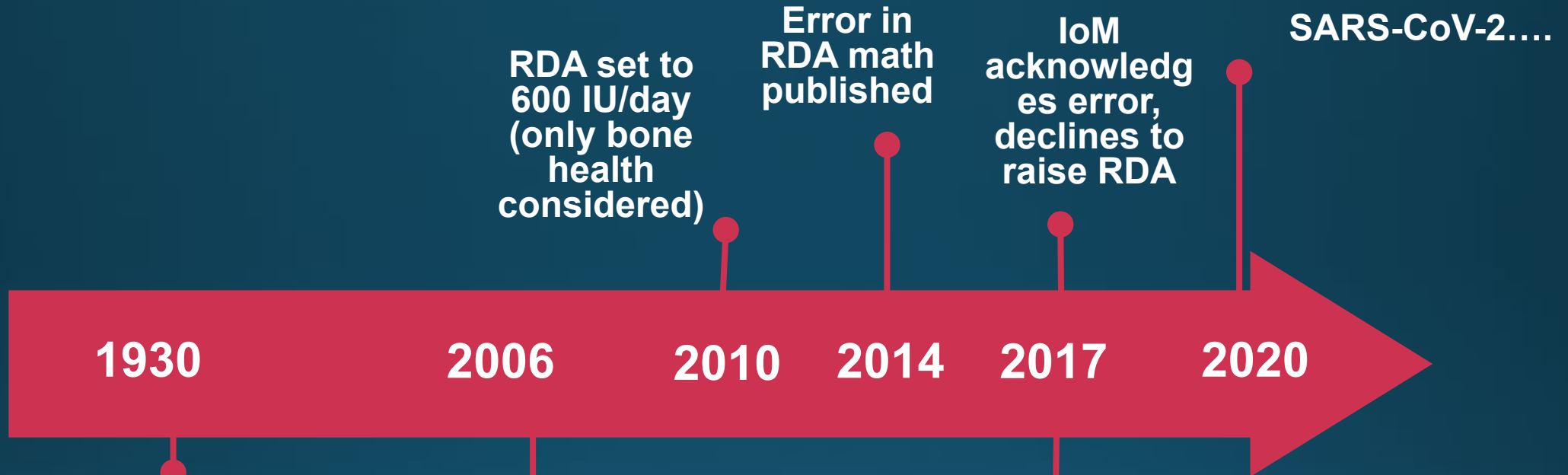
Deficiency linked to most chronic diseases of aging.

Deficiency linked to auto-immune diseases.

Vitamin D acts as a hormone & exhibits not only endocrine signaling but also paracrine & autocrine.

Some vitamin D history

*RDA
timeline:*



RDA set to 600 IU/day (only bone health considered)

Error in RDA math published

IoM acknowledges error, declines to raise RDA

SARS-CoV-2....

1930

2006

2010

2014

2017

2020

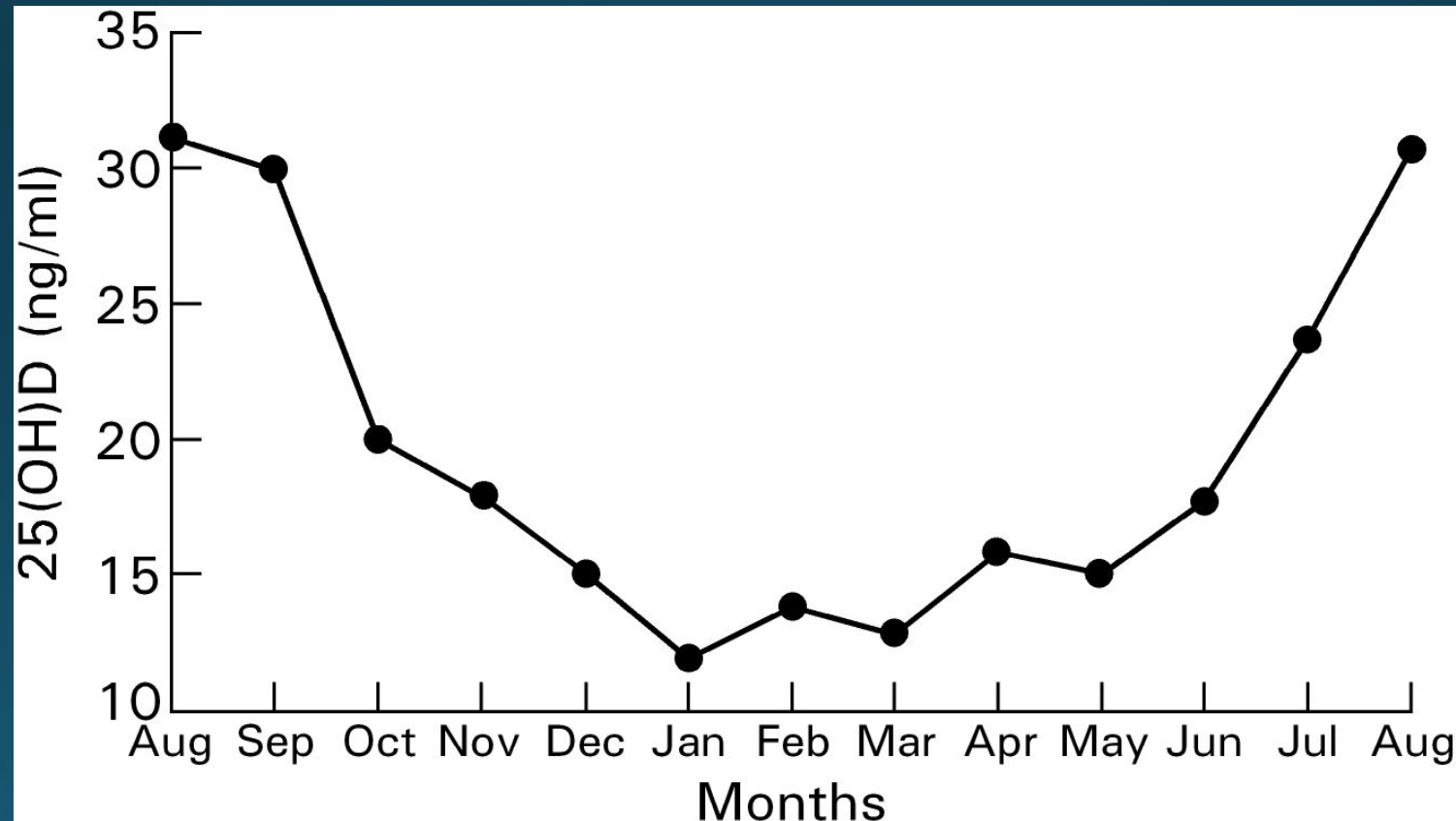
*immune
health
timeline:*

Cod liver oil (rich in D) prevented respiratory infections

Vitamin D effects on influenza seasonality

Meta-Analysis: Vit D supplementation helps prevent acute respiratory tract infections

Seasonal variation of 25(OH)D levels – Vitamin D deficiency is common in winter



Vitamin D Controversy

(Part 2.)

Vitamin D has been a huge controversy in health & medicine for decades

History:

- observational studies vs dozens of health conditions
- “correlation doesn’t imply causation”
- failed large RCTs for many big chronic diseases
- emerging understanding of bad RCT trial design (see next slide)
- (throughout) lack of education on this topic in formal med school curriculums

Current status:

- one side believes it’s only proven for bone health (this side controls public health policy, inc. RDAs)
- the other side believes low D was a global pandemic health catastrophe for years (long before Covid)

The latter side is (too slowly) gaining ground:

- increasing understanding of mechanisms & relevant biology
- definitive [paper](#) (just published, BMJ): vitamin D lowers autoimmune disease risk
- consensus turning on cancer: eg German consensus that vitamin D could prevent 30,000 deaths annually in that country, based on 3 meta-analyses

Why have Vitamin D Studies yielded mixed results?

Trial methodology used for novel drugs inappropriate:

- Not testing D levels at baseline
- Excluding the deficient from studies
- Dose response different from drugs: giving too little to severely deficient or any amount to baseline high dilutes effect sizes
- Invalid assumption that study is only source of D

Re-analysis of many studies in proper ways did show benefits, eg cancer, T2D.

For more details see:

- [Boucher. "Why do so many trials of vitamin D supplementation fail?"](#)
- [Grant et al. "A Narrative Review of the Evidence for Variations in Serum 25-Hydroxyvitamin D Concentration Thresholds for Optimal Health" \(just published\)](#)

No government group held accountable for eradicating deficiency

- Deficiency rates of roughly $\frac{1}{3}$ (USA) or more of society have been allowed to continue for decades in most countries.
- Government blood recs & intake recs incompatible (see next slide).
- (In the US) No agency has a mandate to explore the potential for vitamin D to protect against infectious diseases.

No consensus on intake->response

RDA calculation mistake is still not widely enough known.

Intake->response literature clear that RDA not high enough,

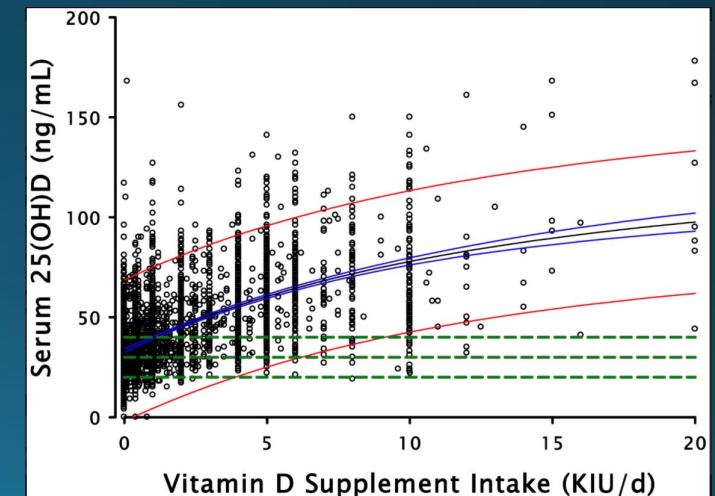
but this also not widely appreciated, even by experts.

No definitive paper & wide disagreement amongst experts, seemingly just due to lack of knowledge of what literature does exist.

RCTs not needed for intake -> response characterization.

Bizarre bias against testing to ensure sufficiency.

IoM'11: 600
Veugelers'14: 8895
Zitterman'14: 720, but not clear it gets 97.5%
Heaney'15: 3875, of supplement
Veugelers'15: 2909, more if overweight
Cashman'17: 1136, but prefer '18 # next
Cashman'18: 1152
Cashman'20: 2408



Vitamin D mistakenly thought to be more dangerous than it is (it's very safe)

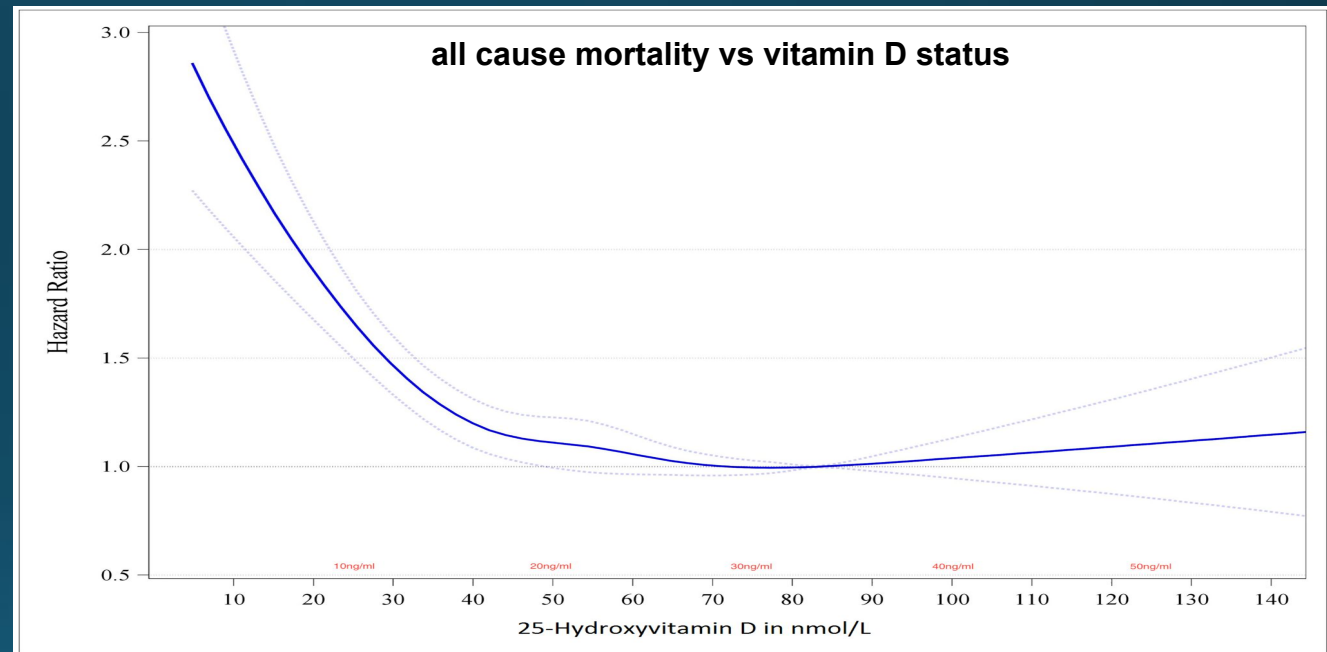
- In 2010, the Institute of Medicine found no evidence of adverse effects for up to 10,000 IU/day vitamin D, set the upper level at 4,000 IU/d out of caution.
- Several studies show no adverse effects from a wide range of doses including several far above 10,000 IU/day.
- Mislabeling of doses or confusing units (mg vs μg) are primary reasons for overdose. Hypercalcemia is usually easily reversed through reducing 25(OH)D levels with no loss of life.
- Deaths or hospitalizations from too much D are so rare they are 1000+x less than from Covid-19 & would be even with universal robust supplementation

Vitamin D and Aging

(Part 3.)

Low D correlates with higher all cause mortality and with most chronic diseases of aging

all cause mortality:



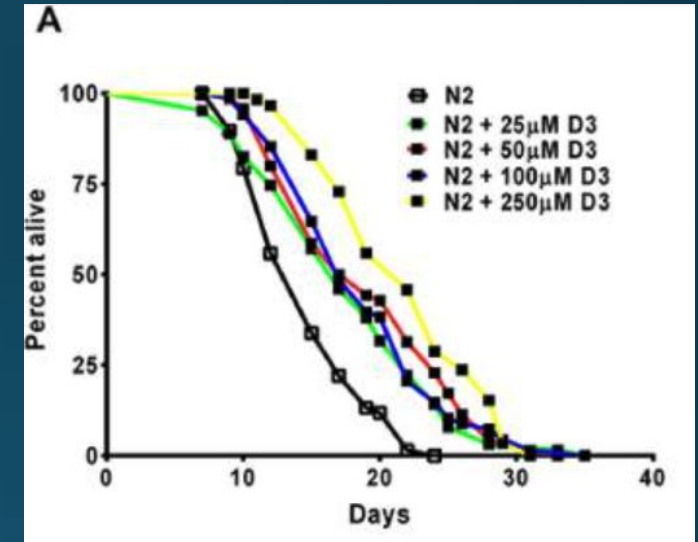
chronic diseases of aging:

CVD, hypertension, cancer, diabetes, Alzheimer's

(see "A Narrative Review of the Evidence for Variations in Serum 25-Hydroxyvitamin D Concentration Thresholds for Optimal Health" 2022)

Vitamin D extends *C.elegans* lifespan

- D extends *C.elegans* lifespan ~33%
- dose dependent fashion
- nematode flatworms have no bones
- MoA at least partially via proteostasis



Published in 2016 by Gordon Lithgow's lab at the Buck Institute

Vitamin D reversed Horvath clock age in (deficient) humans

Fahy et al (2019, TRIIM trial) showed 1.5 year age reversal in n=10 all-male humans using 1 year of treatment with a cocktail of drugs & supplements, with no control group. This made big waves in the longevity community.

Chen et al (2018) showed 1.6-1.8 year age reversal in n=27 D deficient, African Americans of both sexes using 16 weeks of vitamin D (2000-4000IU/d), in an RCT (total n=51). This went unnoticed.

Using early generation aging clocks like this is questionable (eg see Levine), but both results may be real nonetheless.

Vitamin D affects numerous known aging markers/pathways/hallmarks

Aging & insufficient vitamin D both affect, in the same direction:

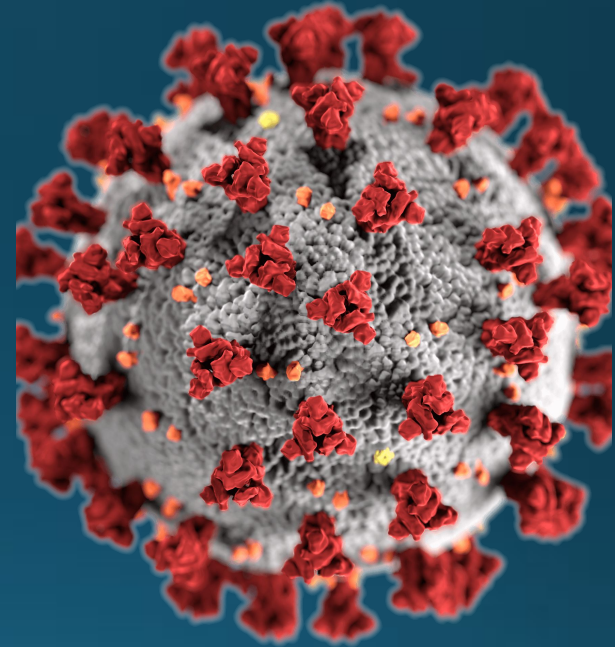
- many markers/pathways (many related to chronic inflammation):
 - Klotho
 - NF- κ B
 - Nrf2
 - SIRT3
 - TNF α
- telomere shortening (2021)

Vitamin D also affects TGF- β (several papers)

Mechanism identified by which vitamin D helps clear A β (2012)

Note: Most (if not all) of these are targets of various aging/longevity biotech companies.

Vitamin D and Covid-19



(Part 4.)

Group correlations: Covid risk groups match VDD risk groups

Covid-19 vs...

latitude

vitamin D deficiency by country

elderly in care homes (96% vitamin D insufficient in 1 US study)

race

obesity

comorbidities

etc. (dozens of published studies)

This was just hypothesis generating, but the data came early.

Individual patient data: Dozens of MAs, millions of patients

See <https://twitter.com/KarlPfleger/status/1486565564671692804>

for links to recent meta-analyses of dozens of observational studies:

- Dec'21: ~50 studies (total n=1,403,715)
VDD -> OR of infection 1.83, of ICU 2.16
- Dec'21: overs ~75 studies (total n=1,976,099)
VDD -> OR of infection 1.46, severe disease 1.90.

Roughly a doubling in odds of ICU for those with Vitamin D Deficiency, across millions of patients & ~50%+ greater odds of infection.

Biological mechanisms:

D helps for Covid19 more than other infections

Reduces risk of SARS-CoV-2 docking at ACE2 receptors.

Stimulates antimicrobial proteins eg cathelicidin

Some D metabolites directly inhibit SARS-CoV-2 replication.

Modulation of Th1 shutdown helps prevent cytokine storm.

Not an exhaustive list.

Dozens of papers at this point.

An early paper by a top vitamin D researcher received ~1000 citations w/in 1st year & now has ~1500.

Causal evidence

- dozens of RCTs for other ARIs (& meta-analyses of them)
- Covid RCTs: Spain (ICU), India (virus clearance)
- Hill's criteria: strength, consistence, temporality, plausibility, etc.
- causal inference modeling
- biological mechanisms
- quasi-experimental studies
- **race/latitude effects** (Kohlmeier: African American Covid-19 deaths over-representation: Wisconsin=5.6x, Michigan=3.6, NewYork=2.2, Alabama=2.1, Louisiana=2.0, Florida=1.3)

Age, obesity, & comorbidities as risk factors unquestioned.

Seatbelts, smoking warnings. Lots of public health w/out RCTs.

Lots of Support of D for Covid

- 200+ international scientists & physicians.
- 150+ Italian scientists & physicians.
- 73 French scientists & physicians (and 6 French national scientific societies).
- Former Surgeon General Richard Carmona, MD, MPH.
- Position statement f/ National Medical Association (largest professional org of African American physicians: 30,000 of them).
- Notable British & Irish academics and American physicians.
- Many of the top vitamin D researchers in the world.

- Former CDC director Tom Frieden and Anthony Fauci both suggested vitamin D is important for immunity. Dr. Fauci said he takes it and would not mind recommending it.

Full list: <https://vitamindforall.org/rollcall.html>

Summary & Take-Homes

(Part 5, last part.)

Lack of D is a disease more than D is a therapeutic

Vitamin D is not a magic bullet (that fixes everything).

But insufficient vitamin D is a sort of evil magic bullet, or poison arrow: something that makes lots of things worse (just like obesity, aging, chronic sleep deprivation, chronic dehydration, smoking, etc. all do also):

- disrupts proper immune function: increases infectious diseases risk & autoimmune risk
- increases risk of most chronic diseases of aging
- *essentially speeds aging*
- plus a bunch of other bad stuff (eg in pregnancy, maybe depression, ...)

D is analogous to water & sleep in this sense, and that should have implications for how interventions to supply it are evaluated.

Low D's prevalence affects much of medicine

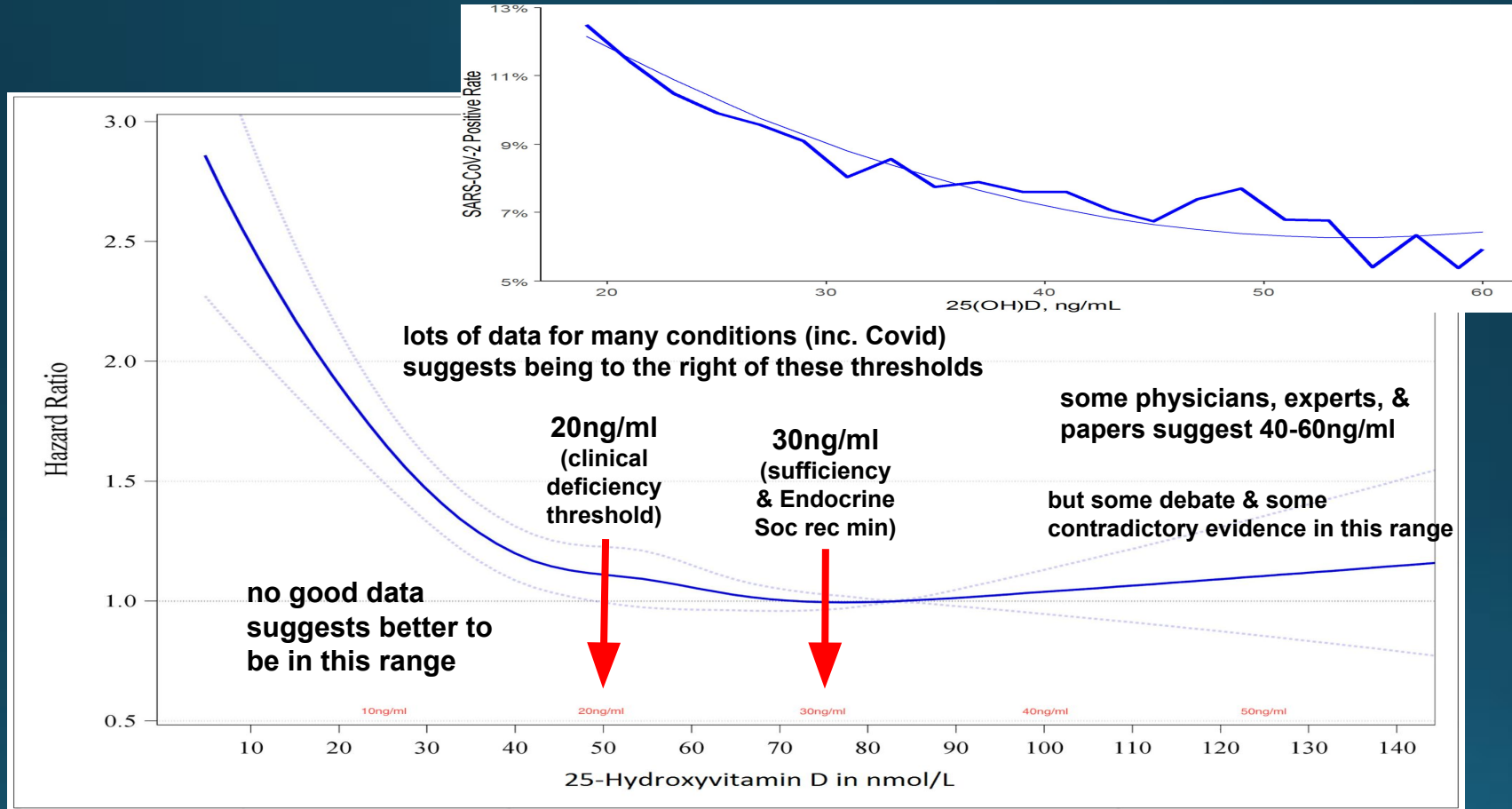
- Compared to other prevalent evil magic bullets / poison arrows (obesity, etc.), insufficient vitamin D is by far the easiest & quickest to correct.
- Since 1 in 2 people globally has clinical D deficiency (~¾ insufficiency): relative to the backdrop of average population, vitamin D could be considered a geroprotective molecule.
- A TAME-like trial of vitamin D could succeed, perhaps even better than metformin, just due to the high fraction of subjects likely starting too low.
- Some (many?) interventions may have overlapping mechanisms of action or may correct downstream problems that are more common with insufficient D. Measured effect sizes in trials of such interventions are artificially increased due to the high prevalence of insufficient D.

Take-home: *Effect sizes seen in studies of other interventions may be lower or absent when limited to subjects with sufficient vitamin D.*

Testing & serum targets

Testing is the surest way to ensure staying in the optimal range. Testing is cheap & easy (eg \$50).

all cause mortality (hazard ratio)



Sun has benefits besides D (eg nitric oxide, melatonin, circadian) & D production from Sun is self limiting. But hard for many to get enough from sun alone, so mix of sun + supplements (or UV lamps) often recommended, varying by season.

Q&A

Resources for more reading/listening (clickable f/ slides):

- [VDD & Covid Twitter thread](#) with many links (pinned to my Twitter profile as of 2/22/22)
- [list of a few podcasts on vitamin D & Covid science](#) (appropriate for lay audiences)
- [best up-to-date review of vitamin D levels & top killer diseases](#) (Grant et al, *Nutrients*, 2/2/22)
- [list of scientific papers on vitamin D intake -> serum response](#)
- [VitaminDforAll.org Covid letter](#) signed by 200+ physicians & scientists with their personal intakes
- [list of pages with useful guidelines for getting D from sun](#) (from non-profit scientific org Grassroots Health)