

# How to Design, Conduct, and Analyze Vitamin D Clinical Trials

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# Disclosure

- I receive funding from Bio-Tech Pharmacal, Inc. (Fayetteville, Arkansas, USA), a supplier of research-grade vitamin D3.

# Outline

- Background
  - Problems with observational studies
  - few successful vitamin D trials
- Reason: based on guidelines for drugs resulting in vitamin D dose being used.
- Should be based on 25(OH)D concentrations
- Examples: cancer; premature birth
- Steps involved for trials based on 25(OH)D
- Colorectal cancer survival
- Coronary heart disease

# Observational Studies

- Observational studies based on 25(OH)D concentrations have provided evidence for beneficial effects of vitamin D for many health outcomes, but are considered weak evidence for establishing causality.
- 25(OH)D concentrations could be due to:
  - Dietary vitamin D sources such as meat and eggs having health effects
  - Non-vitamin D effects of UV exposure
  - Exercise
  - Obesity (generally corrected)

# Background

“Our findings suggest that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes in **unselected** community-dwelling individuals by more than 15%.

Future trials with similar designs are unlikely to alter these conclusions.”

- Bolland MJ, Grey A, Gamble GD, Reid IR. Lancet Diabetes Endocrinol. 2014

# Ongoing Major Vitamin D Clinical Trials

- VITamin D and OmegA-3 TriaL (VITAL) (U.S.)
- D-Health Trial (Australia)
- Vitamin D Assessment (ViDA) Study (N.Z.)
- Vitamin D and Type 2 Diabetes (D2d) study (U.S.)
- Finnish Vitamin D Trial (FIND)
- These trials will finish data collection and publish results in the next 1-3 years.

# Problems with Traditional Vitamin D Clinical Trials

- 1 – Based on the inappropriate guidelines for pharmaceutical drugs
  - The trial is the only source of the agent
  - There is a linear dose-response relationship
- 2 – Doses often too low
- 3 – Baseline 25(OH)D concentration often too high
- 4 – Poor compliance

# Heaney's [2014] Rules for individual clinical studies of nutrient effects - 1

1. Basal nutrient status must be measured, used as an inclusion criterion for entry into study.
2. The intervention must be large enough to change nutrient status and must be quantified by suitable analyses.
3. The change in nutrient status produced in those enrolled in the trials must be measured and recorded.



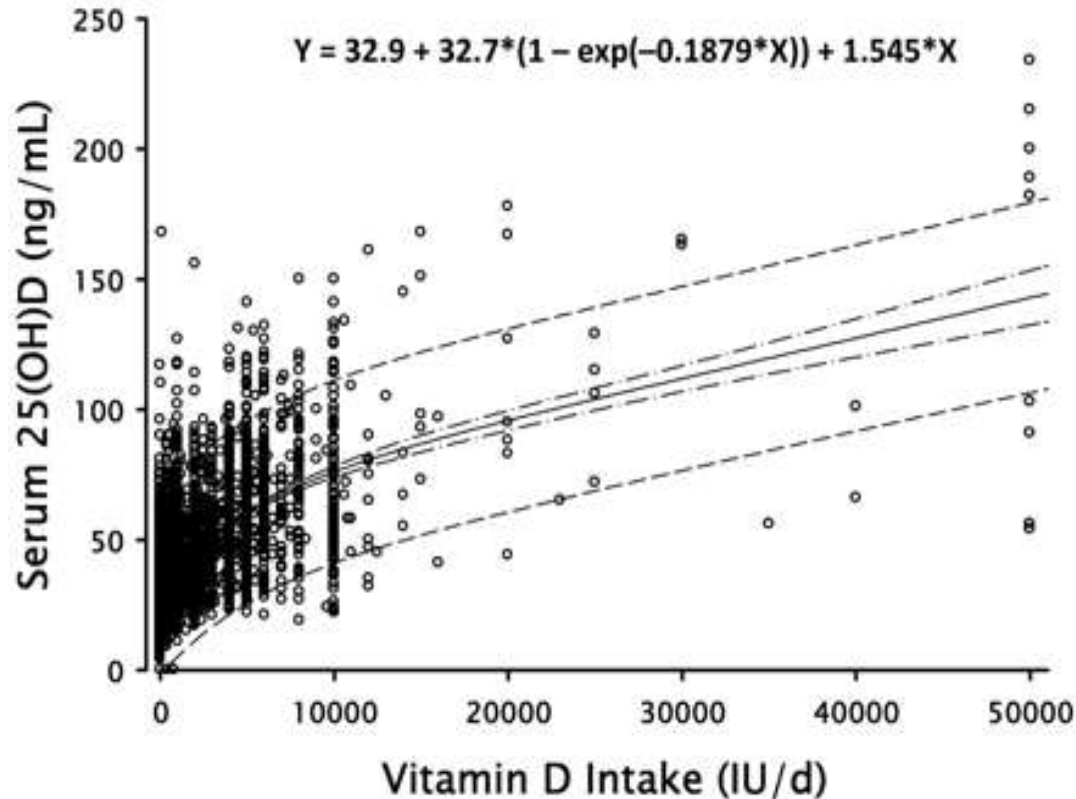
# Heaney's [2014] Rules for individual clinical studies of nutrient effects - 2

4. The hypothesis to be tested must be that a change in nutrient status produces the sought-for effect.
  5. Conutrient status must be optimized in order to ensure that the test nutrient is the only nutrition related, limiting factor in the response.
- Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev. 2014;72(1):48-54.

# Nonlinearities Related to Vitamin D

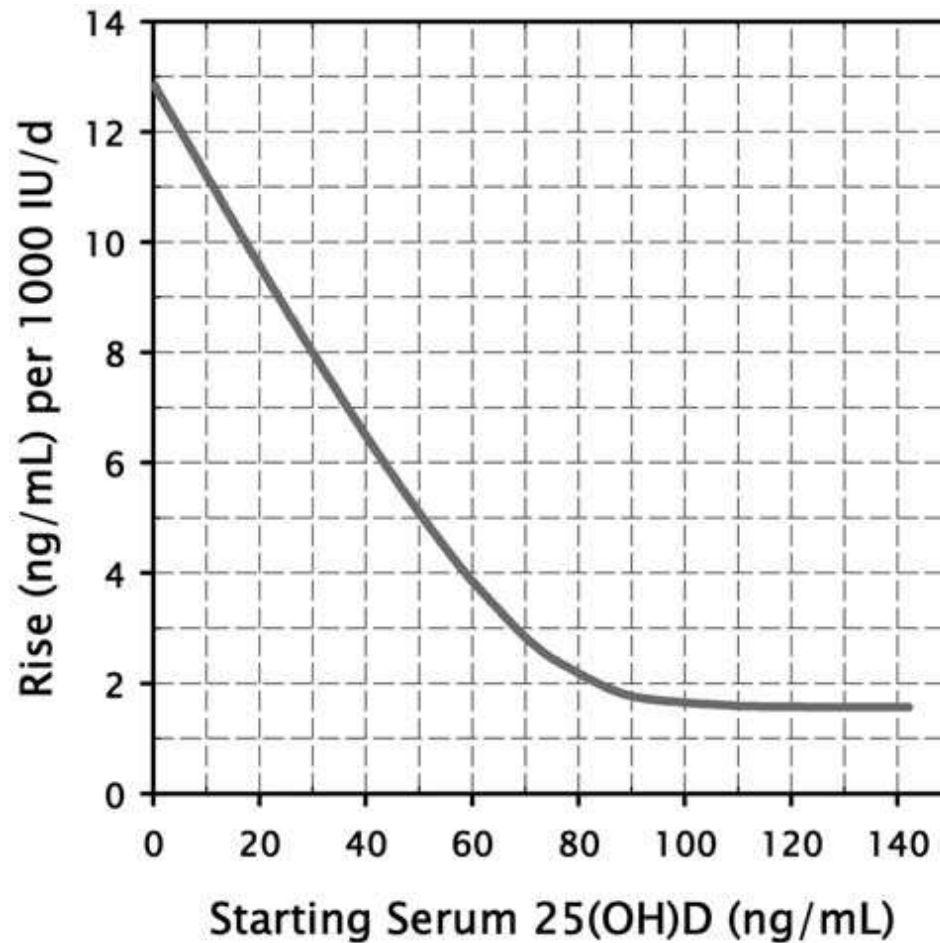
- There is no simple relationship between oral vitamin D dose and serum 25(OH)D concentration.
- The 25(OH)D concentration-health outcome relationships are very nonlinear.
- Thus, vitamin D dose is a poor index to use in clinical trials.

# Variation of 25(OH)D Concentration with Oral Vitamin D Intake

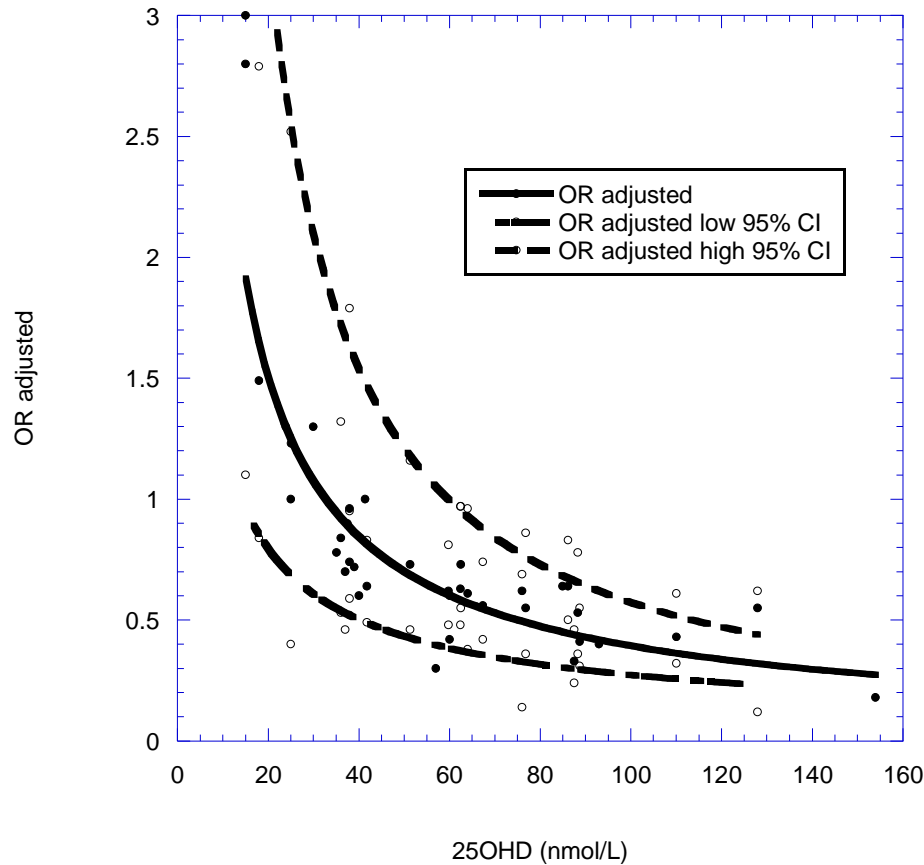


Garland CF, French CB, Baggerly LL, Heaney RP.  
Anticancer Res. 2011 Feb;31(2):607-11.

# Expected Changes in 25(OH)D Concentration for 1000 IU/d vitamin D3



# Breast Cancer Incidence Odds Ratio vs. 25(OH)D Concentration



Grant WB, Boucher BJ. PLoS One. 2017 May 1;12(5):e0176448.

# Proposal: Base Vitamin D Clinical Trials on 25(OH)D Concentration

- The proposal is that vitamin D clinical trials be based on 25(OH)D concentrations, not vitamin D dose.
- 25(OH)D should be measured perhaps 2X/yr.
- Basing them on concentrations would have to be stated in the protocol; otherwise journals may not accept the results.
  
- Grant WB, Boucher BJ, Bhattoa HJ, Lahore. Why vitamin D clinical trials should be based on 25-hydroxyvitamin D concentrations. JSBMB. J Steroid Biochem Mol Biol. 2017 Aug 22. pii: S0960-0760(17)30223-6.

# Clinical Trial: 4 yrs with 2000 IU/d Vitamin D3 + 1500 mg/Ca vs. Placebo

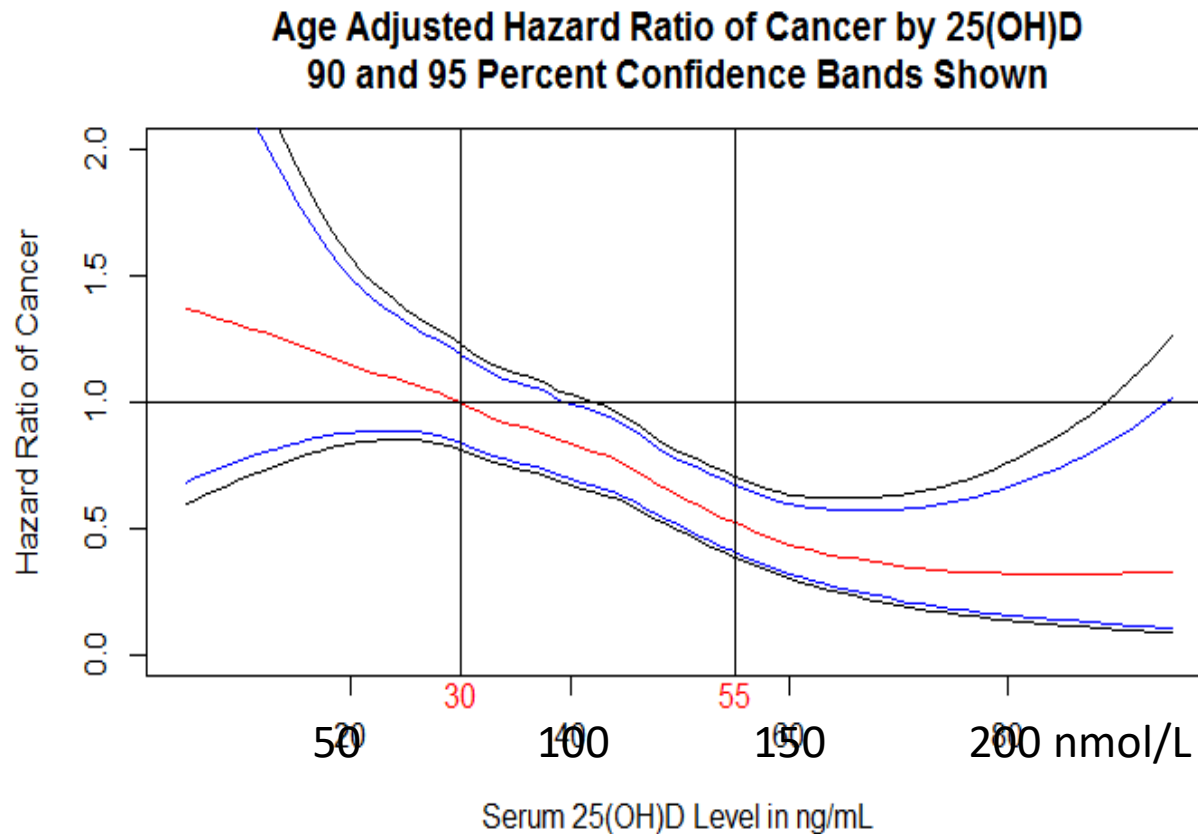
- Among 2303 randomized women (mean age, 65.2 yrs; mean baseline serum 25(OH)D level, 33 ng/mL), mean BMI, 30 kg/m<sup>2</sup>. At year 1, serum 25(OH)D levels were 44 ng/mL in the vitamin D3 + calcium group and 32 ng/mL in the placebo group. A new diagnosis of cancer was confirmed in 109 participants, 45 (3.9%) in the vitamin D3 + calcium group and 64 (5.6%) in the placebo group.

# Clinical Trial: 4 yrs with 2000 IU/d Vitamin D3 + 1500 mg/Ca vs. Placebo

- Kaplan-Meier incidence over 4 years was 0.042 (95% CI, 0.032 to 0.056) in the vitamin D3 + calcium group and 0.060 (95% CI, 0.048 to 0.076) in the placebo group;  $P = 0.06$ .
- Unfortunately, insignificant at  $P = 0.05$  level.
- Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, Baggerly K, McDonnell SL. JAMA. 2017;317(12):1234-1243

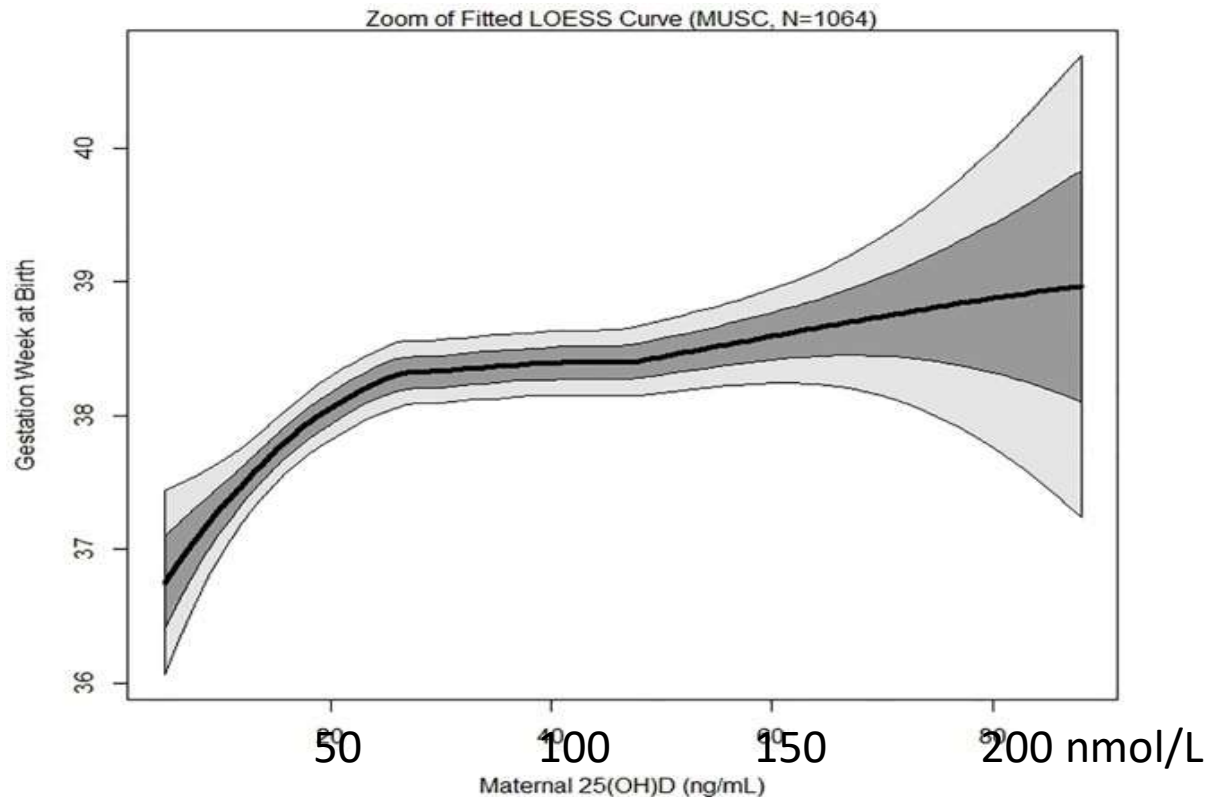


# Results from the Lappe Study Based on 25(OH)D Concentrations (online only)



Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, Baggerly K, McDonnell SL. JAMA. 2017 Mar 28;317(12):1234-1243.

# Gestation Week vs. 25(OH)D Concentration



McDonnell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, Baggerly LL, Ebeling MD, Rittenberg CS, Goodier CG, Mateus Niño JF, Wineland RJ, Newman RB, Hollis BW, Wagner CL. PLoS One. 2017 Jul 24;12(7):e0180483.

# Steps Involved

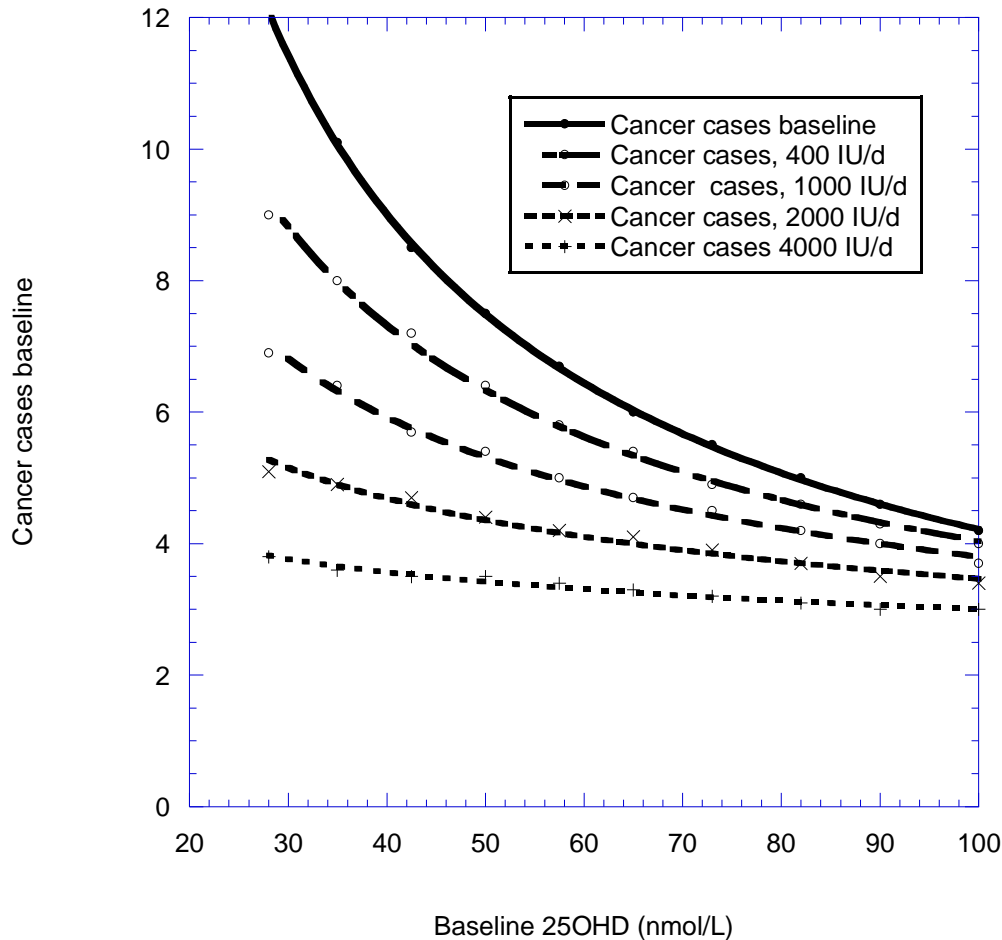
- 1 – Obtain 25(OH)D concentration-health outcome of interest relationship.
- 2 – Determine the range of baseline and achieved 25(OH)D concentrations desired.
- 3 – Determine the 25(OH)D concentration distribution of the population of interest (and those likely to be included in the trial).

# Obtain Population Data on 25(OH)D concentration

Obtain data on known population distributions of serum 25OHD concentrations, e.g. for Canadians aged 50-79 yrs [Grant, 2016].

Decile	25OHD (nmol/L)	Decile	25OHD (nmol/L)
1	28	6	65
2	35	7	73
3	42.5	8	82
4	50	9	90
5	57.5	10	100

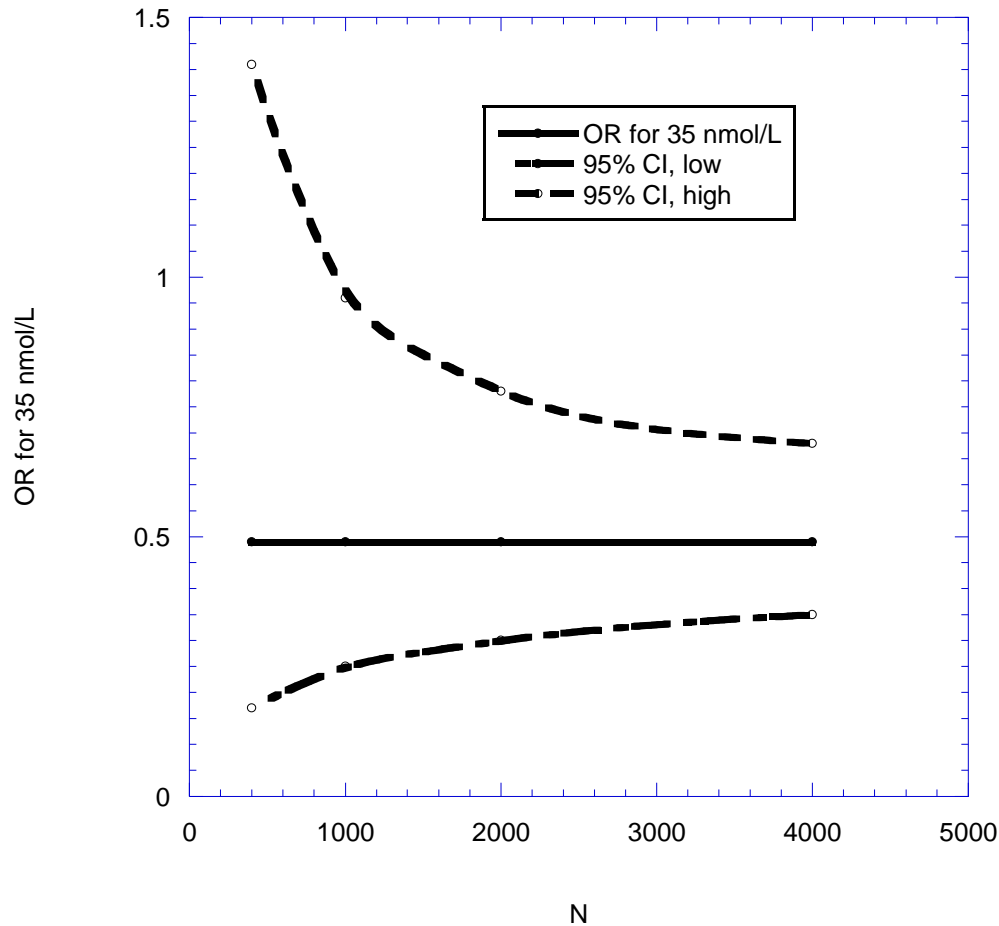
# Calculate the Expected Incidence vs. 25(OH)D with Supplementation



# Relative Risk Calculations

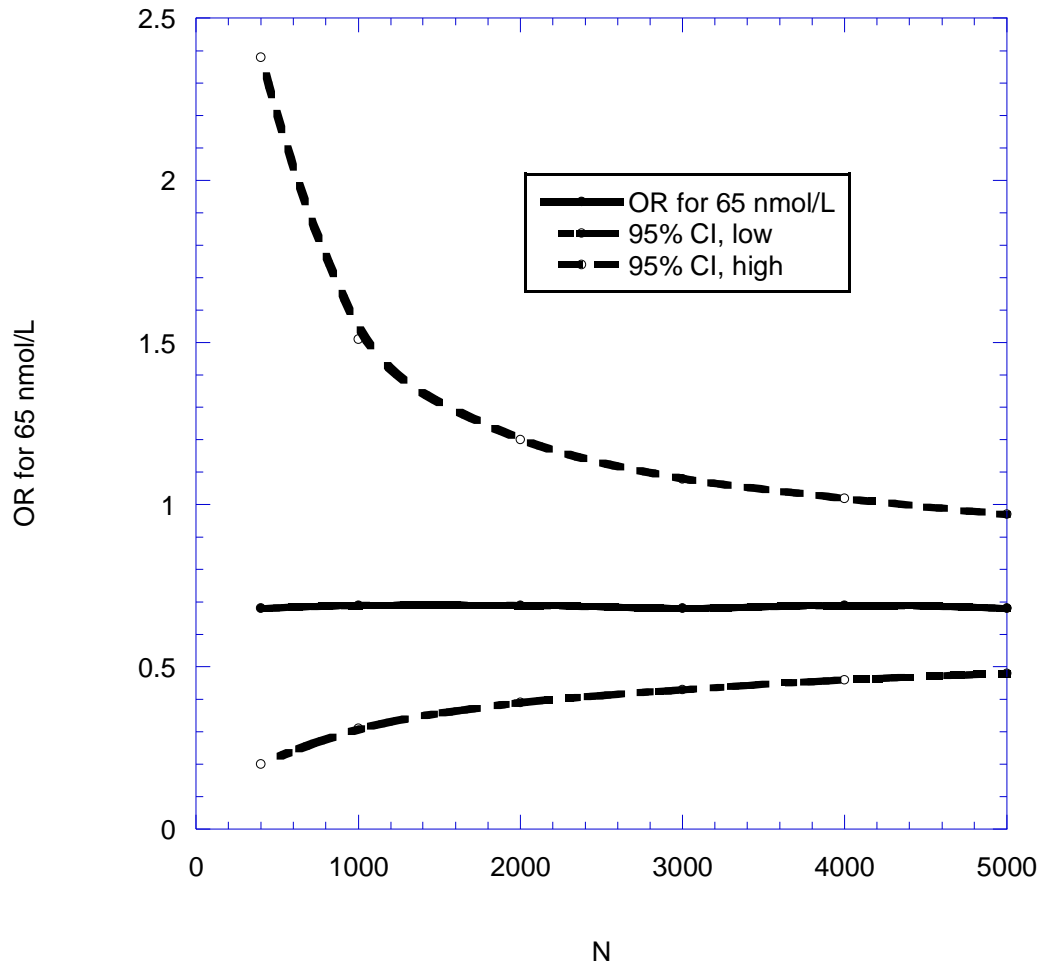
- - Calculate relative risk (RR) using, e.g., <http://www.vassarstats.net/odds2x2.html>
- The number of participant-years can be varied to find the number required to achieve significant results at the  $p=0.05$  level. Allow additional numbers to cover poor compliance, drop outs, undue lag times, etc.
- The lower the baseline 25(OH)D concentration, the fewer people needed.

# Results for Baseline 25(OH)D = 35 nmol/L, 2000 IU/d



Approximately  
1000 participant  
years required

# Results for Baseline 25(OH)D = 65 nmol/L, 2000 IU/d



Approximately  
5000 participant  
years required



# Use 25(OH)D Results During Trial to Titrate/Adjust the Vitamin D Dose

- Since there are large individual variations in 25(OH)D with respect to vitamin D dose, it is important to adjust the vitamin D dose after 3-6 months of the trial using 25(OH)D measurements.
- In addition, doing so overcomes objections that results based on 25(OH)D concentrations are merely an observational study.

# Additional Points to Consider

1. Seek participants with low baseline serum 25(OH)D values.
2. Use vitamin D3, not vitamin D2 and at sufficiently high doses, 1000–6000 IU/d.
3. Consider giving a loading dose of vitamin D3 to reach target 25(OH)D concentrations rapidly.

# Additional Points to Consider

4. Measure baseline serum 25(OH)D concentrations and repeat at suitable intervals to assess compliance and the achievement of target 25(OH)D values.
5. If calcium and/or magnesium are given, give them in both arms.

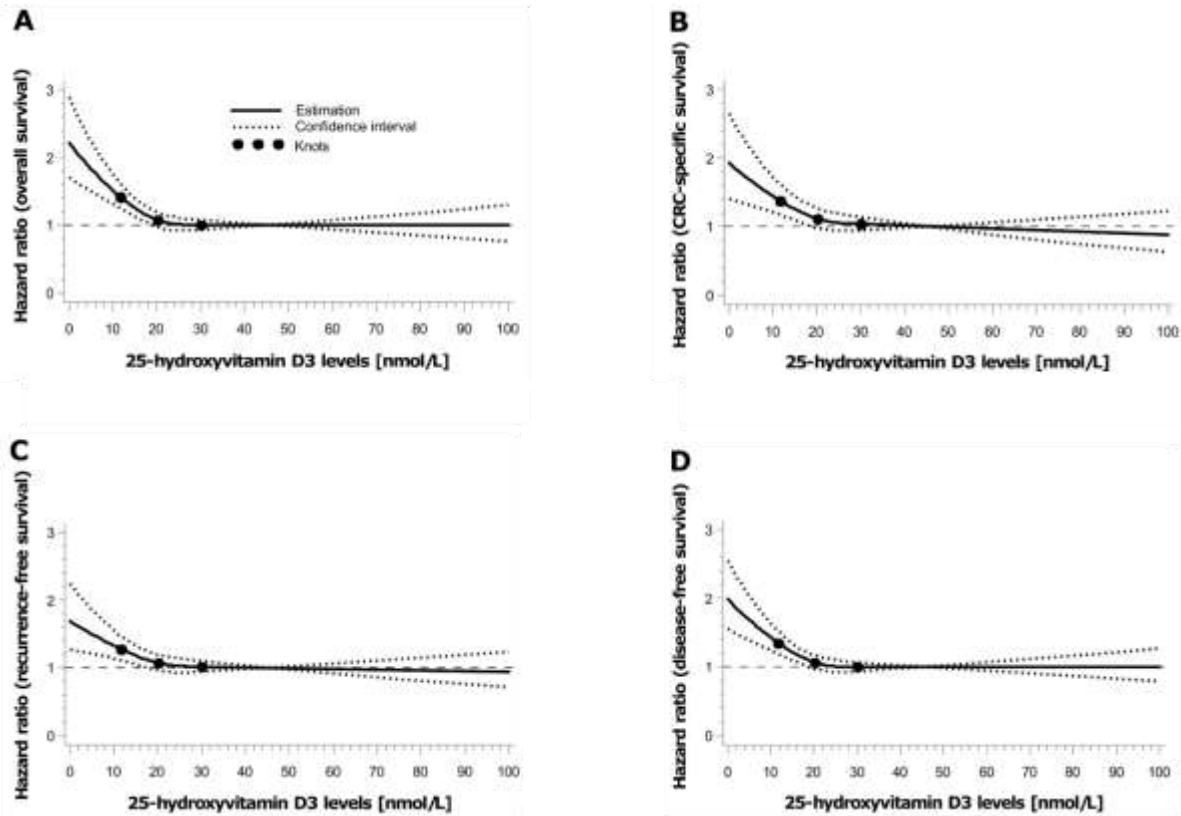
# Additional Points to Consider

6. Monitor participants' UVB exposure , as well as dietary and supplemental intakes of vitamin D3 and potential confounders, including obesity and genetic variants.
7. Allow for the natural history of disease development in planning RCT duration and dosing, and for subject age.
8. Analyze results in terms of 25(OH)D values at baseline, at completion, and at intervals before disease diagnosis, rather than solely with vitamin D3 dose.

# Additional Points to Consider

9. Carefully consider vitamin D dosing interval with respect to compliance and physiological effect. Daily or weekly are likely best.
10. If, for ethical reasons, participants in the control are given 400 IU/d vitamin D, the resulting increase in 25(OH)D concentration should be factored into the selection of participants and into outcome analyses.

# Colorectal Cancer Survival

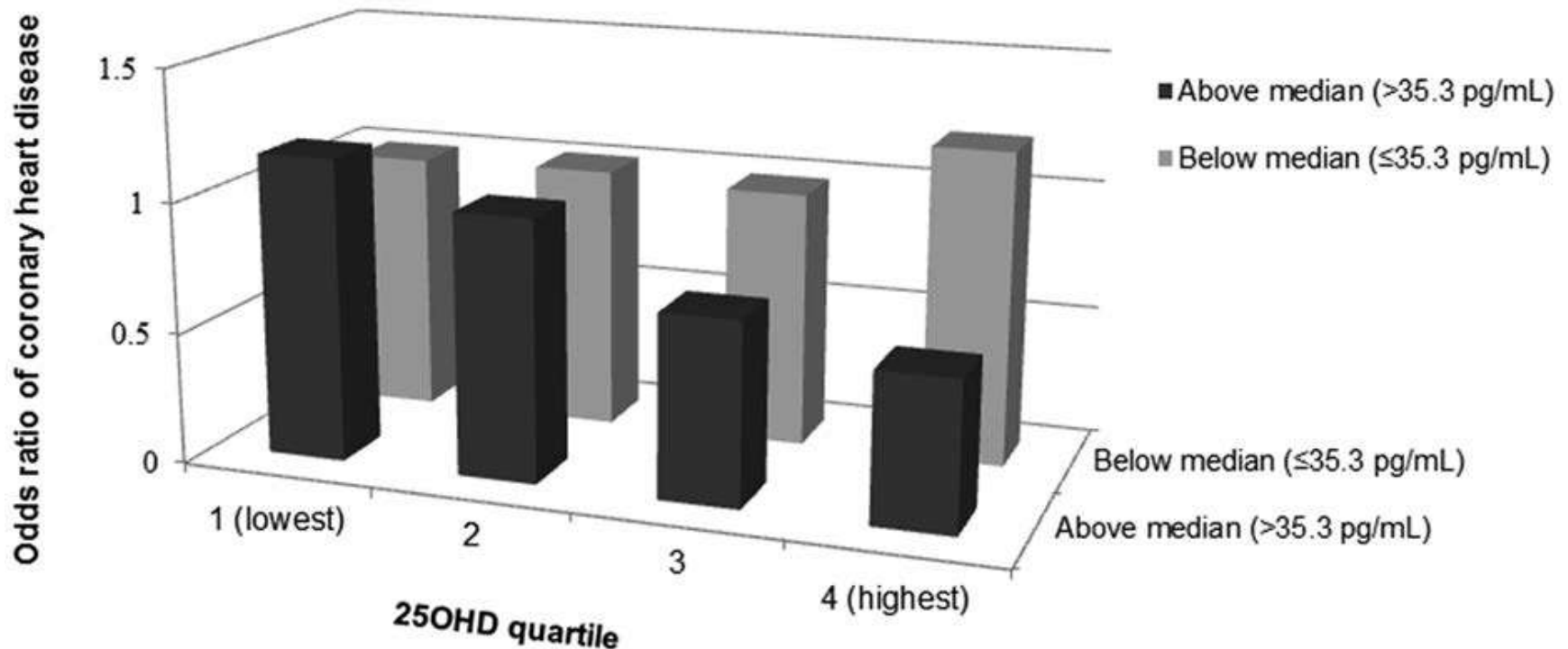


Maalmi H, Walter V, Jansen L, Chang-Claude J, Owen RW, Ulrich A, Schöttker B, Hoffmeister M, Brenner H. Relationship of very low serum 25-hydroxyvitamin D<sub>3</sub> levels with long-term survival in a large cohort of colorectal cancer patients from Germany. *Eur J Epidemiol.* 2017 Sep 7. doi: 10.1007/s10654-017-0298-z. [Epub ahead of print]

# Cardiovascular Disease

- Cardiovascular disease (coronary heart disease, stroke, etc.) have not been shown to be prevented by vitamin D supplementation.
- It may be that only those with very low 25(OH)D concentrations would benefit.
- Or, perhaps, the trials were not properly designed or analyzed.

# 25(OH)D, PTH and Risk of Coronary Heart Disease



Mean 25(OH)D for quartiles: 43, 58, 69, 84 nmol/L

Qi L et al. Independent and Synergistic Associations of Biomarkers of Vitamin D Status With Risk of Coronary Heart Disease. *Arterioscler Thromb Vasc Biol.* 2017 Sep 7



# Summary and Conclusion

- Observational studies in the past decade indicate that vitamin D has many important health effects.
- Vitamin D clinical trials have confirmed some of these effects, but were often poorly designed, conducted, and analyzed.
- Basing vitamin D clinical trials on 25(OH)D concentrations should lead to confirmation of vitamin D's benefits in disease prevention and treatment.