



# *Vitamina D para TODOS?*

**Dra Victória Z. Cochenski Borba**

*Professora Adjunta de Endocrinologia UFPR*

*Vice-Presidente ABRASSO*

*Diretora do Departamento de Metabolismo Ósseo da SBEM*



[www.sempr.org.br](http://www.sempr.org.br)  
vzcborba@gmail.com

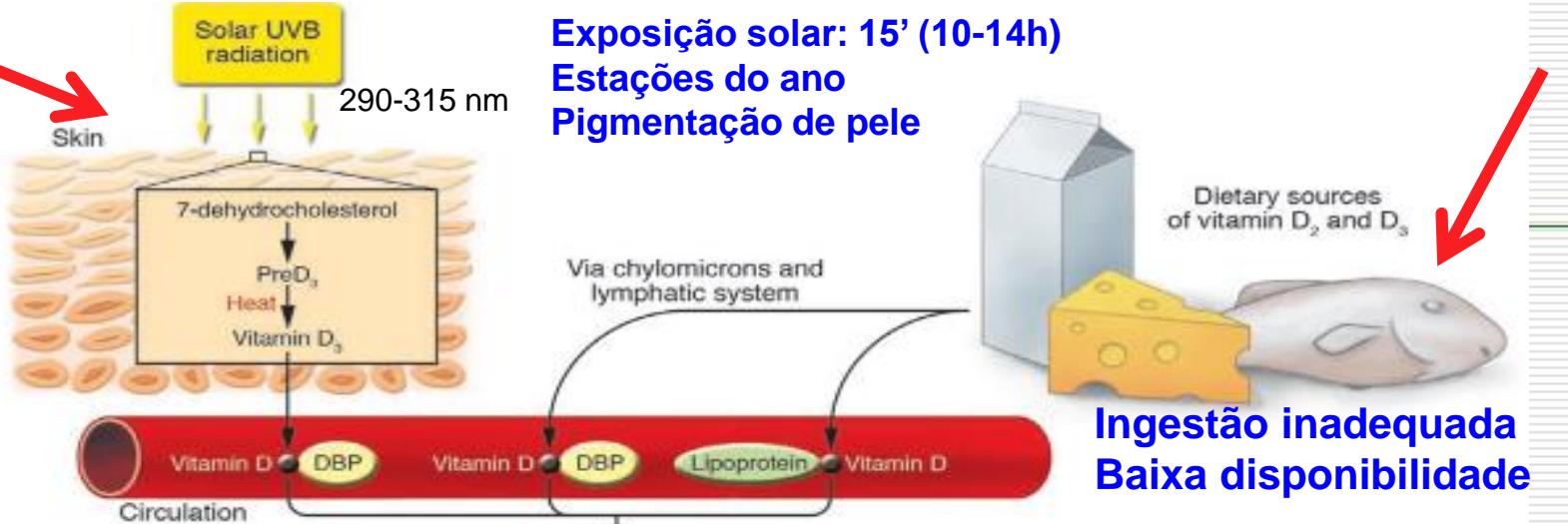


# Conflitos de Interesse

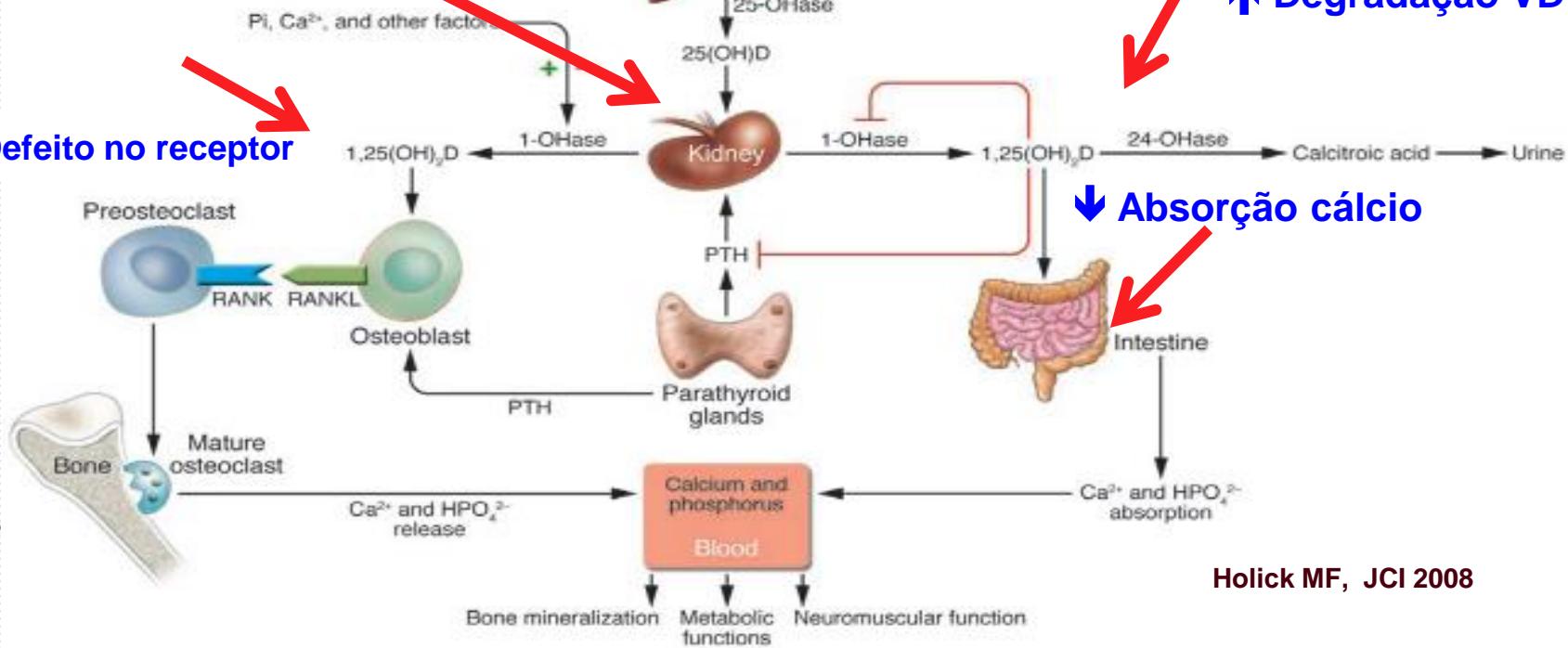
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- Board Laboratórios:
  - Mantecorp
  - Lilly
  - Sandoz
- Palestrante para os Laboratórios:
  - Mantecorp
  - Lilly



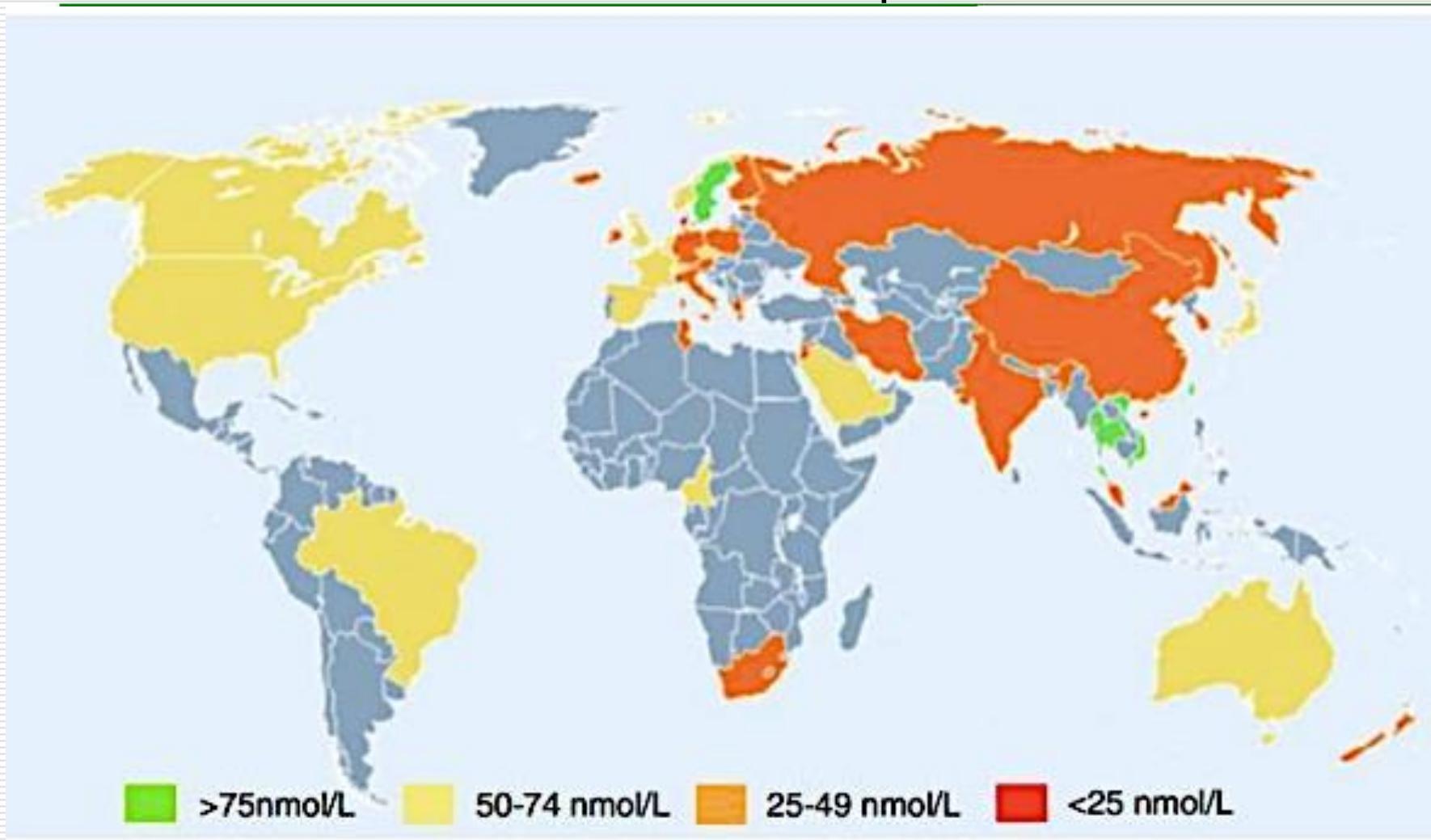


↓ 25OH → 1,25OH<sub>2</sub>D  
↓ Função renal



# População Geral

Vitamina D ao redor do mundo após o inverno

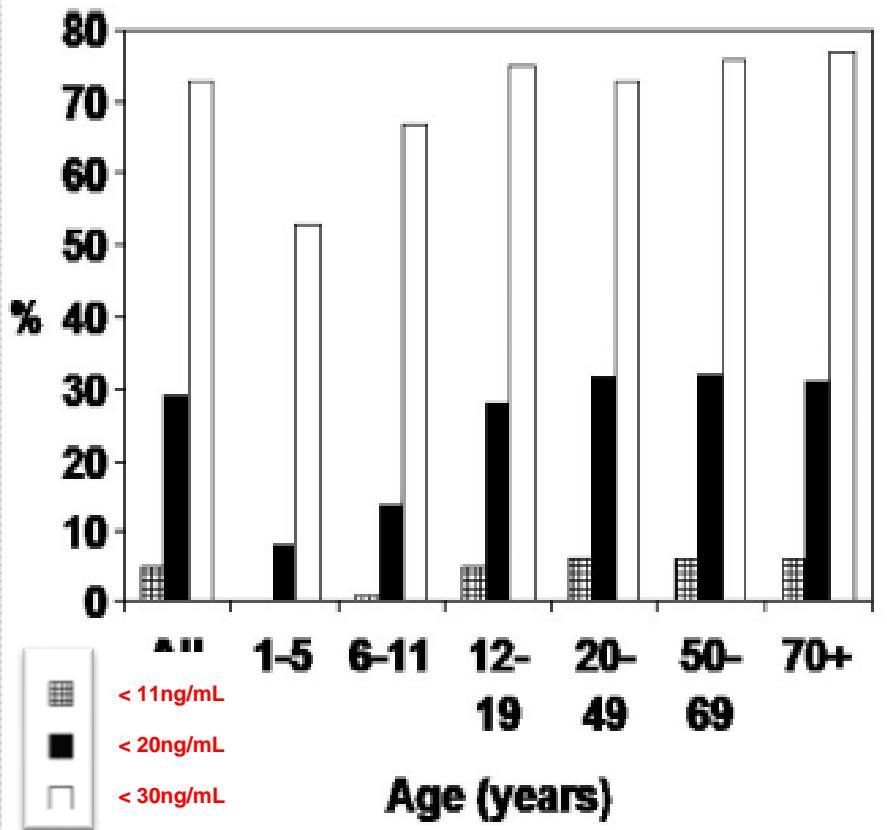


# Assessing the vitamin D status of the US population

Elizabeth A Yetley

# Vitamin D status in central Europe

Pludowski P



## Europa Central

- Pessoas saudáveis da comunidade
  - Inverno  $25\text{OHD} = 21\text{--}23 \text{ ng/mL}$  → todos os grupos idade
- ⑩ ↑ verão
  - $42 \text{ ng/mL}$  (0–9 anos)
  - **$21 \text{ ng/mL}$  (80-89 anos)**

# Fontes alimentares são pobres em Vitamina D

**Necessidades diárias: 400 a 2000 UI**

**Tabela 1.** Fontes alimentares de vitamina D

**Recomendação diária: 400 a 2000 UI**

## ESTUDO BRAZOS:

Recordatório alimentar de 24 hs - 2344 indivíduos  
≥ 40 anos, todas regiões brasileiras

**Ingestão média= 80 UI/dia**

(Pinheiro e col, Nutrition J 2009)

Ossos secos do sol

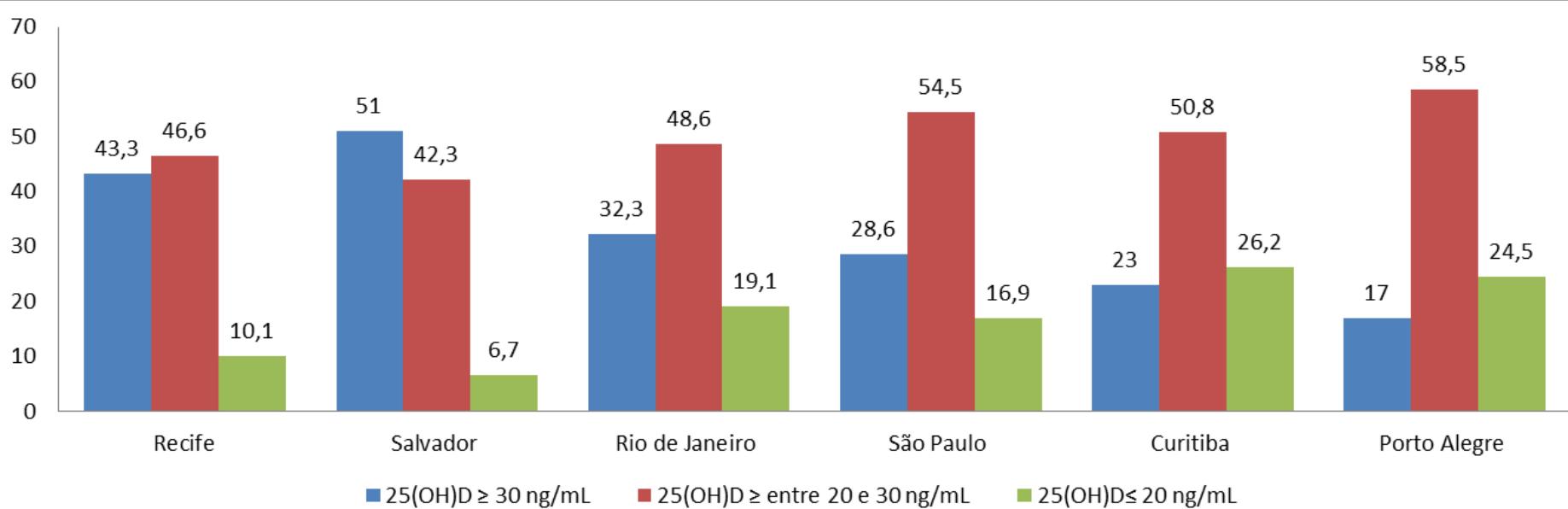
100 g

> 1.000 UI de vitamina D<sub>2</sub>



## Correlation between 25-hydroxyvitamin D levels and latitude in Brazilian postmenopausal women: from the Arzoxifene Generations Trial

H. P. Arantes • C. A. M. Kulak • C. E. Fernandes •  
C. Zerbini • F. Bandeira • I. C. Barbosa • J. C. T. Brenol •  
L. A. Russo • V. C. Borba • A. Y. Chiang •  
J. P. Bilezikian • M. Lazaretti-Castro

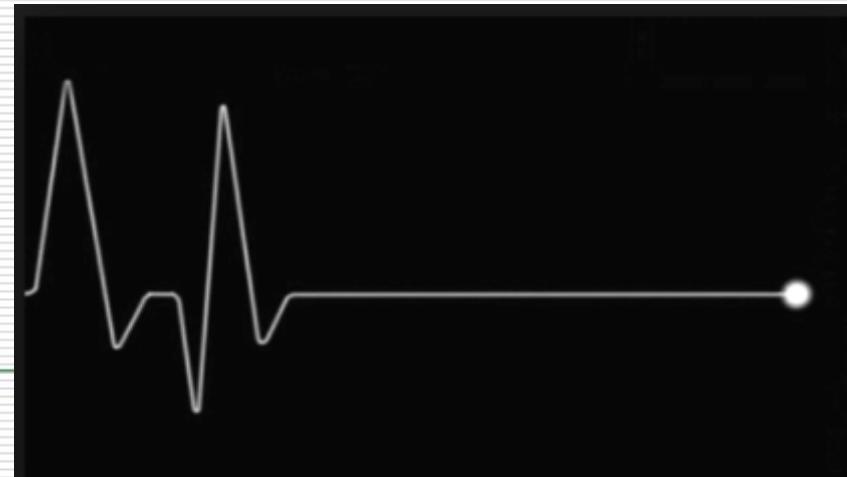




# Consequências para saúde .....



# Consequências.....



# Doentes Crônicos

Furuie IN, Mauro MJJ, Petruzziello S, Riechi SC, Petterle RR, Boguszewski CL, Borba VZC. **Two threshold levels of vitamin D and the prevalence of comorbidities in outpatients of a tertiary hospital.** Osteoporos Int. 2018 Feb;29(2):433-440.

Pereira CP, Amaral DJC, Funke VAM, Borba VZC. **Pre-sarcopenia and bone mineral density in adults submitted to hematopoietic stem cell transplantation.** Rev Bras Hematol Hemoter. 2017 Oct - Dec;39(4):343-348.

Costa TL, Paganotto M, Radominski RB, Kulak CM, Borba VC. **Calcium metabolism, vitamin D and bone mineral density after bariatric surgery.** Osteoporos Int. 2015 Feb;26(2):757-64. doi: 10.1007/s00198-014-2962-4. Epub 2014 Nov 12. PubMed PMID: 25388022.

Campos DJ, Biagini GL, Funke VA, Bonfim CM, Boguszewski CL, Borba VZ. **Vitamin D deficiency in children and adolescents submitted to hematopoietic stem cell transplantation.** Rev Bras Hematol Hemoter. 2014 Mar;36(2):126-31.

Campos DJ, Boguszewski CL, Funke VA, Bonfim CM, Kulak CA, Pasquini R, Borba VZ. **Bone mineral density, vitamin D, and nutritional status of children submitted to hematopoietic stem cell transplantation.** Nutrition. 2014 Jun;30(6):654-

Franco CB, Paz-Filho G, Gomes PE, Nascimento VB, Kulak CA, Boguszewski CL, Borba VZ. **Chronic obstructive pulmonary disease is associated with osteoporosis and low levels of vitamin D.** Osteoporos Int. 2009 Nov;20(11):1881-7.

Souza HN, Lora FL, Kulak CA, Mañas NC, Amarante HM, Borba VZ. **[Low levels of 25-hydroxyvitamin D (25OHD) in patients with inflammatory bowel disease and its correlation with bone mineral density].** Arq Bras Endocrinol Metabol. 2008 Jun;52(4):684-91.

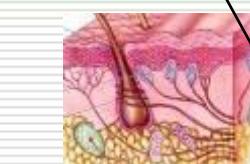
Borba VZ, Vieira JG, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M. **Vitamin D deficiency in patients with active systemic lupus erythematosus.** Osteoporos Int. 2009 Mar;20(3):427-33.

Kulak CA, Borba VZ, Bilezikian JP, Silvado CE, Paola Ld, Boguszewski CL. **Bone mineral density and serum levels of 25 OH vitamin D in chronic users of antiepileptic drugs.** Arq Neuropsiquiatr. 2004 Dec;62(4):940-8

**25OHD**  
Maior metabolito circulante



**1,25(OH)<sub>2</sub>D**  
Biologicamente Ativa



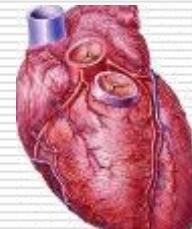
**1,25(OH)<sub>2</sub>D**  
Biologicamente  
Ativa

Possível Efeito

Efeitos  
Imunomoduladores



Efeitos  
Cardiovasculares



Crescimento  
e Regulação



Antiproliferativo  
Prodiferenciação  
Apoptótico  
Anti-angiogênico

Saúde Óssea



Efeitos  
neuromusculares



Homeostase  
Ca e P

Massa  
muscular  
Força  
Equilíbrio

Esclerose Múltipla  
DM 1

Psoríase

AR

DII

Periodontite

↓ Risco  
HAS  
DM 2  
ICC



Câncer  
Próstata  
Côlon  
Mama

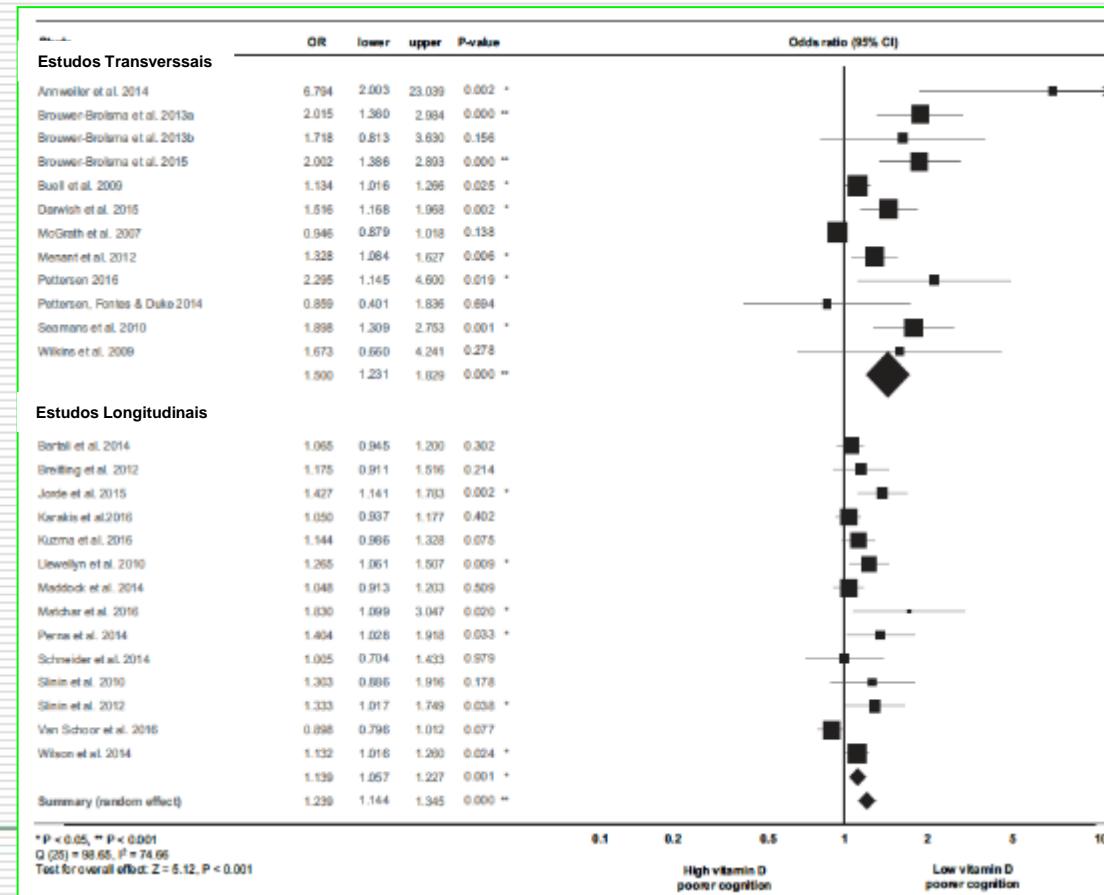


# Cognição.....

## A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition

Goodwill A M, J Am Geriatr Soc 2017

9556 indivíduos  
29 estudos



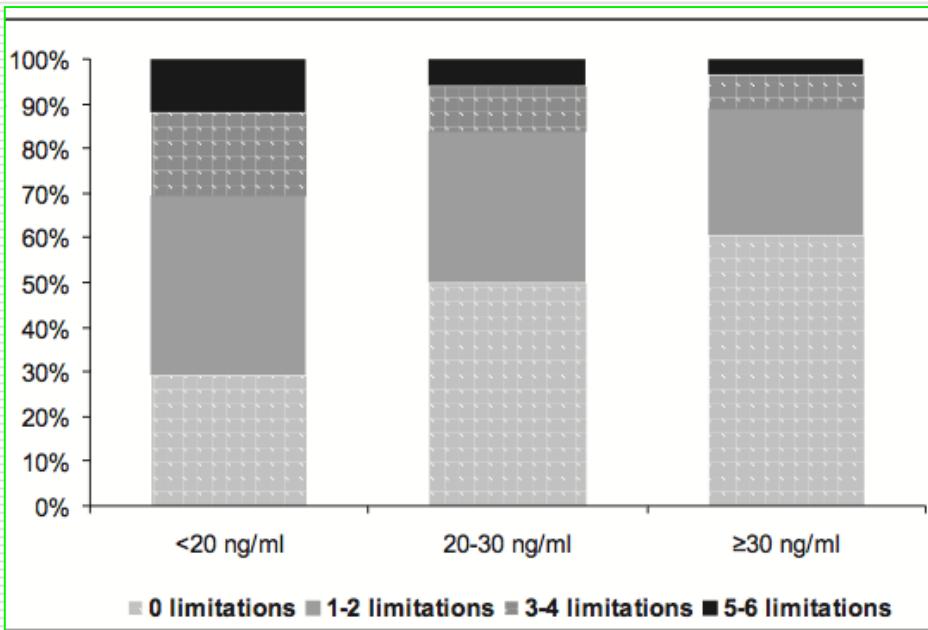


# Quedas e Fraturas

## Vitamin D Status Is Associated With Functional Limitations and Functional Decline in Older Individuals

E. Sohl e cols JCEM, July 2013

1237, 65-88 anos



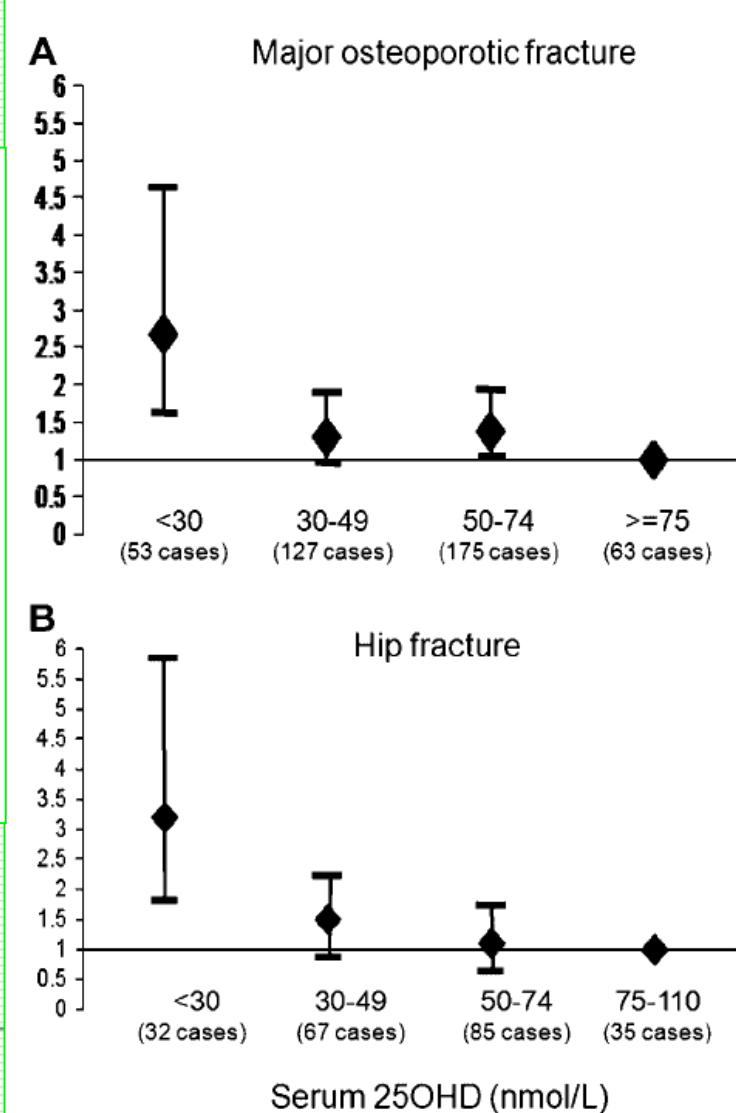
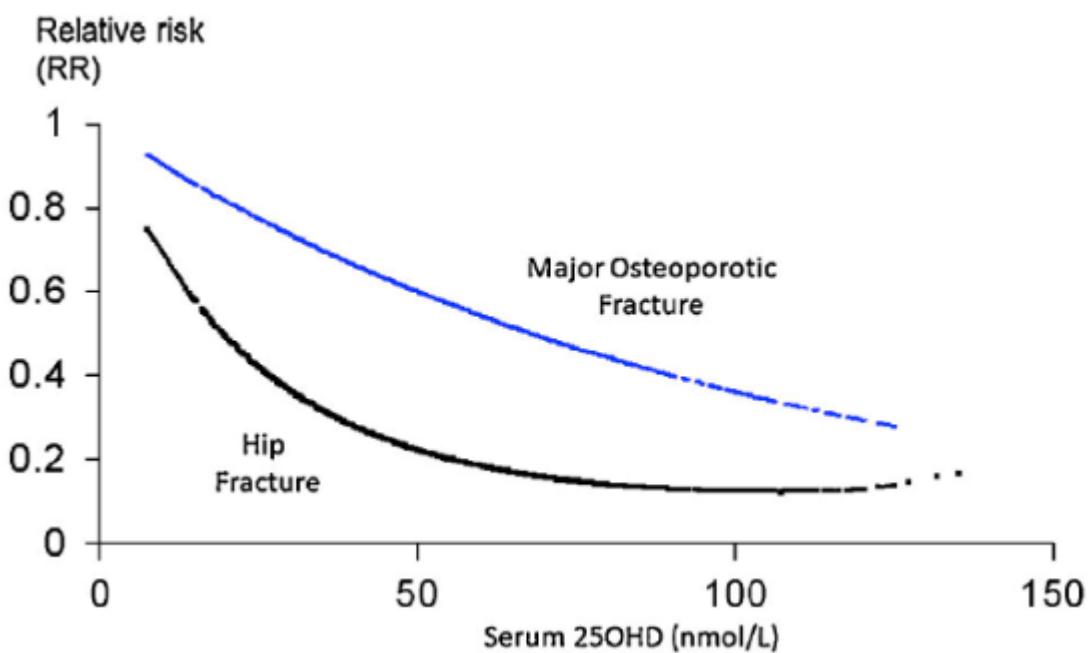
Fatores de risco para quedas recorrentes ( $\geq 2$ /ano) em idosos brasileiros da comunidade (SPAH study, seguimento: 4 anos)

Machado KL e cols. Osteoporosis Int 2015

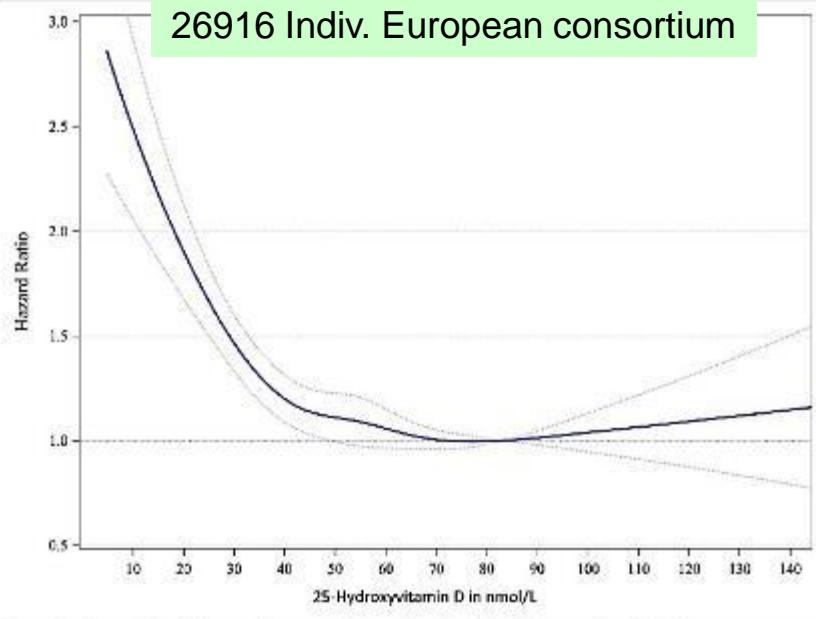
Risk factors	OR	95 % CI	p value
Visual impairment	2.49	1.30–4.74	0.006
Use of psychotropic drugs	2.47	1.36–4.49	0.003
Clinical fracture	2.78	1.48–5.20	0.001
Persistent 25OHD<20 ng/mL	1.71	1.10–2.64	0.016
Loss of total hip BMD	1.21	1.17–1.25	0.035

# Serum 25-Hydroxyvitamin D and Risk of Major Osteoporotic Fractures in Older U.S. Adults

Anne C Looker  
JBMR May, 2013



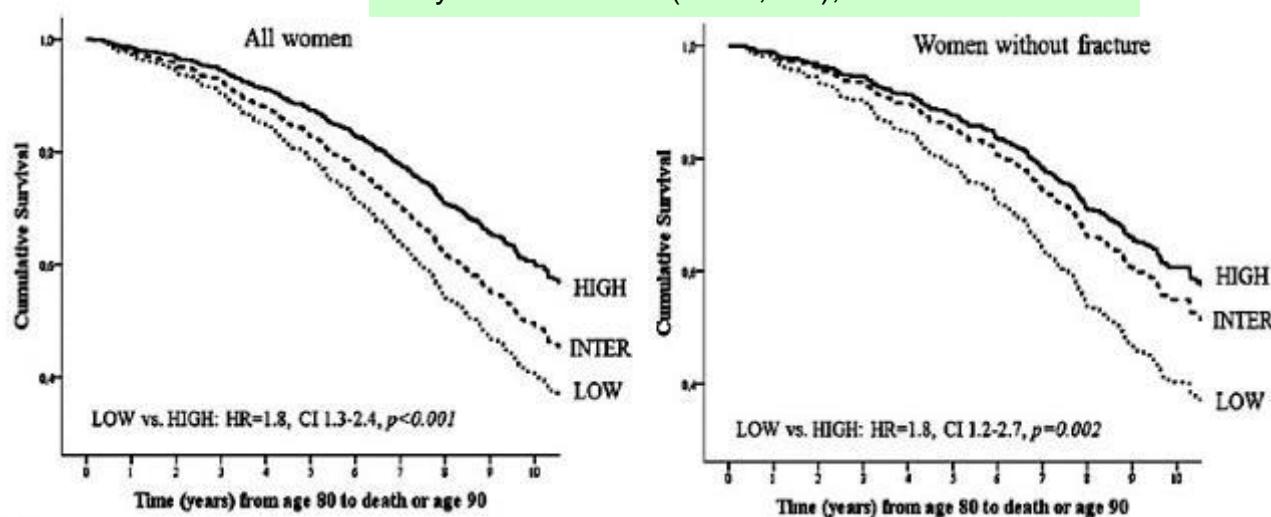
26916 Indiv. European consortium



# Mortalidade

Martin Gaksch, PLOS ONE February 16, 2017

75-year-old women (N = 1,044), 75 → 85 anos.

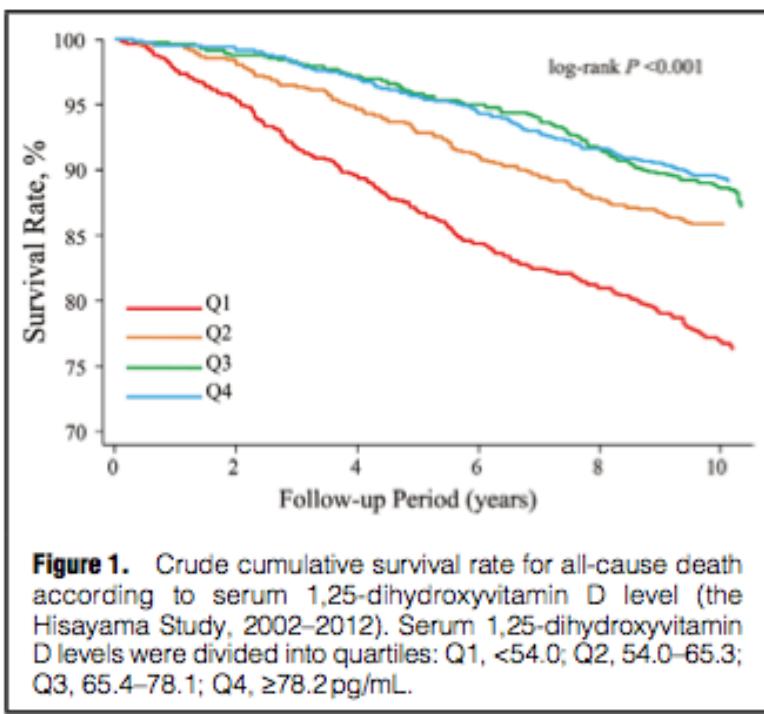


David Buchebner, J Am Geriatr Soc 64:990–997, 2016.

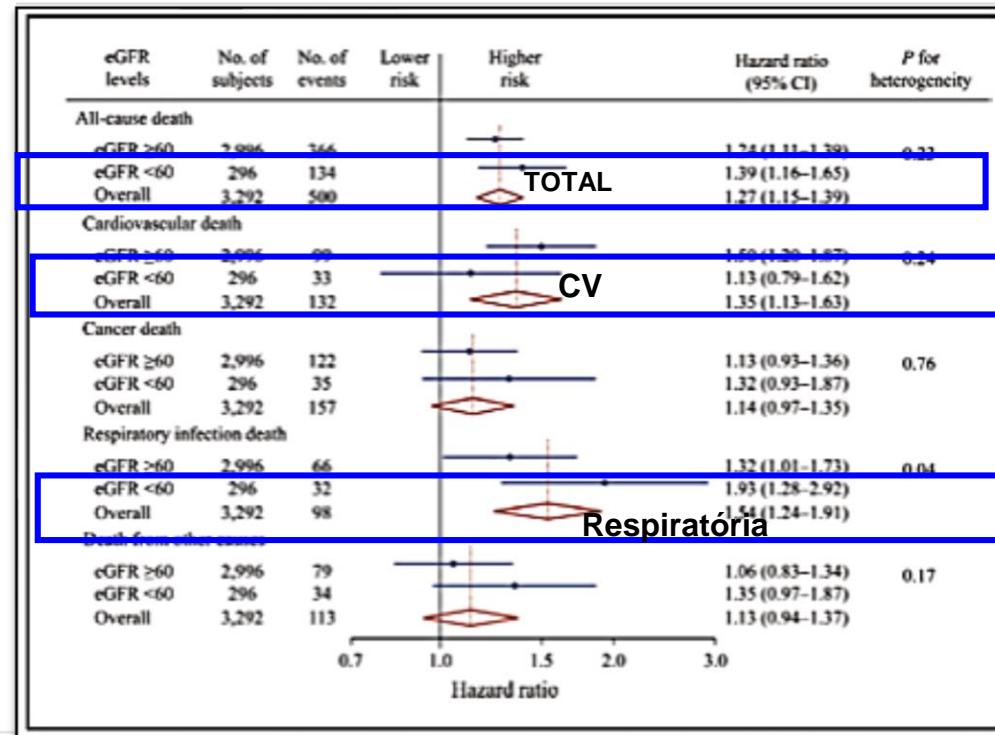
# Vitamina D e Mortalidade em População Japonesa

UMEHARA K et al. *Circ J* 2017; doi:10.1253/circj.CJ-16-0954

- 3292 japoneses > 40 anos
- Avaliação de 1,25-OH-VD e mortalidade geral e específica em 10 anos de follow up



**Figure 1.** Crude cumulative survival rate for all-cause death according to serum 1,25-dihydroxyvitamin D level (the Hisayama Study, 2002–2012). Serum 1,25-dihydroxyvitamin D levels were divided into quartiles: Q1, <54.0; Q2, 54.0–65.3; Q3, 65.4–78.1; Q4, ≥78.2 pg/mL.



- Aumento de mortalidade geral, CV e respiratória;
- Não verificaram aumento de morte por câncer ou outras causas

# Vitamina D vs. Câncer, Doenças autoimunes e metabólicas

- Expressão e Ação: receptores em diversos tecidos: mama, cólon, próstata, cérebro, etc...;
- Controle direto/indireto da 1,25-OH-VD - > 200 genes proliferação celular; angiogênese, apoptose;
- 1,25-OH-VD: ação imuno-moduladora (exposição de monócitos e macrófagos – TBC) inibição da síntese de renina; estimulação da secreção de insulina e estimulação da contratilidade miocárdica
- Deficiência de Vit. D vs. Doenças inflamatórias, metabólicas e neoplásicas
  - ✓ Aumento de 30-50% risco de CA de mama, cólon e próstata
  - ✓ WHI: risco 253% maior de CA colo-retal (8 anos de follow up)
  - ✓ DM2: reposição de VD e cálcio = < risco de 33%
  - ✓ **Esclerose Múltipla = reduziu o risco em 41% com > de 20ng/dl na 25(OH)**
  - ✓ **Artrite reumatóide e osteoartrite = achados semelhantes**
  - ✓ **DM1 → 1º ano de vida (2000UI de VD) – redução do risco de 80%**
  - ✓ **DM1 → crianças deficientes de 25(OH)VD - < risco de 200%**
  - ✓ **DCV: elevação de marcadores inflamatórios (PCR e IL) e ICC**

Hazard ratios (HRs) for total and site specific<sup>\*</sup> cancer according to quarters of plasma vitamin D

	Quarters of plasma vitamin D					P for trend
	1 (low)	2 (second)	3 (third)	4 (high)		
<b>All cancer</b>						
No of cases	840	792	795	874		
HR (95% CI) <sup>†</sup>	1 (reference)	0.84 (0.73 to 0.97)	0.79 (0.68 to 0.91)	0.80 (0.69 to 0.93)	0.003	
HR (95% CI) <sup>‡</sup>	1 (reference)	0.81 (0.70 to 0.94)	0.75 (0.65 to 0.87)	0.78 (0.67 to 0.91)	0.001	
<b>Liver cancer</b>						
No of cases	47	43	41	34		
HR (95% CI) <sup>†</sup>	1 (reference)	0.72 (0.46 to 1.13)	0.65 (0.41 to 1.04)	0.45 (0.27 to 0.77)	0.004	
HR (95% CI) <sup>‡</sup>	1 (reference)	0.70 (0.44 to 1.13)	0.65 (0.40 to 1.06)	0.45 (0.26 to 0.79)	0.006	
<b>Lung cancer</b>						
No of cases	109	87	88	112		
HR (95% CI) <sup>†</sup>	1 (reference)	0.70 (0.51 to 0.96)	0.65 (0.47 to 0.89)	0.75 (0.55 to 1.03)	0.08	
HR (95% CI) <sup>‡</sup>	1 (reference)	0.63 (0.45 to 0.87)	0.56 (0.40 to 0.79)	0.72 (0.52 to 1.00)	0.06	
<b>Prostate cancer</b>						
No of cases	67	65	69	62		
HR (95% CI) <sup>†</sup>	1 (reference)	0.81 (0.54 to 1.22)	0.79 (0.53 to 1.20)	0.64 (0.41 to 1.00)	0.06	
HR (95% CI) <sup>‡</sup>	1 (reference)	0.81 (0.53 to 1.23)	0.81 (0.53 to 1.25)	0.64 (0.41 to 1.02)	0.07	
<b>Breast cancer</b>						
No of cases	72	59	46	62		
HR (95% CI) <sup>†</sup>	1 (reference)	0.82 (0.57 to 1.18)	0.61 (0.41 to 0.92)	0.75 (0.51 to 1.11)	0.08	
HR (95% CI) <sup>§  </sup>	1 (reference)	0.98 (0.66 to 1.47)	0.69 (0.45 to 1.05)	0.78 (0.51 to 1.21)	0.12	
<b>Premenopausal:</b>						
No of cases	35	27	12	12		
HR (95% CI) <sup>**</sup>	1 (reference)	1.14 (0.62 to 2.09)	0.42 (0.20 to 0.90)	0.56 (0.25 to 1.24)	0.03	
<b>Postmenopausal:</b>						
No of cases	29	28	31	40		
HR (95% CI) <sup>**</sup>	1 (reference)	0.91 (0.51 to 1.60)	0.94 (0.54 to 1.64)	0.97 (0.56 to 1.71)	0.98	

Plasma 25-hydroxyvitamin D concentration and subsequent risk of total and site specific cancers in Japanese population: large case-cohort study within Japan Public Health Center-based Prospective Study cohort.

Budhathoki S<sup>1</sup>, et al

Japan Public Health Center-based Prospective Study Group.

BMJ. 2018 Mar 7;360:k671.

# Níveis de Vit.D após 10 anos da Cirurgia bariátrica



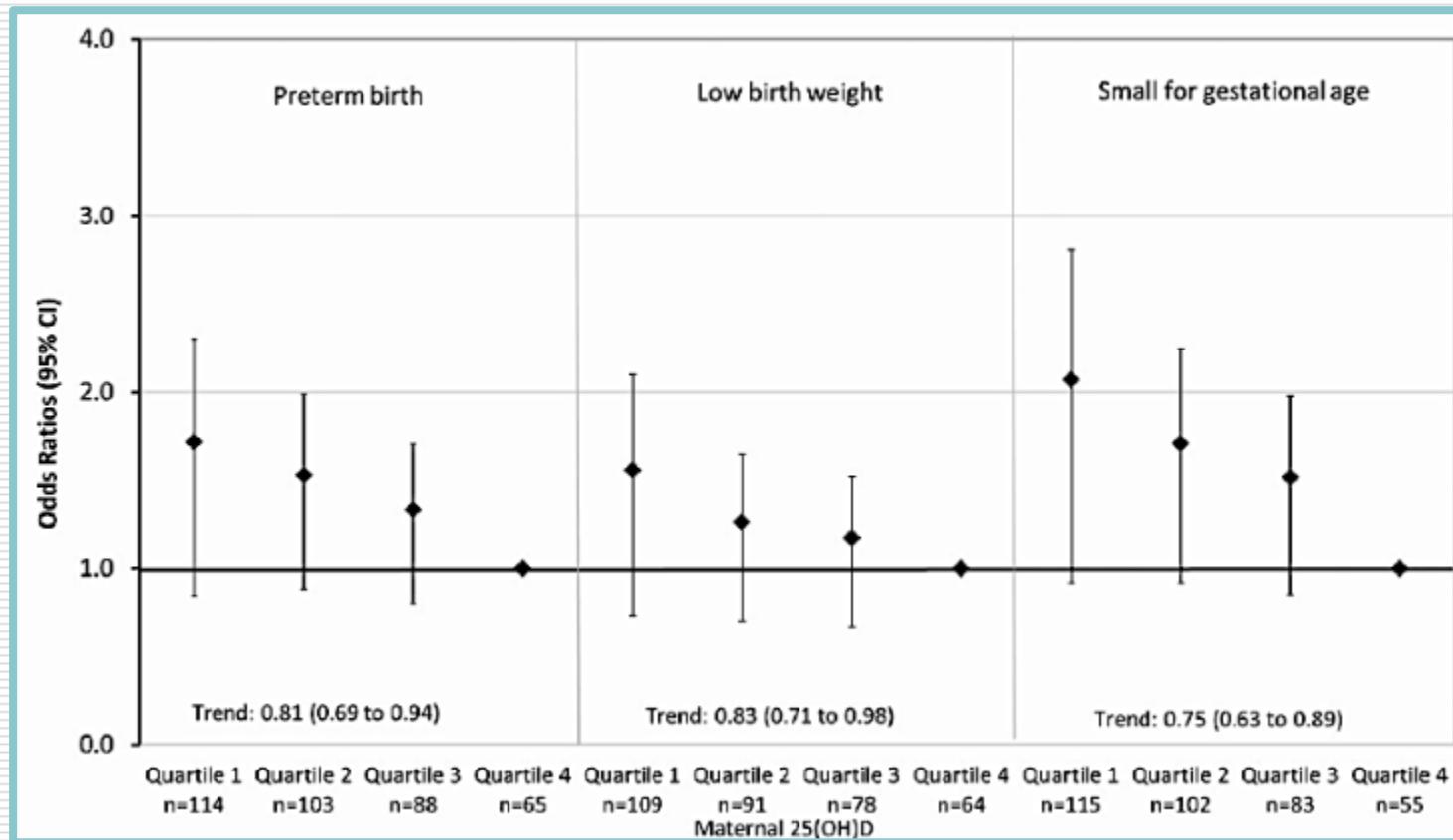
- Estudo prospectivo 10 anos (1993 – 2003) – Suécia
- 537 pacientes submetidos à Y-Roux (“bypass”)
- **65%: deficiência de Vitamina D após 10 anos**
- **69% PTH elevado (Hiperpara 2º)**
- **IMC > 43 kg/m<sup>2</sup>: preditor independente**

## Recomendações SBEM

Cirurgia bariátrica: obesos são população de risco para deficiência e após a cirurgia bariátrica isso se agrava, levando a hiperparatiroidismo secundário e ↑ no risco de fraturas (Evidência A). A avaliação da 25(OH)D é útil para titulação das doses diárias de vitamina D, que podem chegar a até 10 vezes as doses habituais (Evidência D).

# Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes

Holanda – 7098 gestantes e RN 25(OH)D - 20.3 sem (range:18.5–23.3 sem)

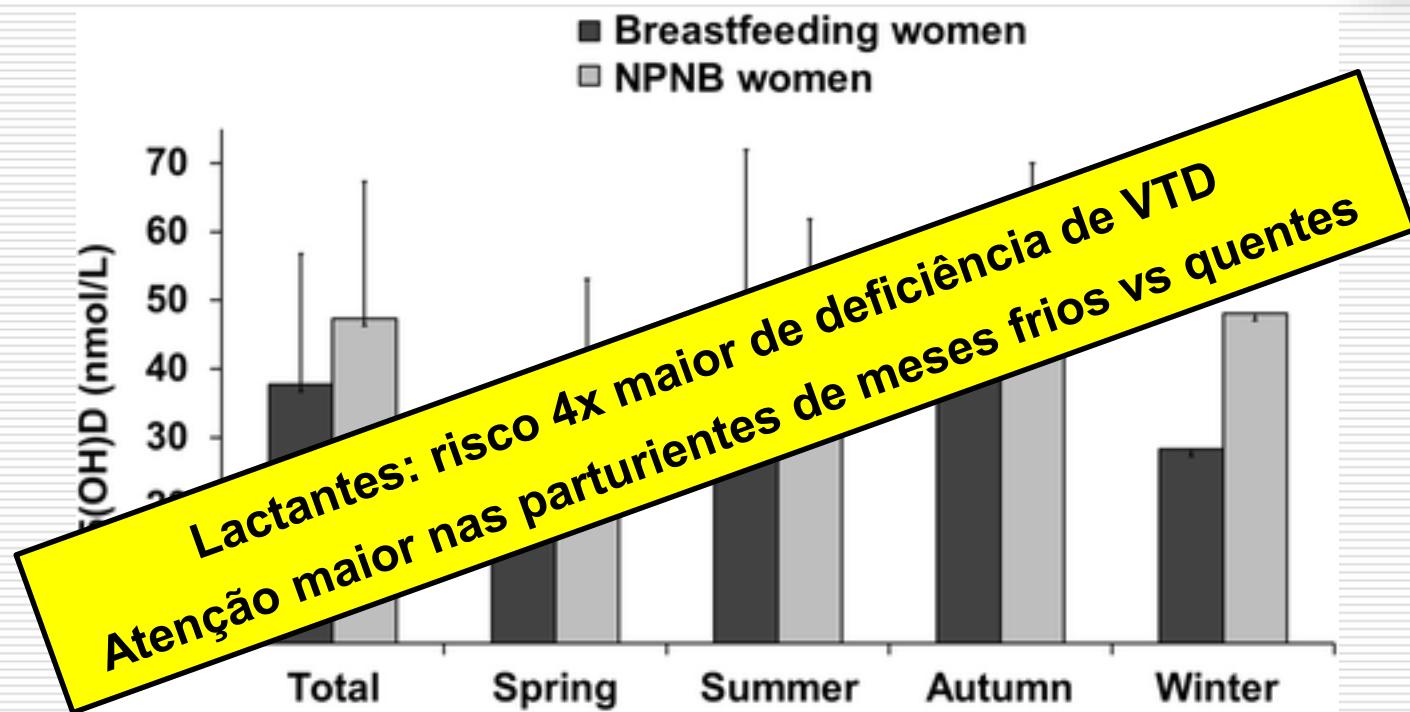


# Vitamin D status in Breastfeeding woman

Gellert S, et al. Int Breastfeed J 2017 Apr;12:19.



## Results



- Breastfeeding women: 4.0-fold higher OR for vitamin D deficiency than NPNB women.
- The risk of vitamin D deficiency was **higher in the winter** and spring months.



E a Reposição.....

**Melhor resposta é para quem precisa!!!!!!**



## Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari,  
Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad,  
and Connie M. Weaver

Group	US RDA	Endocrine Society Daily requirement	Maximum dose tolerable
RN (bebês) < 1 ano	400ui	400 - 1000 ui	2000 ui
Crianças (1-8 anos)	600 ui	600 – 1000 ui	4000 ui
Homens/mulheres (9-18 anos)	600 ui	600 - 1000 ui	4000 ui
Homens/mulheres (> 19-70 anos)	600 ui	1500 - 2000 ui	10.000 ui
Homens/mulheres (>70 anos)	800 ui	1500 - 2000 ui	10.000 ui
Gestante / Lactante	600 ui	1500 - 2000 ui	10.000 ui

National Osteoporosis Foundation:

50 years and older: at least 800 – 1000 units (20-25 mcg) /day, for goal 25OHD > 30 ng/mL (75 nmol/L)

# Impacto da Suplementação de VD nos níveis de 25OHVD após 8 semanas

- 116 homens adultos, saudáveis; média de 70 kg.
- 25OHVD basal 27 ng/mL em média

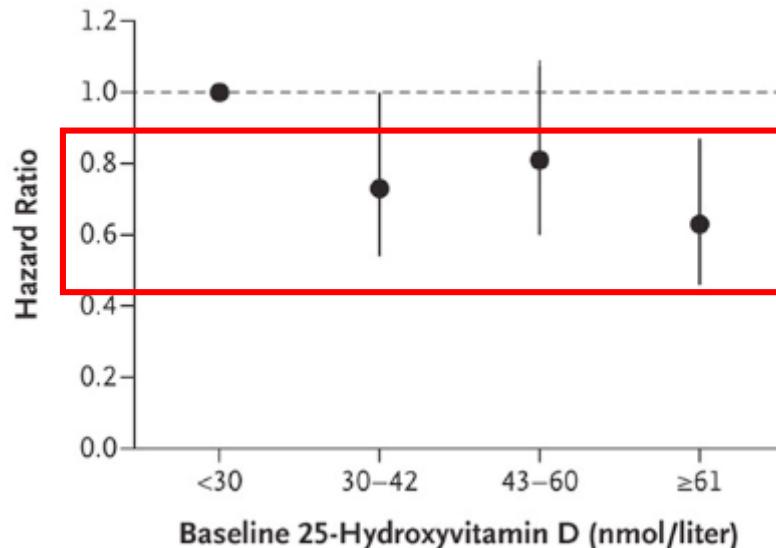


Dose de VITAMINA D	Elevação esperada no nível de 25OHVD sérico
400 ui / dia	4 ng/mL
800 ui / dia	9 ng/mL
1700 ui /dia	12 ng/mL
2400 ui / dia	23 ng/mL
4000 ui / dia	22 ng/mL
100.000 ui / dose única*	4.9 → 30.8 ng/mL

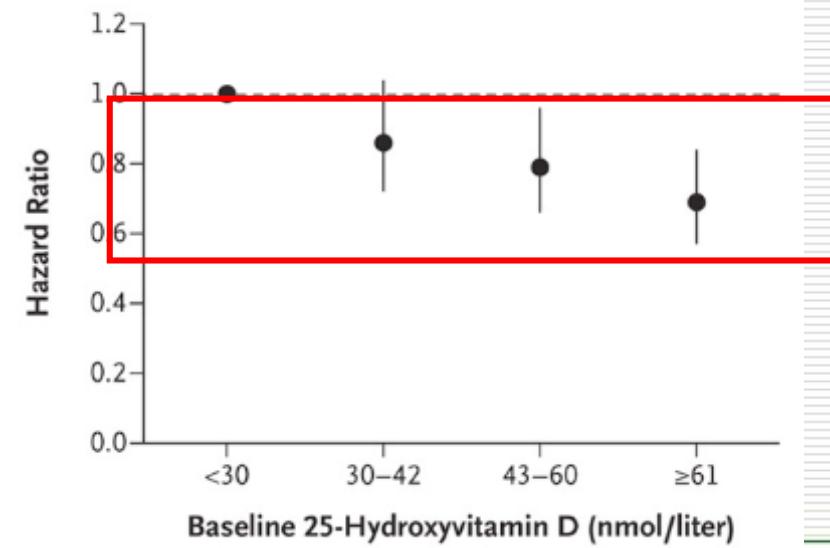
# Prevenção de Fratura

- 31.022 pacientes; Metanálise de 11 RCTs
- 1.111 fraturas de fêmur; 3770 fraturas não-vertebrais
- Vitamina D 800UI dia
  - → Redução de 30% fratura de fêmur;
  - → Redução de 10% fraturas não-vertebrais

A Hip-Fracture Events (N=313)

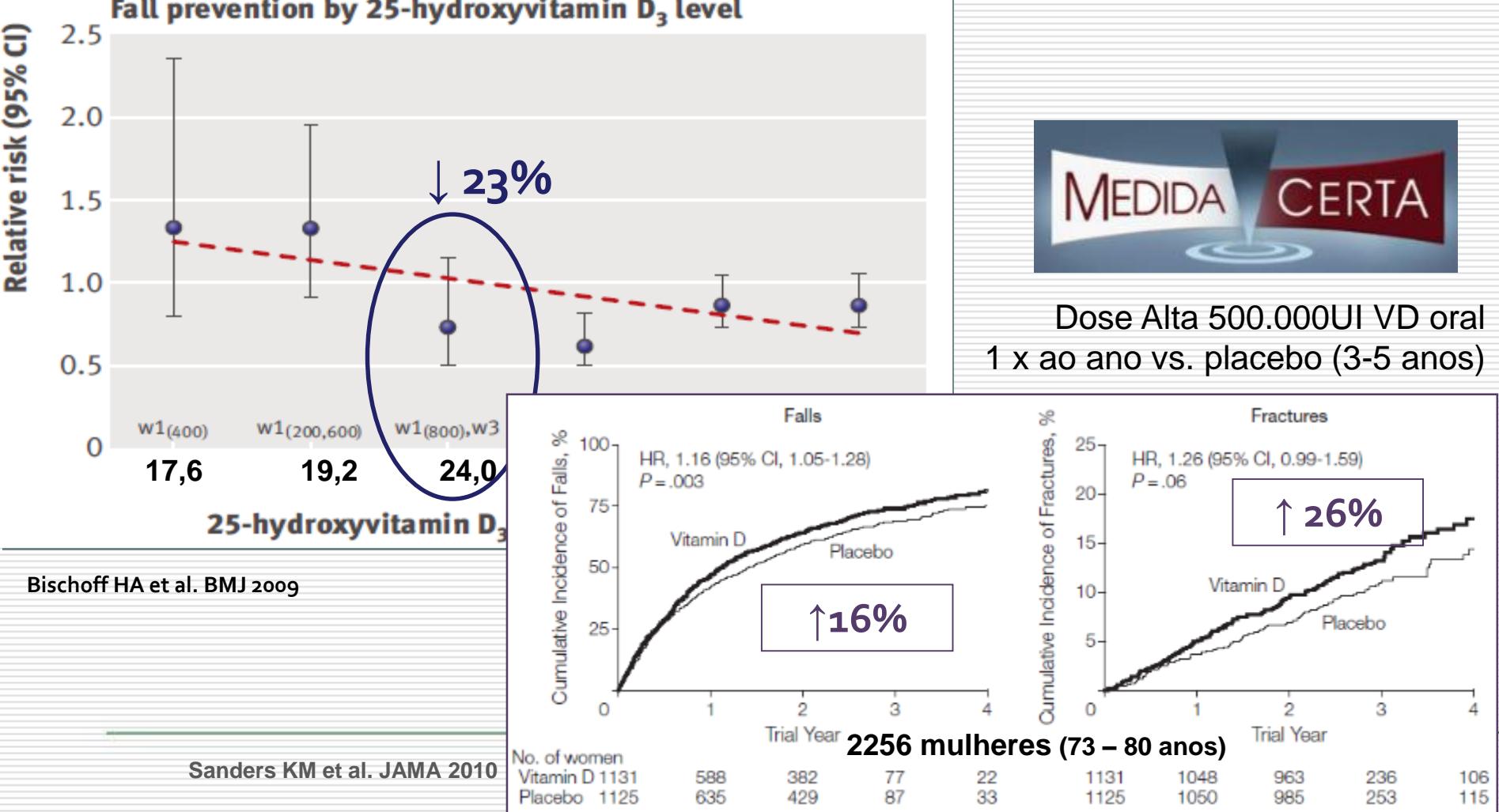


B Nonvertebral-Fracture Events (N=914)



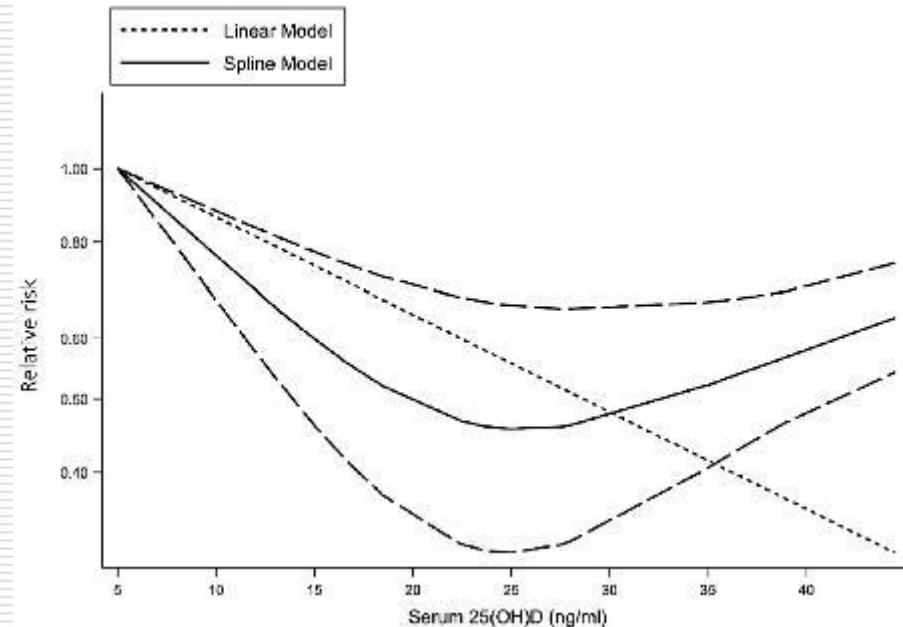
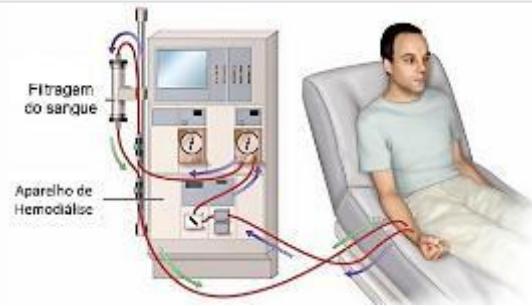
# Prevenção Quedas.....

## Quedas



# 25OHVD e Mortalidade na IRC

- 13 coortes prospectivos; 2 retrospectivos; 1 caso-controle;
- 17.053 participantes → 7517 mortes
- Risco de morte em pacientes com DRC:
  - $25\text{OHVD} < 10 \text{ ng/ml} \rightarrow 1.63 \text{ (95\%CI: } 1.32, 1.94)$
  - $25\text{OHVD } 10\text{-}20 \text{ ng/ml} \rightarrow 1.22 \text{ (95\%CI: } 1.09, 1.35)$
  - $25\text{OHVD } 20\text{-}30 \text{ ng/ml} \rightarrow 1.12 \text{ (95\%CI: } 1.06, 1.18)$
- Maior risco de morte em pacientes em diálise



## Vitamin D supplementation for prevention of mortality in adults (Review)

Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C

- 56 RCTs incluindo 95.286 participantes
- Idade variando de 18 a 107 anos; maioria acima de 70a
- Vitamina D usada por 4.4 anos em média
- Vitamina D reduziu morte em 56 trials; RR 0.97
- Redução de 12% de morte por câncer (RR 0.88) (4 trials)
- Risco de nefrolitíase na associação Cálcio + VTD (RR 1.17)

# Vitamin D Supplementation and Small for Gestational Age (SGA)



- 5405 participantes
- Doses: 800-5.000UI/d; 35000-50.000UI/sem; 60.000- 200UI/mês ou 2/2/meses
- ↓ SGA (RR, 0.72; 95% CI, 0.52 to 0.99) sem risco para RN
- RN > nível de 25(OH)D - 13.50 ng/mL; 95%CI, 10.12 a 16.87 ng/mL), cálcio (0.19mg/dL; 95%CI, 0.003 a 0.38mg/dL),
  - > peso
    - nascer (75.38 g; 95%CI, 22.88 a 127.88 g)
    - 3 m (0.21 kg; 95%CI, 0.13 a 0.28 kg)
    - 6 m (0.46 kg; 95%CI, 0.33 a 0.58 kg)
    - 9 m (0.50 kg; 95%CI, 0.01 a 0.99 kg)
    - 12 m (0.32 kg; 95%CI, 0.12 a 0.52 kg)

# Vitamin D Supplementation and Small for Gestational Age (SGA)



## A Timing of vitamin D supplementation

Source	Experimental Group, No.	Control Group, No.	RR (95% CI)		
	Events	Total	Events	Total	
During pregnancy: initiation at <20 weeks of gestation					
Dawodu et al, <sup>15</sup> 2013	5	84	4	42	0.63 (0.18-2.21)
<b>Subtotal</b>		<b>84</b>		<b>42</b>	<b>0.63 (0.18-2.21)</b>
<b>Total events</b>	<b>5</b>		<b>4</b>		

Heterogeneity: not applicable

Test for overall effect:  $z=0.73$ ;  $P=.47$

## During pregnancy: initiation at ≥20 weeks of gestation

Source	Experimental Group, No.	Control Group, No.	RR (95% CI)		
	Events	Total	Events	Total	
Brooke et al, <sup>12</sup> 1980					
Hasheimpour et al, <sup>19</sup> 2014	0	55	1	54	0.33 (0.01-7.86)
Hossain et al, <sup>21</sup> 2014	19	86	18	89	1.09 (0.62-1.94)
Sablok et al, <sup>31</sup> 2015	9	108	11	57	0.43 (0.19-0.98)
Yu et al, <sup>36</sup> 2009	17	120	10	59	0.84 (0.41-1.71)
<b>Subtotal</b>	<b>428</b>		<b>326</b>	<b>0.72 (0.52-1.01)</b>	
<b>Total events</b>	<b>54</b>		<b>59</b>		

Heterogeneity:  $\chi^2=4.57$ ;  $P=.33$ ;  $I^2=13\%$

Test for overall effect:  $z=1.89$ ;  $P=.06$

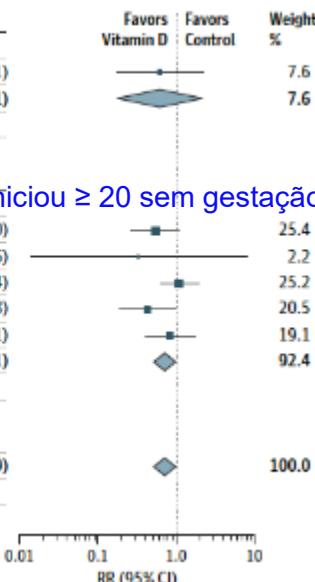
**Total** 512 368 0.72 (0.52-0.99)

**Total events** 59 63

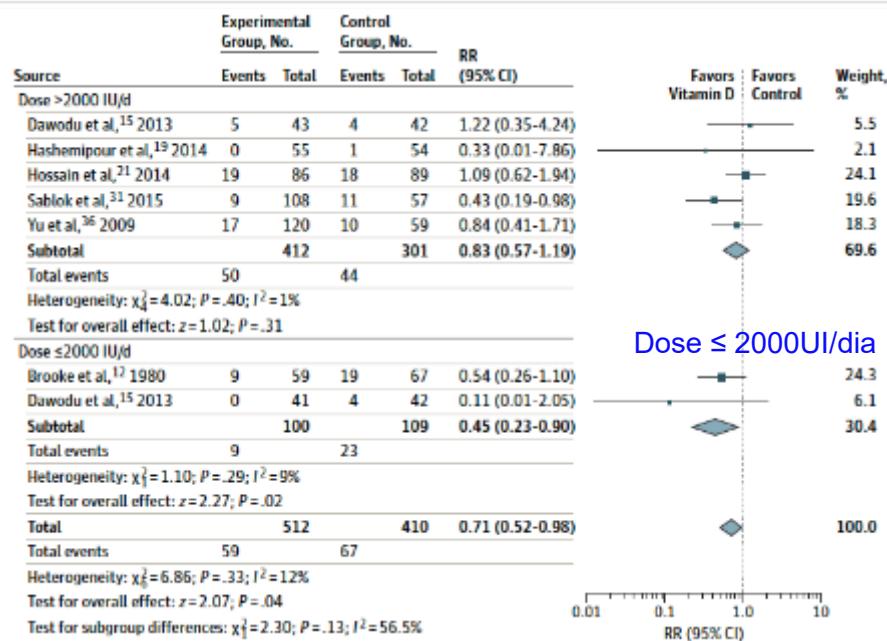
Heterogeneity:  $\chi^2=4.63$ ;  $P=.46$ ;  $I^2=0\%$

Test for overall effect:  $z=2.02$ ;  $P=.04$

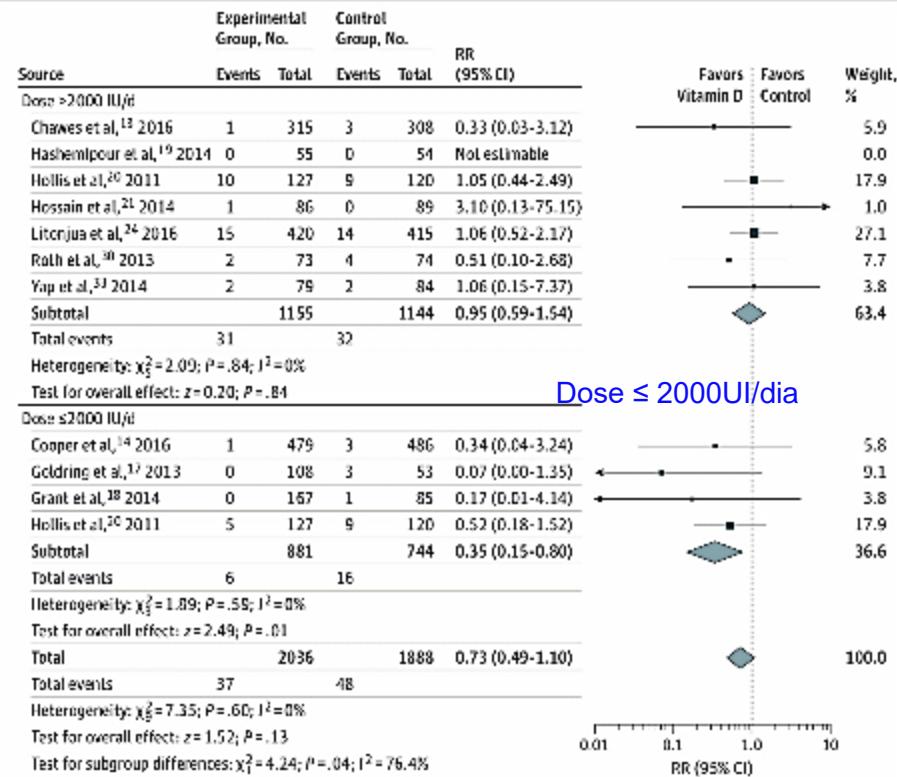
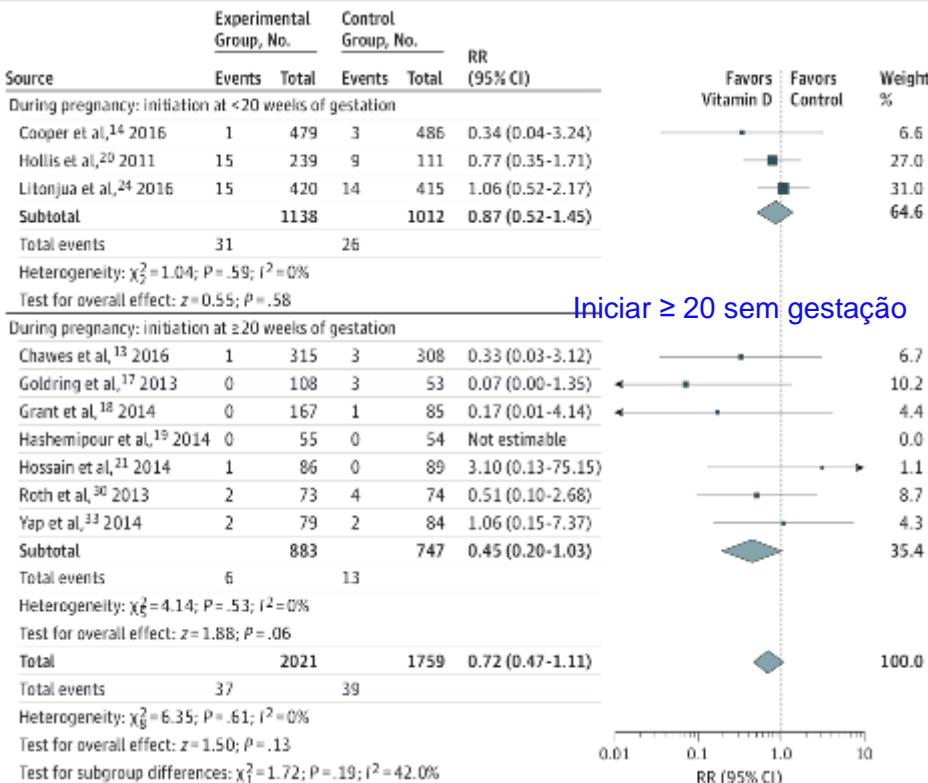
Test for subgroup differences:  $\chi^2=0.05$ ;  $P=.83$ ;  $I^2=0\%$



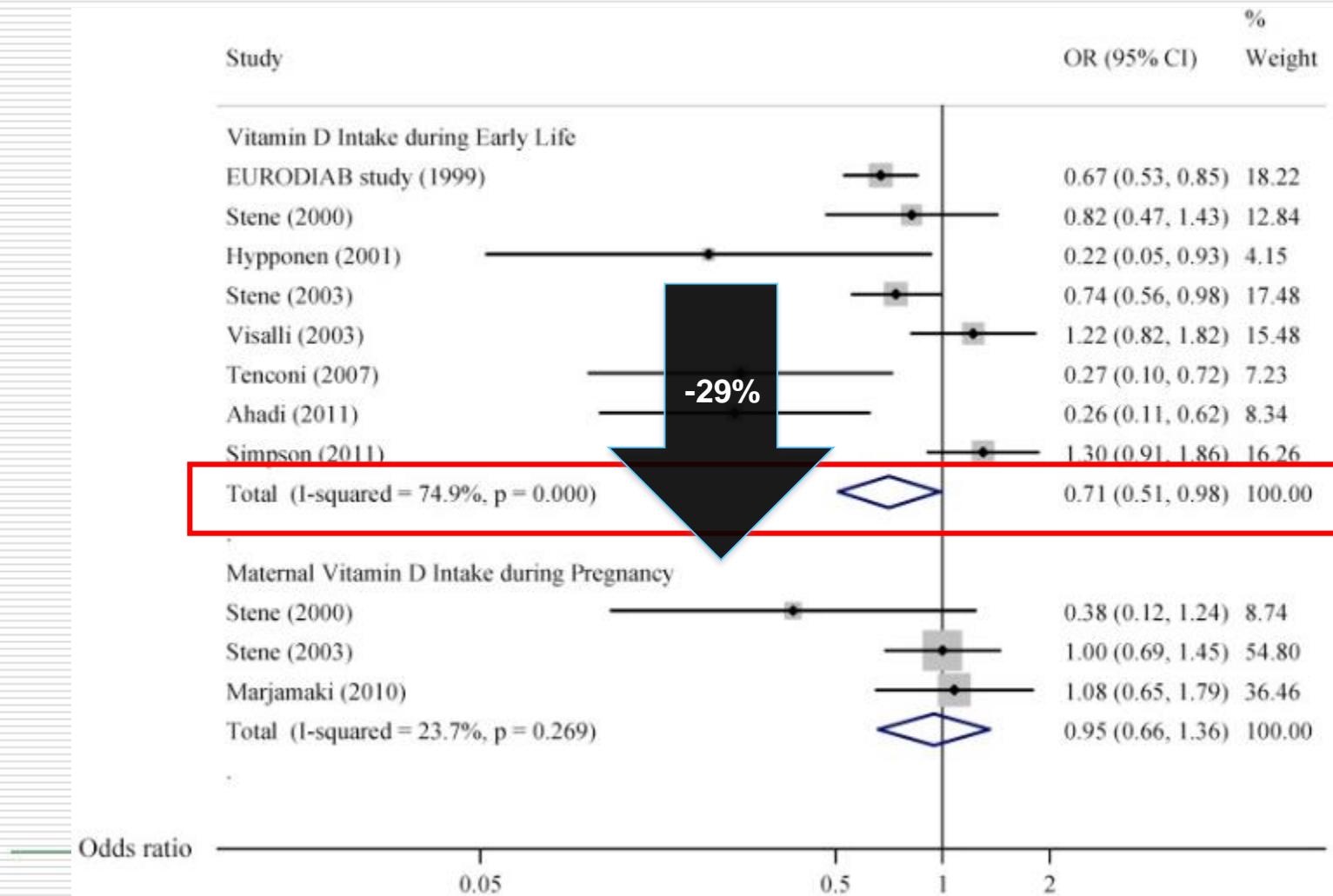
Iniciou ≥ 20 sem gestação



# Association Between Vitamin D Supplementation and Fetal or Neonatal Mortality



# Suplementação precoce de Vit.D 2000ui/dia em crianças reduziu risco de DM1

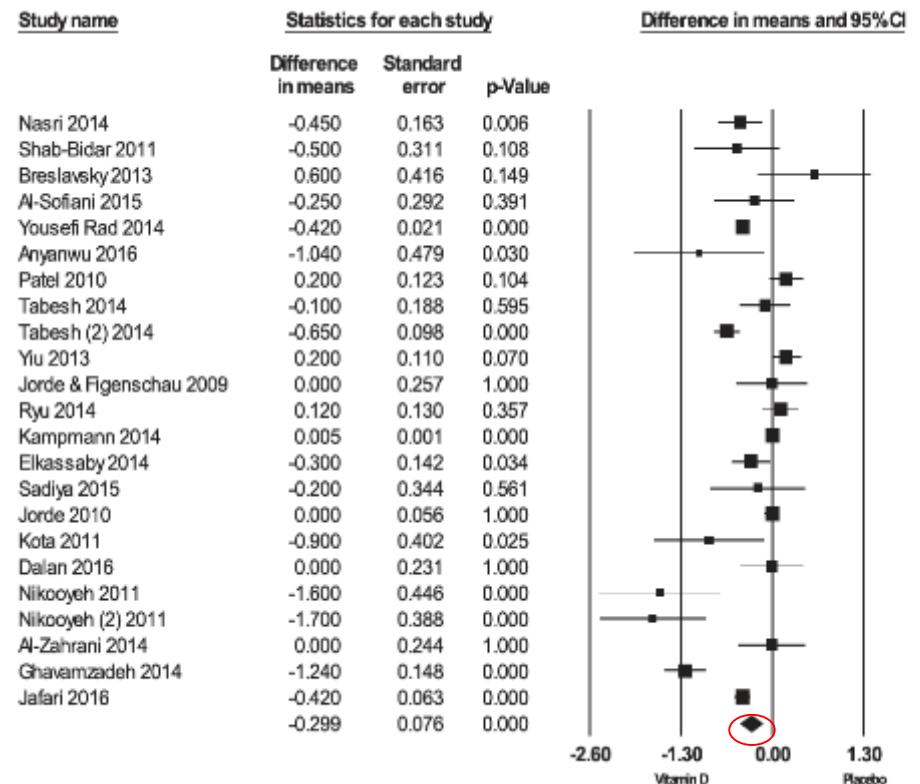


# The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis

N. Mirhosseini

- 1528 indivíduos DM2 40-67 anos
  - VD doses variáveis
    - $\uparrow 17.6 \pm 2.4 \text{ ng/mL}$
    - 4000UI /dia
- 
- HbA1c  $\downarrow 0.3\% (0.45 - 0.15)$
  - GI jejum  $\downarrow 4.9 \text{ mg/dL} (8.1 - 1.6)$
  - HOMA –IR  $\downarrow 0.66; (1.06 - 0.26)$

## HbA1c



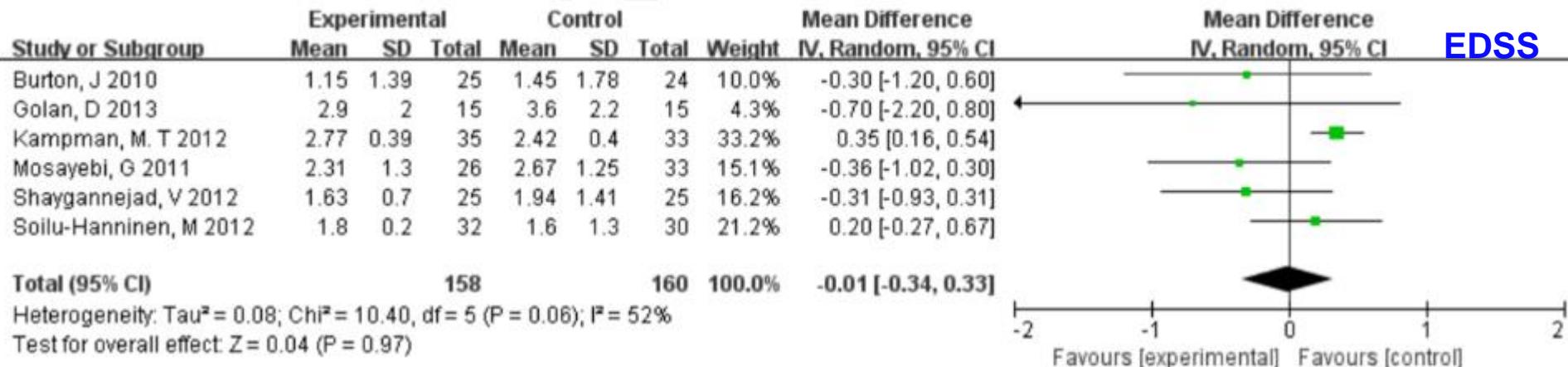
# The efficacy of vitamin D in multiple sclerosis: a meta-analysis

Chao Zheng , Liang He , Lingling Liu , Jie Zhu , Tao Jin

January 2018



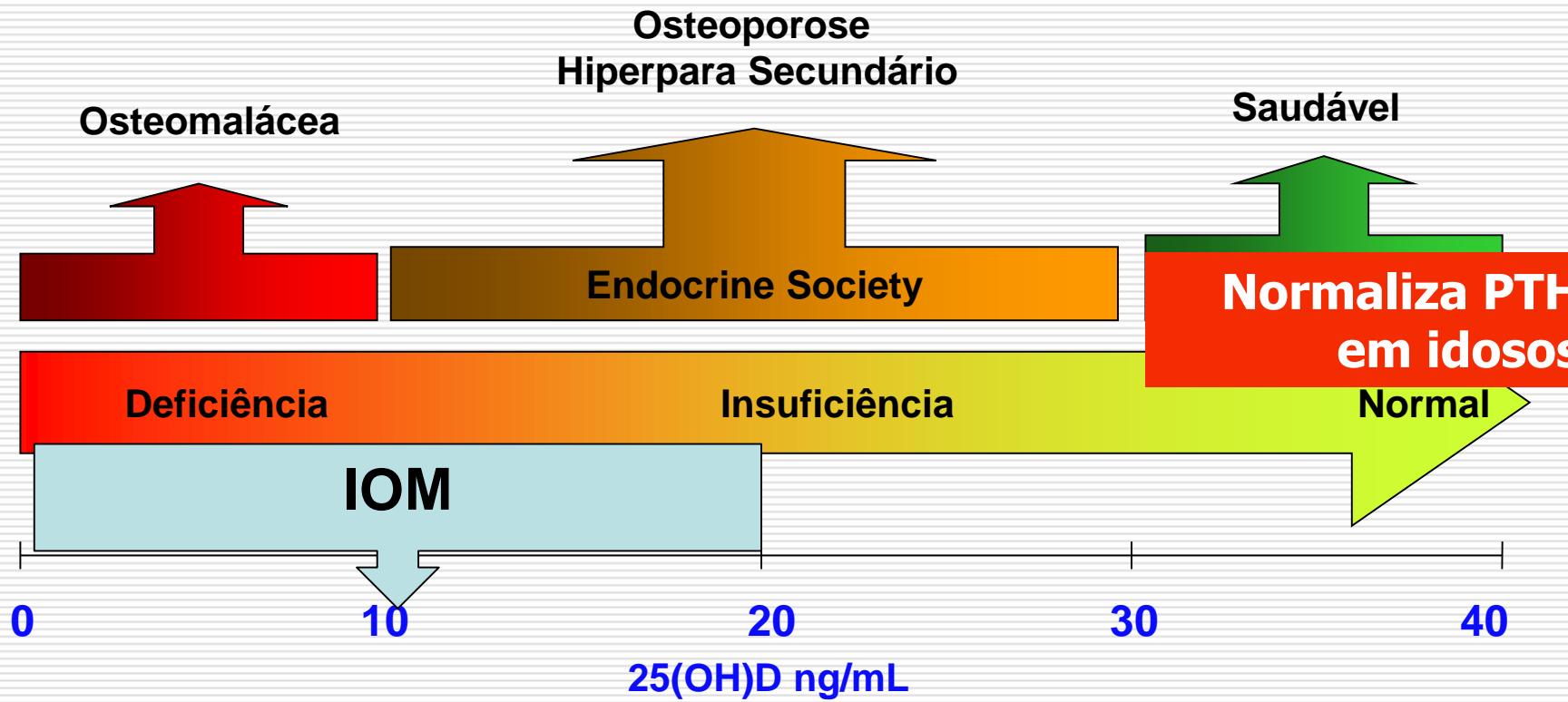
Expanded Disability Status Scale (EDSS) score and annual relapse rate (ARR) → sem diferença



# Quanto de Vitamina D?



# Metas recomendadas pelas Endocrine Society e Soc. Bras Endocrinol e Metabolismo (SBEM) para as concentrações plasmáticas de 25OHD em populações de risco



Nota para conversão:

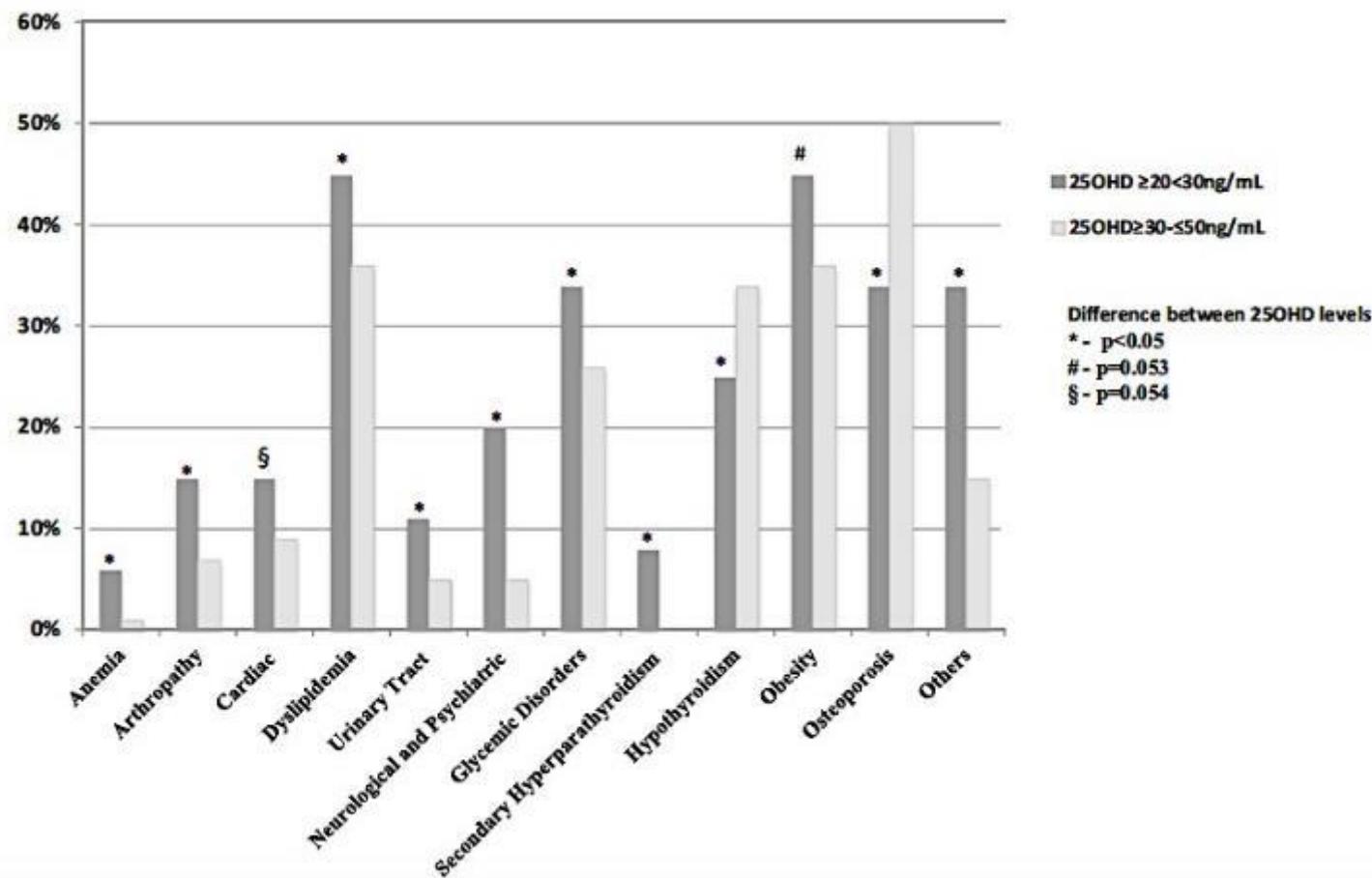
$$\text{_____ ng/ml} \times 2,5 = \text{_____ nmol/l}$$

$$\text{_____ } \mu\text{g/dia} \times 40 = \text{_____ UI/dia}$$

ORIGINAL ARTICLE

## Two threshold levels of vitamin D and the prevalence of comorbidities in outpatients of a tertiary hospital

I. N. Furui<sup>1</sup> • M. J. J. Mauro<sup>1</sup> • S. Petruzzello<sup>1</sup> • S. C. Riechi<sup>2</sup> • R. R. Petterle<sup>3</sup> •  
C. L. Boguszewski<sup>4</sup> • V. Z. C. Borba<sup>4</sup>



# Consensus – reference ranges of vitamin D [25(OH)D] from the Brazilian medical societies. Brazilian Society of Clinical Pathology/Laboratory Medicine (SBPC/ML) and Brazilian Society of Endocrinology and Metabolism (SBEM)

*Posicionamento oficial da Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial (SBPC/ML) e da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM) sobre intervalos de referência da vitamina D [25(OH)D]*

Carlos Eduardo S. Ferreira<sup>1,2</sup>; Sérgio S. Maeda<sup>3</sup>; Marcelo G. Batista<sup>4</sup>; Marise Lazaretti-Castro<sup>5</sup>; Leonardo S. Vasconcellos<sup>6</sup>; Miguel Madeira<sup>4,5</sup>; Lilian M. Soares<sup>8</sup>; Victoria Z. C. Burda<sup>7</sup>; Carolina A. Moreira<sup>7</sup>

- **Idosos >60 anos**
- **Sem exposição solar**
- **Quedas e /ou fraturas recorrentes**
- **Grávidas e lactantes**
- **Osteoporose**
- **Doença óssea metabólica**
- **IRC**
- **Malabsorção (Cgia bariátrica, Dça inflamatória intestinal)**
- **Uso de medicações que interferem com metabolismo VD( Anticonvulsivantes, TARV, GCT)**

## Em resumo...

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- Existe alta prevalência de deficiência de 25OHD
- 25OHD deve ser administrada para indivíduos em risco de hipovitaminose D
- 25OHD faz diferença:
  - Gestantes e RN
  - Osteoporose
  - IRC
  - DM
  - Doentes crônicos



**Reserve a data!**

Obrigada !  
[vzcborba@gmail.com](mailto:vzcborba@gmail.com)

**10 a 13 de outubro de 2018**  
**Centro de Convenções Frei Caneca**  
**São Paulo**



[www.abrasso.org.br](http://www.abrasso.org.br)