

预防疾病 健康中国

“没有全民健康，就没有全面小康”



维生素类药物的健康效应 慢病防治及联合用药

青岛双鲸药业有限公司医药总监 柴雨力博士

营养性药物功效研究进展及其在慢病防治中的重要作用



营养药物

功能

慢病预防

维生素D

基因调控

骨质疏松症,糖尿病,高血压,心血管病,癌症,老年痴呆

维生素A

基因调控

血栓形成、慢阻肺、癌症、白内障、

维生素B族

DNA合成/血管功能

心血管病、癌症、慢性胃病和慢性呼吸道疾病

维生素C

基因调控和抗氧化

心血管病、癌症、免疫功能、慢性中毒

维生素E

参与抗氧化和血脂代谢

心血管病、生殖疾病、癌症、糖尿病等

多烯酸乙酯

降低血脂/ 营养大脑

高血压、高脂血症、心血管病、老年痴呆

辅酶Q-10

抗氧化/提高能量合成

心血管疾病, 糖尿病等, 慢性心力衰竭

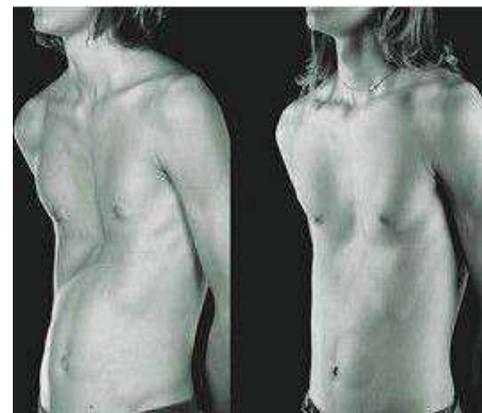
儿童维生素D 缺乏性佝偻病

原因: 低血维生素D → 低血钙

表现: 神经兴奋-肌无力-骨缺钙软化变形



孩子3岁半, X型腿, 中度膝外翻, 韧带松弛和扁平足相关。



2016年发表了新的营养性佝偻病防治全球共识

营养性佝偻病的定义： 由于儿童维生素D缺乏和（或）钙摄入量过低导致生长板软骨细胞分化异常、生长板和类骨质矿化障碍的一种疾病。

营养性佝偻病的诊断： 佝偻病的诊断是基于病史、体格检查和血生化检查得出的，通过X线片确诊。实验室检查的特征为：25-(OH)D、血清磷、血清钙和尿钙下降；血清甲状旁腺素（PTH）、碱性磷酸酶（ALP）和尿磷升高。

维生素D状况分级： 佝偻病是儿童持续维生素D缺乏导致骨骼出现异常的后果。根据血清25（OH）D水平，共识把维生素D状况分为4个等级：充足：>50~250nmol/L；不足：30~50nmol/L；缺乏：<30nmol/L；中毒：>250nmol/L。
当血清25（OH）D水平长期低于30nmol/L(12ng/ml)，有发展为营养性佝偻病的危险。

钙营养状况分级： 缺乏：<300mg/d；不足：300~500mg/d；充足：>500mg/d。

营养性佝偻病的治疗： 维生素D至少2000IU和钙，同时补充，疗程至少3个月。维生素补充时，口服补充为首选方法。特殊情况下，可一次性大剂量注射维生素D。任何一种疗法之后，都需要持续补充维生素D。

营养性佝偻病的预防： 共识建议，无论何种喂养方式的婴儿，均需补充维生素D 400IU/d；12月龄以上儿童至少需要维生素D 600IU/d，提倡儿童天然食物补钙，乳品是最好钙源。

成年人维生素D缺乏骨关节病的预防和治疗

*成人骨质疏松症2.1亿

*骨质疏松发病率近6944万

数据来源：《中国骨质疏松症白皮书2009》

原发性骨质疏松症诊疗指南(2017)

- 预防剂量 800 ~ 1 200 IU /d
- 治疗剂量达到VD水平 $>30 \mu\text{g} /\text{L}$
降低骨关节炎和脆性骨折的风险。



国际骨质疏松基金会IOF推荐维生素D和钙补充预防剂量

General management - nutrition

Recommendations men, women 50+:

- Dietary intake (RNI)
 - Calcium: 1,000 mg/day
 - Vitamin D: 800 IU/day
 - Protein: 1 g/kg body weight
- Supplemental calcium & vitamin D combined
 - Fortified dairy foods (calcium: 400 mg/serving; vitamin D: 200 IU/serving)
 - Supplements (calcium: 0.5-1.2 g/day; vitamin D: 800 IU/day)
- Supplemental vitamin D alone
 - 800 IU/day

美国国家骨质疏松基金会 National Osteoporosis Foundation, NOF

NOF及各国补充维生素D和钙预防骨质疏松症的指南及共识

2011年美国NOF^[65]和2014年波兰骨质疏松症的诊断和处理指南^[7]，2012年中欧国家^[64]、2012年欧洲^[66]的维生素D补充的专家共识明确推荐，需要同时补充**维生素D800-1000IU和钙1200mg**血清25 [OH] D水平 > 30ng/ml(75nmol/L) ，作为预防和药物治疗骨质疏松症必不可少的标准。

2014年美国骨质疏松症基金会的临床医生指南^[3]认为，所有骨质疏松症患者每日摄入充足的钙和维生素D是一种安全和廉价的防治方法，有助于降低骨折风险。**对照的临床试验已经证明，同时补充维生素D和钙可以降低骨折的风险^[67]。**

[7] Głuszko P, et al. Pol Arch Med Wewn, 2014, 124 (5): 255-263

[64] Płudowski P, et al.. Endokrynol Pol, 2013, 64(3): 239-246

[65] Holick MF, et al. J Clin Endocrinol Metab, 2011, 96(7): 1911-1930.

[66] Takacs I, et al. Orv Hetil, 2012, 153 Suppl: 5-26.

[67] Larsen ER, et al. J Bone Miner Res, 2004, 19(3):370-378.

[3] National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014.

中国骨质疏松和骨矿盐学会 COF

●调整生活方式

- (1) 采取防止跌倒的各种措施
- (2) 均衡膳食
- (3) 适当户外活动和日照
- (4) 避免嗜烟、酗酒等骨健康

●基本补充剂

- (1) 钙剂
- (2) 维生素D

原发性骨质疏松症诊疗指南(2017)

维生素D用于骨质疏松症防治:

- 剂量可为 **800 ~ 1 200 IU /d**。建议检测血清 25OHD 水平，以了解患者维生素 D 状态，指导维生素 D 的补充。
- 有研究建议老年人血清 25OHD 水平应 **达到或高于** **75 nmol /L (30 μg /L)**，以降低跌倒和骨折风险。

钙剂用于骨质疏松防治

- 预防性钙补充：营养调查显示我国居民每日膳食约摄入元素钙 400 mg，故尚需补充元素钙约 500 ~ 600 mg /d。
- 骨质疏松症钙剂补充建议：成人每日钙推荐摄入量为 800 mg (元素钙)，50 岁及以上人群每日钙推荐摄入量为 **1 000 ~ 1 200 mg**

维生素D及其类似物临床应用共识2018

骨质疏松症的发生，取决于年轻时获得的峰值骨量和中老年阶段的骨丢失速率，补充VD有助于青壮年人获得更高的骨峰值，减少减慢老年人骨钙丢失和骨折。

目前国际、国内多数机构和专家认为：**> 30 $\mu\text{g/L}$ (> 75nmol/L) 为维生素D充足**，**20~30 $\mu\text{g/L}$ (50~75nmol/L) 为维生素D不足**，**血清25OHD < 20 $\mu\text{g/L}$ (50nmol/L) 为维生素D缺乏**，**< 10 $\mu\text{g/L}$ (< 25nmol/L) 为严重缺乏**。

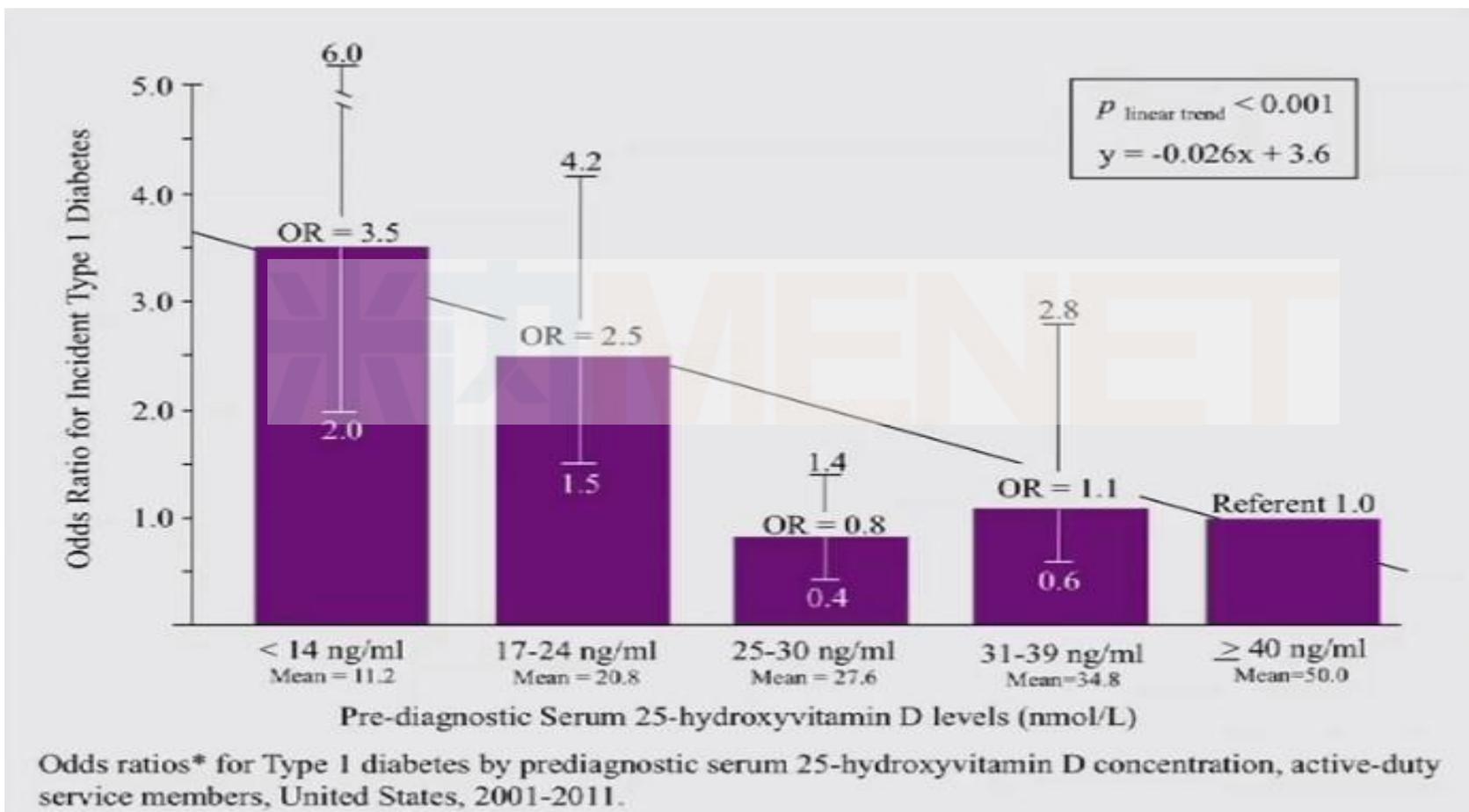
高危人群维生素D补充推荐剂量

年龄	建议补充剂量 (IU/d)	年龄	可耐受摄入上限 (IU/d)
0~1岁	400~1 000	0~6个月	1 000
1~18岁	600~1 000	6个月~1岁	1 500
19~50岁	1 500~2 000	1~3岁	2 500
50~70岁	1 600~2 000	4~8岁	3 000
70岁以上	1 600~2 000	8岁以上	4 000

微信号: CSOBMR

血25-(OH)D水平与1型糖尿病发病率跟踪研究和早期预测

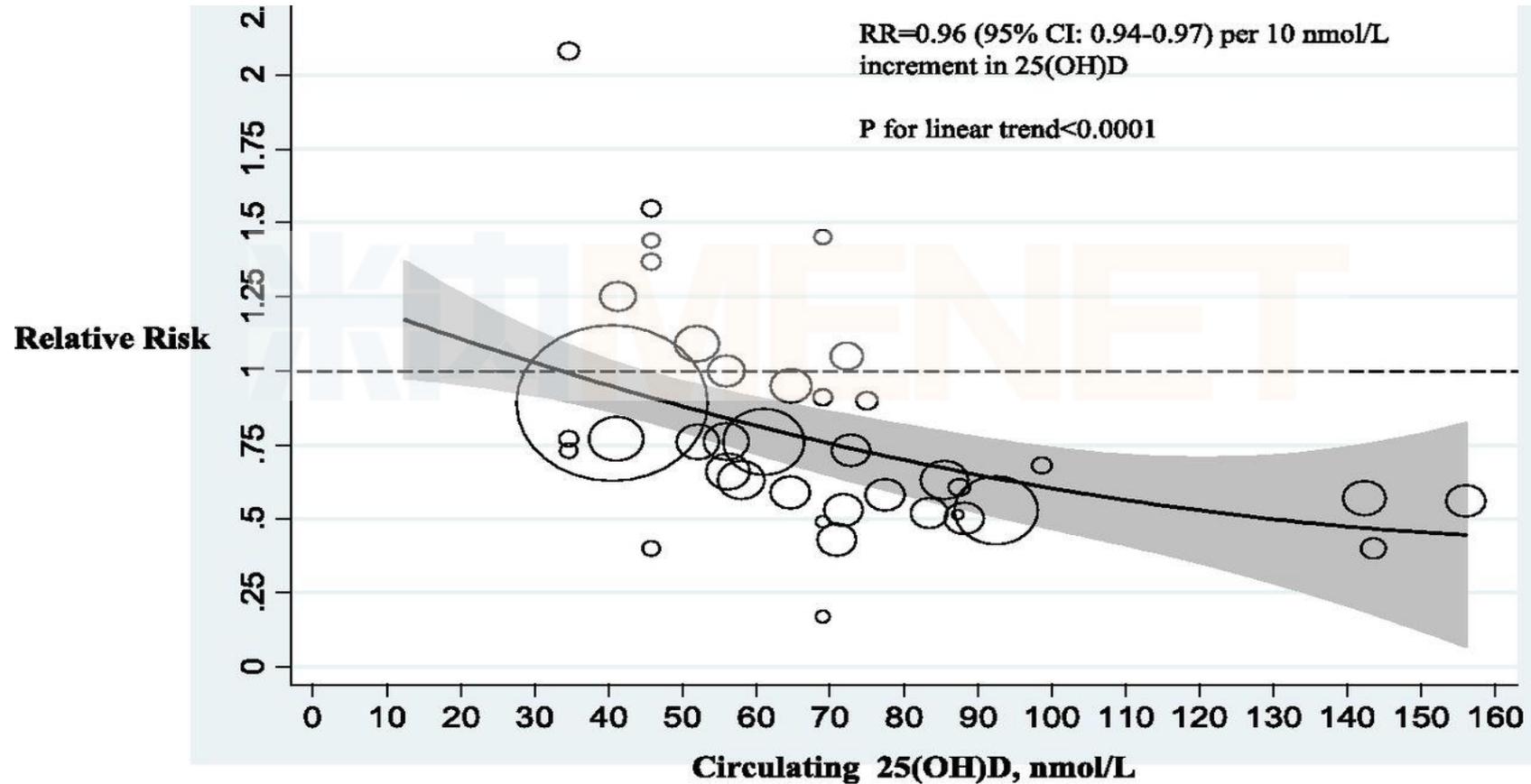
VD < 14 比 > 40 ng/ml 1型糖尿病发病率高出可达6倍



*Using McNemar matched pairs analysis [15-17] in which healthy controls were individually matched to cases by date blood sample was drawn (± 2 days); age (± 3 months); gender; and length of military service (± 30 days). Cases and controls in each pair were on active duty when the case was diagnosed. The number of discordant pairs, from lowest to highest quintile, except the reference quintile, defined as having an odds ratio of 1.0, were 52/15, 50/20, 33/26 and 34/32.

Blood 25-Hydroxy Vitamin D Levels and Incident Type 2 Diabetes. A meta-analysis of prospective studies

VD缺乏者2型糖尿病发病率比充足者高出5-6倍



维生素D治疗1型糖尿病后糖化血红蛋白有统计学意义的降低

每日服用4000IU维生素D，疗程12周，总量330000IU

Glycosylated hemoglobin tertiles by 25-hydroxyvitamin D tertiles at 12 weeks.

		Glycosylated hemoglobin tertiles (%) 糖化血红蛋白三分位数								
25-(OH)D三分位数		>9.9			7.8-9.9			<7.8		
		Female	Male	Total	Female	Male	Total	Female	Male	Total
25-hydroxyvitamin D tertiles (nmol/L)	<35.4	50	50	50	33.3	37.5	34.6	16.7	12.5	15.4
	35.4-51	38.1	16.7	33.3	33.3	66.7	40.7	28.6	16.7	25.9
	>51	25	13.3	18.5	25	26.7	25.9	50	70	55.6

Glycosylated hemoglobin tertiles by 25-hydroxyvitamin D tertiles at 13 weeks.

血25-D水平低于50nmol/L界定为VD缺乏，研究对象被指定服用4000IU的VD/日12周

Vitamin D deficiency was defined as a 25-OHD level of less than 50 nmol/L.¹³ At entry into the study, patients having 25-OHD <50 nmol/L were assigned to receive 4000 IU of vitamin D/d.

美国内分泌学会临床实践指南 (2011年)

参考文献: Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology & Metabolism, 2011, 96(7): 1911-1930.

骨健康保健剂量:

- 1, 1岁以下的婴幼儿每天服用维生素D **400IU**, 大于1-18岁的儿童每天服用**600IU**
- 2, 19-50岁之间的成年人, 每日应最少服用维生素D **600IU**,
- 3, 50-70岁以上的中老年人, 每日应最少服用维生素D **600和800IU**,
- 4, 孕妇和乳母, 每日最少服用维生素D **600IU**。

但是, 以上服用剂量能否满足相应人群骨外健康效应的需求仍未可知。对于这样年龄段的人群来说, 想要使人体内血清 **25(OH)D**浓度保持在 **30 ng/ml (75 nmol/L)**以上, 则需要每日最少服用维生素D **1500-2000IU**。

维生素D缺乏治疗剂量:

- 1, 0-1岁婴幼儿患者: **2000 IU/d**, 或者**50,000 IU/周**, 持续服用**6周**, 使血液**25(OH)D**浓度高于**30 ng/ml**, 然后改为服用**400-1000 IU/d**作为维持治疗。
- 2, 1-18岁儿童及青少年患者: **2000 IU/d**, 持续**6周**; 或者**50,000 IU/周**, 最少持续服用**6周**, 使血液**25(OH)D**浓度高于**30 ng/ml**, 然后改为服用**600-1000 IU/d**作为维持治疗。
- 3, 所有成年患者, **50,000 IU/周**, 持续服用**8周**, 或者**6000 IU/d**, 使血液**25(OH)D**浓度高于**30 ng/ml**, 然后改为服用**1500-2000 IU/d**作为维持治疗。

波兰普通人群和有维生素D缺乏风险人群维生素D补充指南-波兰儿科学会和专家小组的建议, 国家专家顾问和科学院代表参加IC协会-2018年更新

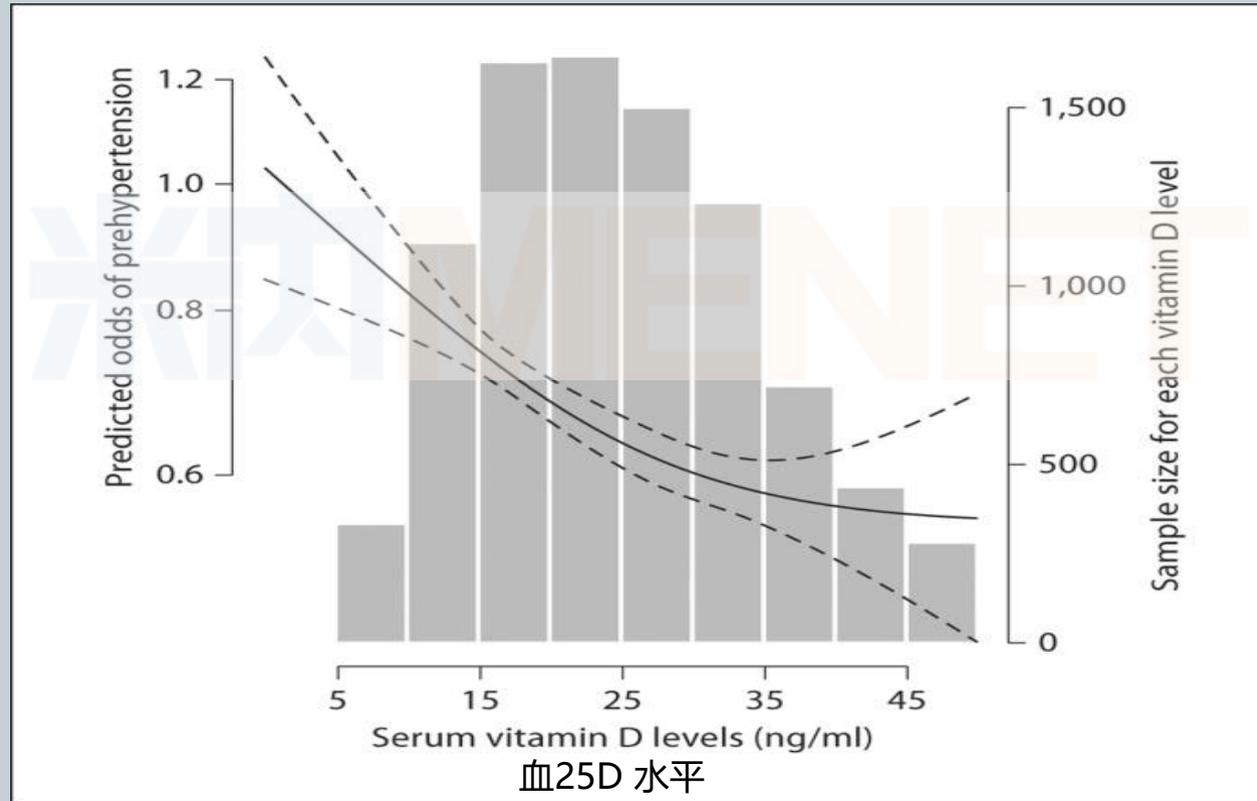
维生素D缺乏症在波兰各年龄段仍然很普遍。目前, 有必要定期补充推荐剂量的维生素D, 并制定有效的缓解人群维生素D缺乏的策略。这些最新建议是针对卫生专业人员和追求全面卫生政策的当局提出的, **纳入预防广泛慢性病的公共卫生计划。**

VITAMIN D SUPPLEMENTATION IN GENERAL POPULATION, IN GROUPS AT RISK OF VITAMIN D DEFICIENCY AND IN PERSONS WITH LABORATORY CONFIRMED VITAMIN D DEFICIENCY – a practical guidelines for prophylactics and therapeutic procedures in Poland								
Vitamin D supplementation in general population and in groups at risk of vitamin D deficiency								
Pregnancy and lactation	Preterm neonates ≤ 32 weeks of gestation	Preterm neonates born at 33–36 weeks of gestation	Neonates and infants	Children 1–10 yrs	Adolescents 11–18 yrs	Adults 19–65 yrs	Seniors > 65–75 yrs	Seniors > 75 yrs
<p>1) Women planning pregnancy should receive adequate vitamin D supply, the same as in the general adult population. If it is possible, the use of 25(OH)D concentration (1@B@);</p> <p>2) When pregnancy is confirmed, supplementation should be carried out under the control of 25(OH)D concentration, to maintain optimal concentrations within ranges of >30–50 ng/ml (2@B@);</p> <p>3) If the assessment of 25(OH)D concentration is not possible, it is recommended to use vitamin D at a dose of 2000 IU/day, throughout pregnancy and lactation (1@B@);</p>	<p>1) It is recommended to start supplementation at a dose of 400 IU/day from the first days of life (if enteral nutrition is possible), regardless the way of feeding (1@B@);</p> <p>2) Supplementation should be carried out under the control of 25(OH)D concentration, both during hospitalization (the first control after 4 weeks of supplementation), as well as in the outpatient care (1@B@);</p> <p>3) When achieving a total dose of 1000 IU/day, containing supplements and diet, there is a risk of vitamin D overdose, particularly in neonates with birth weight <1000 g (1@B@);</p>	<p>1) 400 IU/day from the first days of life, regardless the way of feeding (1@B@);</p> <p>2) There is no need to assay 25(OH)D concentrations routinely (1@B@);</p> <p>3) Supplementation carried out under the control of 25(OH)D concentration should be considered in children in the risk groups (parenteral nutrition >2 weeks, bronchopneumonia >2 weeks, anticonvulsant treatment, cholestasis, birth weight <1500g) (2@B@);</p>	<p>1) 0–6 months: 400 IU/day from first days of life, regardless the way of feeding (1@B@);</p> <p>2) 6–12 months: 400–600 IU/day, depending on daily amount of vitamin D taken with food (1@B@);</p> <p style="text-align: center;">1 µg = 40 IU</p>	<p>1) In the period from May to September, if guidelines for lactation are met, supplementation is not necessary, although still recommended and safe (1@B@);</p> <p>2) If lactation guidelines are not fulfilled, supplementation of 600–1000 IU/day is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1@B@);</p> <p>3) These children require 1200–2000 IU/day, depending on severity of obesity (1@B@);</p>	<p>1) In the period from May to September, if guidelines for lactation are met, supplementation is not necessary, although still recommended and safe (1@B@);</p> <p>2) If lactation guidelines are not fulfilled, supplementation of 600–2000 IU/day is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1@B@);</p> <p>3) These adolescents require 1600–4000 IU/day, depending on severity of obesity (1@B@);</p>	<p>1) In the period from May to September, if guidelines for lactation are met, supplementation is not necessary, although still recommended and safe (1@B@);</p> <p>2) If lactation guidelines are not fulfilled, supplementation of 400–2000 IU/day is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1@B@);</p> <p>3) These adults require 1600–4000 IU/day, depending on severity of obesity (1@B@);</p>	<p>1) Due to decreased efficacy of the skin synthesis, supplementation of vitamin D in the dose of 600–2000 IU/day, based on body weight and the dietary vitamin D intake, is recommended throughout a year (1@B@);</p> <p>2) These seniors require 1900–4000 IU/day, depending on severity of obesity (1@B@);</p>	<p>1) Due to decreased efficacy of the skin synthesis, potential supplementation of vitamin D in the dose of 2000–4000 IU/day, based on body weight and the dietary vitamin D intake, is recommended throughout a year (1@B@);</p> <p>2) These oldest seniors require 4000–8000 IU/day, depending on severity of obesity (2@B@);</p>
<p>Supplementation in groups at risk of vitamin D hypersensitivity</p> <p>1) Prior to initiating the supplementation, the probability of vitamin D hypersensitivity should be assessed (hypercalcaemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, CYP24A1 gene mutation, SLC34A1 gene mutation or history of other types of vitamin D hypersensitivity in an individual or family members). This recommendation applies to all age groups as well as to groups at the risk of vitamin D deficiency (1@B@);</p> <p>2) In groups at the risk of vitamin D hypersensitivity, supplementation should be supervised and carried out carefully and in an individual manner, preferably under the control of calcium-phosphate parameters, particularly calcemia, calciuria, PTH, 25(OH)D and 1,25(OH)₂D (1@B@);</p>								
Vitamin D supplementation and treatment regimes in relation to 25(OH)D concentration								
Severe Deficiency 0–10 ng/ml (1@B@);	Deficiency >10–20 ng/ml (1@B@);	Suboptimal >20–30 ng/ml (1@B@);	Optimal >30–50 ng/ml (1@B@);	High >50–75 ng/ml (2@B@);	High >75–100 ng/ml (2@B@);	Toxic >100 ng/ml (1@B@);		
<p>1) Therapy in relation to age and body weight; control assay of 25(OH)D concentration should be performed after 1–3 months of therapy (1@B@);</p> <p>2) Recommended therapeutic doses:</p> <ul style="list-style-type: none"> > 0–12 months of age: 2000 IU/day (1@B@); > 1–10 years: 3000–6000 IU/day (1@B@); > 10 years: 4000 IU/day (1@B@); <p>3) Treatment should be carried out for 3 months or until the 25(OH)D concentration of >30–50 ng/ml is reached, then it is recommended to use consecutive maintenance dose, i.e. a prophylactic dose recommended for general population, in relation to age and body weight (1@B@);</p> <p>4) In patients with skeletal symptoms and bone mineral disorders (bone deformations, bone pain, history of fragility fractures), it is necessary to assess calcium-phosphate metabolism (Ca, P, ALP, PTH, Calcitonin ratio in urine), and, if available – bone mineral density using DXA (2@B@);</p>	<p>1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2@B@);</p> <p>2) If vitamin D supplementation was appropriate, it is recommended to increase the dose by 100% and to assess 25(OH)D concentration in 3 months' time (2@B@);</p> <p>3) If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at maximal doses recommended for peers from the general population and to assess 25(OH)D concentration in 3 months' time (2@B@);</p> <p>4) In patients with skeletal symptoms (bone deformations, bone pain, history of fragility fractures), it is indicated to assess calcium-phosphate metabolism (Ca, P, ALP, PTH, Calcitonin ratio in urine), and, if available – bone mineral density using DXA (2@B@);</p>	<p>1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2@B@);</p> <p>2) If vitamin D supplementation was appropriate, it is recommended to increase the dose by 50%, and to consider the assessment of 25(OH)D concentration in 6 months' time (2@B@);</p> <p>3) If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at doses recommended for peers from the general population (2@B@);</p> <p style="text-align: center;">1 ng/ml = 2.5 nmol/L</p>	<p>1) Continue previous management (2@B@);</p> <p>General recommendations</p> <p>Prophylactic doses of vitamin D in the general population should be individualized depending on age, body weight, metabolic disease, time of year, sun exposure of an individual, dietary habits and lifestyle (1@B@). Prophylactic dosing of vitamin D in the risk groups at risk of D deficiency should be individualized according to anthropometric and general population data. If no specific practice guidelines are available, then the general population data are recommended for use in the risk groups at risk of vitamin D deficiency (2@B@). In the general population, in case of vitamin D deficiency, the maximum dose of vitamin D should be based on those dependent on the disease, medical therapy, and body weight (1@B@). In the risk groups at risk of vitamin D deficiency, the maximum dose of vitamin D should be based on laboratory assays, should be individualized, and should be based on the patient's age and weight with regard to the nature of the disease, medical therapy, and body weight (1@B@). In 25(OH)D assays, fasting are not established and 25(OH)D concentrations are subject to diurnal variation. In the risk groups, the maximum dose of vitamin D is based on 25(OH)D concentration assays, is recommended (1@B@).</p>	<p>1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2@B@);</p> <p>2) If vitamin D supplementation was appropriate, it is recommended to reduce the dose by 50%, and to consider assessment of 25(OH)D concentration within the consecutive 3 months-period (2@B@);</p> <p>3) If vitamin D was supplemented at doses higher than recommended, it is recommended to reduce the dose by 50%, and to consider assessment of 25(OH)D concentration within the consecutive 3 months-period (2@B@);</p> <p>4) There is a possibility to re-entrance vitamin D supplementation at minimal doses recommended for peers from the general population, after 1–2 months or, in case of neonates, infants and toddlers after reaching 25(OH)D concentrations <50 ng/ml (2@B@);</p>	<p>1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2@B@);</p> <p>2) Vitamin D intake should be suspended for 1–2 months (2@B@);</p> <p>3) In neonates, infants and toddlers, calcemia and calciuria should be assessed, vitamin D hypersensitivity should be evaluated and the control assay of 25(OH)D concentration should be carried out (2@B@);</p> <p>4) There is a possibility to re-entrance vitamin D supplementation at minimal doses recommended for peers from the general population, after 1–2 months or, in case of neonates, infants and toddlers after reaching 25(OH)D concentrations <50 ng/ml (2@B@);</p>	<p>1) Vitamin D supplementation has to be absolutely terminated, calcemia and calciuria should be assessed, and 25(OH)D concentration should be assessed in the state in which the 25(OH)D concentration = 600 ng/ml is accompanied by hypercalcaemia, hypercalciuria and apparent PTH suppression (1@B@);</p> <p>2) In case of clinical symptoms of vitamin D intoxication, a treatment should be immediately initiated (1@B@);</p> <p>3) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2@B@);</p> <p>4) There is a possibility to re-entrance vitamin D supplementation at doses recommended for peers from the general population, after reaching normocalcaemia, normocalciuria and 25(OH)D concentrations <50 ng/ml, followed by assaying vitamin D (2@B@);</p>		
<p>GRADE: 1 – strong recommendation (application to the general population and in all patients in most circumstances, benefits clearly outweigh the risks); and 2 – weak recommendation (possesses opinions of working group or to be considered, the best action may depend on circumstances, benefits and risk clearly balanced or uncertain). Quality of evidence was assessed as follows: @B@ high quality (prospective cohort or RCT studies, at low risk of bias); @C@ moderate quality (retrospective cohort studies, case-control studies, case series, or cross-sectional studies); @D@ low quality (expert opinion, case reports, or case series); @E@ very low quality (expert opinion, case reports, or case series).</p>								

维生素D对早期高血压病的预防治疗作用

Lower serum vitamin D levels are associated with prehypertension

早期高血压病风险率



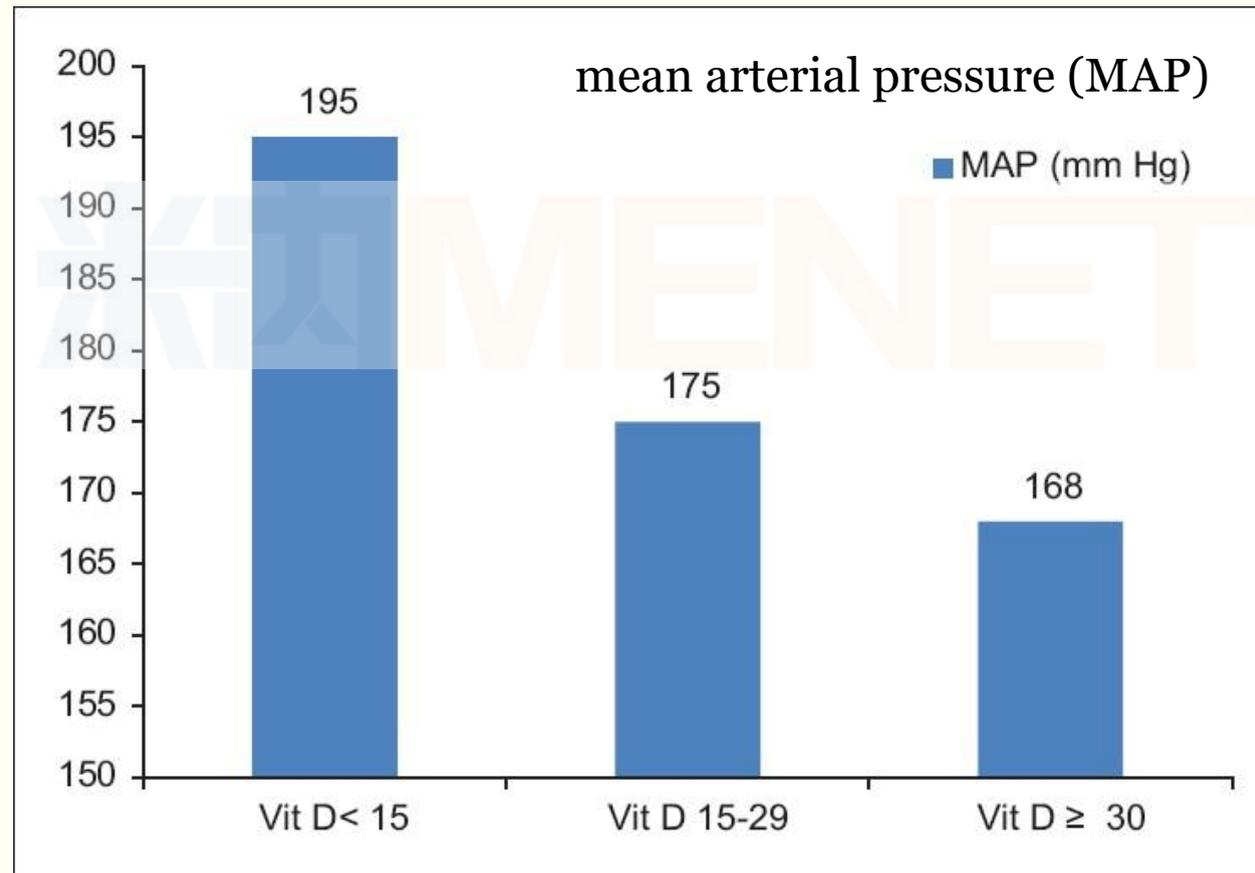
不同水平25D样本量

Participants of the 3rd National Health and Nutrition Examination Survey >20 years of age and free of hypertension (n = 9,215, 53.5% women) and clinical cardiovascular disease were examined. Serum vitamin D levels were analyzed as quartiles. Prehypertension (n = 3,712) was defined as systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg.

营养药物在慢病防治中的作用



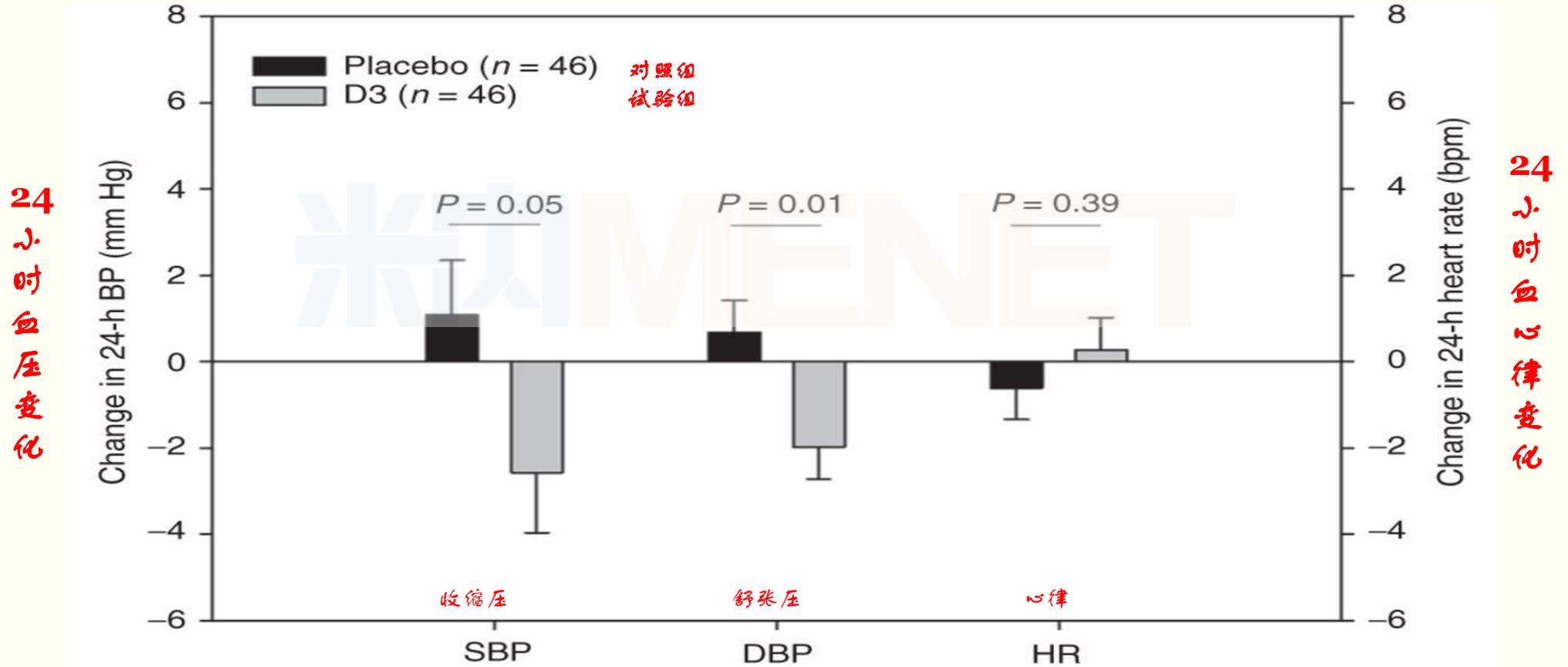
维生素D能有效降低血压 - 防治高血压病



investigated the effect of 75µg (3,000 IU) cholecalciferol per day in a randomized, placebo-controlled, double-blind study in 130 hypertensive patients. Ambulatory BP (24-h BP) and arterial stiffness were measured before and after 20 weeks of treatment.

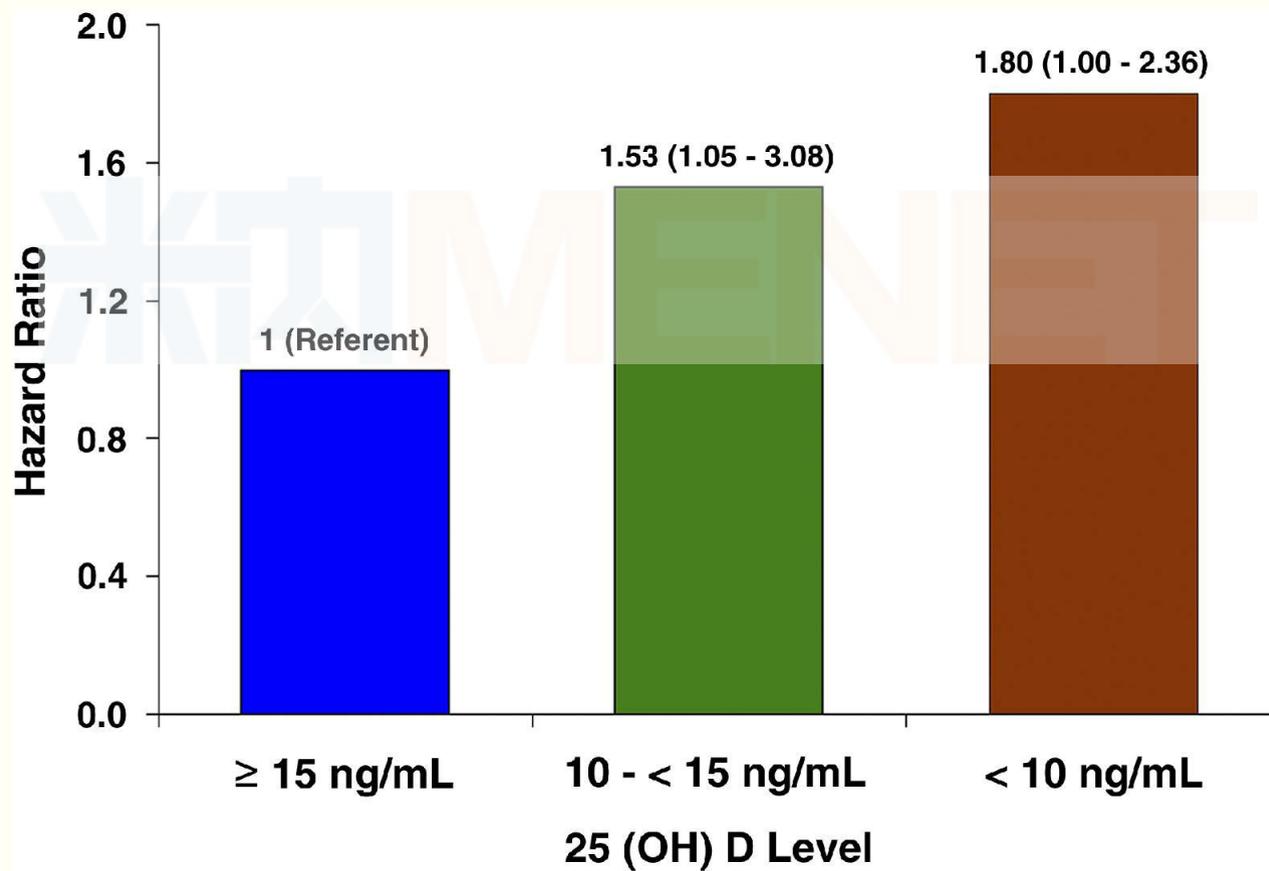
维生素D3治疗高血压病的效果观测: 随机双盲试验: 每天3000IU, 共服20周

In patients with p-25(OH)D <32 ng/ml at baseline (placebo: n = 46; cholecalciferol: n = 46), 24-h BP was reduced by 4/3 mm Hg (P = 0.05/0.01)



Ambulatory blood pressure (BP) and heart rate in patients with plasma concentrations of 25-hydroxy-vitamin D <80 nmol/l at baseline (n = 92). Mean values and s.e.m. after treatment with cholecalciferol and placebo. bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

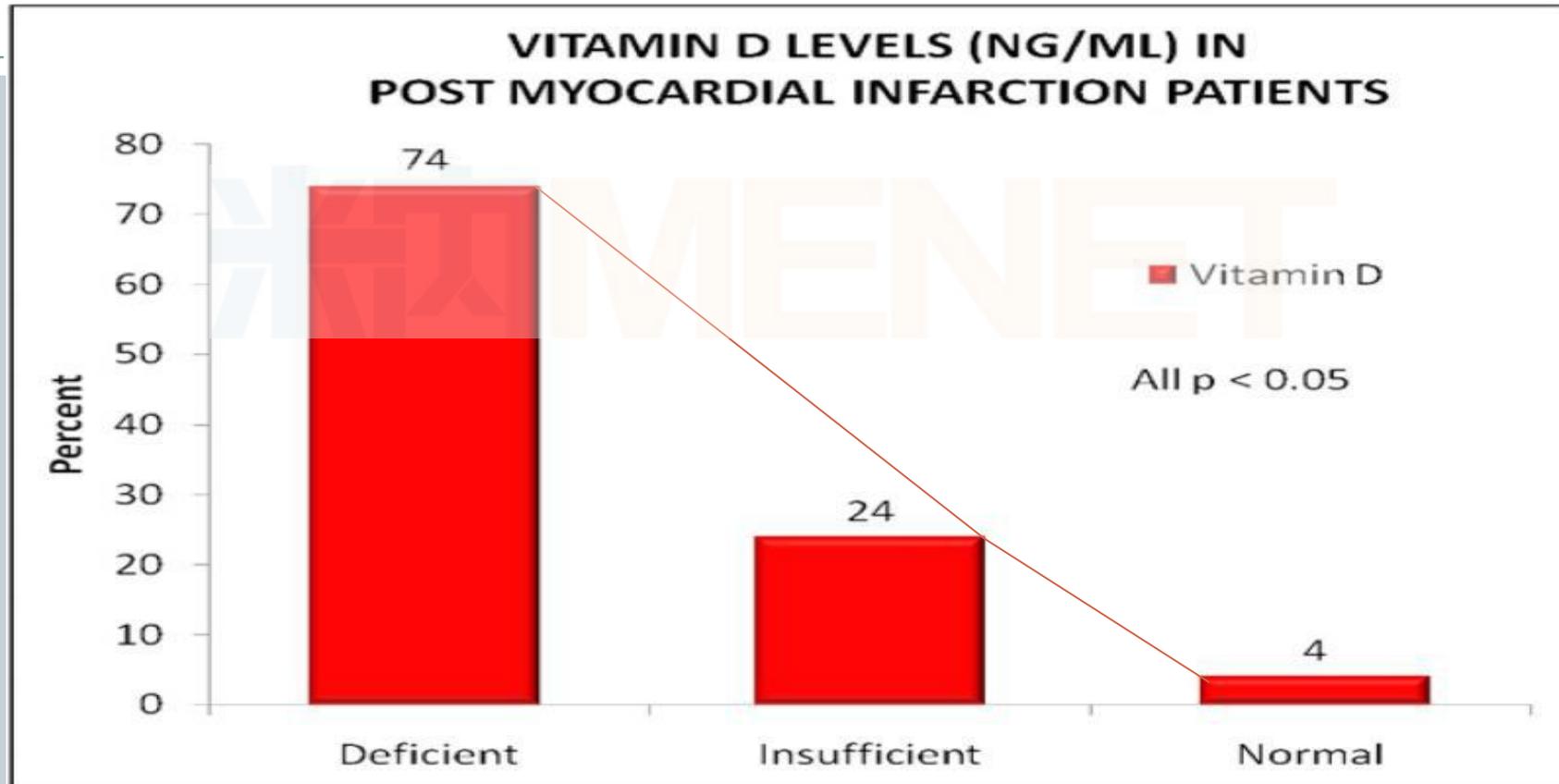
维生素D降低心血管病发病风险 - 防治心血管疾病



维生素D缺乏是心肌梗死的危险因素

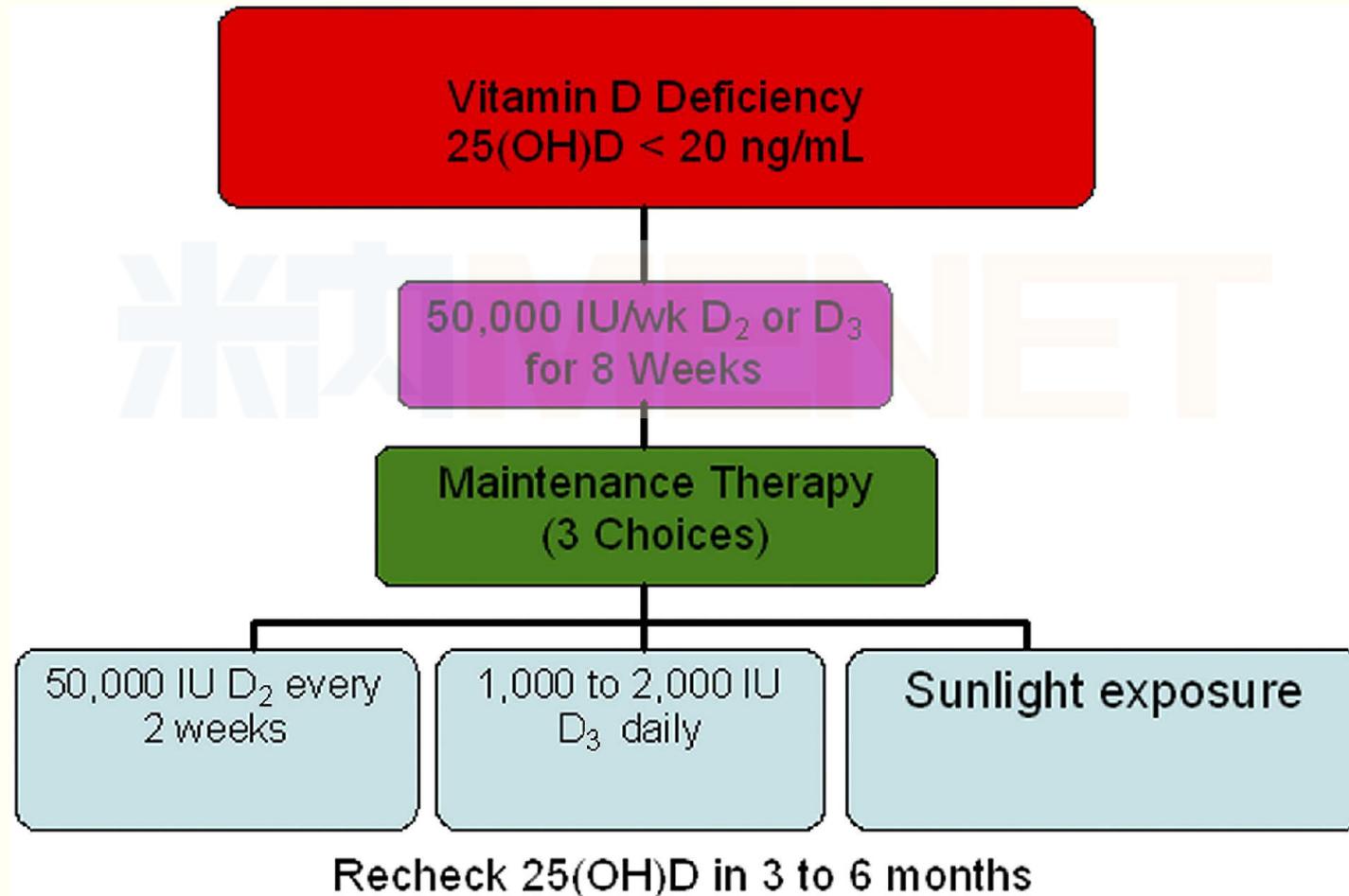
补充充足的维生素D降低70%的心肌梗死发生率

In this study, 25(OH)D was assessed in 239 subjects enrolled in a 20-hospital prospective myocardial infarction registry.

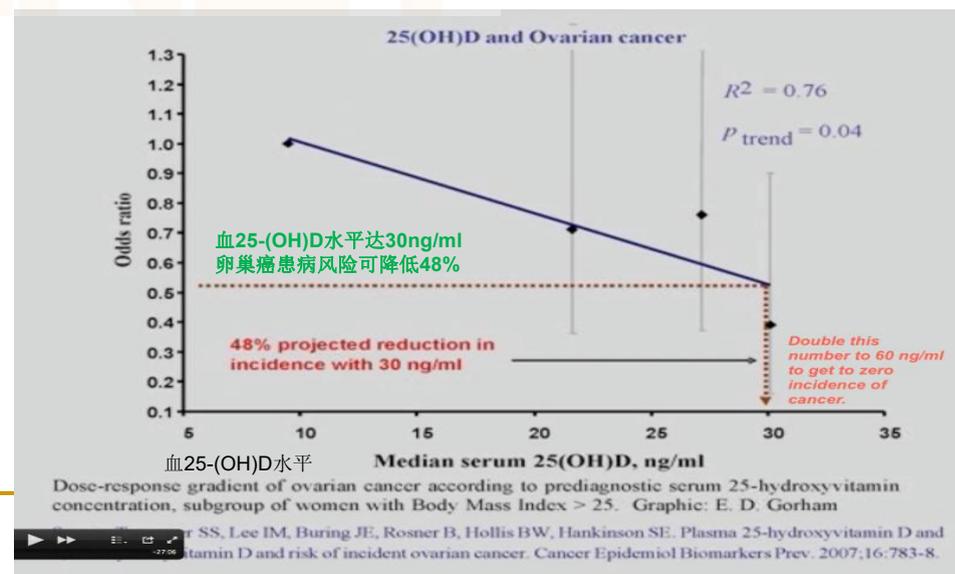
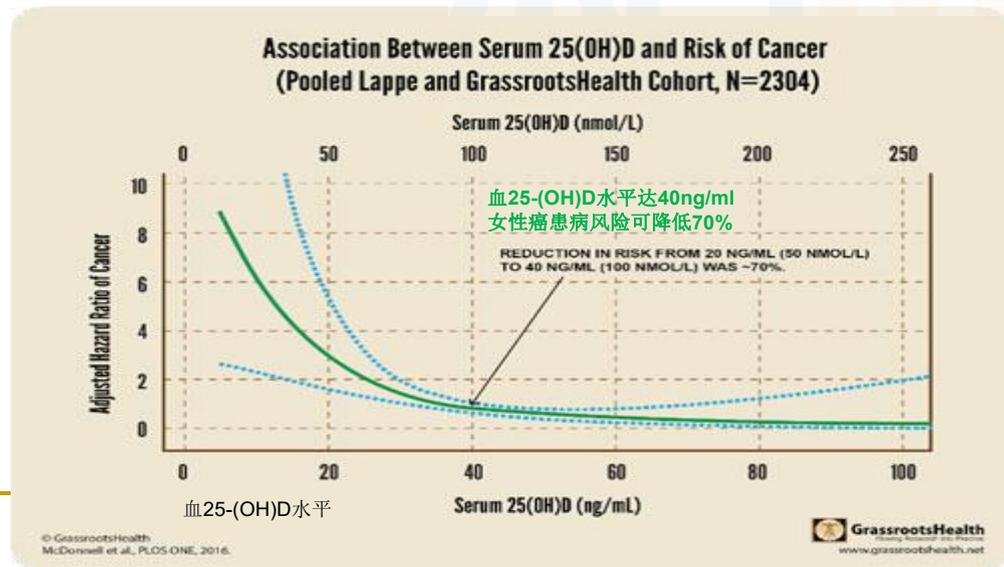
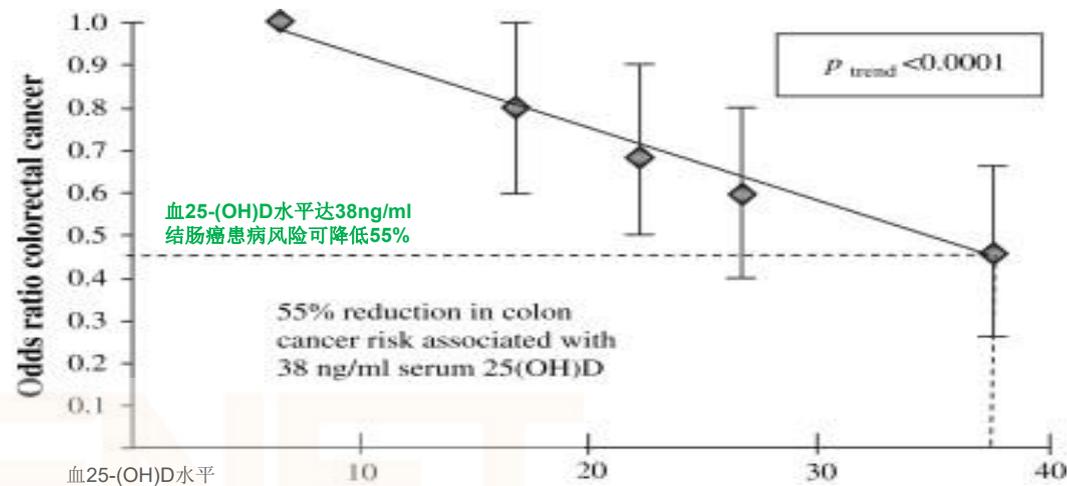
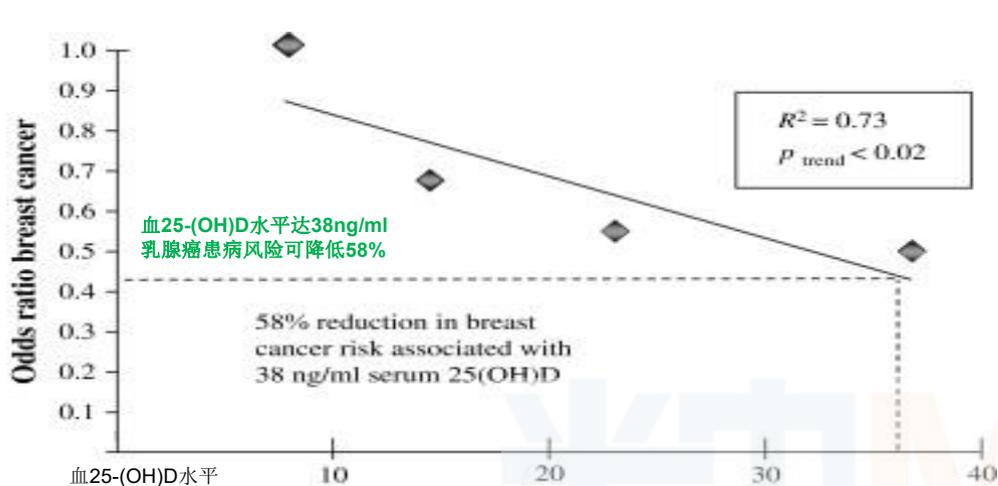


美国心血管疾病预防指南 - 治疗性推荐VD剂量

Treatment Recommendations for Vitamin D Deficiency $25(\text{OH})\text{D} < 20\text{ng/ml}$

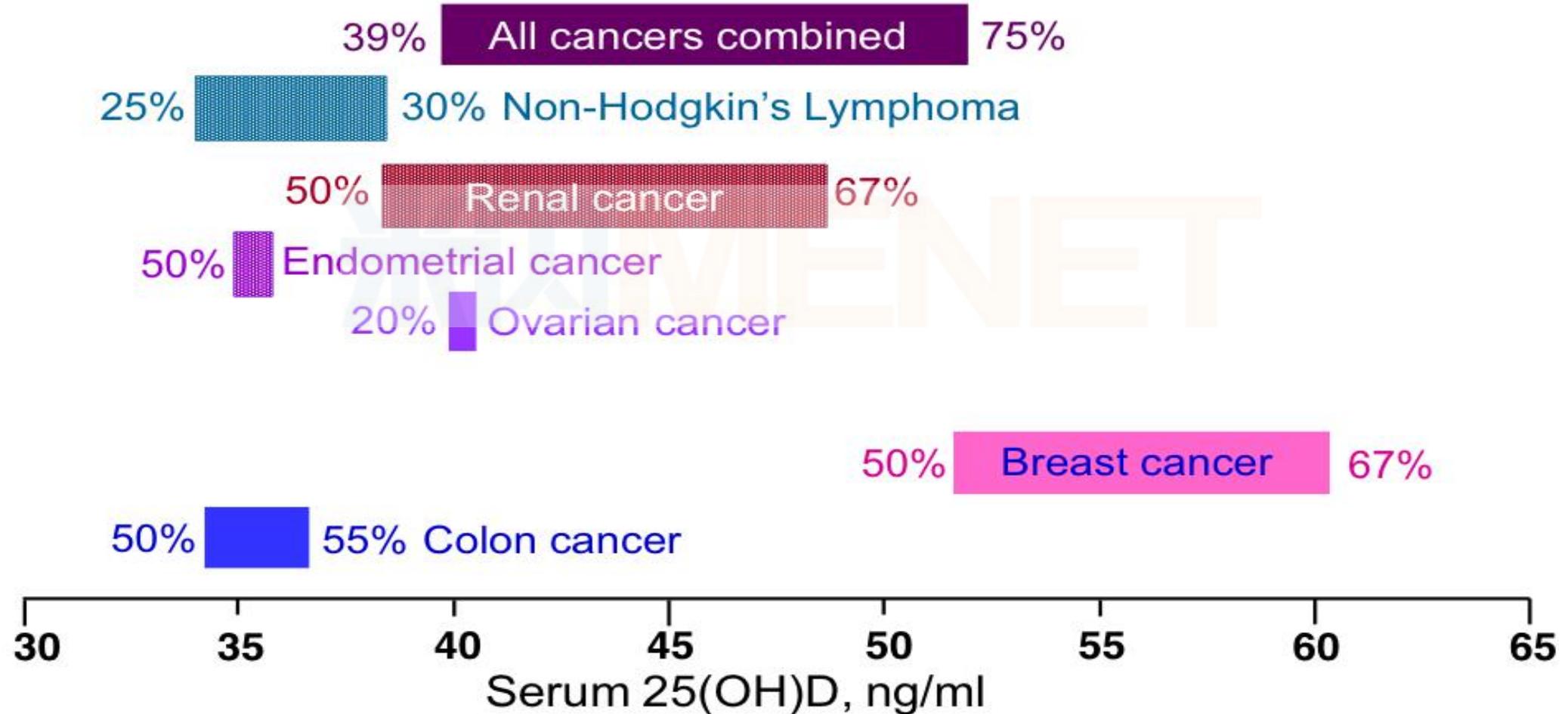


维生素D水平与癌症发病风险的关系



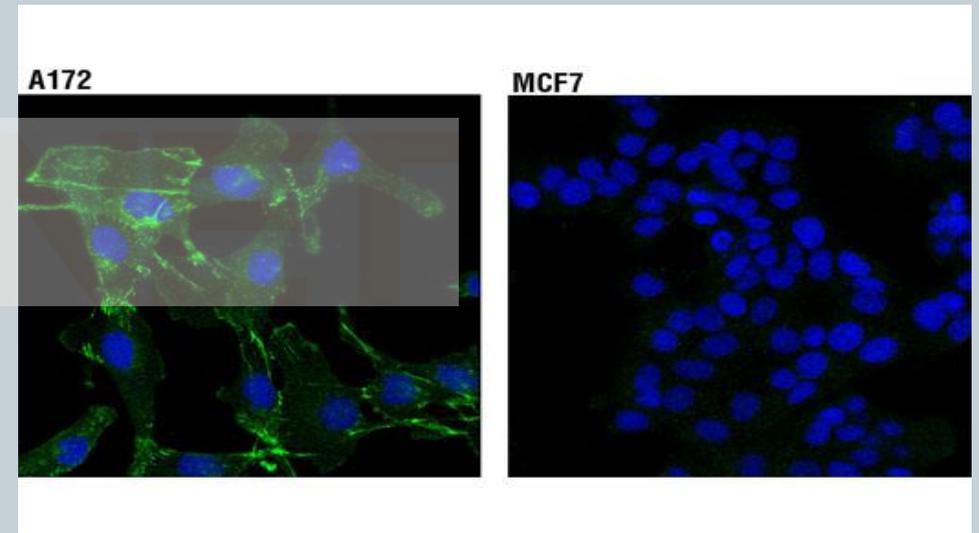
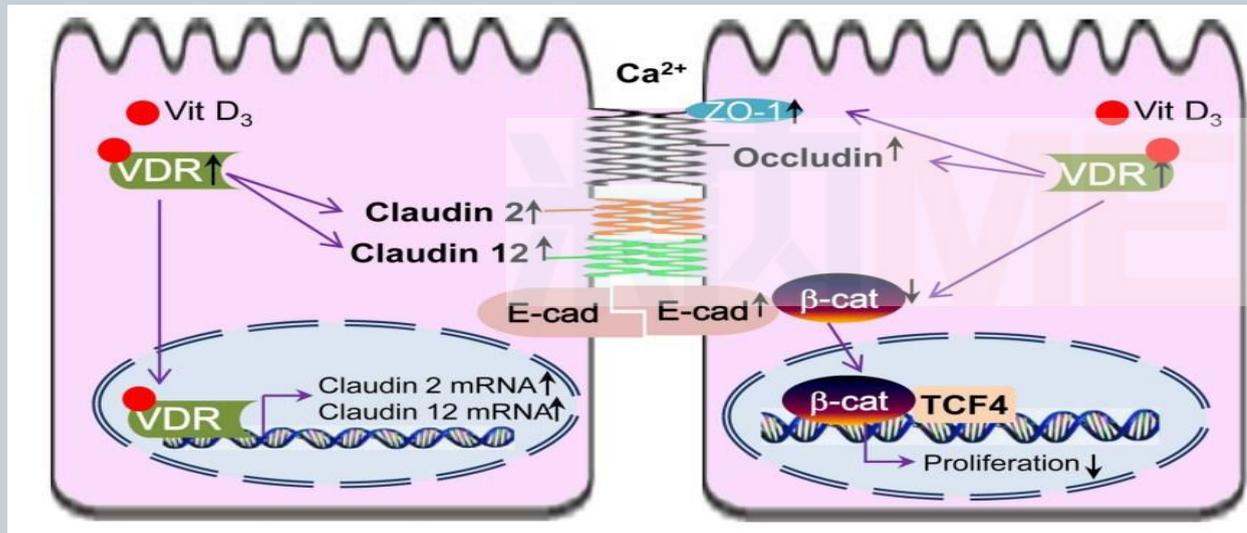
维生素D能预防多种癌症-降低癌症发病率

Estimated Proportion of Cancers Preventable by Serum 25(OH) D Range



维生素D3缺乏**钙粘素**减少，促进癌细胞转移和扩散

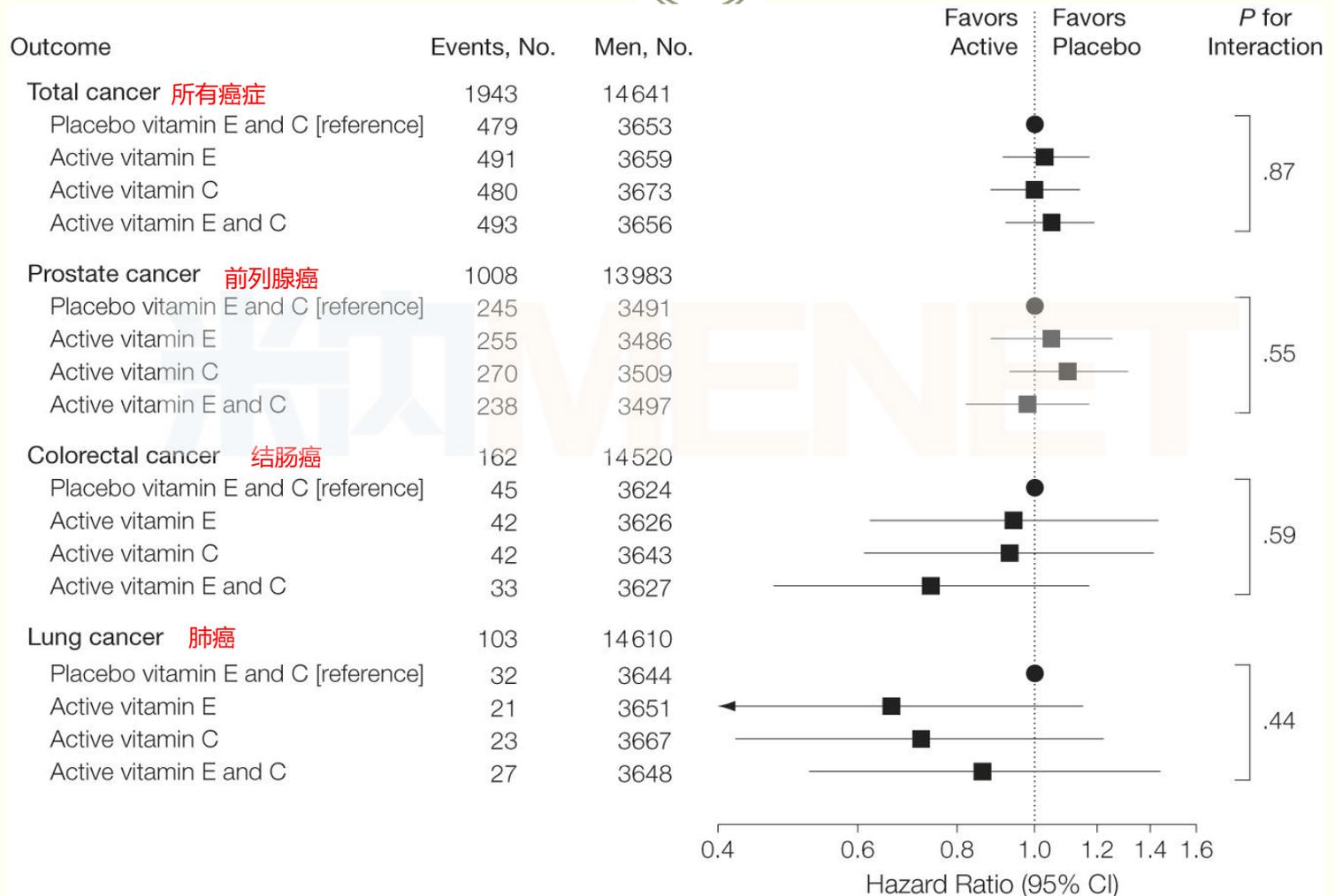
Vitamin D, Vitamin D Receptor, and Tissue Barriers



Recent studies of vitamin D and its receptor revealed different cellular functions of VDR that are based on multiple intracellular signaling pathways and molecular targets of this protein. Specifically, VDR appears to regulate molecular composition and functions of different epithelial junctions. As summarized in Figure 1, VDR has physical interaction with P-catenin. Activation of VDR suppresses the activity of P-catenin, thus decreasing nuclear P-catenin and inhibiting cell proliferation. VDR status is also directly associated with the expression level and functions of TJ proteins, such as claudin2 and 12. Increased VDR level leads to increased claudin2 and 12, which may play roles in calcium homeostasis and barrier function (Figure 1). The other cell junction proteins involved in the vitamin D/VDR include E-cadherin, Occludin, and ZO-1.

添加补充维生素E和C对中老年人多种癌症有预防作用

Conclusions In this large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of prostate or total cancer. These data provide no support for the use of these supplements for the prevention of cancer in middle-aged and older men.



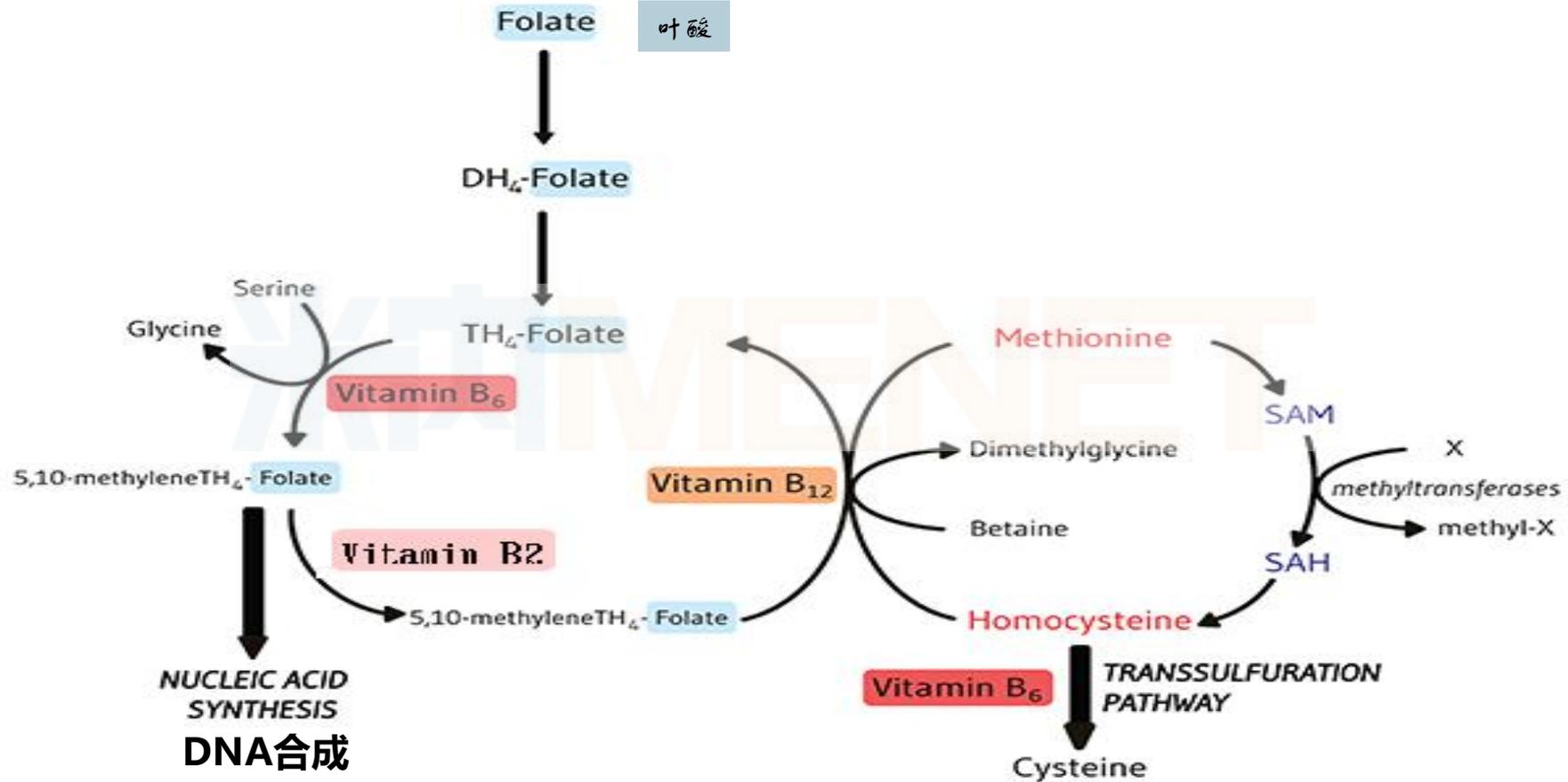
维生素A缺乏与慢病的关系



维生素A调控的部分基因及其编码蛋白的生理作用

基因名称	生理功能	相关疾病防治作用
生长发育相关基因		
HOX基因	诱导细胞分化	畸形 癌症
免疫相关基因		
补体因子4	稳定免疫功能	糖尿病/慢性肾病/风湿病
抗凝相关基因		
血栓调节蛋白基因 纤溶酶原激活蛋白基因	抗血栓形成 溶解血栓	心脑血管病

VB族参与核酸代谢和酶功能 - 缺乏导致畸形, 代谢紊乱, 癌症等多种疾病



5,10-methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential for many biological methylation reactions, including DNA methylation. Methylene tetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH₄-Folate, Tetrahydrofolate.

VC/VE/Q10 抗氧化作用 – 保护细胞分子结构

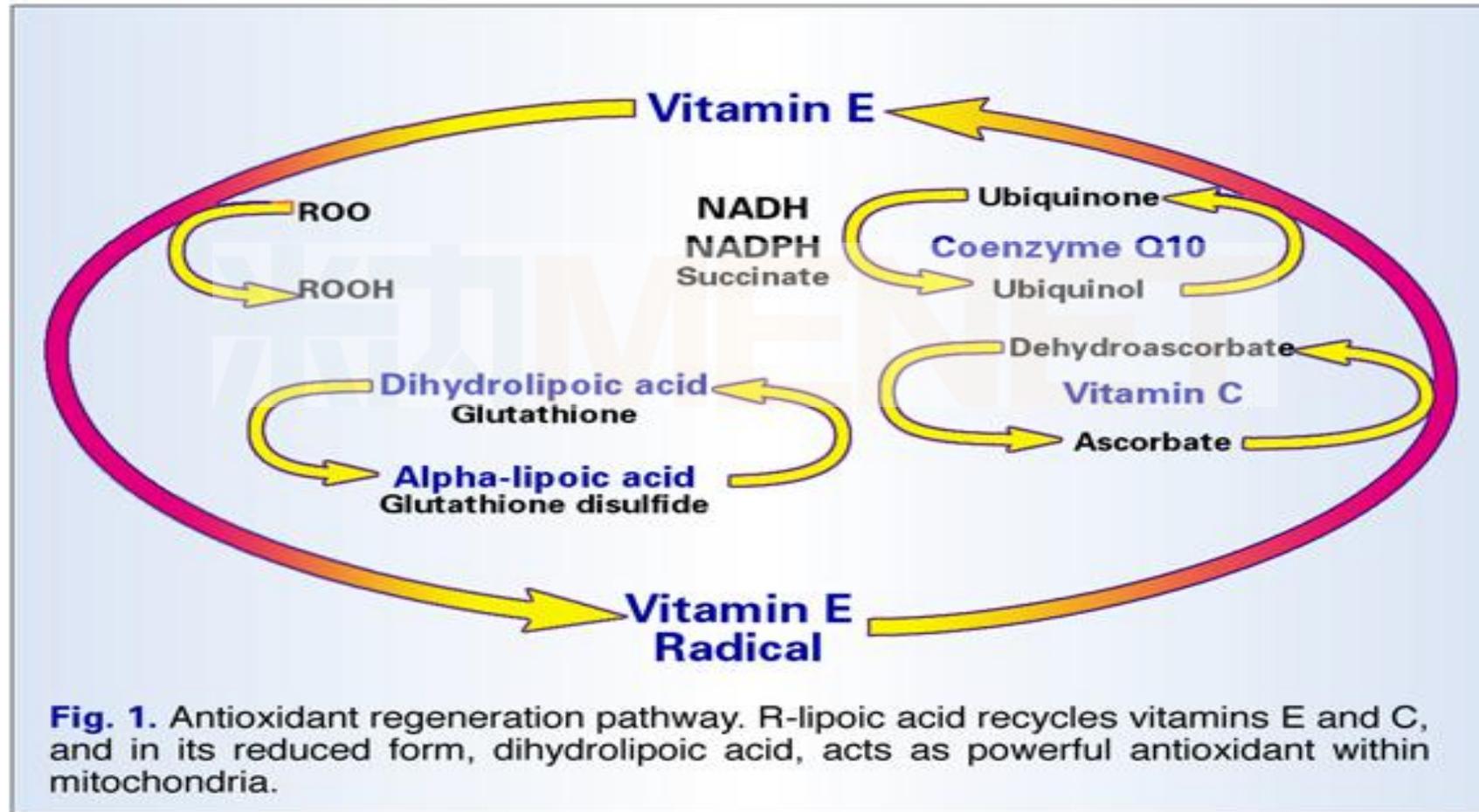
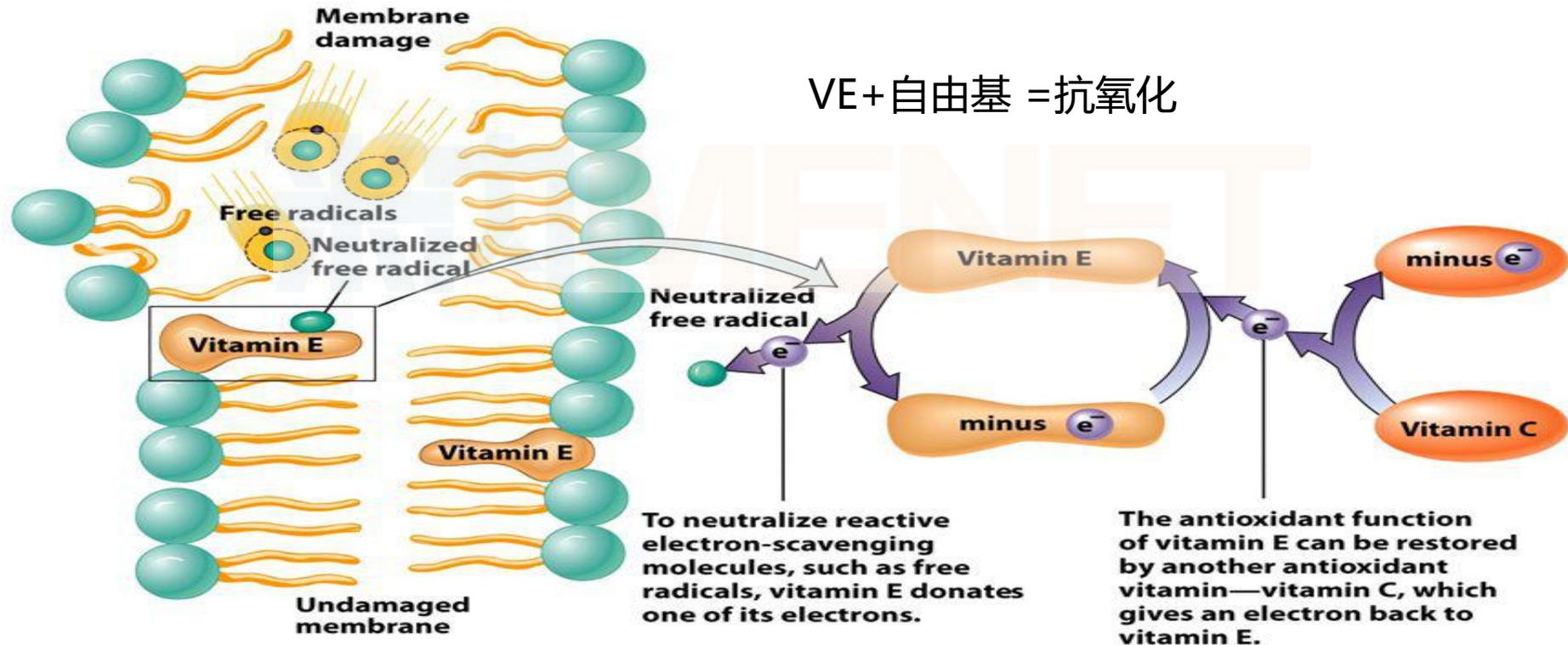


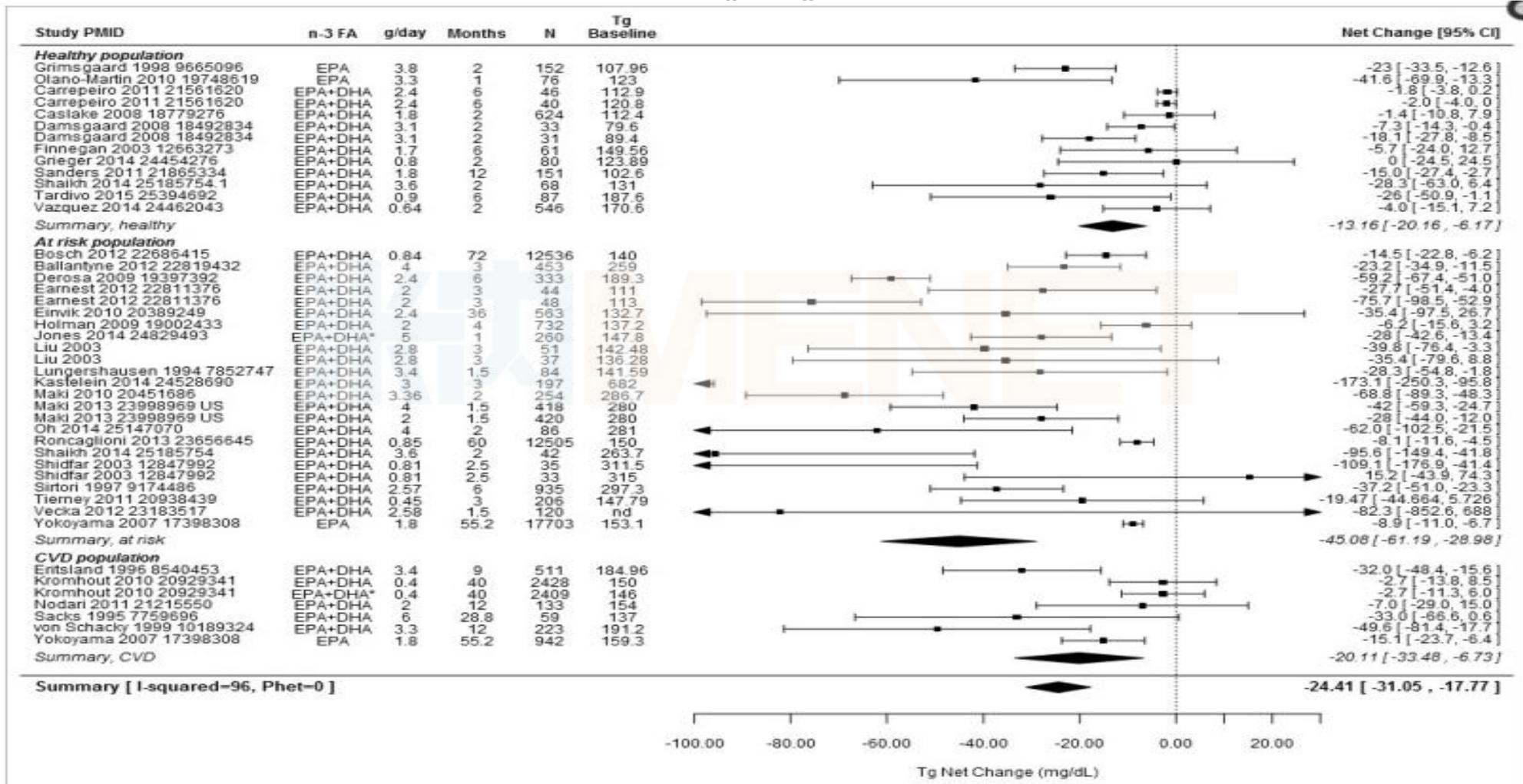
Fig. 1. Antioxidant regeneration pathway. R-lipoic acid recycles vitamins E and C, and in its reduced form, dihydrolipoic acid, acts as powerful antioxidant within mitochondria.

VC+VE - 保护细胞结构完整性 - 预防心脑血管病/糖尿病/癌症等

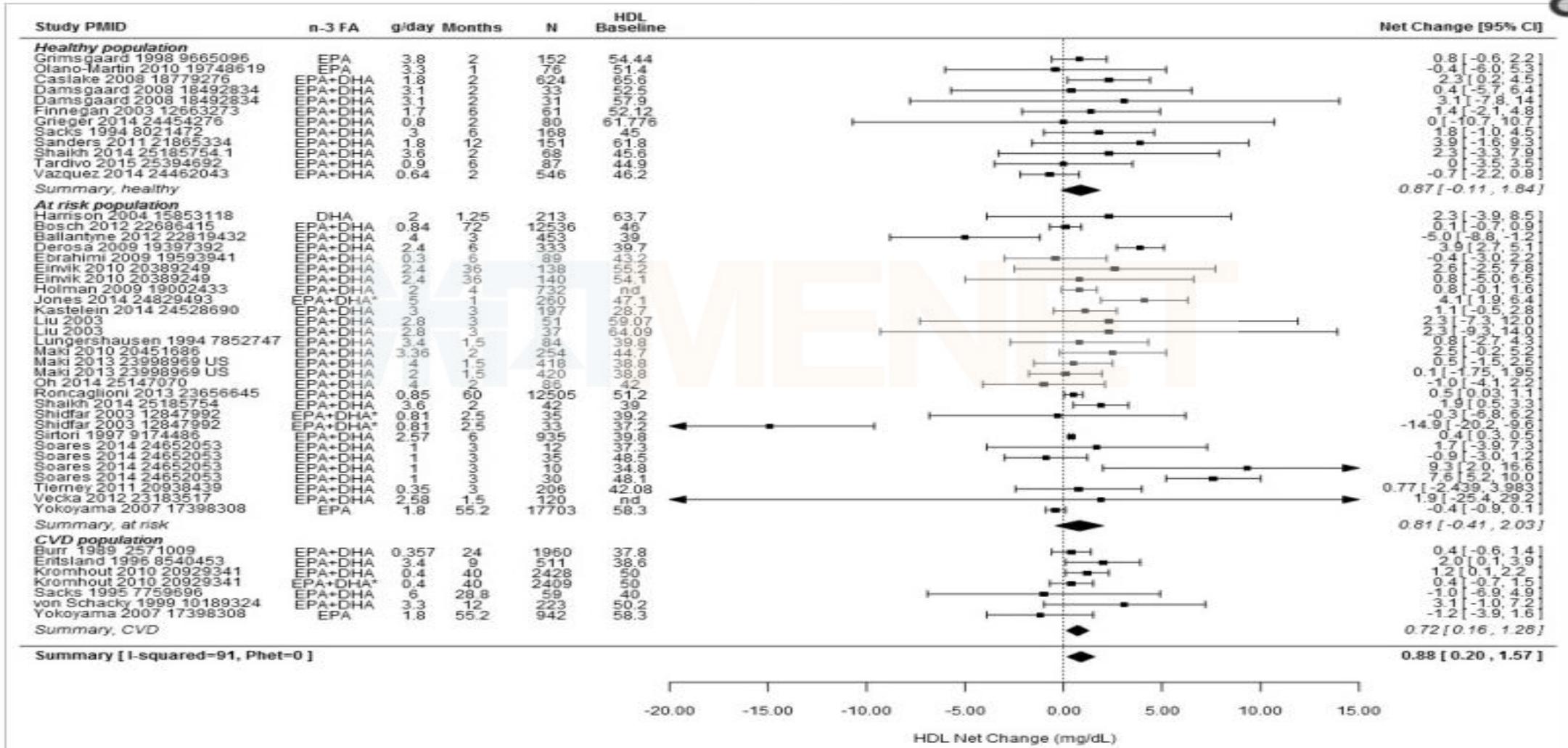
Vitamin E as an Antioxidant



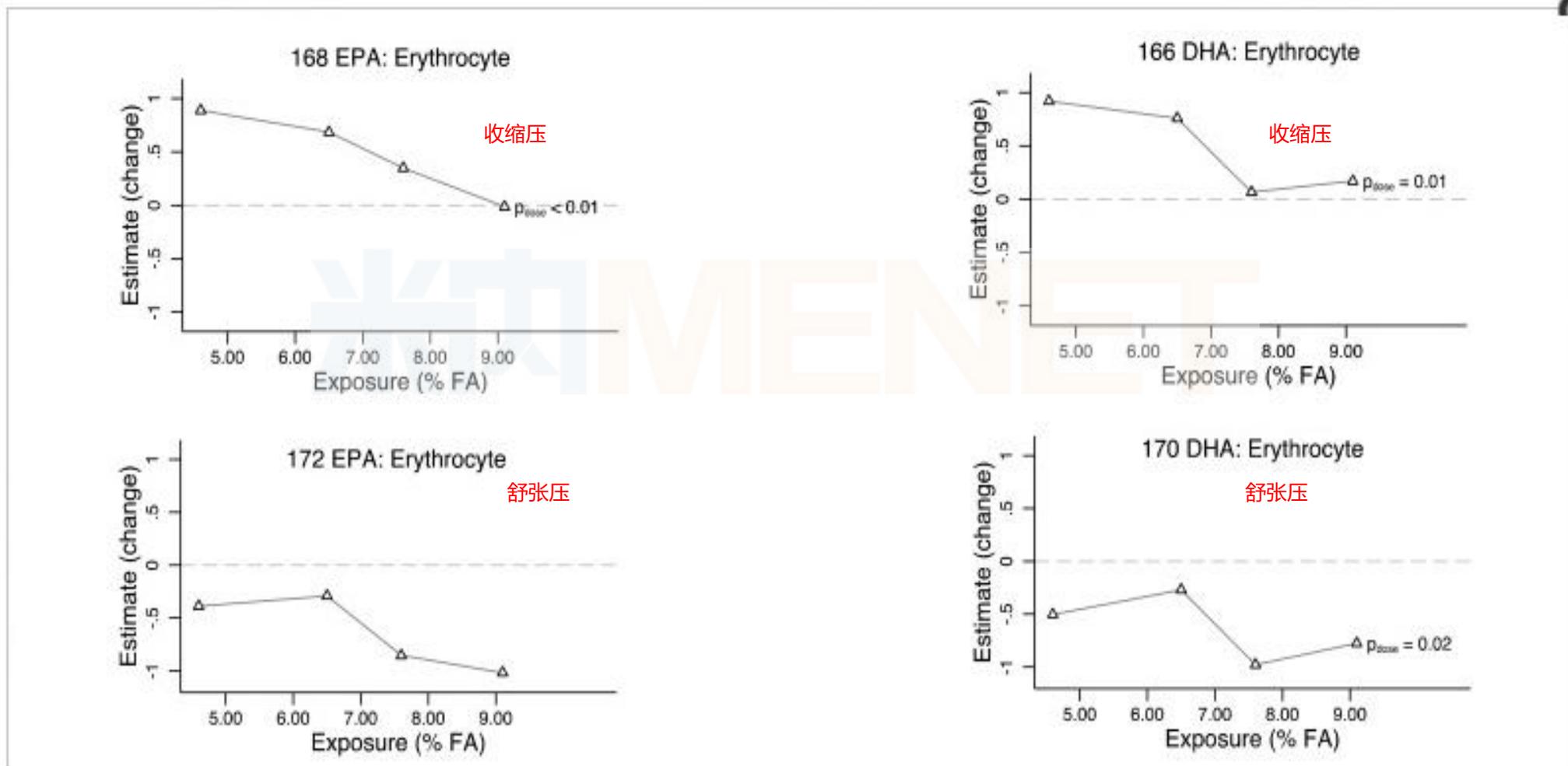
多烯酸乙酯(EPA/DHA)降低胆固醇/甘油三酯 /低密度脂蛋白- 防治心脑血管疾病



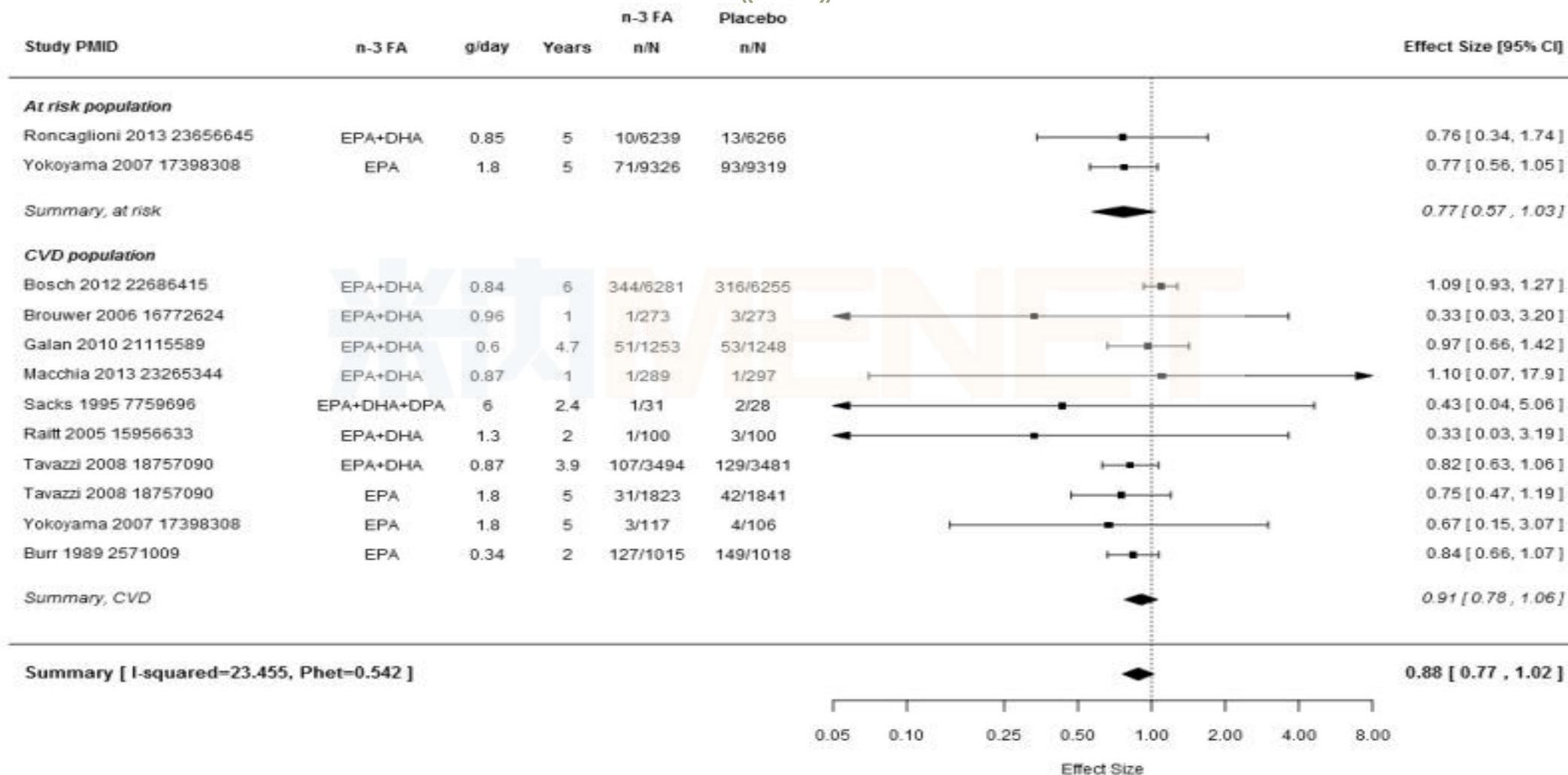
多烯酸乙酯(EPA/DHA)增加高密度脂蛋白 - 防治心血管疾病



多烯酸乙酯(EPA/DHA)降低血压 – 预防治疗高血压病



多烯酸乙酯(EPA/DHA) 抗血栓 – 降低心血管事件发生率和死亡率



99%预防佝偻病



14 83%降低感冒风险



71%降低1型糖尿病风险
50%减低2型糖尿病风险



63%降低帕金森病



99%防治骨质软化症



50%降低心梗



76%降低癌症风险



50%预防骨质疏松



50%降低妊娠并发症

Infertility and placental insufficiency
Preeclampsia and Bacterial vaginosis
Gestational diabetes
Intrauterine growth retardation
Physiology & function
Metabolic disorders
Twins
(current) abortions,
caesarean section
is associated with
by during pregnancy



30%预防骨折



78%降低高血压风险

维生素类药品的安全性

- * 人体本身需要的营养物质,是维持生命活动所必需,没有毒性作用
- * 大多医用维生素来自天然食物中提取,符合人体需要
- * 即使是大剂量误服一般只有不良反应,不会致病.

营养性药物有广泛的联合用药空间



维生素D	基因调控	骨质疏松症, 糖尿病, 高血压, 心血管病, 癌症, 老年痴呆
维生素A	基因调控	血栓形成、慢阻肺、癌症、白内障、
维生素B族	DNA合成/血管功能	心血管病、癌症、慢性胃病和慢性呼吸道疾病
维生素C	基因调控和抗氧化	心血管病、癌症、免疫功能、慢性中毒
维生素E	参与抗氧化和血脂代谢	心血管病、生殖疾病、癌症、糖尿病等
多烯酸乙酯	降低血脂/ 营养大脑	高血压、高脂血症、心血管病、老年痴呆
辅酶Q-10	抗氧化/提高能量合成	心血管疾病, 糖尿病等, 慢性心力衰竭



谢谢各位聆听

营养性药物用于慢病防治OTC市场巨大



- 1, 慢病发病率在世界范围内持续上升, 中国居高不下
- 2, 越来越多的医学研究证明慢病与微营养素缺乏密切相关
- 3, 医药学研究证明微营养素对多种高发慢病有预防治疗作用
- 4, 营养性药物资源已成为世界范围抢夺的紧缺健康资源
- 5, 与日俱增的健康需求和不匹配的医疗技术和资源
- 6, 健康知识的普及人群教育水平的提高

人类健康现状与医学模式的转变



医学模式的转变

- ✚ 关注疾病 —— 关注健康 - 保健
- ✚ 关注疾病的发病率 —— 关注疾病起源 - 病因
- ✚ 关注疾病治疗 —— 关注疾病预防 - 预防

印度儿科学会 (IAP) 指南 (2017年)

预防佝偻病，

- 1, 新生儿每日需要服用**400 IU**的维生素D和200 mg的钙。早产儿每天需要服用400 IU的维生素D和150-220 mg / kg的钙，
- 2, 1-18岁的孩子，每日应服用**600IU**维生素D和600-800mg钙。
- 3, 治疗佝偻病：早产新生儿期，婴儿期到1岁以内和1-18岁的孩子维生素D的日推荐服用剂量分别为**1000 IU, 2000 IU和3000-6000 IU; 持续6周**。早产儿新生儿期每日服用70-80 mg / kg的钙，新生儿期以后每日服用500-800mg钙。3个月至18岁可以给予较大治疗剂量的维生素D，**每周60,000 IU**。

参考文献：From Indian Academy of Pediatrics 'Guideline for Vitamin D and Calcium in Children' Committee., Khadilkar A, Khadilkar V, et al. Prevention and Treatment of Vitamin D and Calcium Deficiency in Children and Adolescents: Indian Academy of Pediatrics (IAP) Guidelines. Indian Pediatr, 2017, 54(7):567-573.

维生素D与成年人骨骼健康应用指南 (2014标准版)

维生素D预防治疗骨质疏松的用量和服用方法

【治疗标准】 1, 血清25OHD < 30 nmol/L (12 ng/mL)

【治疗负荷量】 : 达到总量约300000 IU, 可以每周或每日分开给予。

- | | | |
|---------------|------|--------------------|
| ① 50000 IU 胶囊 | 每周1次 | 连续共6周 (300000 IU)。 |
| ② 20000 IU 胶囊 | 每周2次 | 连续共7周 (280000 IU)。 |
| ③ 800 IU 胶囊 | 每日5次 | 连续10周 (280000 IU)。 |

【治疗维持量】 : 可以在负荷量补足后1个月开始给予。维持剂量为每日800~2000 IU;

下面给药方法已证明无效, 或无效和中毒的风险增加, 因此不推荐: ①应用单次超剂量 (300000 IU 或更高) 使患者快速达到负荷量的方法; ②采用肌肉注射或口服维生素D的年储备给药方法; ③使用活性维生素D制剂 (骨化三醇和阿法骨化醇)。

2015年韩国骨矿物研究学会声明（2015年）

- 1 绝经期妇女和50岁以上的男性必须每日服用足量钙剂和维生素D，以预防骨质疏松症的发生。
- 2 我们建议每日服用钙剂**800-1000mg**，食物依然是获取钙的最好来源。如果饮食不能满足，那么应该额外服用钙剂。
- 3 我们建议每日至少服用**800IU**维生素D，这样可以有效降低骨折风险。
- 4 如果担心体内维生素D不足，我们建议及时查体检验血清中25（OH）D水平。
- 5 我们建议未来预防骨质疏松，体内血清中25（OH）D水平不得低于20ng/ml。**如果能够达到或者高于30ng/ml，则能有效地预防骨质疏松，降低骨折和跌倒风险。**

参考文献：

Kyoung Min Kim, Han Seok Choi, Mi-Ja Choi, et al. Calcium and Vitamin D Supplementations: 2015 Position Statement of the Korean Society for Bone and Mineral Research. J Bone Metab, 2015, 22(4):143-149.

营养药在慢病防治中的应用有巨大扩展空间健康效益

中国的“小康”被“健康”困扰

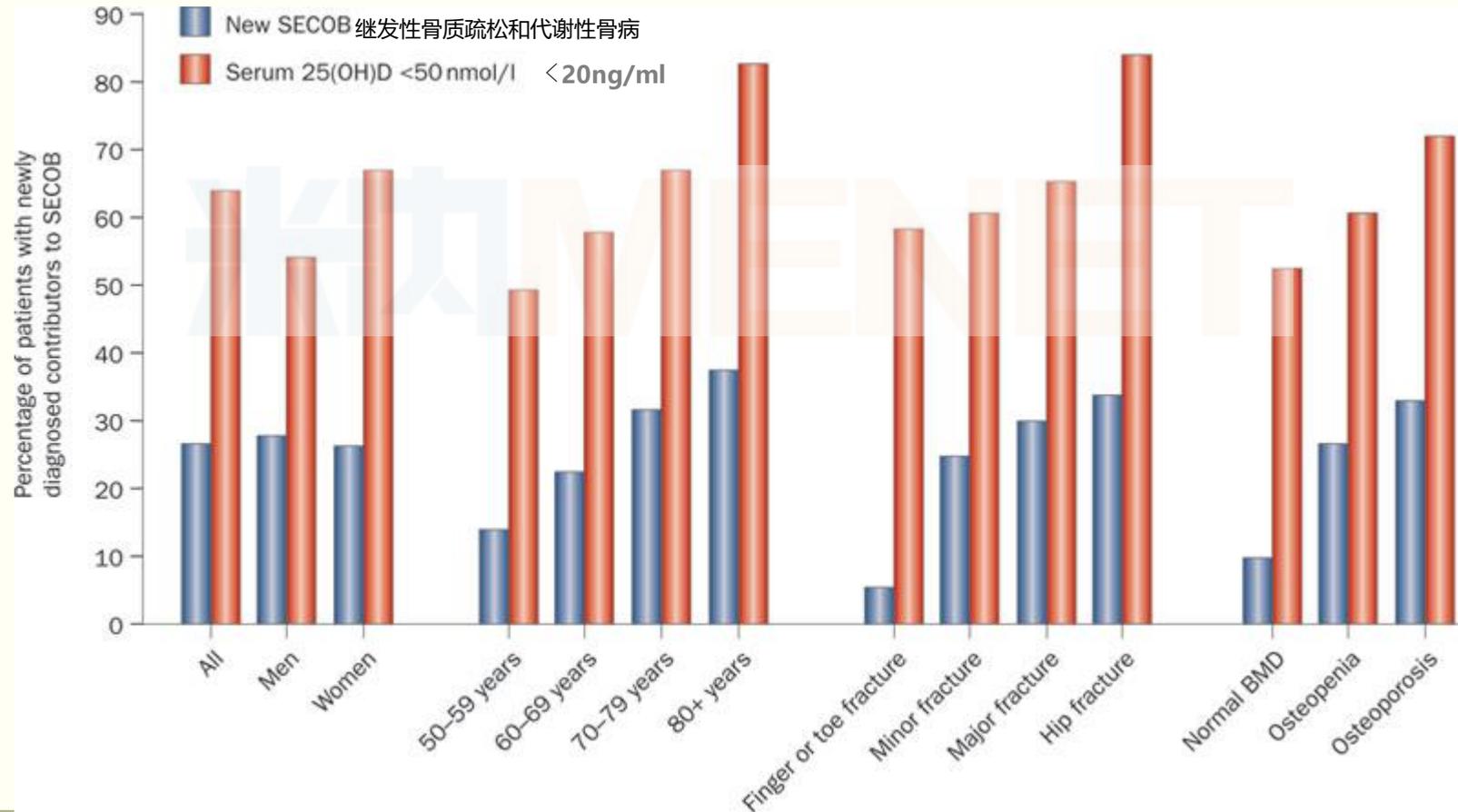
- 国家卫计委发布《中国居民营养与慢性病状况报告（2015年）》，中国居民慢性病死亡率占总死亡人数的**86.6%**。其中心脑血管病、癌症和慢性呼吸系统疾病为主要死因，占总死亡的**79.4%**。
- **中国慢病患者率排名，其中4中与VD缺乏密切相关**
 - 1、高血压心血管疾病：约**2.9亿**（中国循环杂志,2016,31:624-632），高血脂**1.6亿**
 - 2、糖尿病：约**1.1亿**（来自《中国居民营养与慢性病状况报告2015年》），血糖受损**2千万**
 - 3、骨质疏松症：约**1.1亿**（来自中国骨骼健康公益项目），在**上升**
 - 4、癌症：约**700万**（2015年中国癌症统计数据报告），在**上升**
 - 5、慢阻肺 约**1亿**

合计：**6.17亿**

维生素D预防骨质疏松/骨折的健康作用

CONCLUSION:

At presentation with a fracture, 26.5% of patients have previously unknown contributors to secondary osteoporosis and metabolic bone diseases (SECOB), which are treatable or need follow-up, and more than 90% of patients have an inadequate vitamin D status and/or calcium intake. Systematic screening of patients with a recent fracture identifies those in whom potentially reversible contributors to SECOB and calcium and vitamin D deficiency are present.



维生素D降低心血管病事件发生率和死亡率

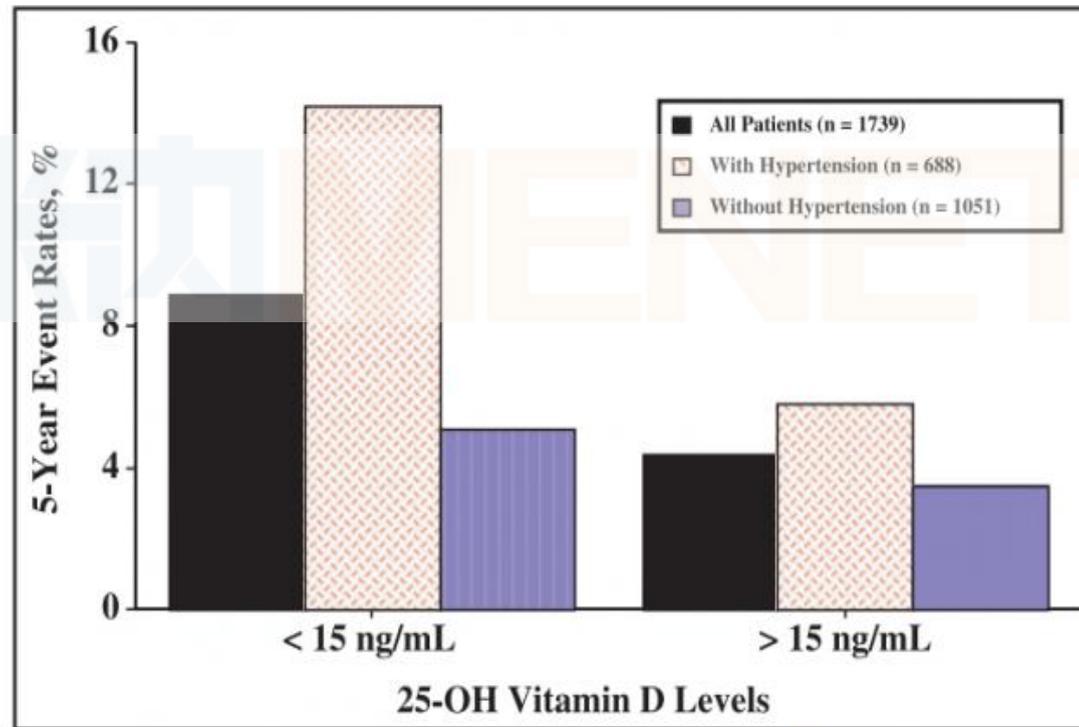


Figure 1. Five-year cardiovascular event rates (%) according to varying levels of 25-hydroxyvitamin D in the Framingham Offspring Study. Rates were adjusted for age and sex and grouped according to the presence or absence of hypertension. Modified with permission from Wang et al.⁷