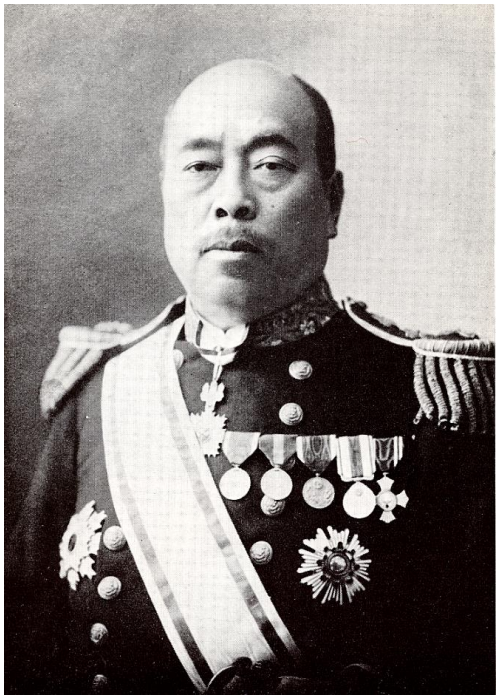
疾病予防のための微量栄養素のエビデンス

東京慈恵会医科大学　浦島充佳

Case 1



高木兼寛

ビタミンが発見される前に白米に栄養が偏ることにより脚気を生じ、これを麦飯に変え、おかずを増やして蛋白摂取を増やすことにより脚気を激減させることを戦艦を使った臨床試験で証明し、さらに脚気を撲滅した。

Case 1

帰国そして脚気との戦い（1880～1890）

- 学生や兵隊に多く，とくに海軍ではつねに兵員の三分の一がそれにかかっているといってよい状況であった．
- 症状としては，全身の倦怠感にはじまり，手足の運動麻痺，感覚麻痺，浮腫が進行し，運動をするとはげしく動悸して，次第に寝たきりの状態になっていく，あるいは脚気衝心といって胸部から腹部にかけて痙攣がおこり，はげしい苦悶のうちに死んでいくという恐ろしいものであった。
- 死亡率も低くなく，つねに脚気患者の3%近くをしめていた。
- 脚気はこのように恐ろしい病気であったが，当時はまだ原因が分からず，治療法といえばまったくの対症療法しかなく，効果はほとんど期待されなかった．
- **兼寛は．なんとかしてこの病気の原因を明らかにし，その予防法，治療法を確立したいと考えた．**

Case 1

取掛かり

- 「将校，下士卒，囚人等を区別して取り調べてみると，その囚人のごときは最も脚気患者が多く，下士卒がこれに次ぎ，将校にあっては殆どこの病気にかかることはない」

下士卒	生徒	准士官	士官
1対28	1対25	1対20	1対20

- 「パークス氏のいわゆる健康標準食なるものは窒素1に対して炭素が約15の割合になっているのに，これを基準にして脚気患者の食事を調べてみると窒素1に対して炭素がなんと28にもなっている．しかも15，20，22，23のあたりでは脚気患者が出ていない．してみればこの病気の原因はもしかしたらこの辺にあるのではないか，であるからして若し食物中の窒素と炭素の割合をほぼI対15に近い食物を献立して，供給すれば，この病気は防ぐことが出来るのではないか，という考えがでて参ったのであります」

Case 1

研究のヒントを逃さない

- 明治15年（1882）年12月19日
- 376人の乗組員
- 遠洋航海(ニュージーランド，チリ，ペルー，ハワイ（ホノルル）
- 全行程272日
- （病者多し航海できぬ金送れ）という悲痛な電報
- 169名の脚気患者が発生し，そのうち25名が死亡

- ところが，ホノルルで一ケ月間停泊し，それまでの食糧を全部捨て，ここで積み込んだ肉，野菜を乗組員に与えたところ，脚気患者は全員元気をとりもどし，無事品川港に滞ってくることができたのであった.

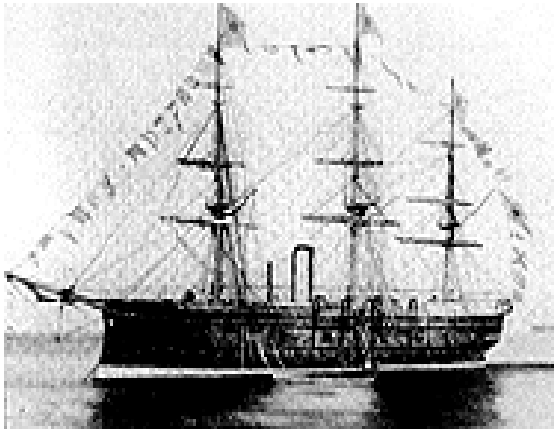


写真8　龍驤
高木兼寛伝　巻頭グラビア
軍艦（龍驤）．明治16年のニュージーランド，南米，ホノルルを回る航海で，多くの脚気患者（乗組員376人中169人），脚気死亡者（25人）を出した．

Case 1

龍驤艦での脚気患者の発生状況，とくにハワイで食料を変える前後の変化

階　級	ハワイまで		ハワイから品川	
	食　糧 窒素炭素比	脚気患者数 （死亡者数）	食　糧 窒素炭素比	脚気患者数 （死亡者数）
下士卒 準士官	1対20 ～28	169 (25)	1対11～16	0
士官	1対20	0	1対11	0
乗組員は総数376人				

Case 1

軍艦筑波での検証

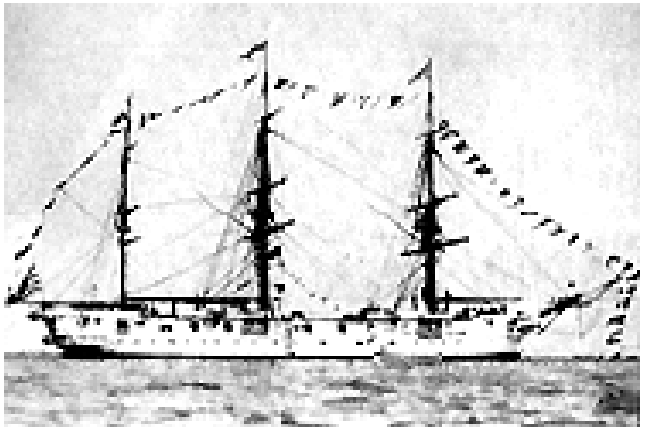


写真9　筑波
高木兼寛伝　巻頭グラビア
軍艦〈筑波〉．明治17年，高木兼寛の改善食を積んで，〈龍驤〉と同じコースを航海した．〈筑波〉からは〈病者1人もなし，安心あれ〉という電報が送られてきた．

- 龍驤艦と同じ航路
- 食事：炭水化物対蛋白　　＝17：1

電報：
「ビヤウシヤーニンモナシアンシンアレ」
（病者一人もなし安心あれ）

Case 1

龍驤艦と筑波艦での脚気患者発生状況の違い，とくに食糧との関係

艦　名	食　糧 窒素炭素比	脚気患者数（死亡者数）	
		全航程	チリ・ハワイ間
龍　驤	1対20～28	169 (25)	150 (23)
筑　波	1対17	10 (0)	1 (0)
両艦の乗組員はそれぞれ376人，333人である			

「下士卒273名（全員333名）中、脚気にかかりたる者10名のみ，しかも死亡に陥りたる者全くえれなく，その10名にしても8名は始め全く肉類を食する能わずして後に僅少の鮮肉を喫せし者なり」

Case 1

予防医学の実践

- 高木は海軍兵食の改善を強力に推し進めていった．はじめ主食はほとんどパンであったが，これに抵抗して食べない者もいたため，高木はパンをあきらめ，パンの原料であり蛋白質の多い麦を与えることにした（麦に蛋白質が多いことは多くの改善献立をつくったときから熟知していた）．結果はますます良好で，明治18年（1885）以降，海軍から脚気病を完全に駆逐してしまったのである

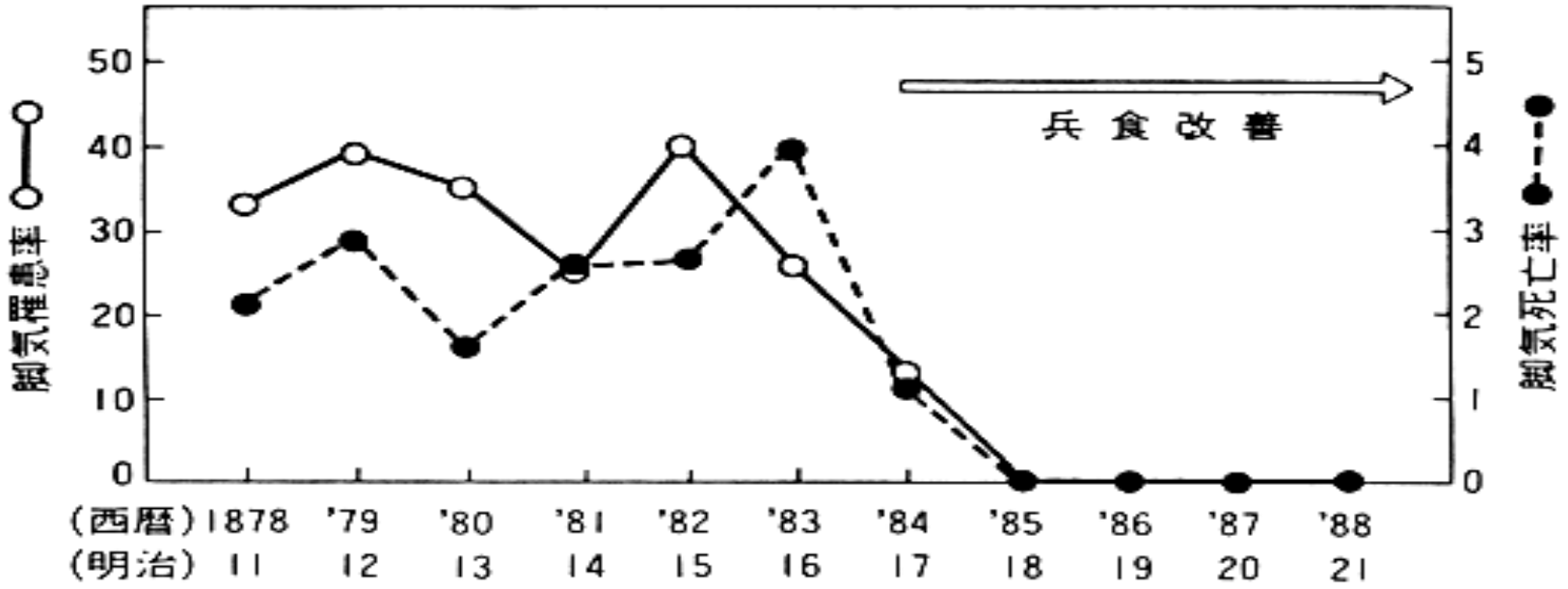
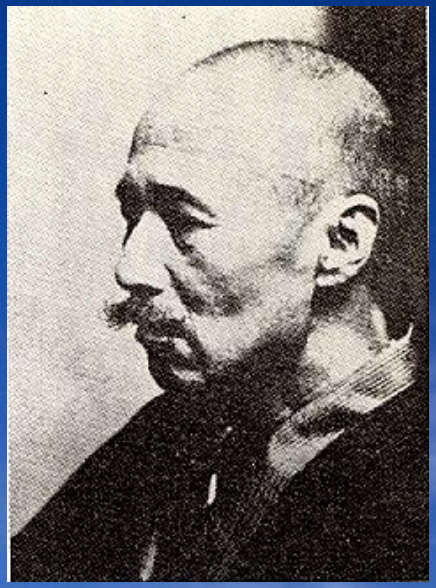


図1．　海軍での脚気病罹患率と死亡率の推移．

脚気病栄養説
イギリス医学
病人を診る学問

脚気病細菌学説
ドイツ医学
病気を観る学問



明治27年　日清戦争

海軍
脚気患者　＝　0人

陸軍
脚気死亡　＝　4064人

明治37年　日露戦争

海軍
脚気患者　＝　105人

陸軍
脚気による死亡　＝　27，800人

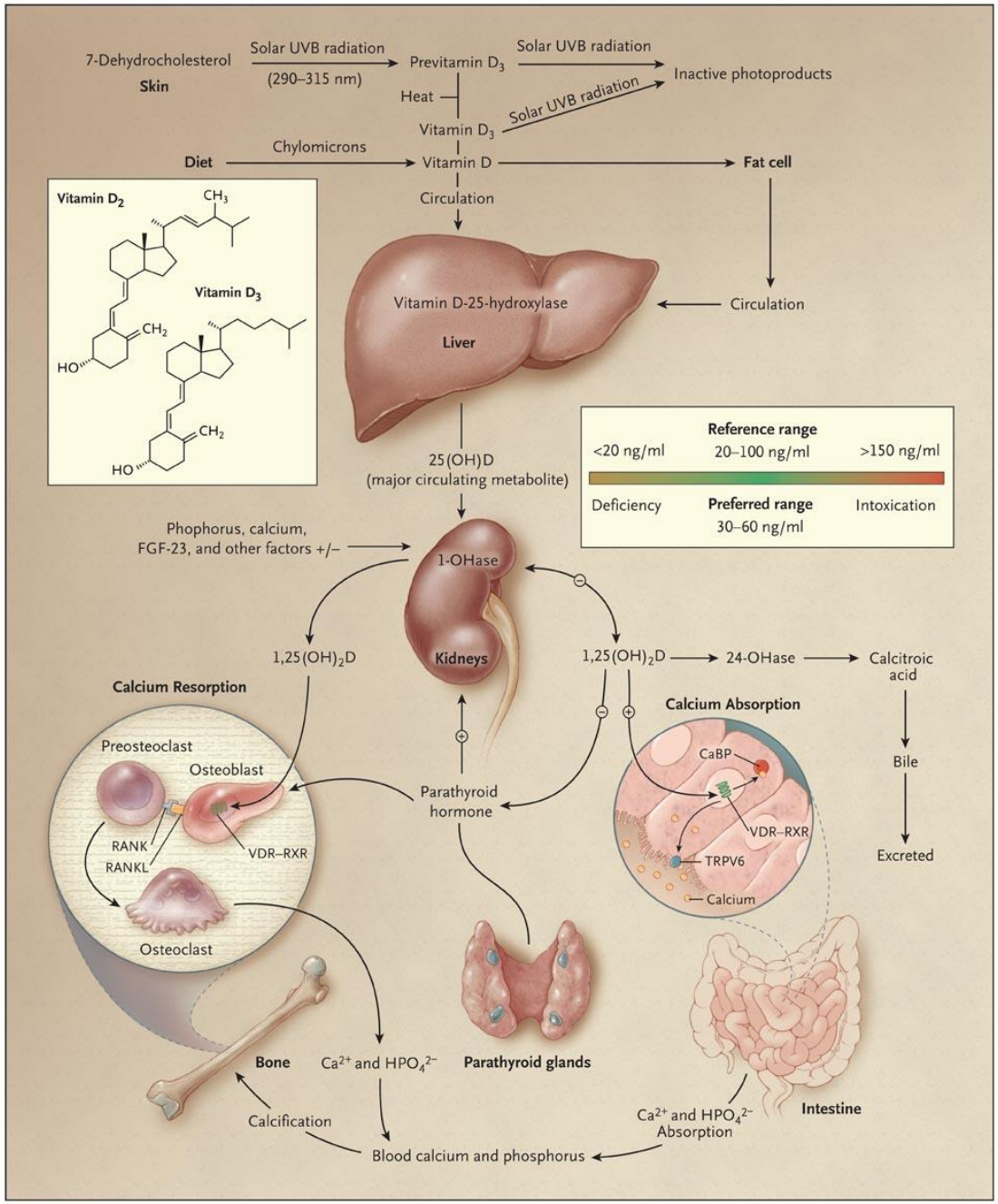
古今東西ノ戦役中殆ト類例ヲ見サル

Case 2

栄養素による
７つの
ランダム化臨床試験

Case 2

0. ビタミンD の代謝および不足状態



日光　　食事

夏　　冬　　干ししいたけ
サケ、イワシ、サバなど油の多い魚

ビタミンD　　日照、食事により変化
2倍以上変動

↓

25(OH)D　　30 ng/ml

↓

腎臓　1,25(OH)D　　活性型

↓

20 – 60 pg/ml

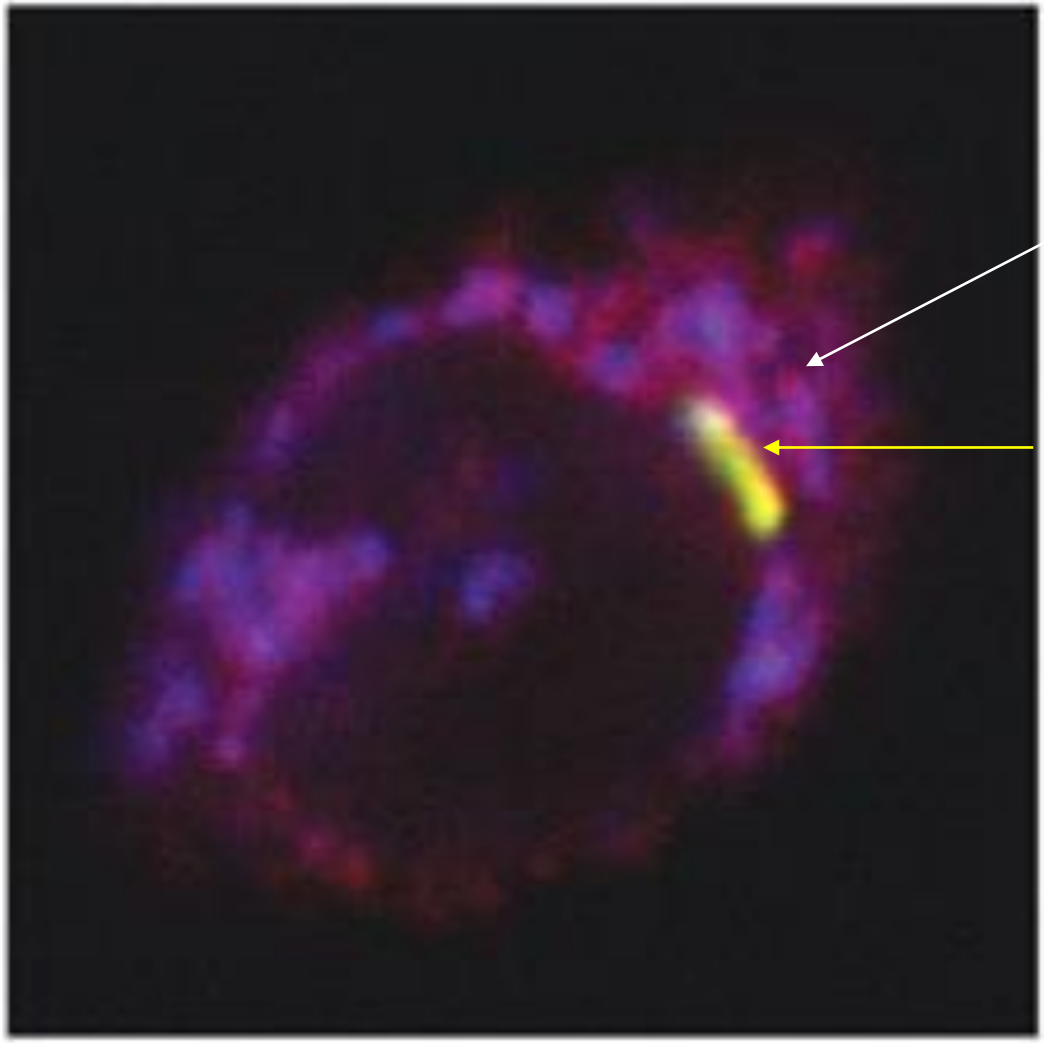
↓

骨の成長

ネガテフィブ・フィードバックによりタイトにコントロール

Case 2

マクロファージ



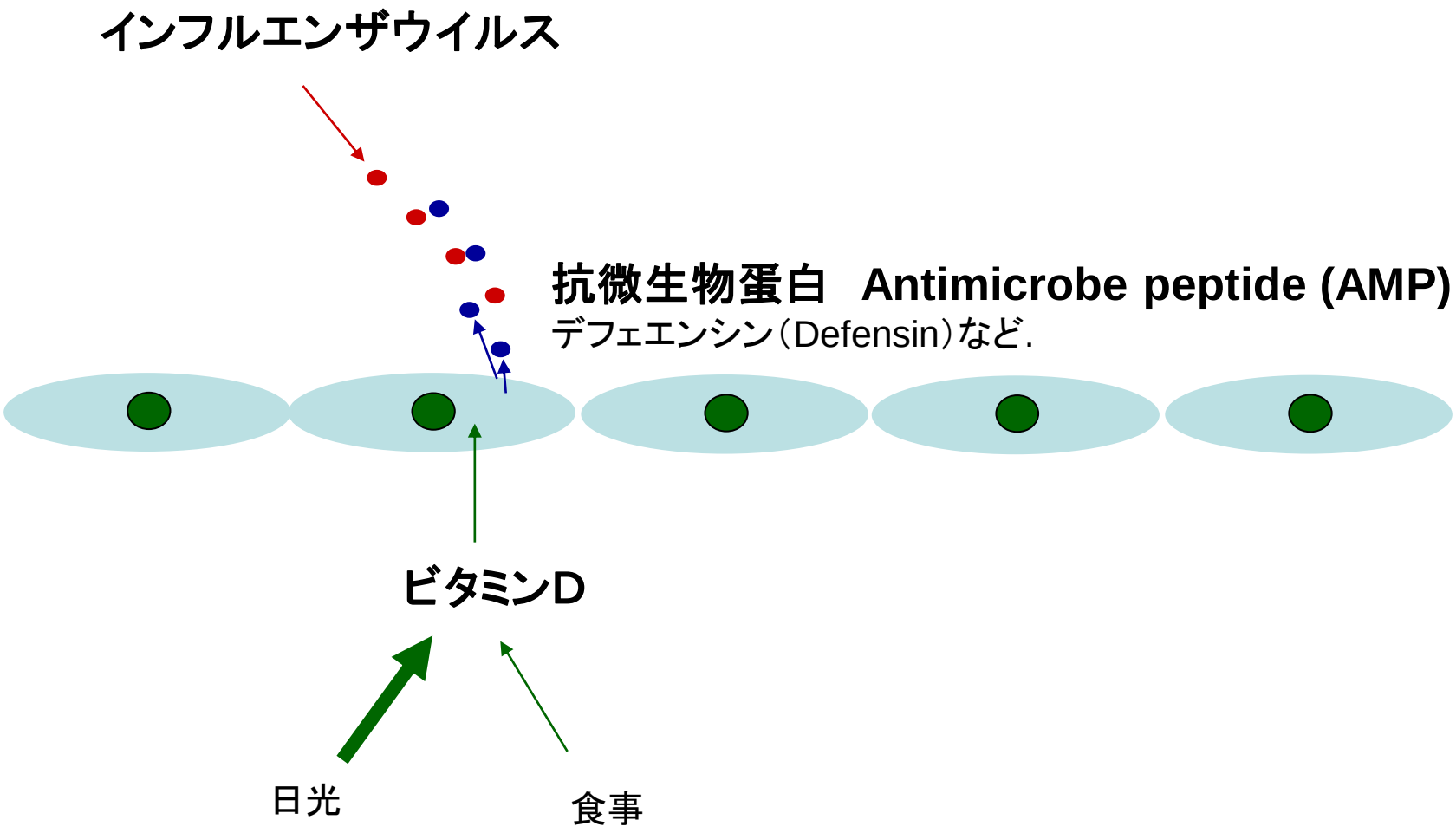
ビタミンDの刺激により分泌

カセリシジン (赤)

結核菌

Science. 2006 Mar 24;311(5768):1770-3.

Case 2



日頃からの体力づくりが大切

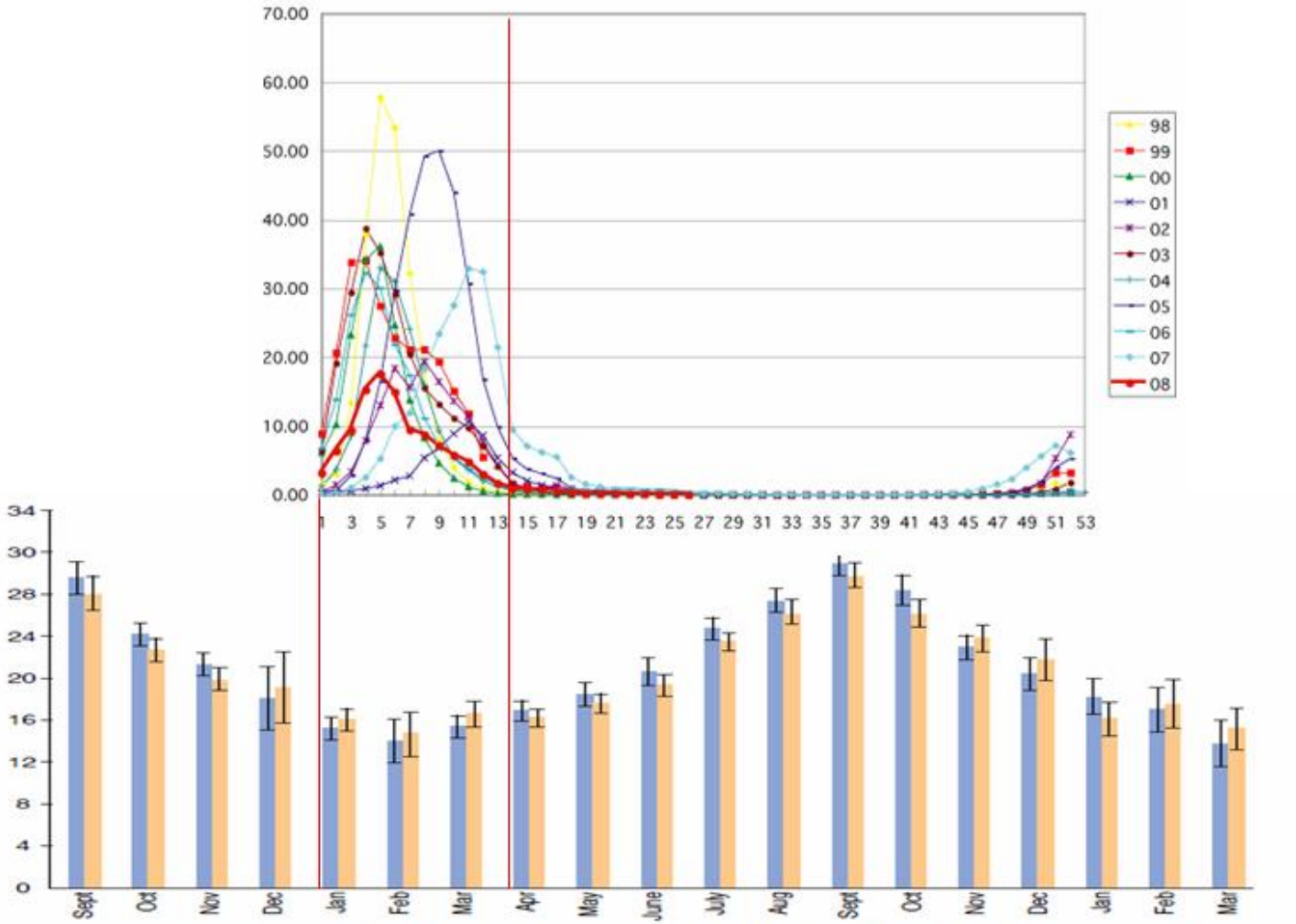
Nat Immunol. 2010 Jan;11(1):76-83.

Nat Immunol. 2005 Oct;6(10):995-1001.

Case 2

Ⅱ. インフルエンザ発症予防の可能性

インフルエンザ A 流行時期と血清ビタミン Dレベルの低下する時期が一致する



Geometric mean monthly variations in serum 25-hydroxyvitamin D [25(OH)D] concentration in men (blue, n=3723) and women (orange, n=3712) in a 1958 British (England, Scotland, and Wales) birth cohort at age 45. Adapted from: Hypponen E, Power C. Hypovitaminosis D in British adults at age 45y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007;85:860-868. Used with permission.

国立感染症研究所情報センターホームページ

Am J Clin Nutr 2008; 85: 860-868.

Case 2

25OHDレベルが高いとインフルエンザに罹り難くなる

Case 2

ビタミンDを使った
ランダム化プラセボ比較試験

Case 2

二重盲検

ビタミンDの入ったサプリメント vs. プラセボ

Case 2

Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren[1–3]

Mitsuyoshi Urashima, Takaaki Segawa, Minoru Okazaki, Mana Kurihara, Yasuyuki Wada, and Hiroyuki Ida

ABSTRACT

Background: To our knowledge, no rigorously designed clinical trials have evaluated the relation between vitamin D and physician-diagnosed seasonal influenza.

Objective: We investigated the effect of vitamin D supplements on the incidence of seasonal influenza A in schoolchildren.

Design: From December 2008 through March 2009, we conducted a randomized, double-blind, placebo-controlled trial comparing vitamin D_3 supplements (1200 IU/d) with placebo in schoolchildren. The primary outcome was the incidence of influenza A, diagnosed with influenza antigen testing with a nasopharyngeal swab specimen.

Results: Influenza A occurred in 18 of 167 (10.8%) children in the vitamin D_3 group compared with 31 of 167 (18.6%) children in the placebo group [relative risk (RR), 0.58; 95% CI: 0.34, 0.99; $P = 0.04$]. The reduction in influenza A was more prominent in children who had not been taking other vitamin D supplements (RR: 0.36; 95% CI: 0.17, 0.79; $P = 0.006$) and who started nursery school after age 3 y (RR: 0.36; 95% CI: 0.17, 0.78; $P = 0.005$). In children with a previous diagnosis of asthma, asthma attacks as a secondary outcome occurred in 2 children receiving vitamin D_3 compared with 12 children receiving placebo (RR: 0.17; 95% CI: 0.04, 0.73; $P = 0.006$).

Conclusion: This study suggests that vitamin D_3 supplementation during the winter may reduce the incidence of influenza A, especially in specific subgroups of schoolchildren. This trial was registered at https://center.umin.ac.jp as UMIN000001373. *Am J Clin Nutr* 2010;91:1255–60.

Case 2

```
. csi 18 31 150 137
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	Exposed	Unexposed	Total
Cases	18	31	49
Noncases	150	137	287
Total	168	168	336
Risk	.1071429	.1845238	.1458333

	Point estimate	[95% Conf.	Interval]
Risk difference	-.077381	-.1524019	-.00236
Risk ratio	.5806452	.3383697	.9963918
Prev. frac. ex.	.4193548	.0036082	.6616303
Prev. frac. pop	.2096774		

chi2(1) = 4.04 Pr>chi2 = 0.0445

Case 2

Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI
Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Improved control of childhood asthma with low-dose, short-term vitamin D supplementation: a randomized, double-blind, placebo-controlled trial

H. Tachimoto[1], H. Mezawa[1,2], T. Segawa[1,3], N. Akiyama[1,3], H. Ida[1] & M. Urashima[1,2]

[1]Department of Pediatrics; [2]Division of Molecular Epidemiology, Jikei University School of Medicine, Tokyo; [3]Department of Pediatrics, Fuji Chuo Hospital, Shizuoka, Japan

Abstract

Background: In our prior randomized trial on preventing influenza, asthma attacks as a secondary outcome occurred less often in the vitamin D group than in the placebo group. We aimed to clarify whether low-dose, short-term vitamin D supplementation, in addition to standard treatments, improves control of childhood asthma.

Methods: We conducted a randomized, double-blind, placebo-controlled trial comparing vitamin D3 supplements (800 IU/day) with placebo for 2 months in schoolchildren with asthma. The primary outcomes were frequency and severity of asthma judging from changes in asthma control levels defined by the Global Initiative for Asthma (GINA) by collaborating doctors at 2 and 6 months.

Results: Japanese schoolchildren with asthma ($n = 89$) were randomly assigned to receive vitamin D ($n = 54$) or placebo ($n = 35$). At 2 months, GINA asthma control was significantly more improved in the vitamin D group compared with the placebo group ($P = 0.015$). Childhood asthma control test (CACT) scores, a secondary outcome, were also significantly ($P = 0.004$) improved in the vitamin D group compared with the placebo group at 2 months, and differences remained significant ($P = 0.012$) at 6 months. The proportion of patients with a peak expiratory flow rate <80% predicted was significantly less in the vitamin D group (8/54: 15%) than in the placebo group (12/35: 34%) at 6 months ($P = 0.032$).

Conclusions: Low-dose, short-term vitamin D supplementation in addition to standard treatment may improve levels of asthma control in schoolchildren.

Case 2

	Vitamin D	Placebo	Total
Cases	16	7	23
Noncases	39	50	89
Total	55	57	112
Risk	.2909091	.122807	.2053571

	Point estimate	[95% Conf.	Interval]
Risk difference	.1681021	.0209026	.3153016
Risk ratio	2.368831	1.056709	5.310224
Attr. frac. ex.	.5778509	.0536655	.811684
Attr. frac. pop	.4019832		

chi2(1) = 4.85 Pr>chi2 = 0.0277

Case 2

Mitsu -- I would be happy to learn more about your research. It may interest you to know that I have family ties to Japan -- though I've not been there in several years. My sister is married to a Japanese man (Yoshimasa) and they have two daughters (Conatsu and Miyuki). They live in Tokyo. :)

Best wishes,
Carlos

Carlos A. Camargo, MD, DrPH
Director, EMNet Coordinating Center
Massachusetts General Hospital
326 Cambridge St, Suite 410
Boston, MA 02114 USA

Case 2

Invitation to collaborate on IPD meta-analysis of vitamin D trials

受信トレイ x urashima@jikei.ac.jp x

Camargo, Carlos Arturo,Jr.,M.D. <CCAMARGO@partners.org> 2013/01/13

To urashima, Adrian

英語 › 日本語 メッセージを翻訳 次の言語で無効にする: 英語

Dear Mitsu,

Happy New Year! I hope this email finds you well.

The reason I write is to ask if you might be interested in joining a collaborative group working on an individual patient data (IPD) meta-analysis of vitamin D trials for the prevention of acute respiratory infections and exacerbations of asthma and COPD. This initiative is being set up by Adrian Martineau in London (cc'd) and myself.

I've attached a formal invitation letter and an outline of the proposal, and look forward to hearing your thoughts.

Best wishes,
Carlos

Carlos A. Camargo, MD DrPH
Professor of Medicine & Epidemiology
Massachusetts General Hospital
Harvard Medical School
326 Cambridge St, Suite 410
Boston, MA 02114

Case 2

Case 2

Case 2

Case 2

Case 2

Case 2

In 2014

Case 2


vitamin D
AND HUMAN HEALTH
Dr Adrian Martineau
Queen Mary University of London
www.smd.qmul.ac.uk

Case 2

Queen Alexandra

President of the London Hospital

1904

Who always took a personal & sympathetic interest in its work and who in 1900 introduced to England

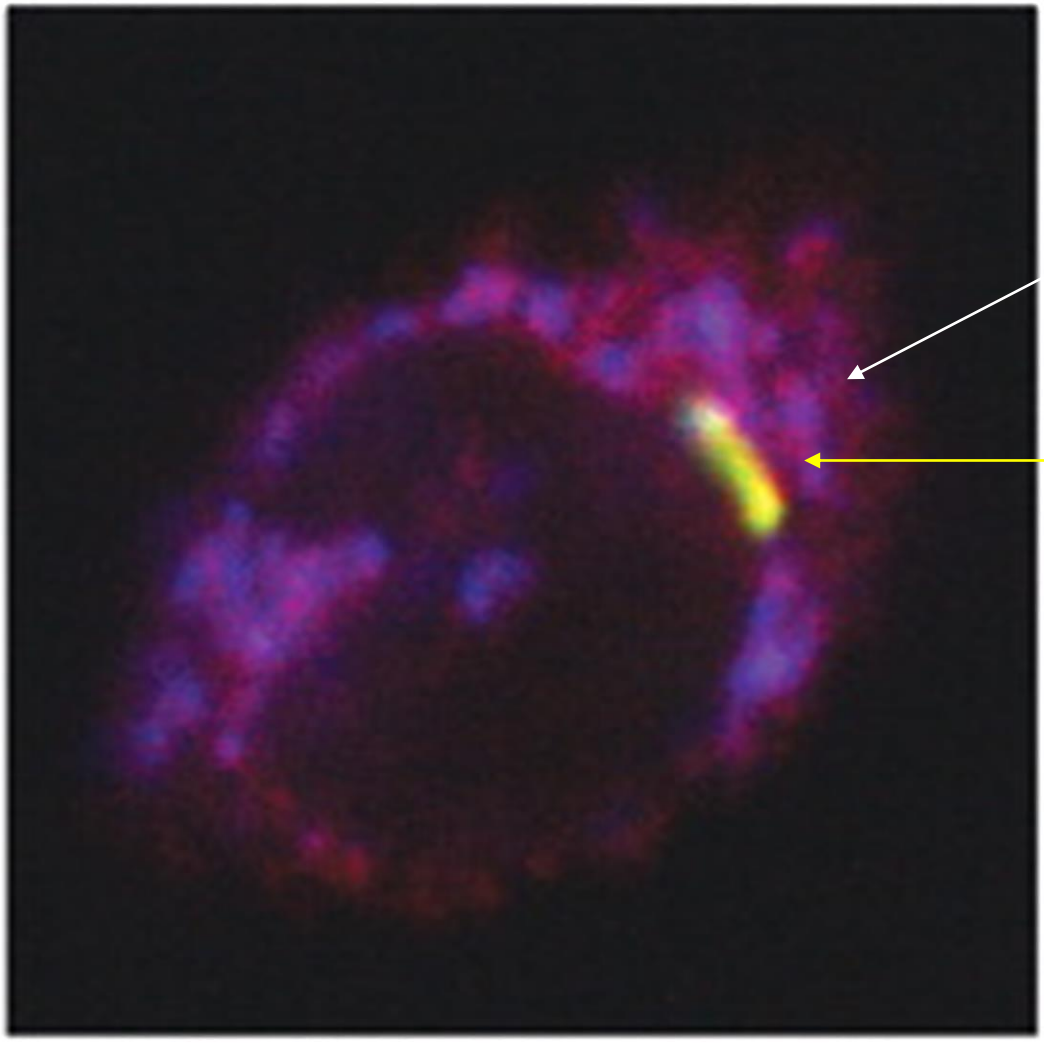
The Finsen Light Cure for Lupus（尋常性狼瘡：皮膚結核）

and preserved the first lamp to this hospital.

1908

Case 2

マクロファージ



ビタミンDの刺激により分泌

カセリシジン (赤)

結核菌

Science. 2006 Mar 24;311(5768):1770-3.

Case 2

Case 2

東慕慈恵医院行啓

満谷国四郎　筆

東京慈恵会　奉納

1887年（明治20年）5月9日

東京慈恵病院

Case 2

国際共同研究
- 日本
- イギリス
- アメリカ
- カナダ
- イスラエル
- ベルギー
- ポーランド
- ニュージーランド
- オーストラリア
- レバノン
- インド

ビタミンDの急性呼吸器感染（上気道炎から肺炎まで）発症予防効果
1人1人のデータを合わせたメタ解析
Effect of vitamin D supplementation on incidence of acute respiratory infection: systematic review and meta-analysis of individual patient data (AVID-ARI)

Case 2

Acute respiratory tract infections：
急性気道感染症

Case 2

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

Adrian R Martineau,[1,2] David A Jolliffe,[1] Richard L Hooper,[1] Lauren Greenberg,[1] John F Aloia,[3] Peter Bergman,[4] Gal Dubnov-Raz,[5] Susanna Esposito,[6] Davaasambuu Ganmaa,[7] Adit A Ginde,[8] Emma C Goodall,[9] Cameron C Grant,[10] Christopher J Griffiths,[1,2,11] Wim Janssens,[12] Ilkka Laaksi,[13] Semira Manaseki-Holland,[14] David Mauger,[15] David R Murdoch,[16] Rachel Neale,[17] Judy R Rees,[18] Steve Simpson,Jr[19] Iwona Stelmach,[20] Geeta Trilok Kumar,[21] Mitsuyoshi Urashima,[22] Carlos A Camargo Jr[23]

For numbered affiliations see end of article.

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Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/bmj.i6583

Accepted: 01 December 2016

ABSTRACT

OBJECTIVES

To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.

DESIGN

Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.

DATA SOURCES

Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry from inception to December 2015.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Randomised, double blind, placebo controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.

RESULTS

25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. IPD were obtained for 10 933 (96.6%) participants. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; P for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83). The body of evidence contributing to these analyses was assessed as being of high quality.

CONCLUSIONS

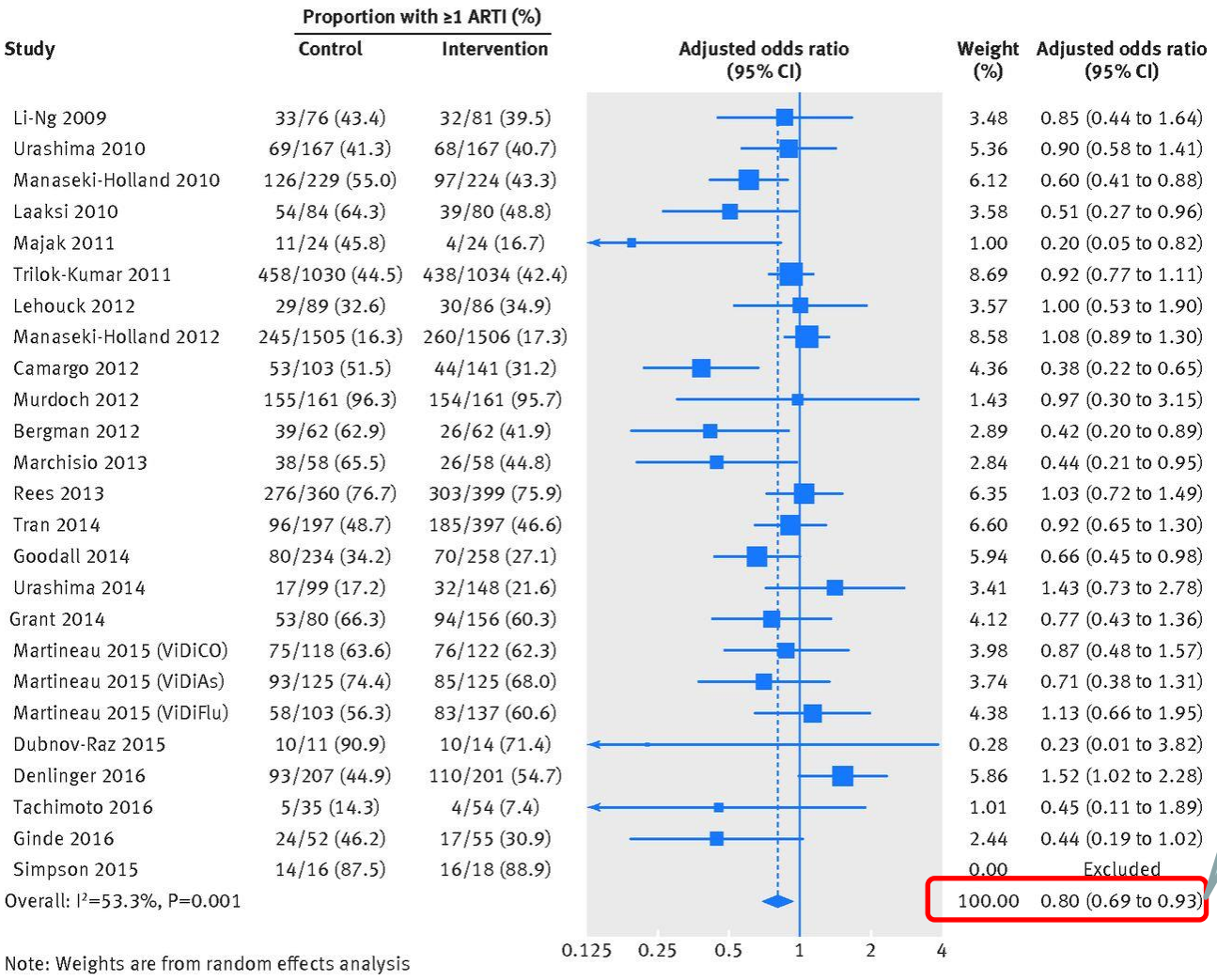
Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42014013953.

Case 2

Fig 2 Two step individual participant data meta-analysis: proportion of participants experiencing at least one acute respiratory tract infection (ARTI).



Note: Weights are from random effects analysis

ビタミンDは急性気道感染症を20%予防する。

Adrian R Martineau et al. BMJ 2017;356:bmj.i6583

Case 2

サブ･グループ解析 II

	プラセボ (%)	ビタミンD (%)	オッズ比 (95% 信頼区間)[1]	P 値	P 相互作用
投与前 25(OH)D (nmol/L)					
<25	64/107 (59.8)	40/127 (31.5)	0.30 (0.17, 0.53)	<0.001	0.006
≥25	477/729 (65.4)	516/874 (59.0)	0.75 (0.60, 0.95)	0.02	

サプリメント投与前にビタミンD不足がある人にビタミンDを投与すると、約7割、急性気道感染症を予防した。
不足が無い場合でも、25%を予防した。

Case 2

Articles

Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data

David A Jolliffe, Lauren Greenberg, Richard L Hooper, Christopher J Griffiths, Carlos A Camargo Jr, Conor P Kerley, Megan E Jensen, David Mauger, Iwona Stelmach, Mitsuyoshi Urashima, Adrian R Martineau

Case 2

	Vitamin D (N)	Vitamin D (events/participant-years [event rate])	Placebo (N)	Placebo (events/participant-years [event rate])	Adjusted incidence rate ratio (95% CI)	Weight (%)
Castro et al[11]	201	24/105·4 (0·23)	207	44/109·0 (0·40)	0·56 (0·34–0·92)	32·89
Martineau et al[12]	125	42/117·4 (0·36)	125	51/116·7 (0·44)	0·85 (0·56–1·28)	48·39
Jensen et al[15]	11	9/4·9 (1·84)	11	13/5·3 (2·47)	0·66 (0·28–1·58)	10·89
Kerley et al[16]	17	9/5·2 (1·72)	22	13/7·0 (1·86)	0·49 (0·18–1·38)	7·82
Tachimoto et al[14]	54	1/26·5 (0·04)	35	0/16·8 (0·0)	(Excluded)	0·00
Overall (I^2=0·0%, p=0·560)					**0·69 (0·52–0·92)**	**100·00**

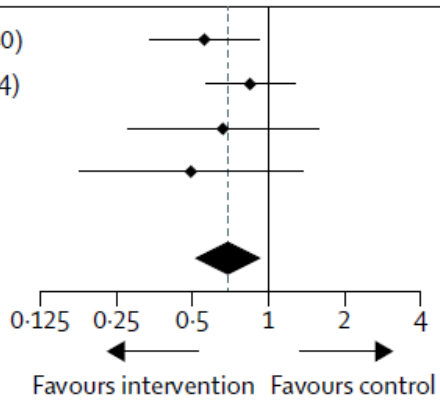


Figure 2: Two-step individual participant data meta-analysis, event rate for asthma exacerbations requiring treatment with systemic corticosteroids

Case 2

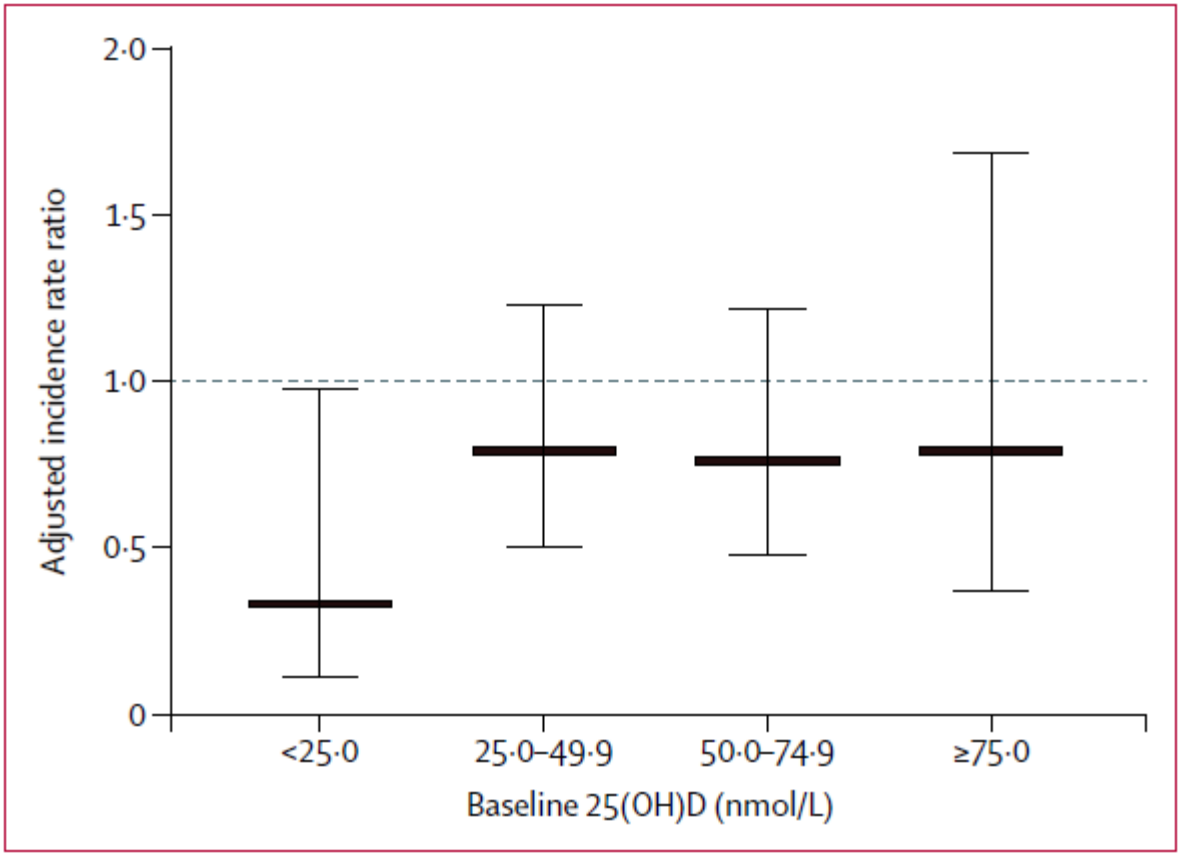


Figure 3: Effects of vitamin D supplementation on asthma exacerbation rate by baseline circulating 25(OH)D concentration categorised by 25 nmol/L strata

Case 2

Lancet Diabetes Endocrinol 2021

Published Online
March 30, 2021
https://doi.org/10.1016/
S2213-8587(21)00051-6

Articles

Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials

David A Jolliffe, Carlos A Camargo Jr, John D Sluyter, Mary Aglipay, John F Aloia, Davaasambuu Ganmaa, Peter Bergman, Heike A Bischoff-Ferrari, Arturo Borzutzky, Camilla T Damsgaard, Gal Dubnov-Raz, Susanna Esposito, Clare Gilham, Adit A Ginde, Inbal Golan-Tripto, Emma C Goodall, Cameron C Grant, Christopher J Griffiths, Anna Maria Hibbs, Wim Janssens, Anuradha Vaman Khadilkar, Ilkka Laaksi, Margaret T Lee, Mark Loeb, Jonathon L Maguire, Paweł Majak, David T Mauger, Semira Manaseki-Holland, David R Murdoch, Akio Nakashima, Rachel E Neale, Hai Pham, Christine Rake, Judy R Rees, Jenni Rosendahl, Robert Scragg, Dheeraj Shah, Yoshiki Shimizu, Steve Simpson-Yap, Geeta Trilok-Kumar, Mitsuyoshi Urashima, Adrian R Martineau

Case 2

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Baseline 25(OH)D concentration, nmol/L*						
<25·0	20	1395/1879 (74·2%)	1433/1898 (75·5%)	0·81 (0·57–1·15)	44·5%	0·017
25·0–49·9	29	3662/5022 (72·9%)	3569/4874 (73·2%)	1·04 (0·94–1·15)	0·0%	0·49
50·0–74·9	30	1929/3279 (58·8%)	1829/3004 (60·9%)	0·88 (0·76–1·02)	9·3%	0·32
≥75·0	26	1072/1742 (61·5%)	1029/1674 (61·5%)	1·00 (0·85–1·18)	0·0%	0·78

Case 2

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Dosing frequency						
Daily	19	1703/3210 (53·1%)	1672/2952 (56·6%)	0·78 (0·65–0·94)	53·5%	0·003
Weekly	6	4482/6421 (69·8%)	4447/6335 (70·2%)	0·97 (0·88–1·06)	0·0%	0·48
Once per month to once every 3 months	12	8147/13 733 (59·3%)	8098/13 515 (59·9%)	0·98 (0·93–1·03)	0·0%	0·57

Case 2

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Daily dose equivalent, IU†						
<400	2	482/1175 (41·0%)	511/1133 (45·1%)	0·65 (0·31–1·37)	86·3%	0·007
400–1000	10	656/1236 (53·1%)	627/1069 (58·7%)	0·70 (0·55–0·89)	31·2%	0·16
1001–2000	16	10 593/16 961 (62·5%)	10 674/16 898 (63·2%)	0·97 (0·93–1·02)	0·0%	0·51
>2000	7	2291/3462 (66·2%)	2250/3444 (65·3%)	1·05 (0·84–1·31)	37·1%	0·15

Case 2

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Trial duration, months						
≤12	29	1977/4887 (40·5%)	1866/4368 (42·7%)	0·82 (0·72–0·93)	38·1%	0·021
>12	8	12 355/18 477 (66·9%)	12 351/18 434 (67·0%)	0·99 (0·95–1·04)	0·0%	0·95

Case 2

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Age, years*						
<1·00	5	875/2901 (30·2%)	839/2796 (30·0%)	0·95 (0·82–1·10)	18·7%	0·30
1·00–15·99	15	4297/5994 (71·7%)	4303/5877 (73·2%)	0·71 (0·57–0·90)	46·0%	0·027
16·00–64·99	21	3137/4876 (64·3%)	3087/4727 (65·3%)	0·97 (0·93–1·09)	11·5%	0·31
≥65·00	17	6023/9665 (62·3%)	6004/9475 (63·4%)	0·96 (0·90–1·02)	0·0%	0·73

Case 2

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Airway disease						
Asthma only	4	203/404 (50·2%)	202/391 (51·7%)	0·73 (0·36–1·49)	71·7%	0·014
Chronic obstructive pulmonary disease only	2	106/208 (51·0%)	104/207 (50·2%)	1·01 (0·68–1·51)	0·0%	0·71
Unrestricted	31	14 023/22 752 (61·6%)	13 911/22 204 (62·7%)	0·92 (0·86–0·99)	33·0%	0·040

Case 3

2019 April 9th

Research

JAMA | Original Investigation

Effect of Vitamin D Supplementation on Relapse-Free Survival Among Patients With Digestive Tract Cancers

The AMATERASU Randomized Clinical Trial

Mitsuyoshi Urashima, MD; Hironori Ohdaira, MD; Taisuke Akutsu, MD; Shinya Okada, MD; Masashi Yoshida, MD; Masaki Kitajima, MD; Yutaka Suzuki, MD

https://jamanetwork.com/journals/jama/fullarticle/2730111

Case 3

JAMA Network™

QUESTION Does vitamin D supplementation improve survival among patients with digestive tract cancer?

CONCLUSION This randomized clinical trial found that vitamin D supplementation did not improve 5-year relapse-free survival in patients with digestive tract cancer.

POPULATION

276 Men
141 Women

Adults with cancers of the digestive tract from esophagus to rectum, stages I to III

Mean age: 66 years

LOCATIONS

1
University hospital in Japan

INTERVENTION

417 Patients randomized

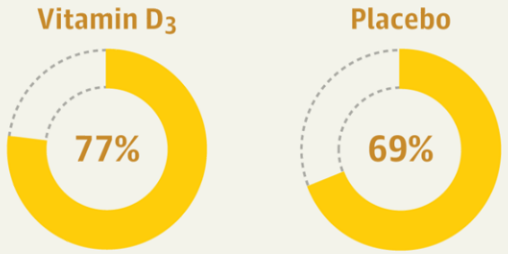
251	166
Vitamin D_3	Placebo
2000 IU/d (2 capsules per day)	(2 capsules per day)

PRIMARY OUTCOME

Relapse-free survival

FINDINGS

Relapse-free survival at 5 years



Between-group difference was not significant.

Hazard ratio: **0.76**
(95% CI, 0.50-1.14; *P* = .18)

Urashima M, Ohdaira H, Akutsu T, et al. Effect of vitamin D supplementation on relapse-free survival among patients with digestive tract cancers: the AMATERASU randomized clinical trial [published April 9, 2019]. *JAMA*. doi:10.1001/jama.2019.2210

Case 3

JAMA Network

QUESTION Does high-dose vitamin D_3 supplementation prolong progression-free survival when added to standard chemotherapy in patients with advanced or metastatic colorectal cancer?

CONCLUSION This randomized clinical trial found a potential role for high-dose vitamin D_3 supplementation in the treatment of patients with advanced or metastatic colorectal cancer that warrant further evaluation in a larger multicenter trial.

POPULATION

79 Men
60 Women

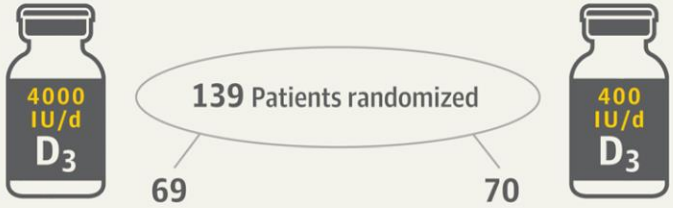
Patients with pathologically confirmed, unresectable advanced or metastatic colorectal cancer

Median age: 56 years

LOCATIONS

11 Cancer centers in the United States

INTERVENTION



High-dose vitamin D_3
Loading dose of 8000 IU/d for cycle 1 followed by 4000 IU/d for subsequent cycles

Standard-dose vitamin D_3
400 IU/d for all cycles

PRIMARY OUTCOME

Progression-free survival, defined as the time from start of protocol treatment to first documented disease progression or death

FINDINGS

Median progression-free survival

High-dose vitamin D_3
13.0 months (49 events)
(95% CI, 10.1-14.7)

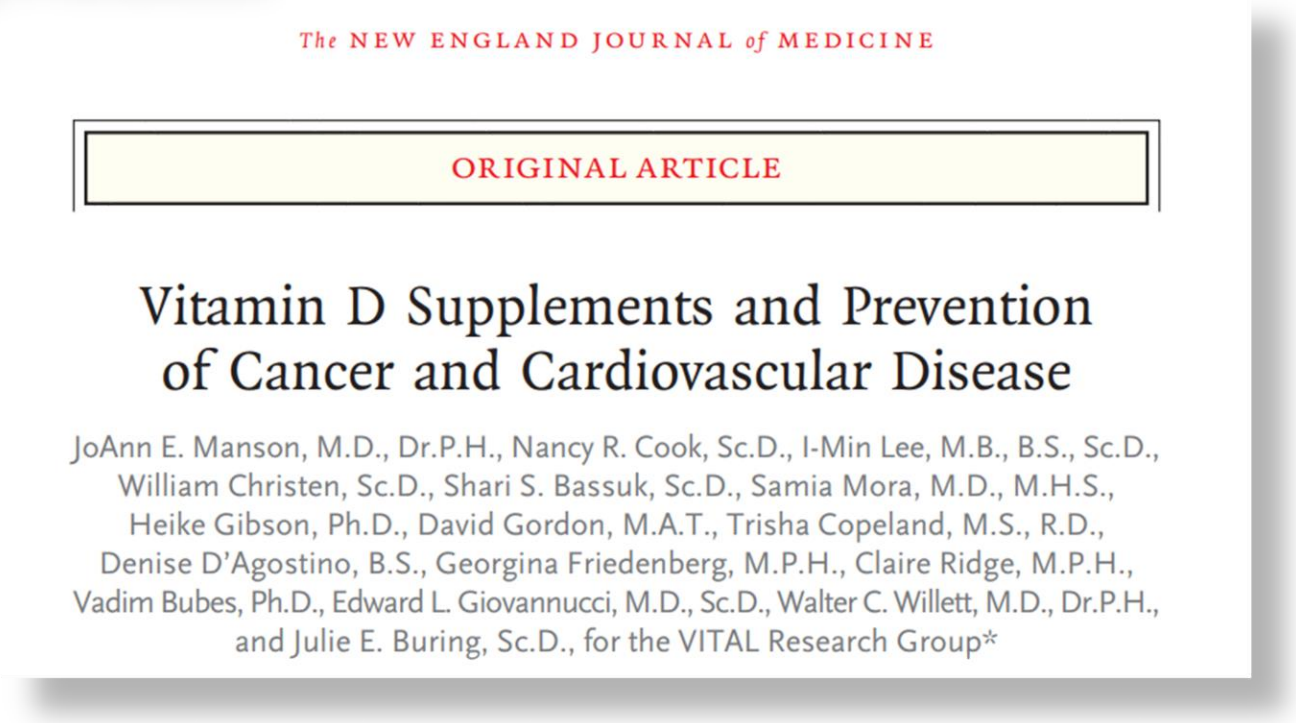
Standard-dose vitamin D_3
11.0 months (62 events)
(95% CI, 9.5-14.0)

1-sided log-rank $P = .07$

Ng K, Nimeiri HS, McCleary NJ, et al. Effect of high-dose vs standard-dose vitamin D_3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the SUNSHINE randomized clinical trial [published April 9, 2019]. *JAMA*. doi:10.1001/jama.2019.2402

Case 3

Primary Prevention



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

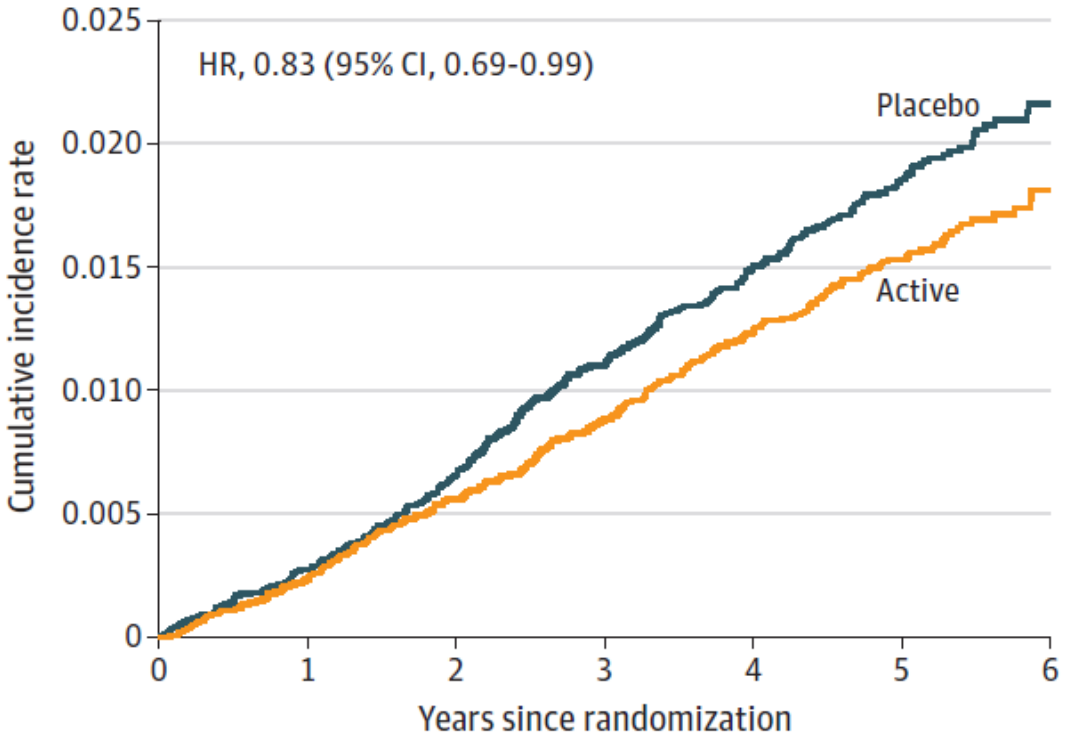
N Engl J Med. **2019 Jan 3**;380(1):33-44.

Primary Prevention

Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to Vitamin D or Placebo, in Intention-To-Treat Analyses.*

End Point	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)	Hazard Ratio (95% CI)
	no. of participants with event		
Cancer			
Primary end point: invasive cancer of any type	793	824	0.96 (0.88–1.06)
Breast cancer	124	122	1.02 (0.79–1.31)
Prostate cancer	192	219	0.88 (0.72–1.07)
Colorectal cancer	51	47	1.09 (0.73–1.62)
Death from cancer	154	187	0.83 (0.67–1.02)
Death from any cause	485	493	0.99 (0.87–1.12)
Analyses excluding the first 2 yr of follow-up			
Invasive cancer of any type	490	522	0.94 (0.83–1.06)
Death from cancer	112	149	0.75 (0.59–0.96)
Major cardiovascular event	274	296	0.93 (0.79–1.09)
Death from any cause	368	384	0.96 (0.84–1.11)

Figure 2. Vitamin D (Active) and Placebo: Cumulative Incidence Rates of Metastatic and Fatal Cancer of Any Type



No. at risk							
Active	12 927	12 738	12 543	12 341	11 992	9557	744
Placebo	12 944	12 765	12 567	12 345	11 985	9543	746

Case 3

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

2019 Feb

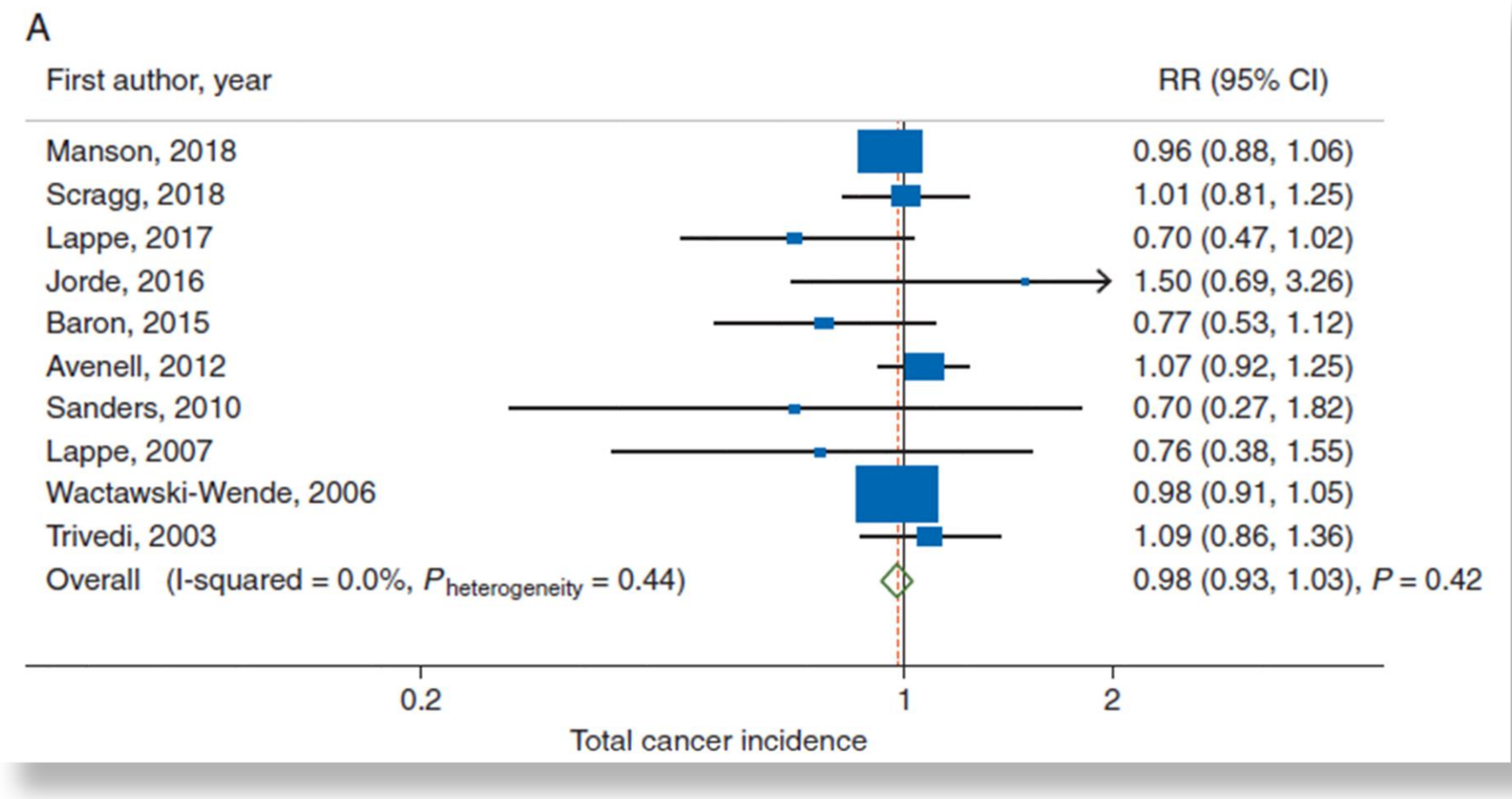
Annals of Oncology 30: 733–743, 2019
doi:10.1093/annonc/mdz059
Published online 22 February 2019

REVIEW

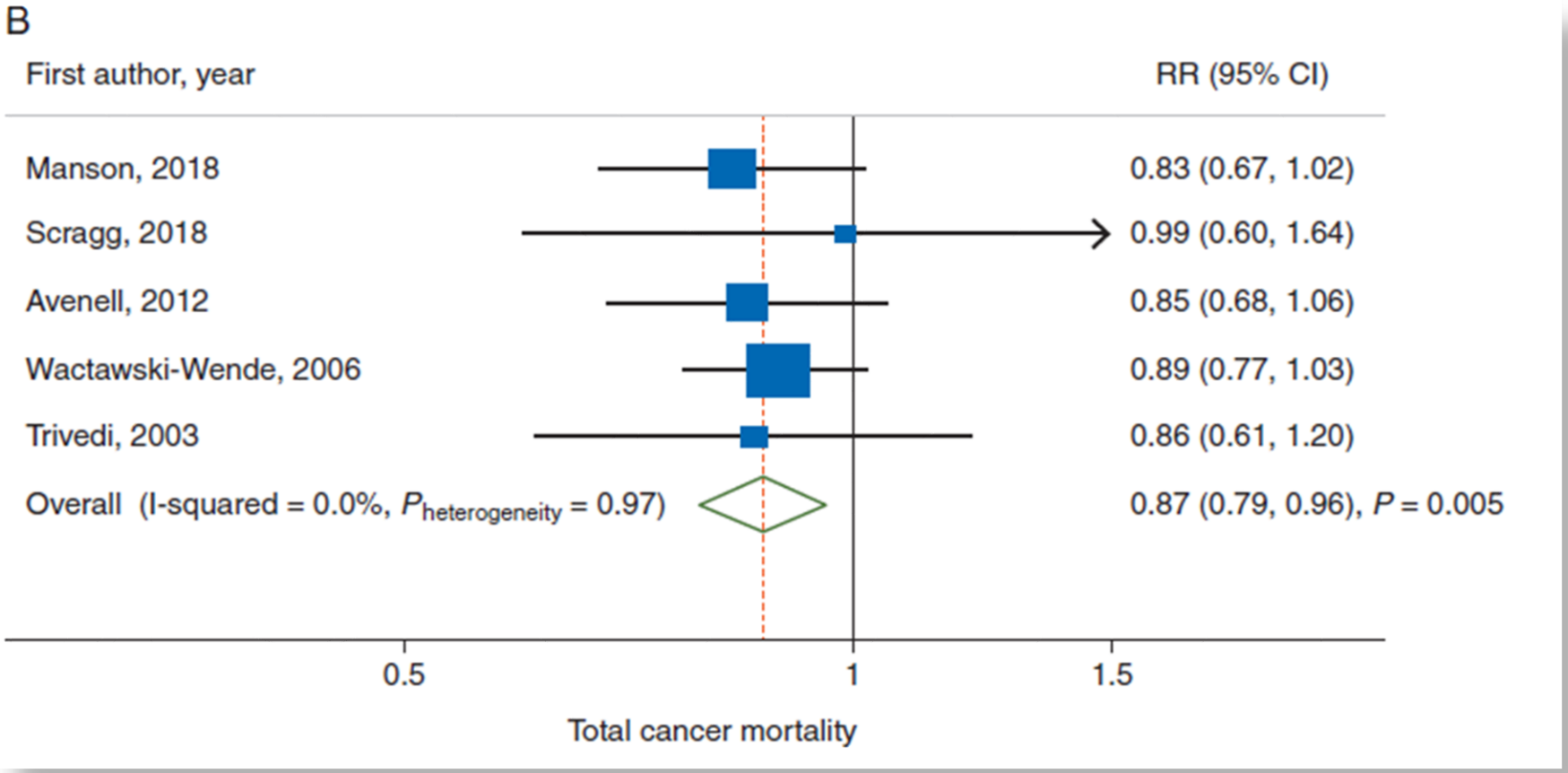
Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials

N. Keum[1,2*], D. H. Lee[1], D. C. Greenwood[3], J. E. Manson[4,5] & E. Giovannucci[1,4,5*]

Case 3


A
First author, year
RR (95% CI)
Manson, 2018
0.96 (0.88, 1.06)
Scragg, 2018
1.01 (0.81, 1.25)
Lappe, 2017
0.70 (0.47, 1.02)
Jorde, 2016
1.50 (0.69, 3.26)
Baron, 2015
0.77 (0.53, 1.12)
Avenell, 2012
1.07 (0.92, 1.25)
Sanders, 2010
0.70 (0.27, 1.82)
Lappe, 2007
0.76 (0.38, 1.55)
Wactawski-Wende, 2006
0.98 (0.91, 1.05)
Trivedi, 2003
1.09 (0.86, 1.36)
Overall (I-squared = 0.0%, $P_{heterogeneity}$ = 0.44)
0.98 (0.93, 1.03), P = 0.42
0.2
1
2
Total cancer incidence

Case 3


B
First author, year
RR (95% CI)
Manson, 2018
0.83 (0.67, 1.02)
Scragg, 2018
0.99 (0.60, 1.64)
Avenell, 2012
0.85 (0.68, 1.06)
Wactawski-Wende, 2006
0.89 (0.77, 1.03)
Trivedi, 2003
0.86 (0.61, 1.20)
Overall (I-squared = 0.0%, $P_{heterogeneity}$ = 0.97)
0.87 (0.79, 0.96), P = 0.005
0.5
1
1.5
Total cancer mortality

Case 3

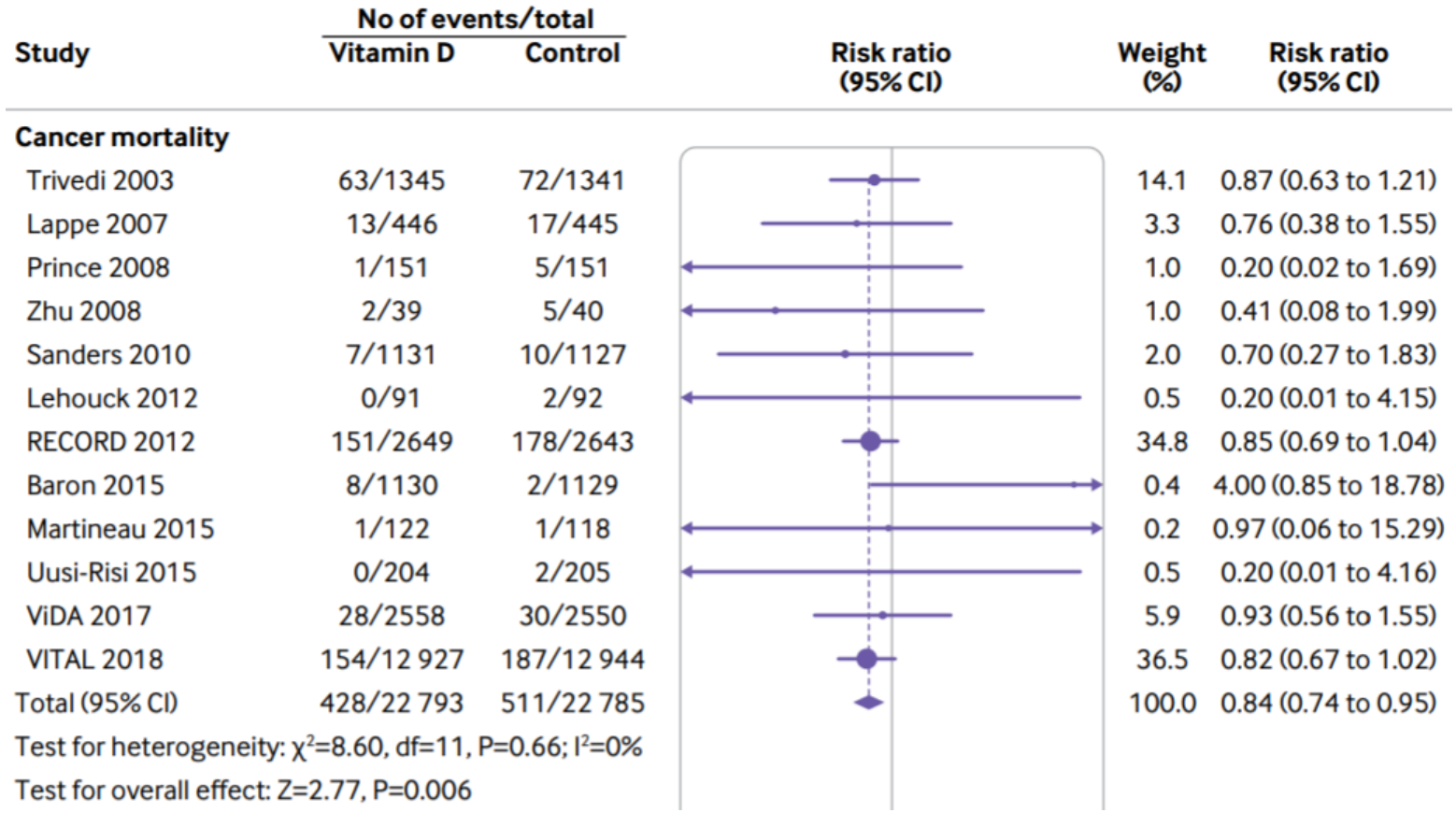
thebmj 2019 July

RESEARCH

Association between vitamin D supplementation and mortality: systematic review and meta-analysis

Yu Zhang,[1] Fang Fang,[2] Jingjing Tang,[3] Lu Jia,[4] Yuning Feng,[1] Ping Xu,[5] Andrew Faramand[6]

Case 3



Study	No of events/total: Vitamin D	No of events/total: Control	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Cancer mortality					
Trivedi 2003	63/1345	72/1341		14.1	0.87 (0.63 to 1.21)
Lappe 2007	13/446	17/445		3.3	0.76 (0.38 to 1.55)
Prince 2008	1/151	5/151		1.0	0.20 (0.02 to 1.69)
Zhu 2008	2/39	5/40		1.0	0.41 (0.08 to 1.99)
Sanders 2010	7/1131	10/1127		2.0	0.70 (0.27 to 1.83)
Lehouck 2012	0/91	2/92		0.5	0.20 (0.01 to 4.15)
RECORD 2012	151/2649	178/2643		34.8	0.85 (0.69 to 1.04)
Baron 2015	8/1130	2/1129		0.4	4.00 (0.85 to 18.78)
Martineau 2015	1/122	1/118		0.2	0.97 (0.06 to 15.29)
Uusi-Risi 2015	0/204	2/205		0.5	0.20 (0.01 to 4.16)
ViDA 2017	28/2558	30/2550		5.9	0.93 (0.56 to 1.55)
VITAL 2018	154/12 927	187/12 944		36.5	0.82 (0.67 to 1.02)
Total (95% CI)	428/22 793	511/22 785		100.0	0.84 (0.74 to 0.95)
Test for heterogeneity: χ^2=8.60, df=11, P=0.66; I^2=0%					
Test for overall effect: Z=2.77, P=0.006					

Case 3

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

Epidemiology

The effect of vitamin D supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials

Peter G. Vaughan-Shaw[1,2], Louis F. Buijs[1,2], James P. Blackmur[1,2], Evi Theodoratou[2,3], Lina Zgaga[4], Farhat V. N. Din[1,2], Susan M. Farrington[1,2] and Malcolm G. Dunlop[1,2]

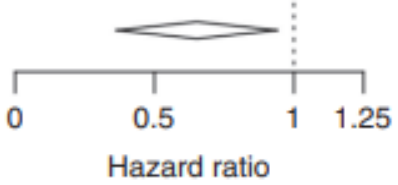
British Journal of Cancer (2020) 123:1705–1712;
https://doi.org/10.1038/s41416-020-01060-8

Case 3

a

Progression-free survival (in CRC patient trials)

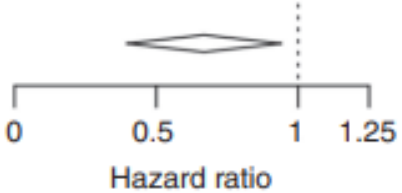
Study	*N*	Deaths	Weight	HR [95% CI]
SUNSHINE	139	111	76%	0.64 [0.00, 0.90]
AMATERASU	201	NA	24%	0.69 [0.39, 1.24]
Subtotal	340			0.65 [0.36, 0.94]



b

Progression-free survival (in all trials reporting PFS)

Study	*N*	Deaths	Weight	HR [95% CI]
VITAL	98	25	12%	0.79 [0.36, 1.75]
SUNSHINE	139	111	67%	0.64 [0.00, 0.90]
AMATERASU	201	NA	22%	0.69 [0.39, 1.24]
Subtotal	438			0.67 [0.40, 0.94]



Challenge & Change

Tokyo Marathon
2017.2.26
4 hr 27 min