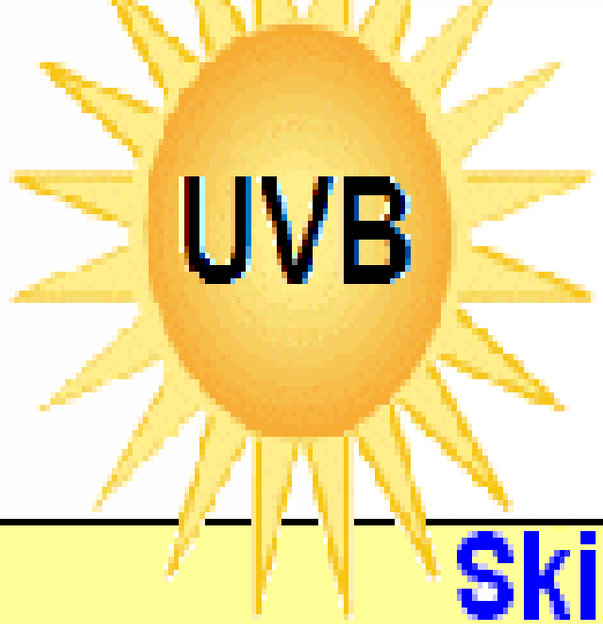
Έλλειψη βιταμίνης D, η νέα επιδημία;
Διαχωρίζοντας τα δεδομένα από την τάση για καθολική θεραπεία

Καλλιόπη Κώτσα

Επικ. Καθηγήτρια Ενδοκρινολογίας-Διαβητολογίας ΑΠΘ



80%

Skin

7-Dehydrocholesterol → Pre Vitamin D3

Diet:

20%

Vitamin D2

Vitamin D3

Vitamin D

25 Hydroxylase

CYP3A4

Liver

- Sunlight: UV B —270-290 nm

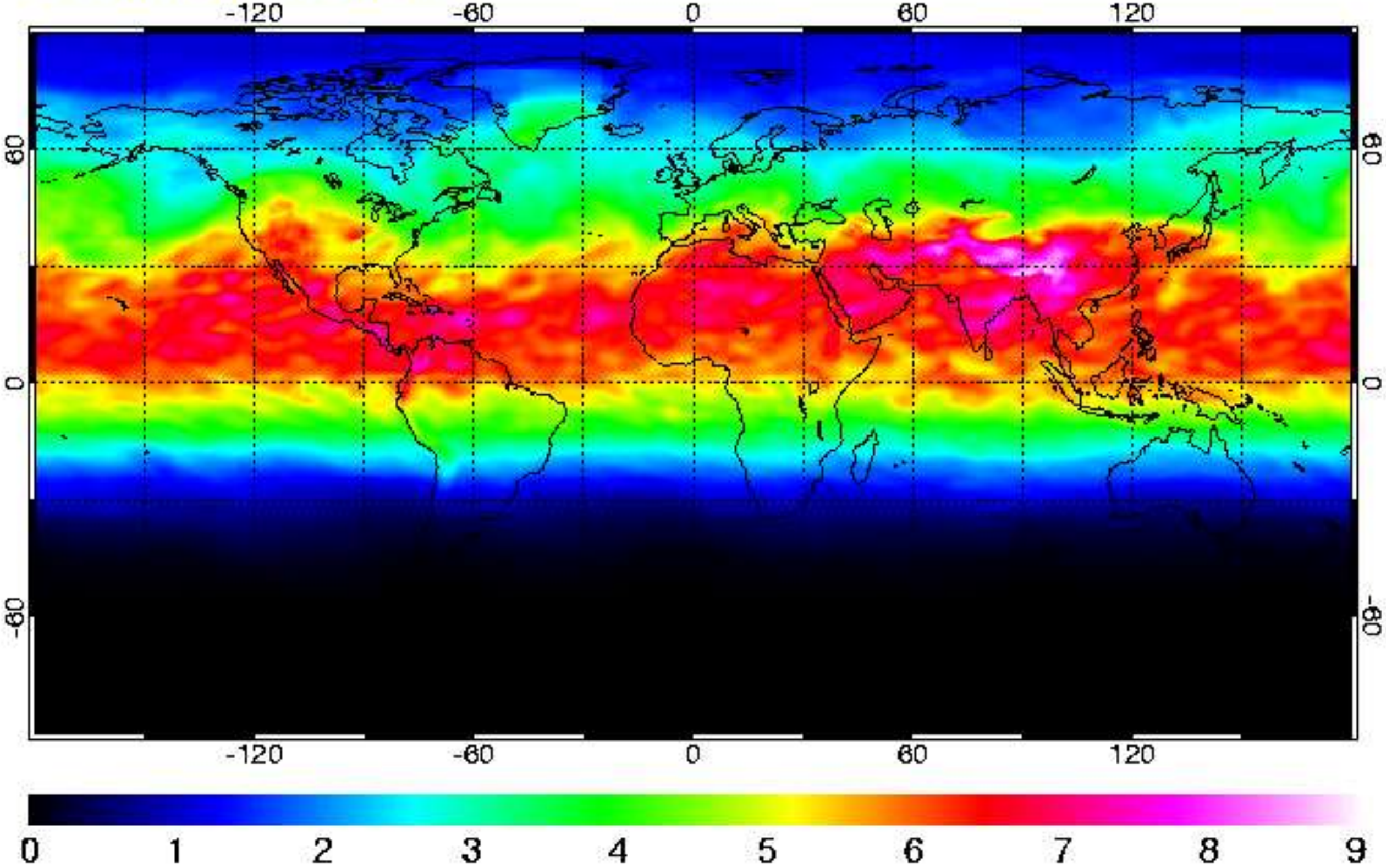
10 minutes of summer sun over the weekend without sunblock makes ~10,000 IU of Vitamin D

25 Hydroxyvitamin D

Vitamin-D UV dose (kJ/m2)

SCIAMACHY - KNMI/ESA

Clear-sky
21 June 2007

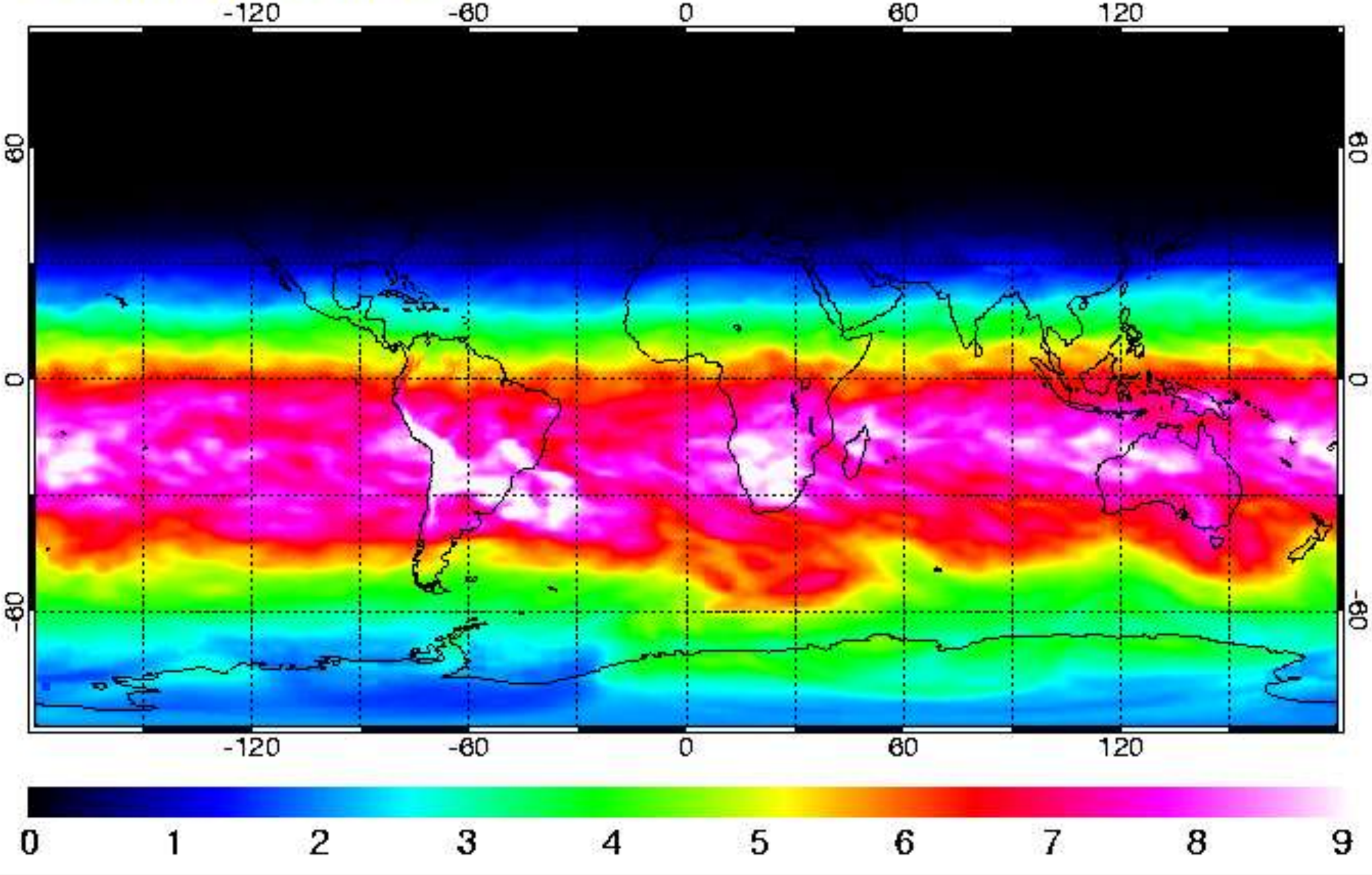


Vitamin-D UV dose (kJ/m2)

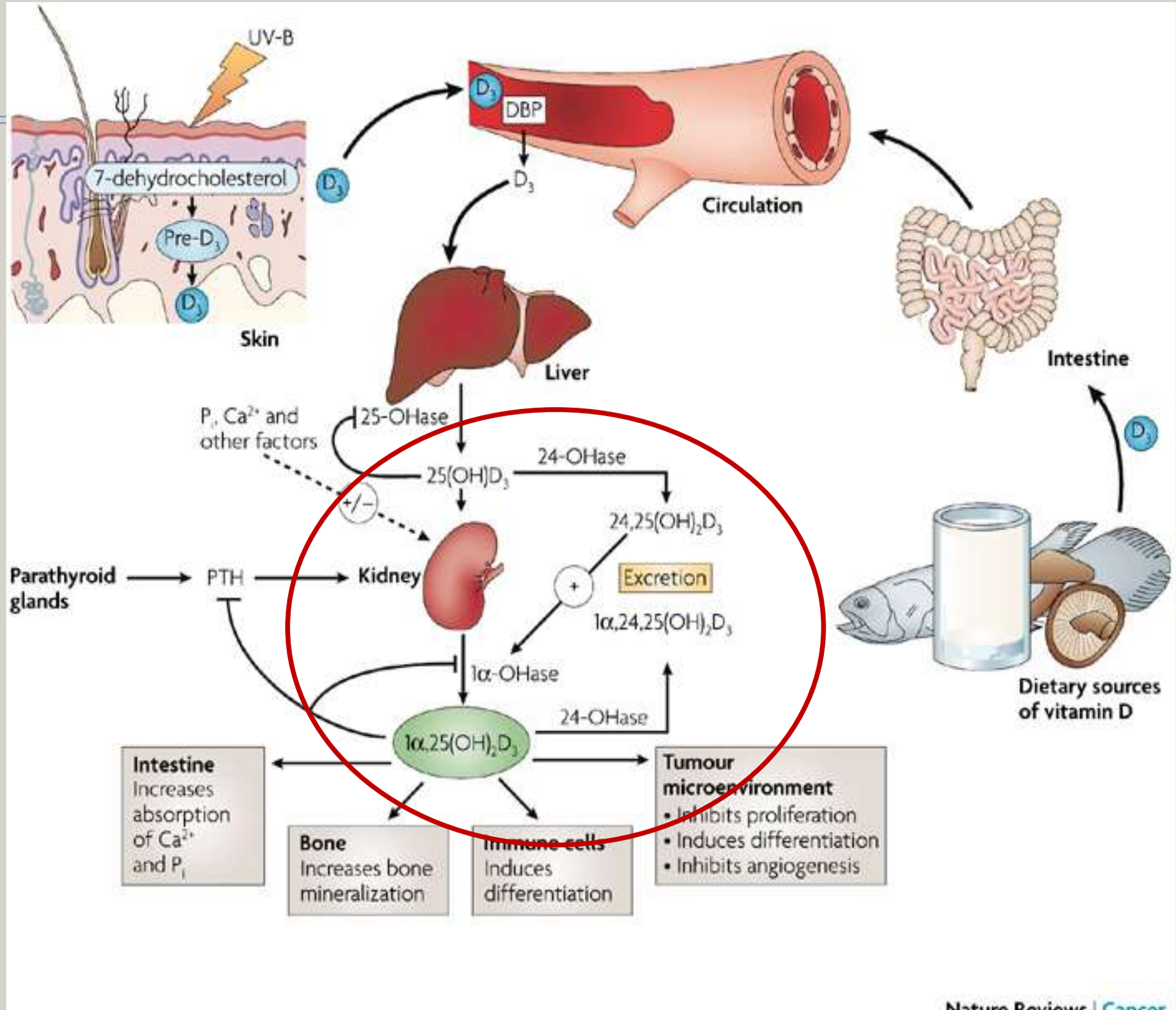
Clear-sky

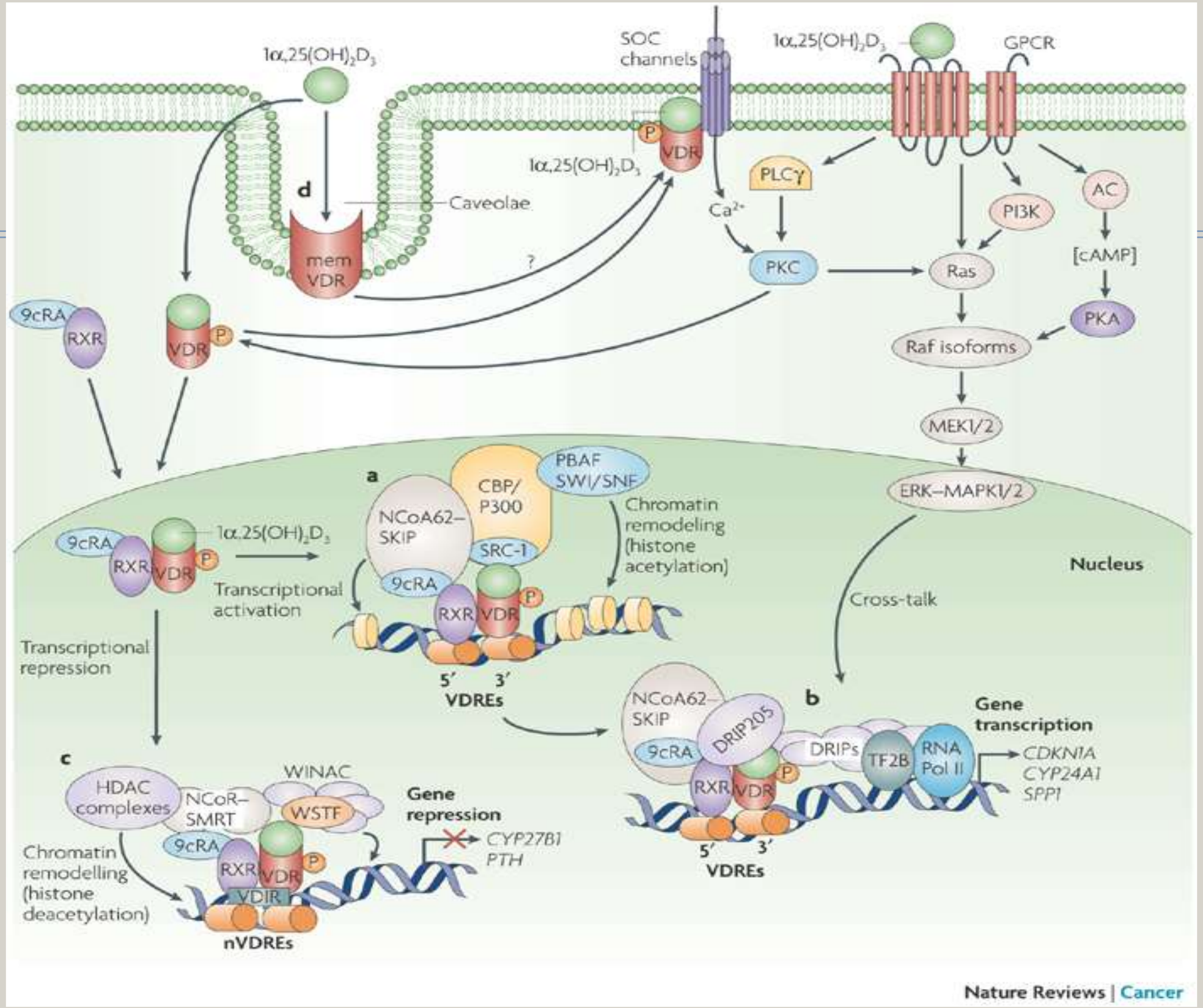
SCIAMACHY - KNMI/ESA

21 December 2006

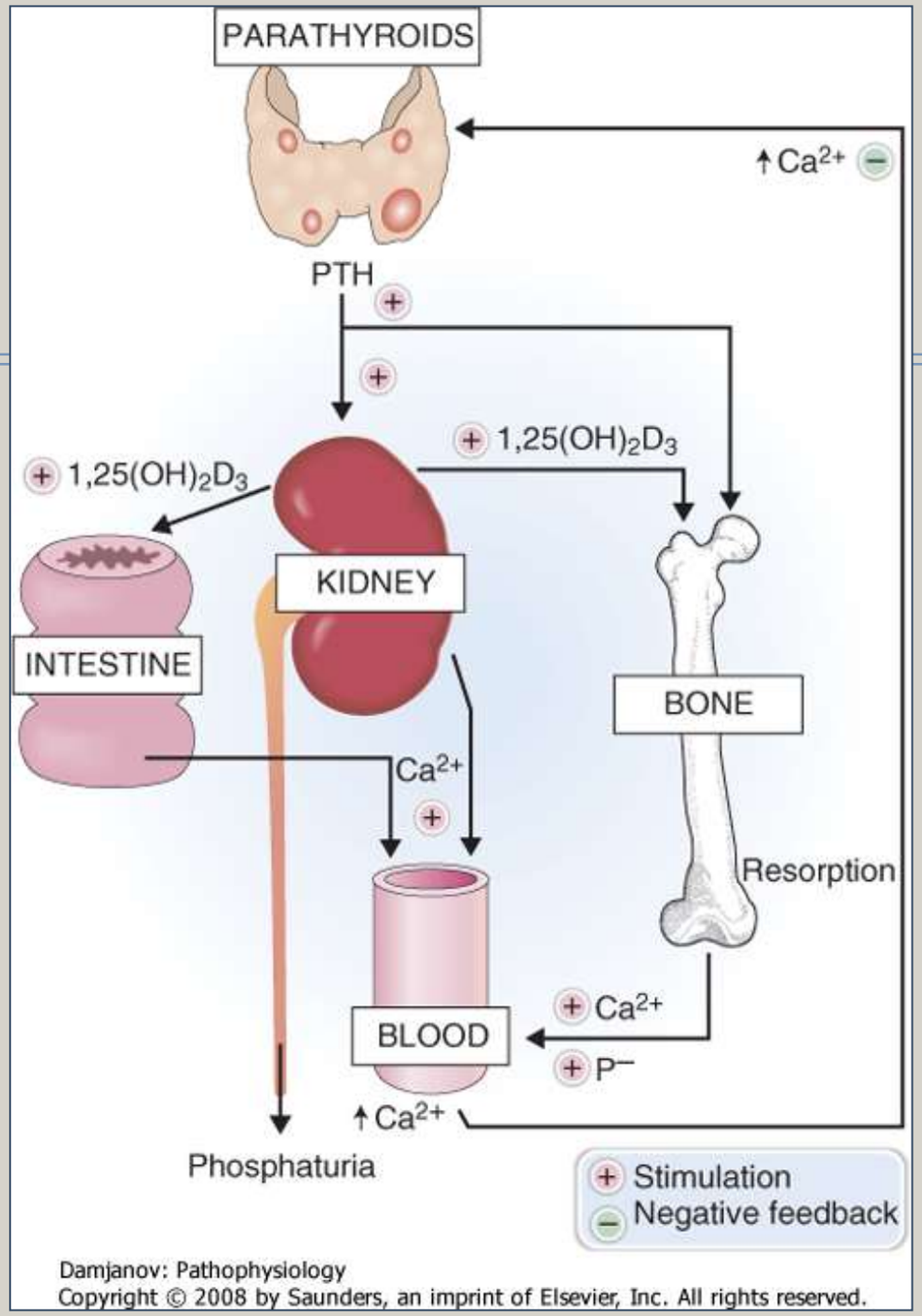


ΠΑΡΑΓΩΓΗ, ΜΕΤΑΒΟΛΙΣΜΟΣ, ΒΙΟΛΟΓΙΚΕΣ ΔΡΑΣΕΙΣ





Nature Reviews | Cancer



The role of parathyroid hormone and vitamin D in the metabolism of calcium. 1,25(OH)2D3, 1,25 dihydroxyvitamin D3; P-, phosphate; PTH, parathyroid hormone. (Modified from Boon NA, Colledge NR, Walker BR, Hunter JAA [eds]: Davidson's Principles & Practice of Medicine, 20th ed. Edinburgh, Churchill Livingstone, 2006, p. 772.)

New Emerging Serum Vitamin D Norms

Vitamin D status	(ng/dL)	(nmol/L)
Deficient (high risk)	<20	<50
Insufficient (moderate risk)	20-29	50-72
Adequate (low risk)	30 or higher	73 or higher

Serum vitamin D test results (25-Hydroxyvitamin D) are shown in these two units.

ΚΑΤΑΝΟΜΗ ΤΩΝ VDR ΣΤΟΥΣ ΙΣΤΟΥΣ

Ανοσολογικό σύστημα
- Τ και Β κύτταρα
- μακροφάγα
- ουδετερόφιλα

Καρδιαγγειακό
- ενδοθήλιο
- λείες μυϊκές ίνες
- μυοκάρδιο

Ενδοκρινικό
- παραθυρεοειδείς
- β κύτταρα παγκρέατος
- θυρεοειδής

Άλλα συστήματα
- εξωκρινικό
- νευρολογικό
- αναπαραγωγικό

Κατανομή των VDR στους ιστούς

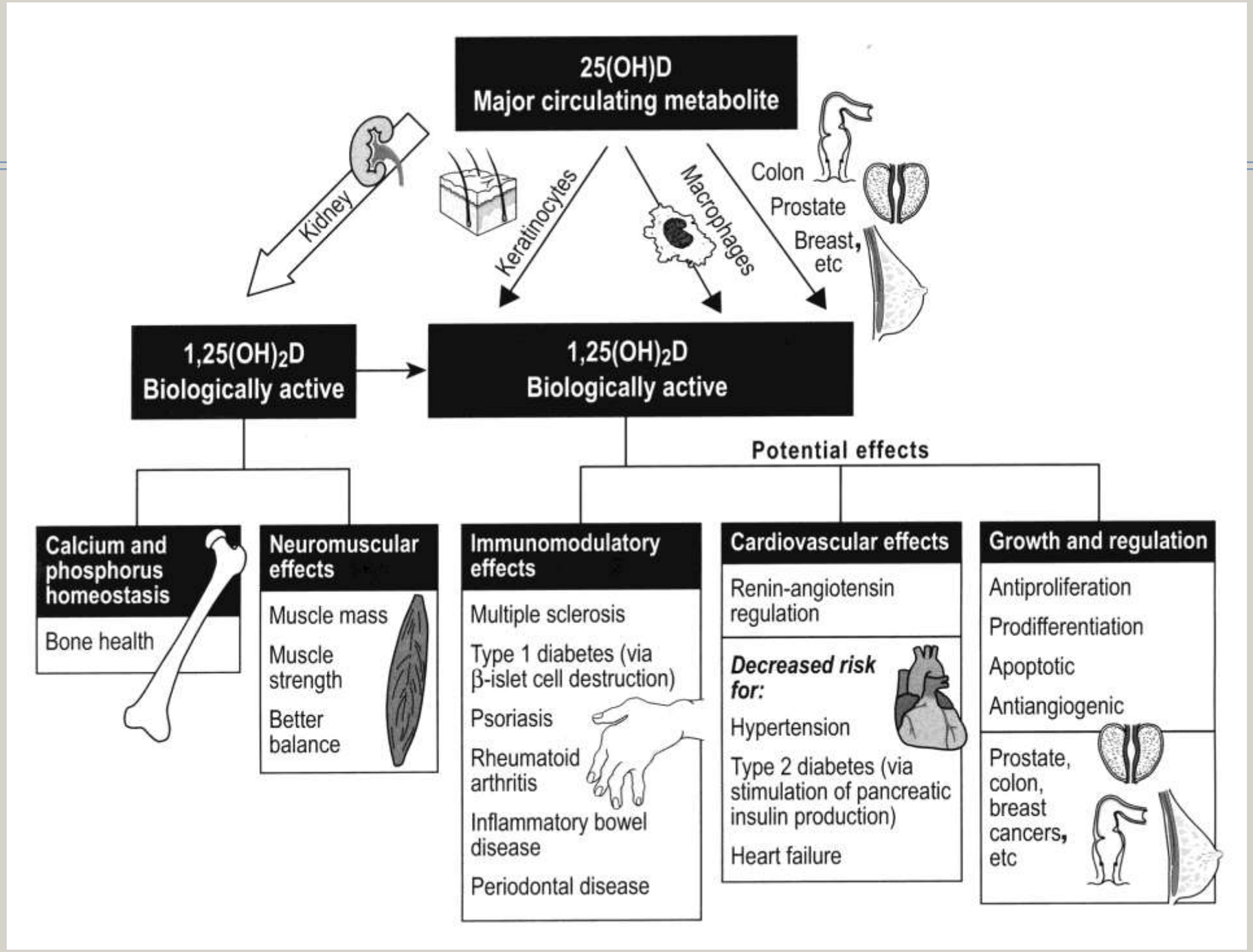
Άλλα συστήματα
- επιδερμίδα
- ήπαρ
- γαστρεντερικό
- αναπνευστικό

Νεφρός
- ποδοκύτταρα
- μεσαγγειακά κύτταρα
- σπειραματικά κύτταρα

Μυοσκελετικό
- οστεοβλάστες
- οστεοκύτταρα
- κύτταρα χόνδρων
- γραμμωτοί μύες

Συνδετικός ιστός
- ινοβλάστες
- διάμεσα κύτταρα

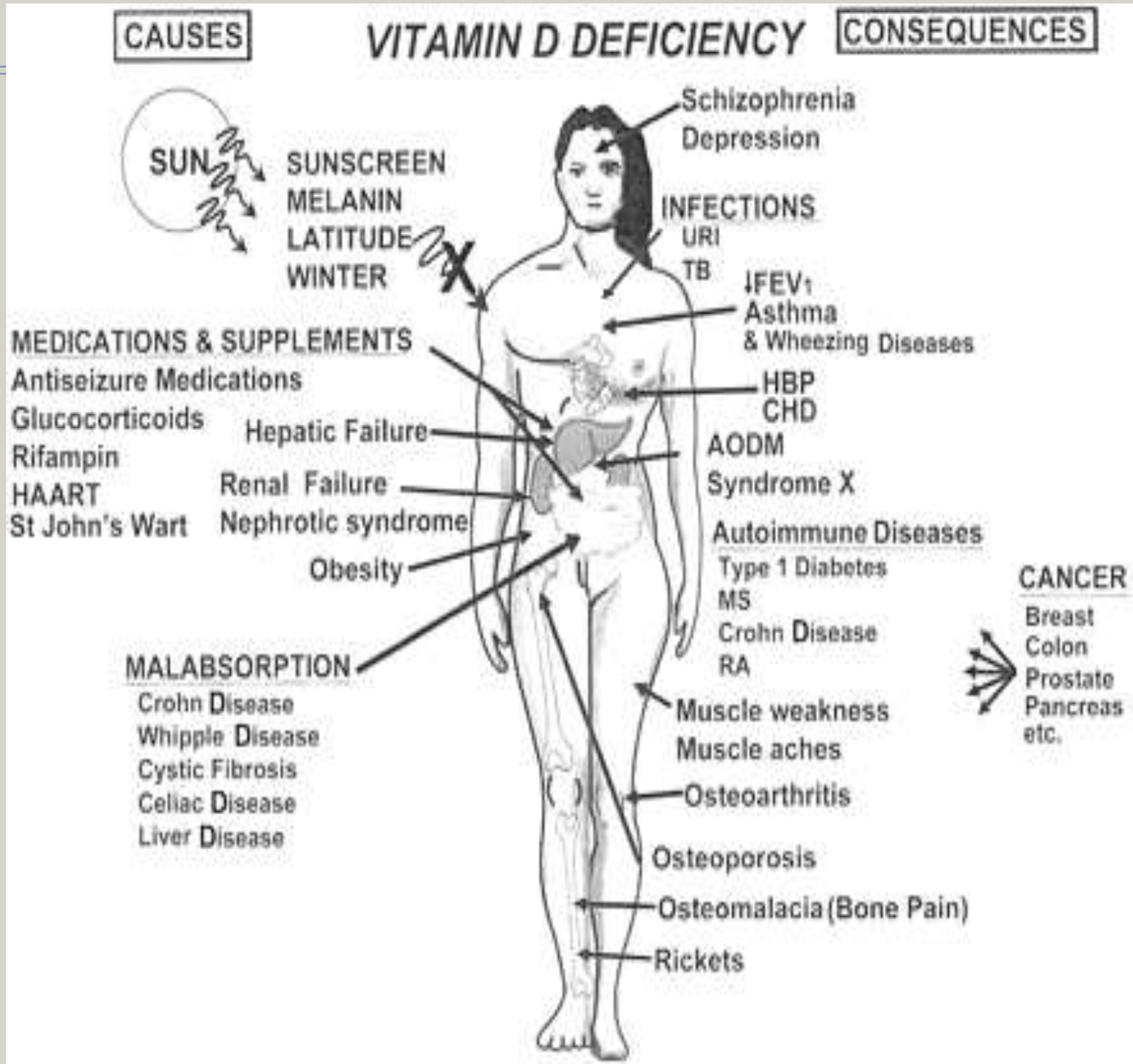
ΕΝΔΟΚΡΙΝΙΚΕΣ ΚΑΙ ΠΑΡΑΚΡΙΝΙΚΕΣ ΔΡΑΣΕΙΣ ΤΗΣ 1,25-dihydroxyvitamin D (1,25[OH]2D)



Holick M F Mayo Clin Proc. 2006;81:353-373

MAYO CLINIC
Mayo Clinic Proceedings

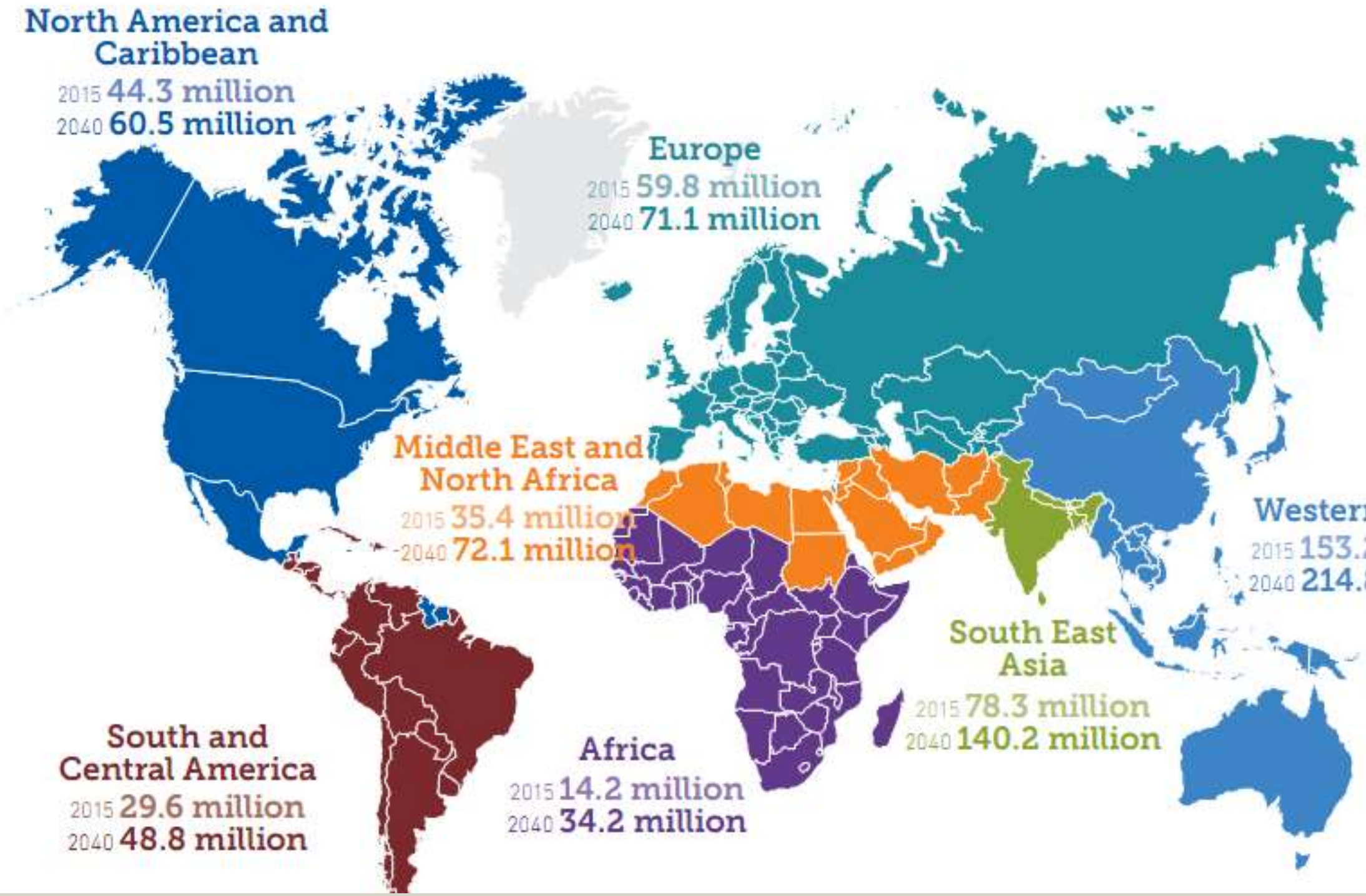
Ανεπάρκεια βιταμίνης D



Diabetes: A global emergency

International Diabetes Federation

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



Diabetes around the world

International Diabetes Federation

The prevalence of diabetes

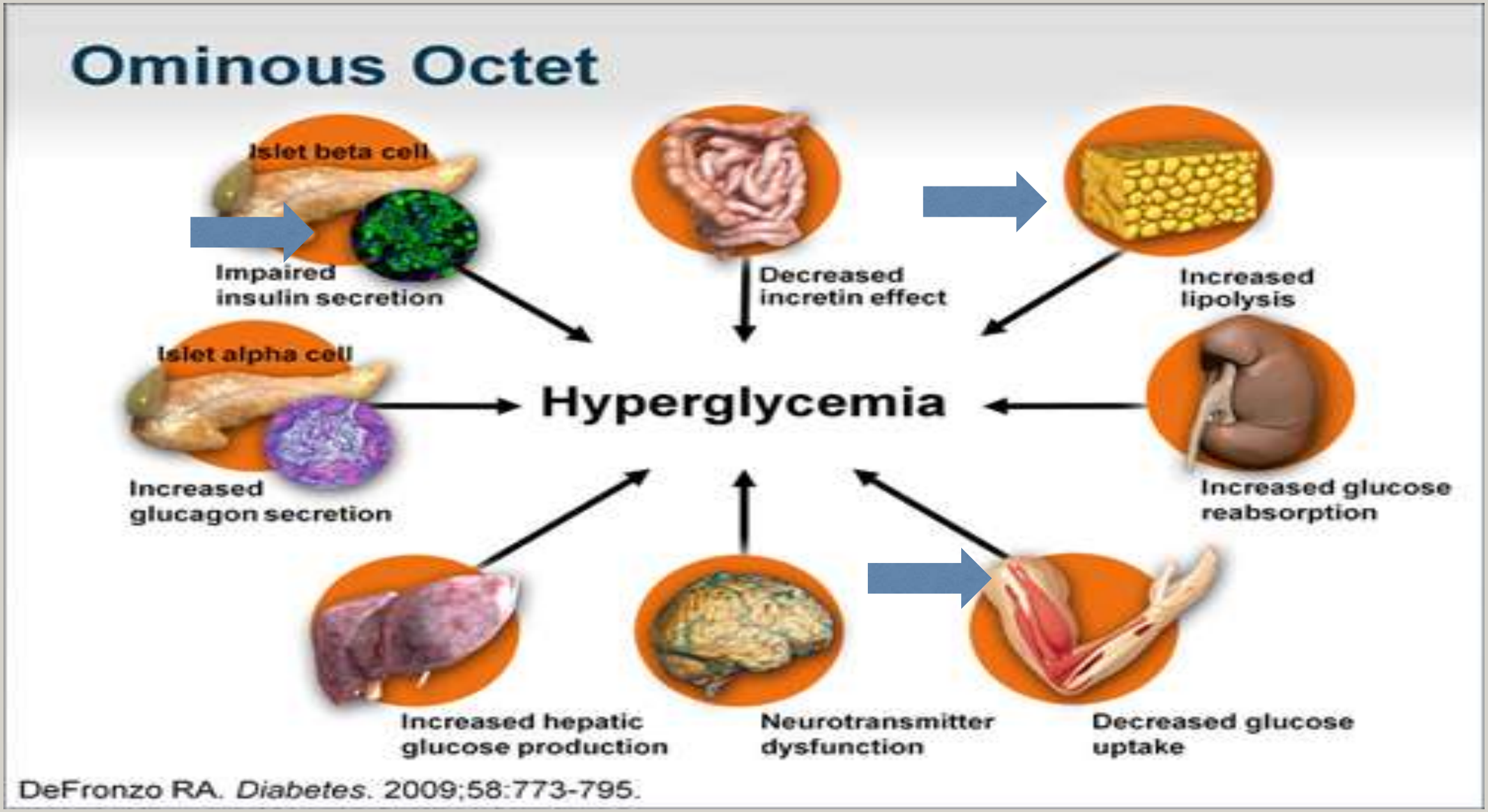
2015

One in **11 adults** has diabetes

2040

One in **10 adults** will have diabetes

Type 2 DM: pathogenesis



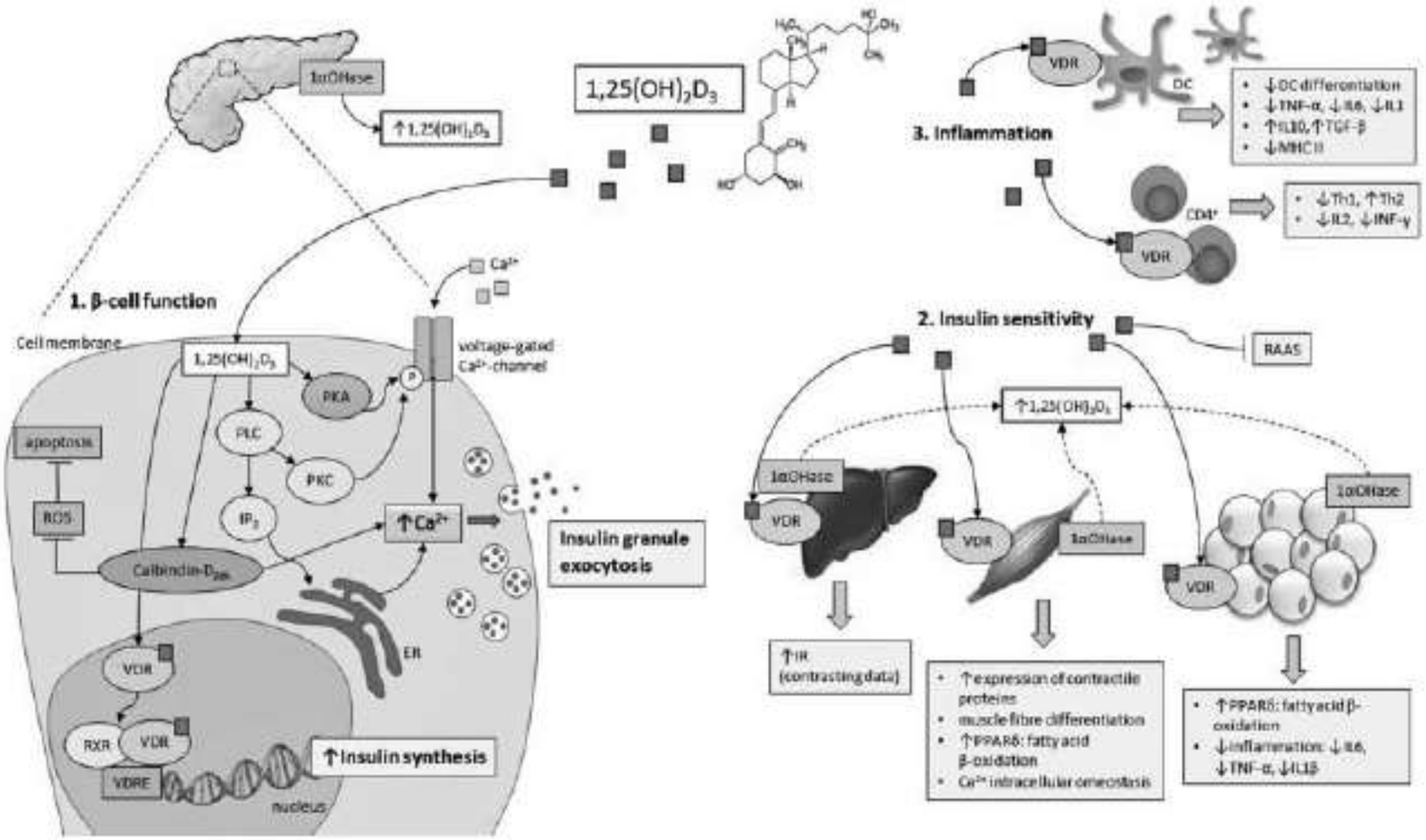


Figure 1. Potential mechanisms by which vitamin D may influence T2DM. Vitamin D could influence T2DM through several pathways distinguished into three major mechanisms: (1) Stimulates insulin secretion by its interaction with VDRE localized in the promoter region of insulin gene, or stimulates indirectly the secretion of insulin granules through the regulation of intracellular calcium concentration. (2) Stimulates insulin sensitivity through the regulation of IRs expression in target cells and the activation of PPAR-δ in skeletal muscle and adipose tissues, which is involved in fatty acid metabolism. Therefore $25(OH_2)D_3$ regulates the correct function of skeletal muscle and reduces inflammation and changes adipokine secretion in adipose tissue. Indirectly, $25(OH_2)D_3$ inhibits the RAAS, with an improvement of insulin resistance. (3) Regulates systemic inflammation through an inhibition of dentritic cells differentiation and proinflammatory cytokines, such as TNFα, IL6, IL1, IL2, and IFNγ. Thus results in a indirect shift in T cells polarization from T helper (Th) 1to Th2 and in a reduction of macrophage infiltration. Abbreviation: 1αOHase: 1-α-hidroxylase; Ca^{2+}: calcium; DC: Dentritic Cell; ER: Endoplasmatic Reticulum; IP_3: inositol 1,4,5-trisphosphate; IR: insulin receptor; PKA: Protein kinase A; PKC: Protein Kinase C; PPAR-δ: peroxisome proliferator-activated receptor gamma; RAAS: Renin-Angiotensin-Aldosteron system; ROS: reactive oxygen species; RXR: Retinoid X Receptor; Th: T helper limphocite; VDR: Vitamin D Receptor; VDRE: vitamin D responsive element.

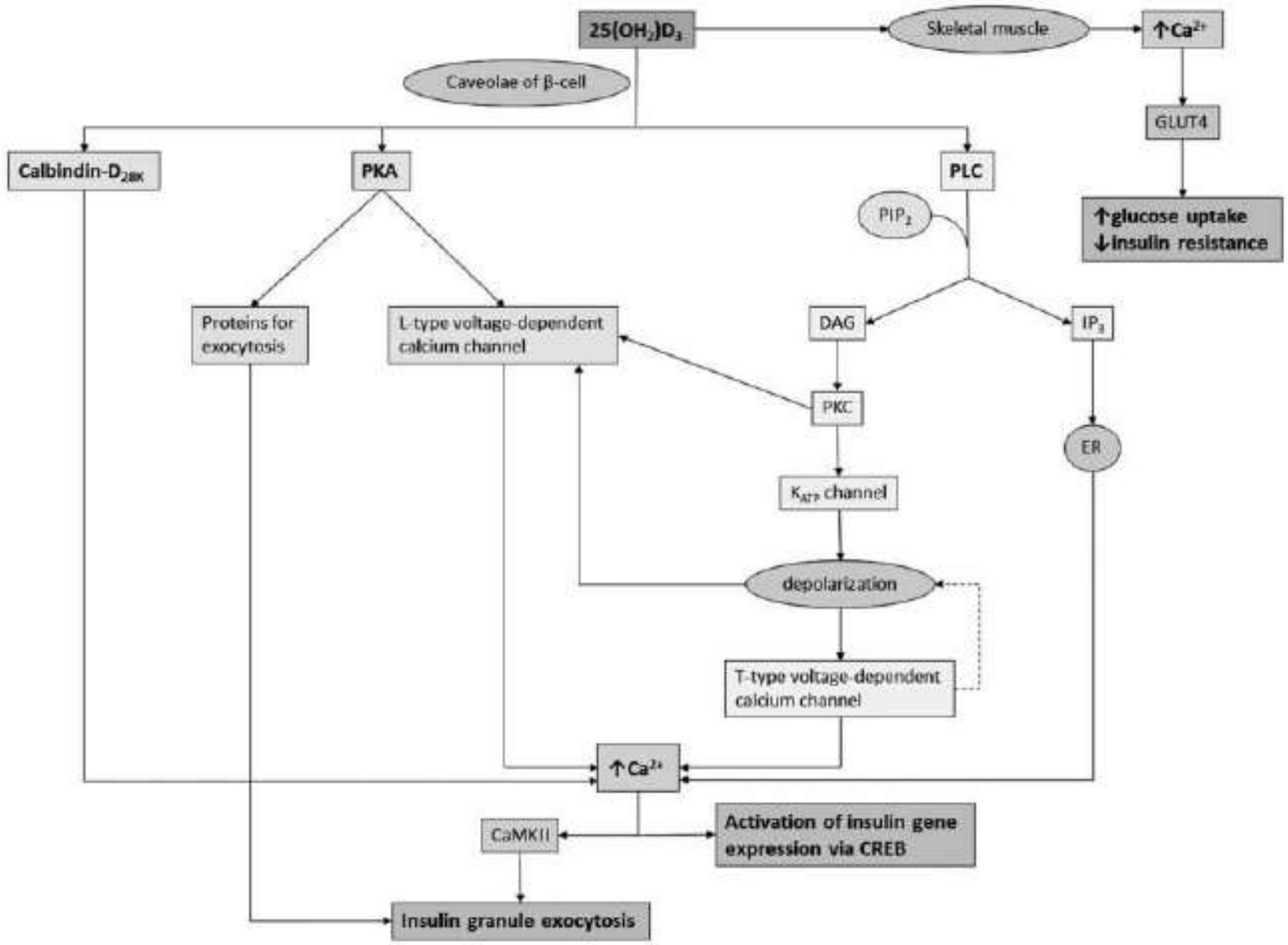
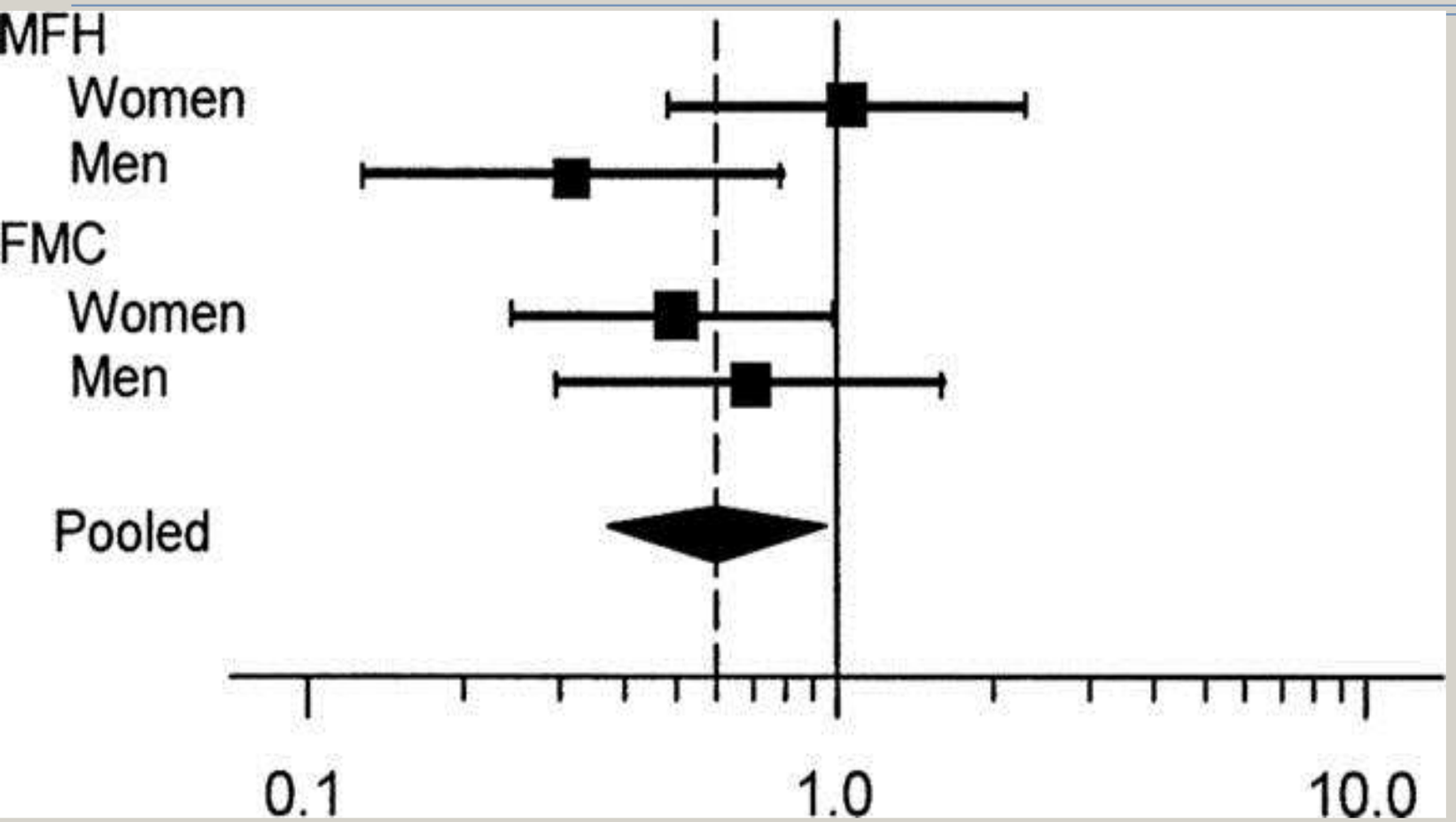


Figure 2. Metabolic pathway of calcium and vitamin D on glucose metabolism. $25(OH_2)D_3$may modulates the increase of intracellular calcium level by the activation of two different signaling pathways mediated by two different protein kinase: PKA and PKC. The PKA mediates the phosphorylation of different proteins, including the L-type voltage-dependent calcium channels and proteins necessary for the exocytotic mechanism. $1,25(OH)_2D_3$ activates the PLC, which cleaves PIP_2 into IP_3, involved in calcium release from the endoplasmic reticulum, and DAG that mediates the activation of the PKC. The PKC phosphorylates the K_{ATP} channels and the L-type voltage-dependent calcium channels causing the depolarization of the cytoplasmatic membrane and the opening of the T-type voltage-dependent. These events increases intracellular calcium. The PKC also mobilizes the secretory vesicles. The increase of intracellular calcium concentration lead to the activation of CaMKII, a protein localized at the insulin secretory granules, which promotes the phosphorylation of several proteins involved in the mobilization of insulin granules resulting in exocytosis. Therefore, the increased of intracellular calcium level activates also the insulin gene expression via CREB. Furthermore, $1,25(OH)_2D_3$ also regulates the expression of calbindin-D_{28k}, a cytosolic calcium-binding protein, which stimulates insulin secretion by regulating intracellular calcium diffusion. Finally, the increased calcium level in muscle cells enhanced the recruitment of GLUT4 to the cell membrane, resulting in a decrease of insulin resistance. Abbreviation: 1αOHase: 1-α-hidroxylase; Ca^{2+}: calcium; CaMKII: calcium-calmodulin-dependent protein kinase II; CREB: Calcium Responsive Element Binding protein; DAG: diacylglycerol; ER: Endoplasmatic Reticulum; GLUT4: Glucose transporter type 4 IP_3: inositol 1,4,5-trisphosphate; K_{ATP} channels: ATP-sensitive potassium channel; PIP_2: phosphoinositides; PKA: Protein Kinase A; PKC: Protein Kinase C (PKC); PLC: phospholipase C.

Σημαντικά κλινικά ερωτήματα

- Προδιαθέτει η έλλειψη βιταμίνης D σε ΣΔ;
- Η αναπλήρωση με βιταμίνη D προλαμβάνει το ΣΔ;
- Η χορήγηση βιταμίνης D βελτιώνει το γλυκαιμικό έλεγχο;

Serum Vitamin D and Subsequent Occurrence of Type 2 Diabetes



Two nested case-control studies, collected by the Finnish Mobile Clinic in 1973–1980. During a follow-up period of 22 years, 412 incident type 2 diabetes cases occurred, and 986 controls were selected by individual matching.

Men had higher serum vitamin D concentrations than women and showed a reduced risk of type 2 diabetes in their highest vitamin D quartile. The relative odds between the highest and lowest quartiles was 0.28 (95% confidence interval = 0.10-0.81) in men and 1.14 (0.60-2.17) in women after adjustment for smoking, body mass index, physical activity, and education. Men in the highest quartile of serum vitamin D had an 82% lower risk compared with those in the lowest quartile after adjustment for body mass index, physical activity, smoking, and education.

Knekt: Epidemiology, Volume 19(5).September 2008.666-671

Epidemiology/Health Services Research
BRIEF REPORT

Plasma 25-Hydroxyvitamin D Concentration and Risk of Incident Type 2 Diabetes in Women

ANASTASSIOS G. PITTAS, MS, MD[1,2]
QI SUN, MD, SCD[3]
JOANN E. MANSON, MD, DRPH[3,4]
BESS DAWSON-HUGHES, MD[1,5]
FRANK B. HU, MD, PHD[3]

date of blood draw. After excluding women with unavailable information on 25-OHD, the final analytical sample consisted of 608 case and 569 control sub-

	1 (lowest)	2	3	4 (highest)	*P* for trend*
Plasma 25-OHD concentration (ng/ml) [median (range)]†	14.4 (6.7–17.8)	20.8 (17.9–23.1)	25.9 (23.2–28.9)	33.4 (29.1–87.6)	
n (case/control subjects)	201/140	193/145	139/144	75/140	
OR (95% CI)					
Crude‡	1.00 (reference)	0.91 (0.67–1.24)	0.65 (0.47–0.90)	0.35 (0.25–0.51)	<0.001
Multivariate model§	1.00 (reference)	1.02 (0.71–1.47)	0.79 (0.54–1.16)	0.40 (0.26–0.62)	<0.001
Multivariate model plus BMI	1.00 (reference)	1.09 (0.74–1.61)	0.95 (0.63–1.45)	0.52 (0.33–0.83)	0.008

*Statistical tests for trend were conducted using the median value of each quartile of plasma 25-OHD concentration as a continuous variable. †To convert 25-OHD concentration from ng/ml to nmol/l multiplied by 2.459. ‡Adjusted for matching variables (age, race, fasting status, month of blood draw, and laboratory batch for plasma 25-OHD). §Adjusted for everything in ‡ plus latitude (residence in southern states [<40°N; California, Florida, and Texas] or northern states [≥40°N; Connecticut, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, and Pennsylvania]), history of hypercholesterolemia (yes or no), history of hypertension (yes or no), family history of diabetes (yes or no), smoking status (never, past, or currently smoking), physical activity (METs/week, in quartiles), alcohol consumption (grams/day, in quartiles), multivitamin use (yes or no), and dietary variables in quartiles (caffeine [mg/day], *trans* fat [g/day], cereal fiber [g/day], heme iron [mg/day], magnesium [mg/day], fish [servings/day], and calcium intake [mg/day]).

Nested case-control study conducted among 608 women with newly diagnosed type 2 diabetes and 559 control subjects in the Nurses' Health Study,

Association between baseline plasma 25-OHD concentration and risk of incident diabetes.

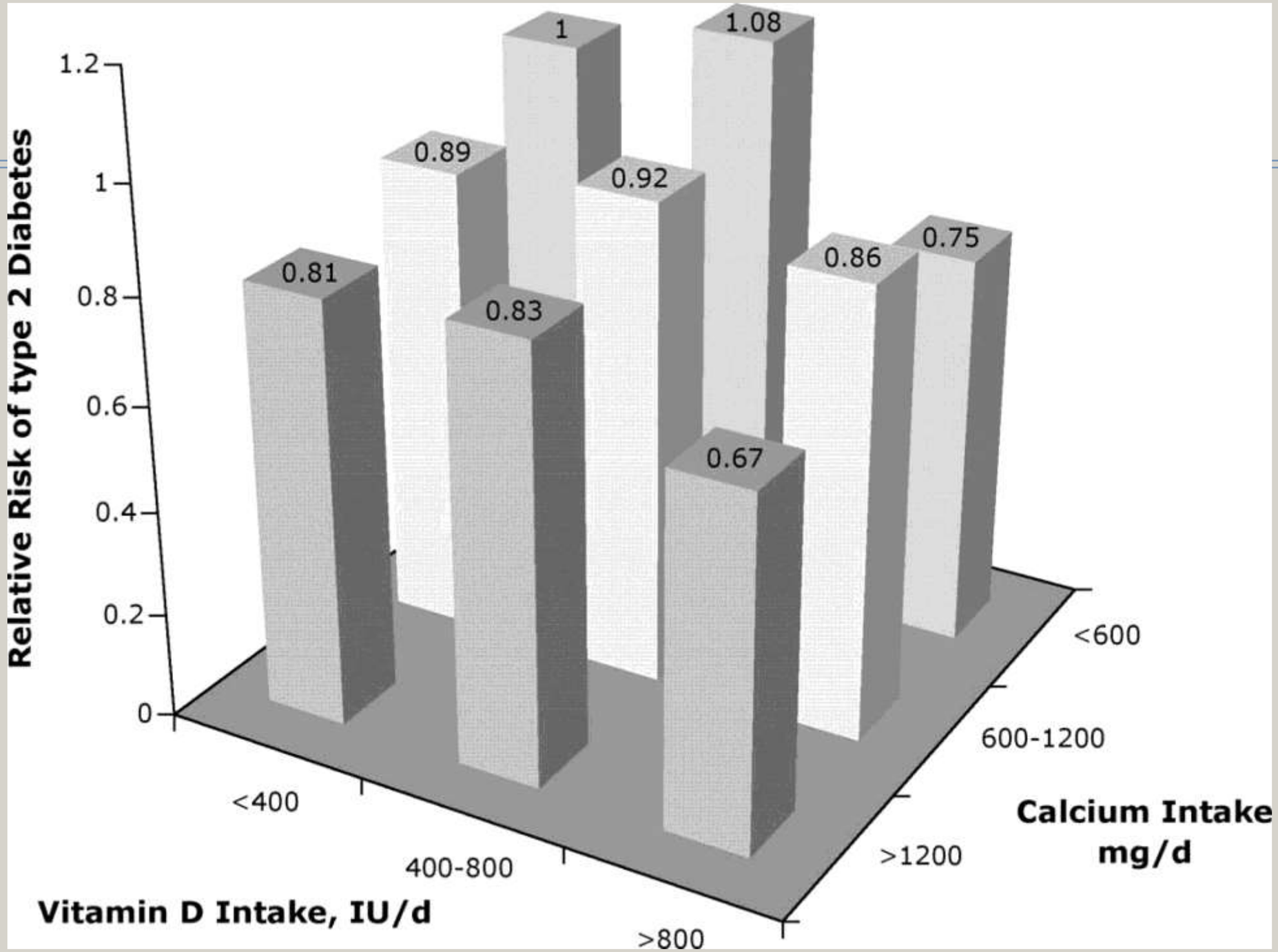
Higher levels of plasma 25-OHD were associated with a lower risk for type 2 diabetes.

The odds ratio for incident type 2 diabetes in the top (median 25-OHD, 33.4 ng/ml) versus the bottom (median 25-OHD, 14.4 ng/ml) quartile was 0.52 (95% CI 0.33–0.83).

The associations were consistent across subgroups of baseline BMI, age, and calcium intake.

Pittas AG et al, Diabetes Care, 33(9) 2010

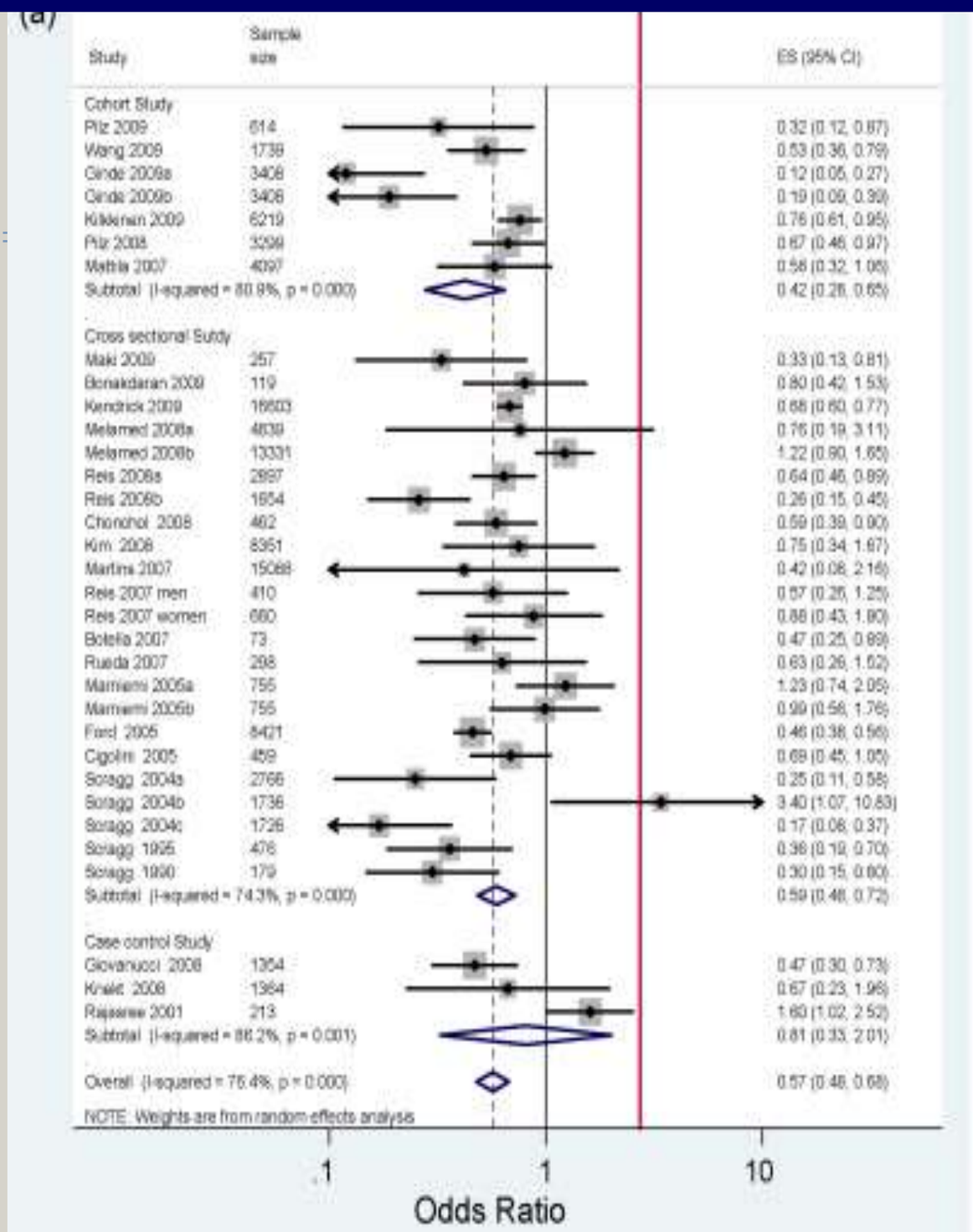
Adjusted relative risk of incident type 2 DM in the Nurses Health Study by calcium and vitamin D intake (52)

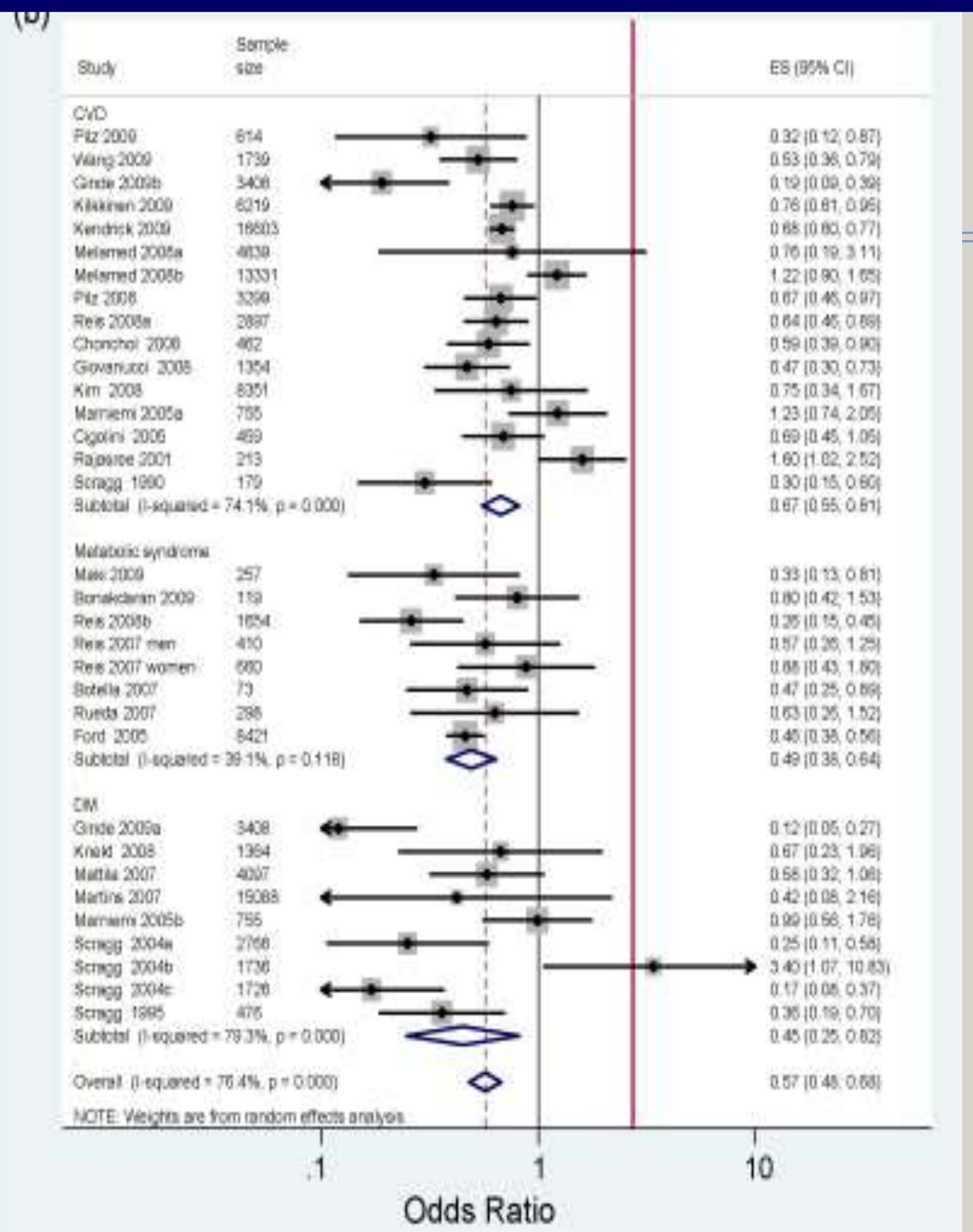


Pittas, A. G. et al. J Clin Endocrinol Metab 2007;92:2017-2029

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis





Parker J et al, Maturitas, 2009

Factors Contributing to Low Vitamin D Levels in Diabetes

Dietary intake	Limited intake of foods high in vitamin D
Sun Exposure	Lack of outdoor physical activity due to possible fatigue, obesity, and or mobility issues
Obesity[a]	More vitamin D is *stored* in the fatty tissues and less is biologically active in the serum
Renal Insufficiency	Less biologically active vitamin D since conversion to the active form occurs in the kidneys
Genetic variations	Polymorphisms of vitamin D binding protein Polymorphisms of CYP2R1 gene (which is necessary to catalyze the formation of the main circulating vitamin D metabolite)

[a]Obesity is associated with inflammation, but low levels of vitamin D are also associated with inflammation. Cytokines and other inflammatory agents have been linked to beta cell damage which then impairs insulin synthesis and secretion.

Penckofer et al. 2008

Σημαντικά κλινικά ερωτήματα

Η αναπλήρωση με βιταμίνη D προλαμβάνει το ΣΔ;

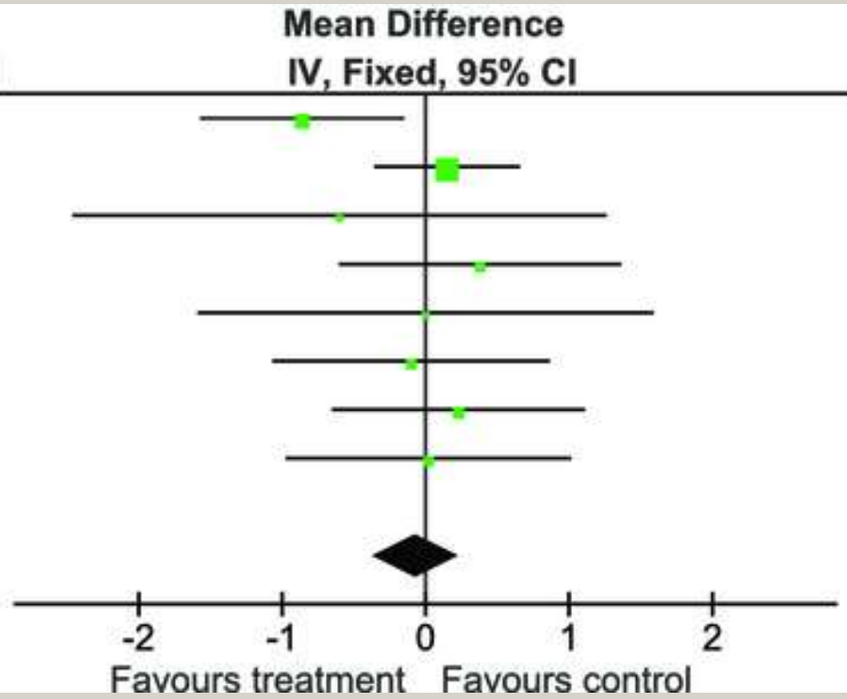
Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis

Mean difference (95% CI) in the change of homeostatic model assessment of insulin resistance for vitamin D supplementation and control

	Treatment			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pittas 2007	0.05	1.27	45	0.91	2.13	47	18.0%	-0.86 [-1.57, -0.15]
De Boer 2008	0.17	2.37	189	0.02	2.7	195	35.5%	0.15 [-0.36, 0.66]
Jorde 2010	-0.5	1.8	34	0.1	5	31	2.6%	-0.60 [-2.46, 1.26]
Harris 2012	0.32	2.36	43	-0.06	2.37	46	9.5%	0.38 [-0.60, 1.36]
Iraj 2012	0.5	2.19	20	0.5	2.89	20	3.6%	0.00 [-1.59, 1.59]
Davidson 2013	0.1	2.19	56	0.2	2.89	53	9.8%	-0.10 [-1.07, 0.87]
Oosterwerff 2014	0.23	2.19	65	0	2.89	65	11.8%	0.23 [-0.65, 1.11]
Dutta 2014	-0.74	2.19	55	-0.76	2.89	49	9.2%	0.02 [-0.97, 1.01]
Total (95% CI)			**507**			**506**	**100.0%**	**-0.06 [-0.36, 0.24]**

Heterogeneity: $Chi^2 = 7.04$, df = 7 (P = 0.43); $I^2 = 1\%$

Test for overall effect: Z = 0.40 (P = 0.69)

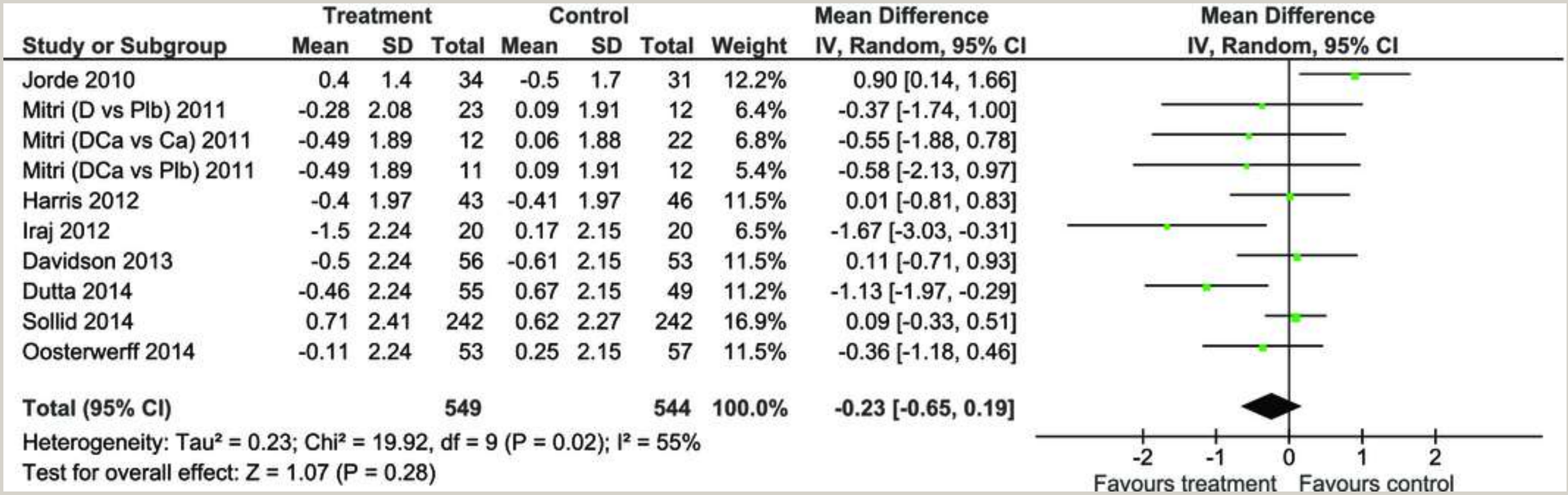


A total of 10 randomized controlled trials were included. Vitamin D did not significantly improve homeostatic model assessment of insulin resistance

Diabetic Medicine
Volume 33, Issue 3, pages 290-299, 6 OCT 2015 DOI: 10.1111/dme.12893
http://onlinelibrary.wiley.com/doi/10.1111/dme.12893/full#dme12893-fig-0002

Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis

Mean difference (95% CI) in the change of 2-h oral glucose tolerance test plasma glucose (mmol/l) for vitamin D supplementation and control.



Eight studies, with 1093 subjects (549 subjects in vitamin D and 544 subjects in control groups), contributed data on the effect of vitamin D supplementation on 2-h plasma glucose after OGTT. Again, vitamin D supplementation failed to show a significant effect on 2-h plasma glucose after OGTT

Diabetic Medicine
Volume 33, Issue 3, pages 290-299, 6 OCT 2015 DOI: 10.1111/dme.12893
http://onlinelibrary.wiley.com/doi/10.1111/dme.12893/full#dme12893-fig-0003

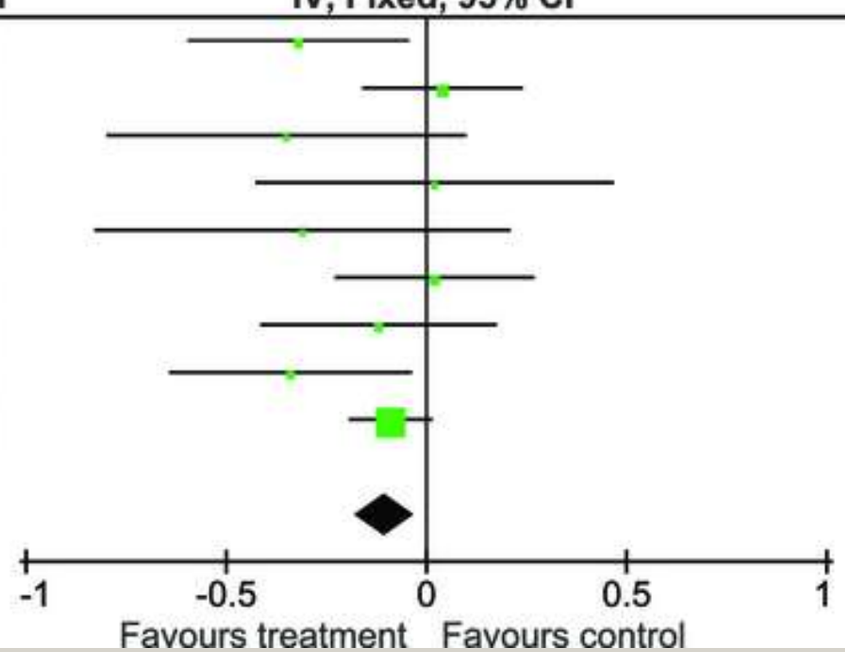
Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis

Mean difference (95% CI) in the change in fasting plasma glucose (mmol/l) for vitamin D supplementation and control.

	Treatment			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Pittas 2007	0.02	0.6	45	0.34	0.75	47	7.2%	-0.32 [-0.60, -0.04]
De Boer 2008	-0.07	1	197	-0.11	1.07	211	13.7%	0.04 [-0.16, 0.24]
Mitri (D vs Plb) 2011	0.12	0.67	23	0.47	0.63	12	2.7%	-0.35 [-0.80, 0.10]
Mitri (DCa vs Ca) 2011	0.16	0.64	12	0.14	0.63	22	2.8%	0.02 [-0.43, 0.47]
Mitri (DCa vs Plb) 2011	0.16	0.64	11	0.47	0.63	12	2.0%	-0.31 [-0.83, 0.21]
Harris 2012	-0.01	0.59	43	-0.03	0.61	46	8.9%	0.02 [-0.23, 0.27]
Davidson 2013	0.07	0.75	56	0.19	0.82	53	6.3%	-0.12 [-0.42, 0.18]
Dutta 2014	-0.28	0.75	55	0.06	0.82	49	6.0%	-0.34 [-0.64, -0.04]
Sollid 2014	-0.07	0.54	242	0.02	0.63	242	50.4%	-0.09 [-0.19, 0.01]
Total (95% CI)			**684**			**694**	**100.0%**	**-0.10 [-0.18, -0.03]**

Heterogeneity: $Chi^2 = 9.72$, df = 8 (P = 0.29); $I^2 = 18\%$

Test for overall effect: Z = 2.76 (P = 0.006)

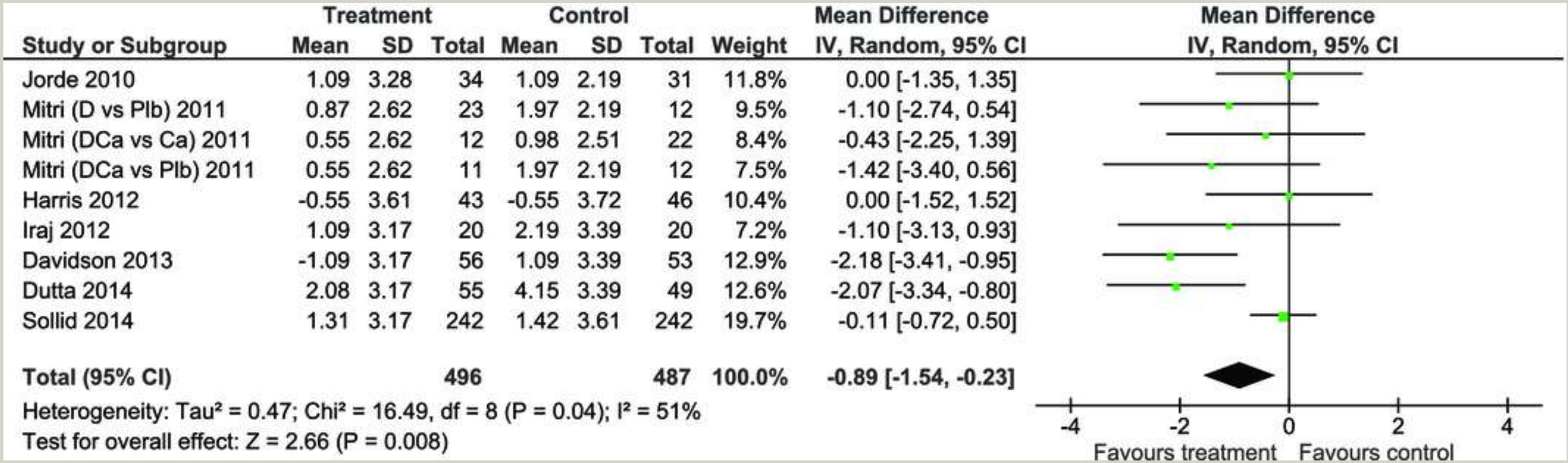


The effect of vitamin D supplementation based on baseline 25(OH)D was inconclusive.

Diabetic Medicine
Volume 33, Issue 3, pages 290-299, 6 OCT 2015 DOI: 10.1111/dme.12893
http://onlinelibrary.wiley.com/doi/10.1111/dme.12893/full#dme12893-fig-0004

Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis

Mean difference (95% CI) in the change of HbA_{1c} (mmol/mol) for vitamin D supplementation and control.



The effect of vitamin D supplementation based on baseline 25(OH)D was inconclusive.

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Volume 33, Issue 3, pages 290-299, 6 OCT 2015 DOI: 10.1111/dme.12893
http://onlinelibrary.wiley.com/doi/10.1111/dme.12893/full#dme12893-fig-0005

Βιταμίνη D και ΣΔ2

- **Η πλειοψηφία των μελετών παρατήρησης στηρίζει τη δράση της βιταμίνης D**
- **Ωστόσο, κάποιες μελέτες ήταν ουδέτερες**
- **Λίγες μελέτες παρέμβασης δεν απέδειξαν όφελος (σχεδιασμός;)**

Σημαντικά κλινικά ερωτήματα

- Η χορήγηση βιταμίνης D βελτιώνει το γλυκαιμικό έλεγχο;

METABOLISM CLINICAL AND EXPERIMENTAL 73 (2017) 67–76

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Vitamin D supplementation and glycemic control in type 2 diabetes patients: A systematic review and meta-analysis

Chunhua Wu, Shanhu Qiu, Xiangyun Zhu, Ling Li*

Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, Medical School, Southeast University, China

a modest reduction of HbA1C after vitamin D treatment in adults with type 2 diabetes albeit with substantial heterogeneity between studies and no difference in FBG

Vitamin D supplementation could be effective at improving glycemic control in vitamin D deficient or non-obese type 2 diabetes patients

Journal of Diabetes and Its Complications 31 (2017) 1115–1126

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Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

The effect of vitamin D supplementation on glucose metabolism in type 2 diabetes mellitus: A systematic review and meta-analysis of intervention studies

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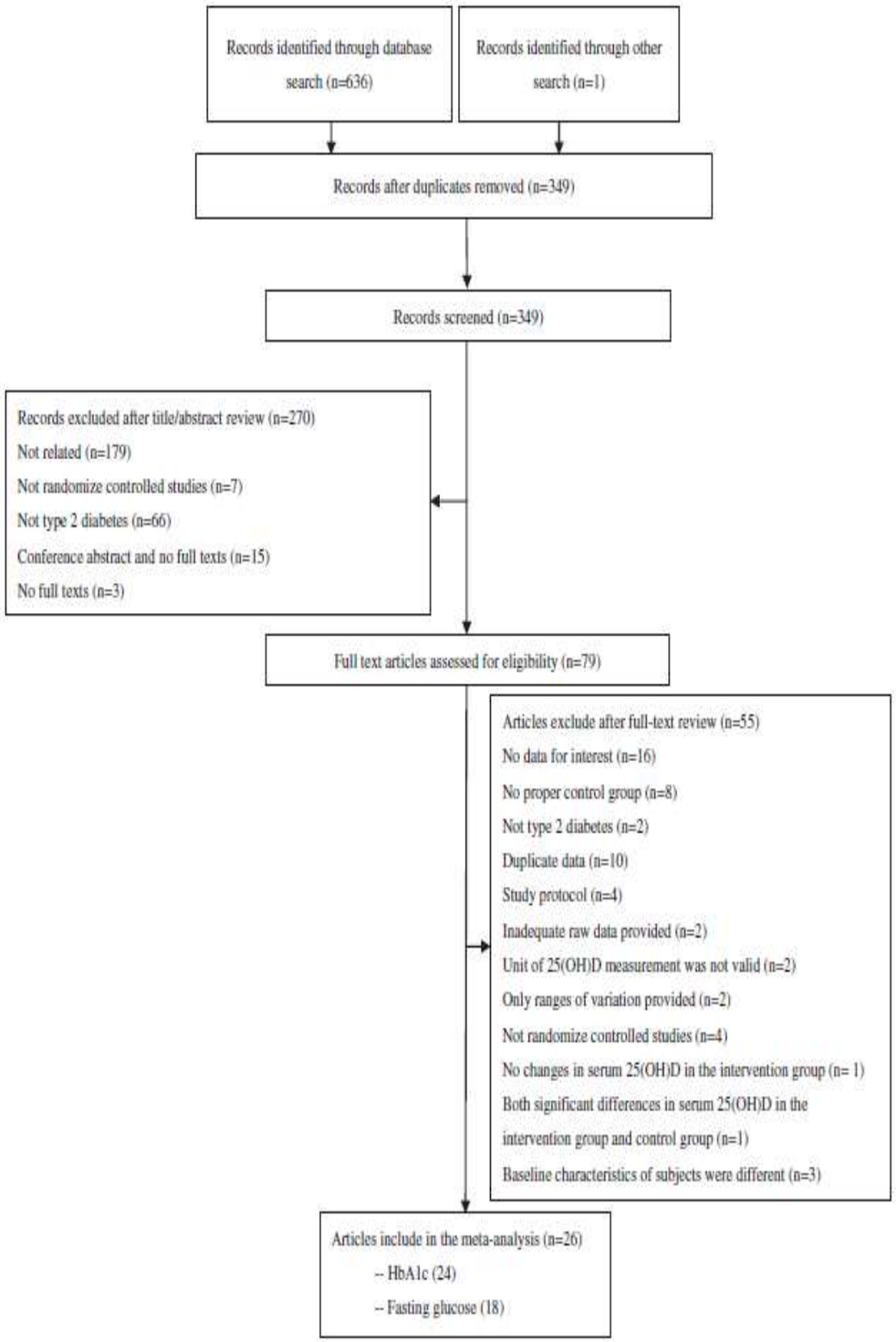


Fig. 1 – Flow chart of the multi-phase process for study selection.

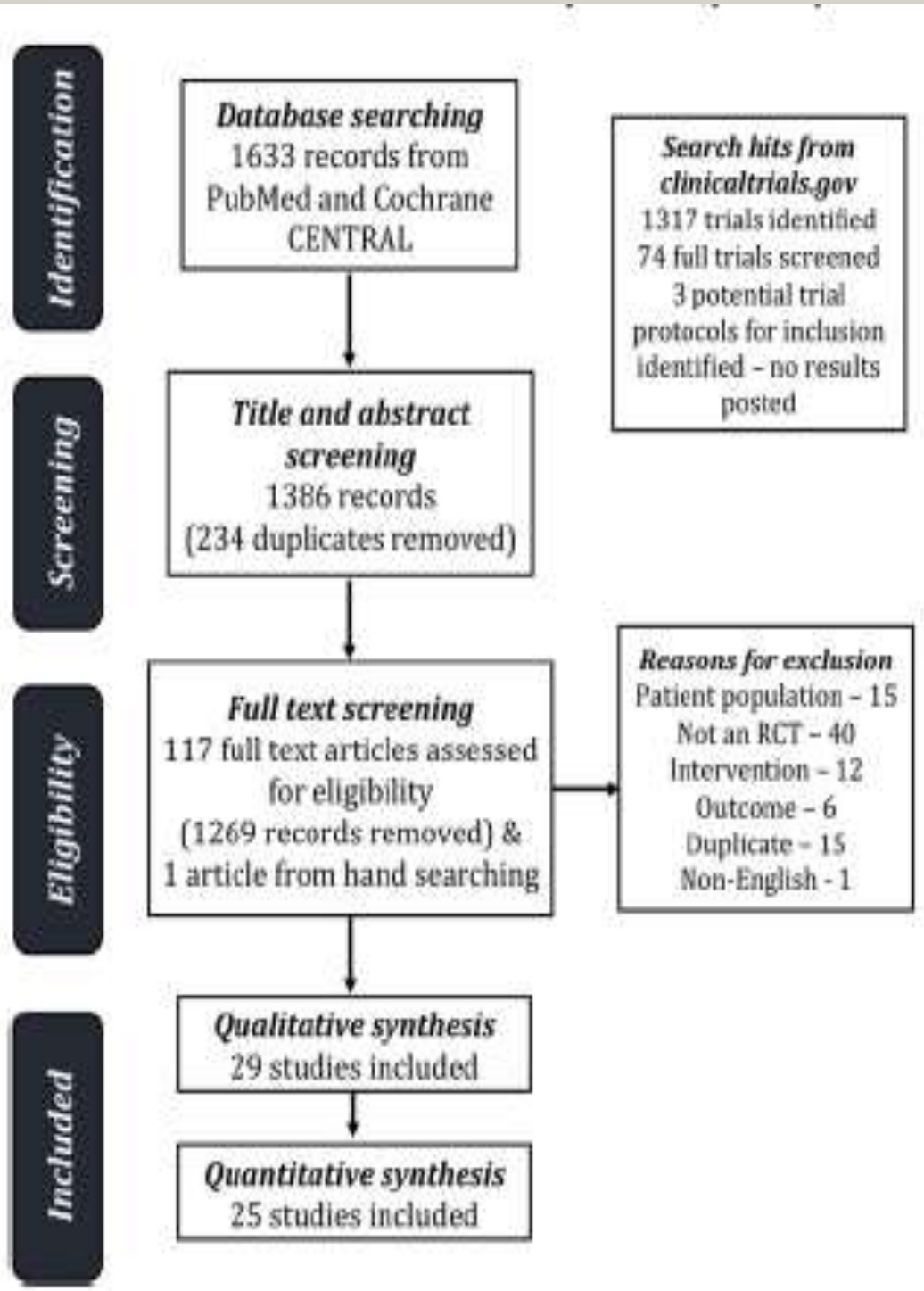


Fig. 1. Flow diagram of search and selection processes.

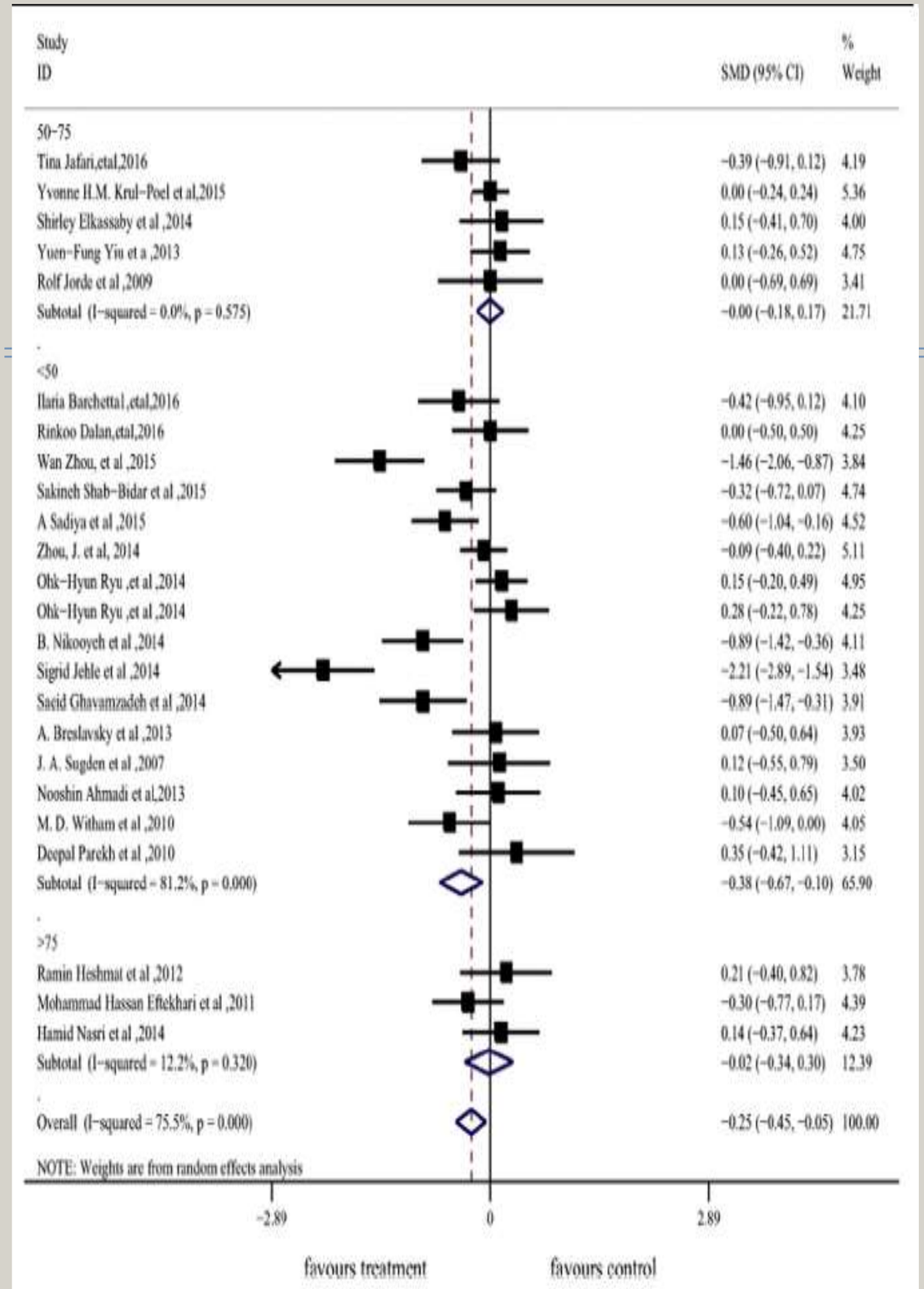


Fig. 2 – Forest plots of meta-analysis of the effect of vitamin D supplementation on HbA1c. Data are pooled SMDs with 95% CIs. HbA1c: hemoglobinA1c; SMD: standardized mean difference, CIs: confidence interval.

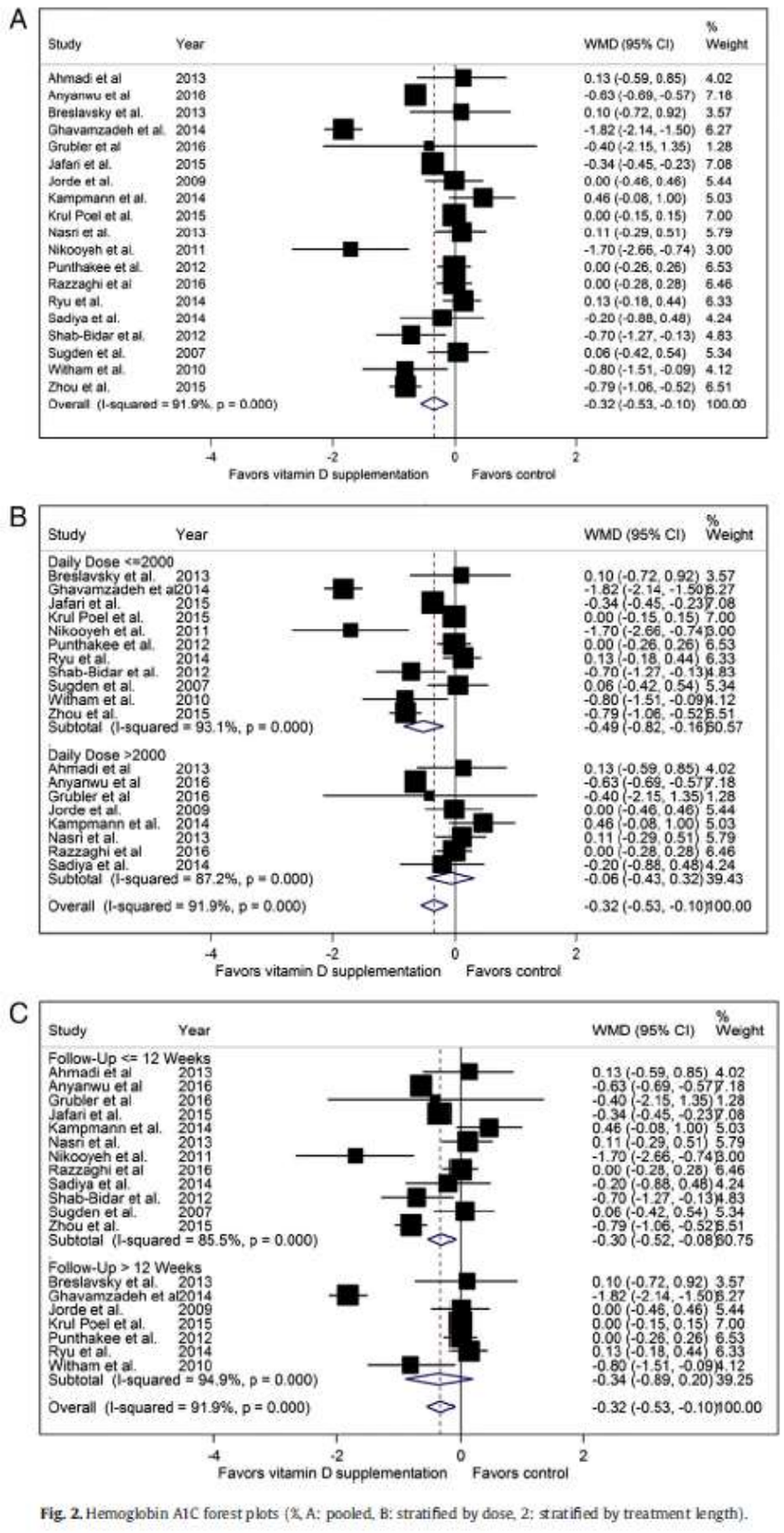


Fig. 2. Hemoglobin A1C forest plots (%, A: pooled, B: stratified by dose, 2: stratified by treatment length).

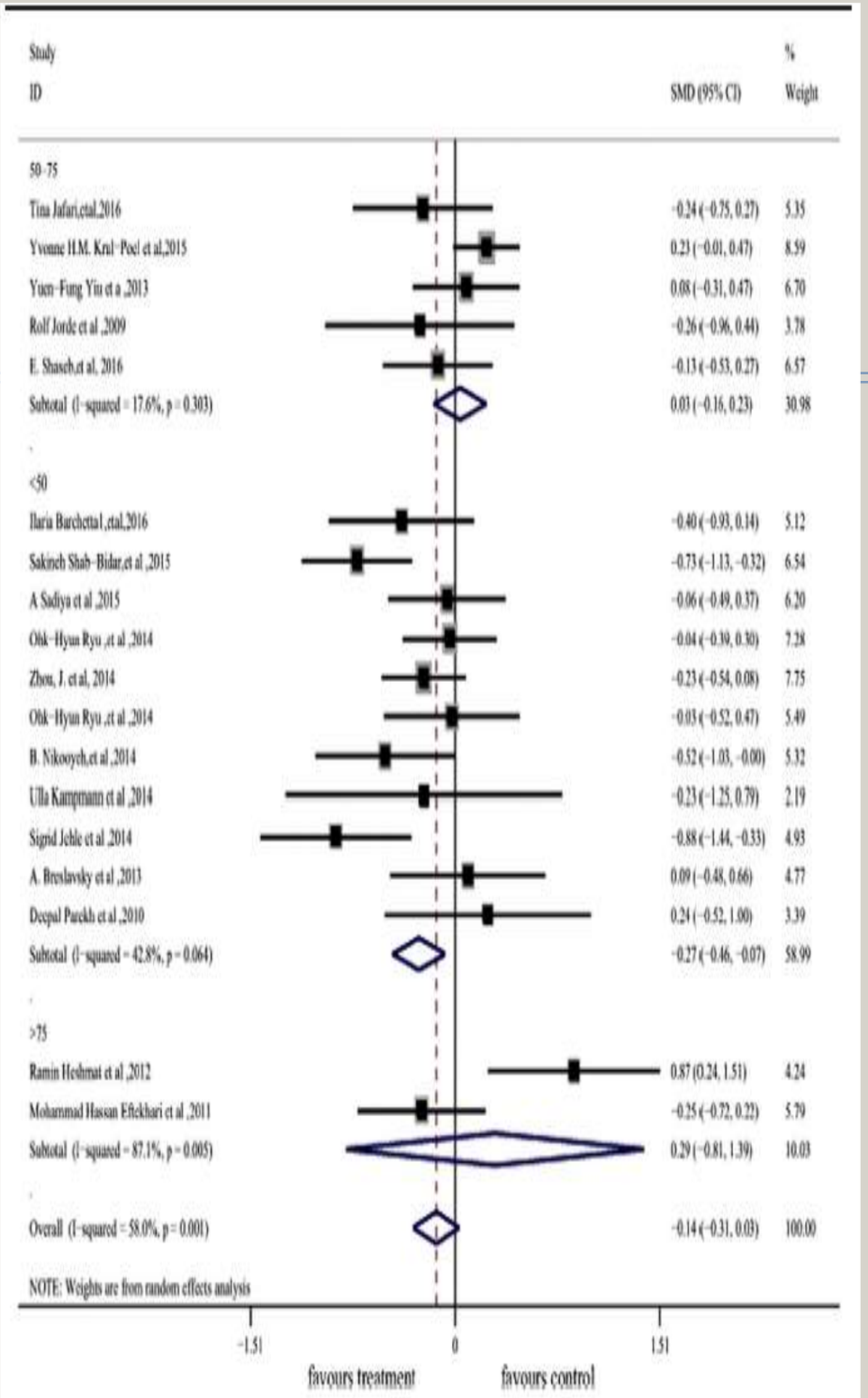


Fig. 3 – Forest plots of meta-analysis of the effect of vitamin D supplementation on FBG. Data are pooled SMDs with 95% CIs. FBG: fasting blood glucose SMD: standardized mean difference, CIs: confidence interval.

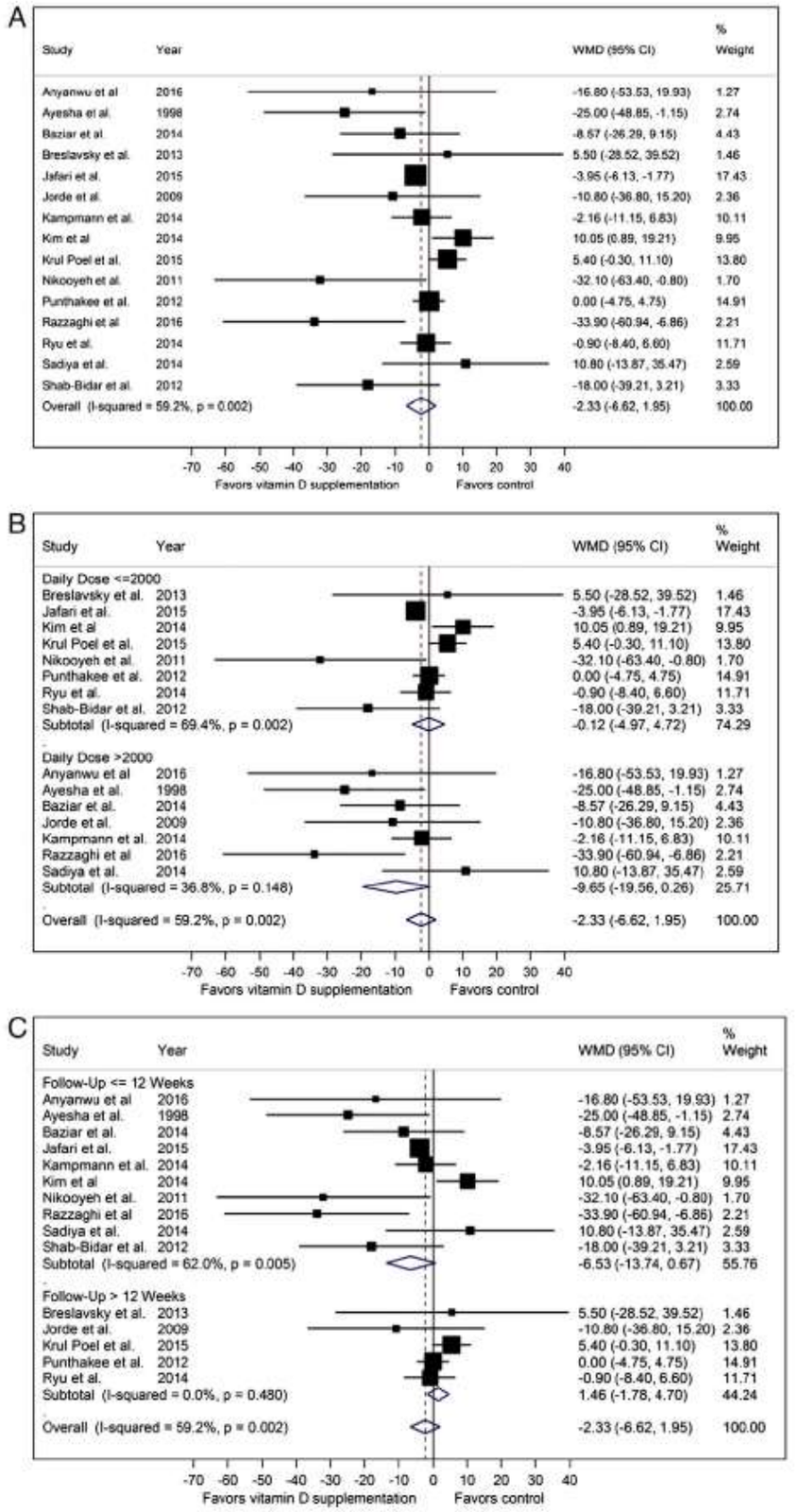
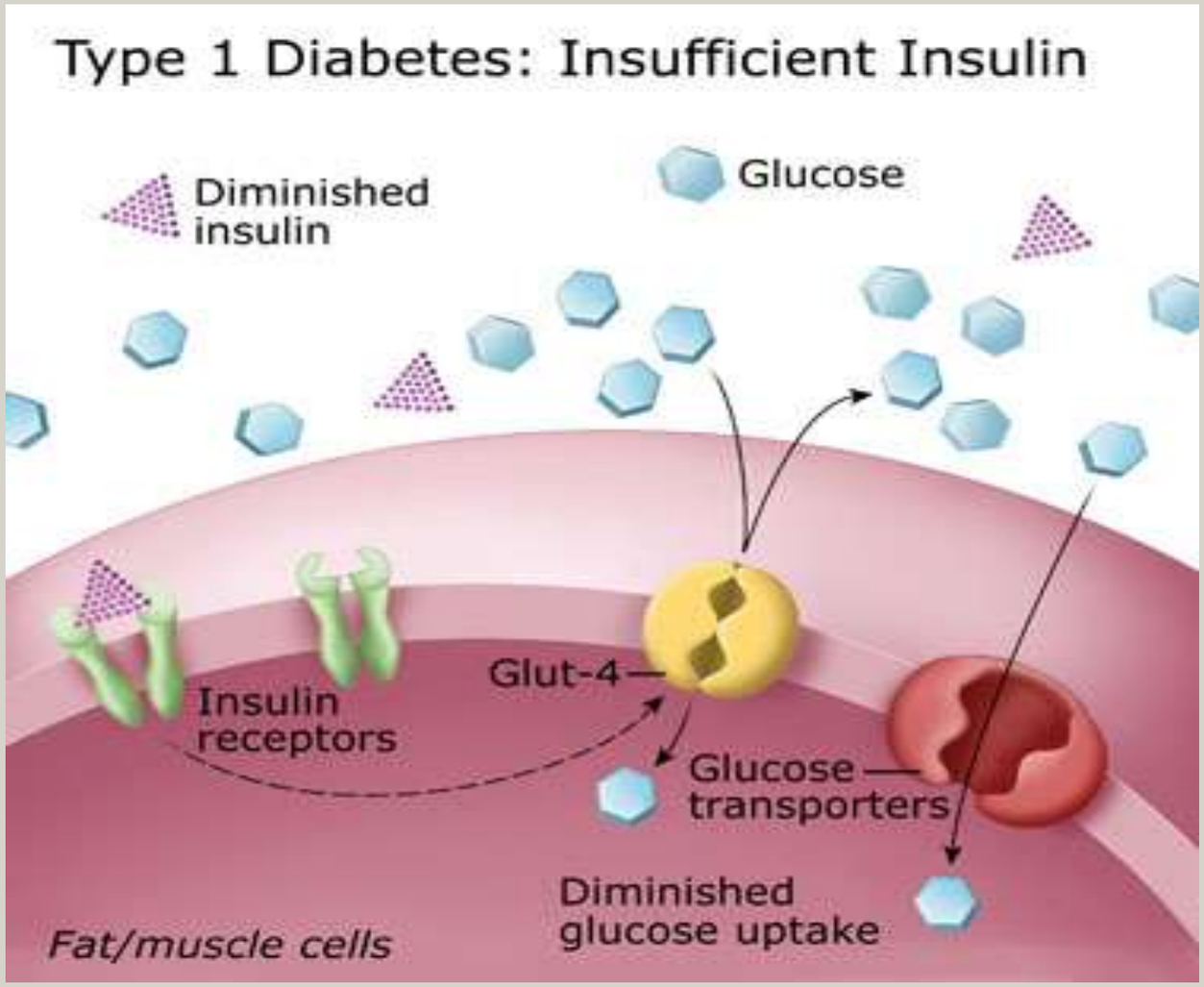


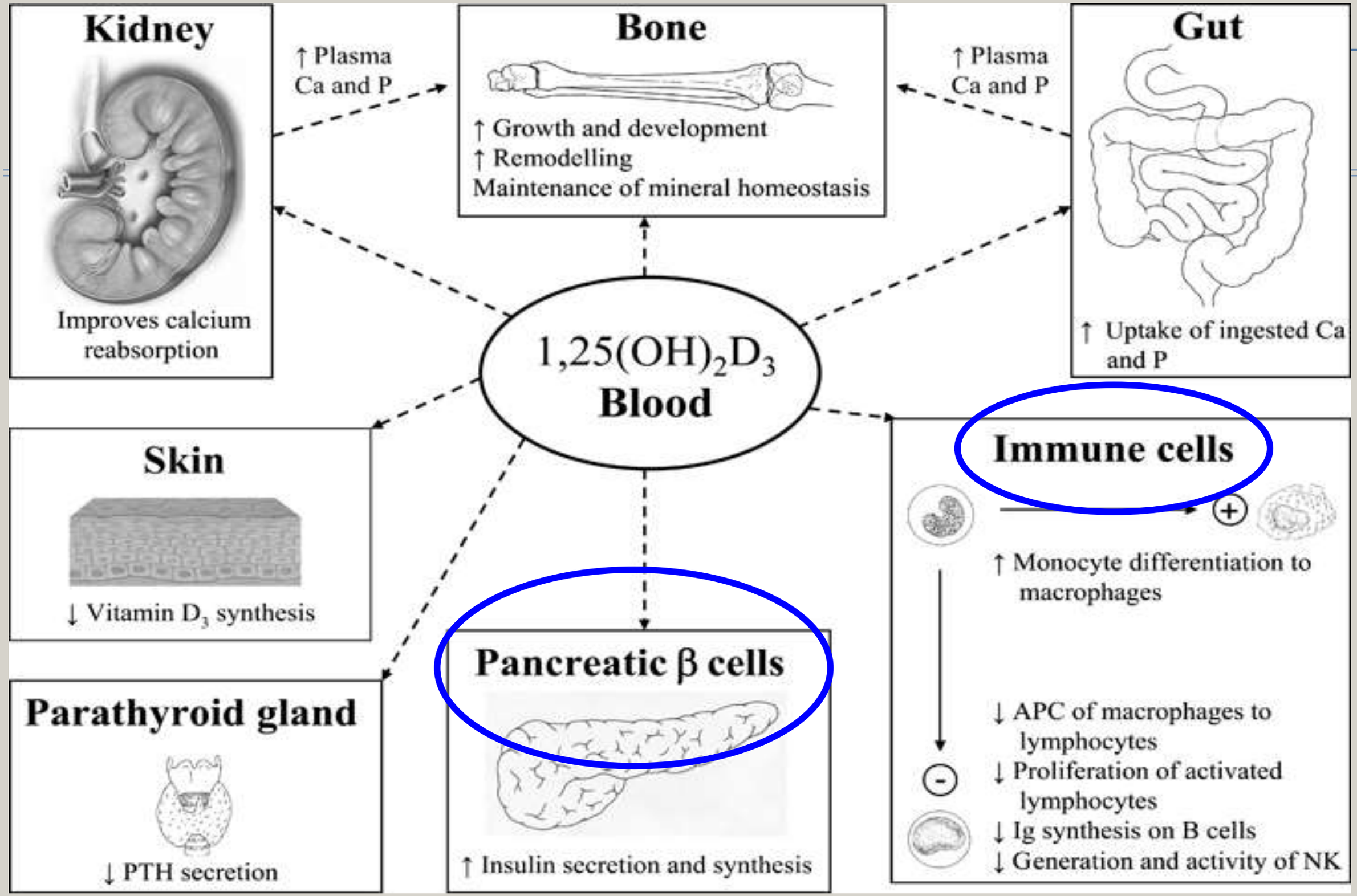
Fig. 3. Fasting blood glucose forest plots (mg/dl, A: pooled, B: stratified by dose, C: stratified by treatment length).


Frustration
Just Ahead

Τι συμβαίνει στο ΣΔ1;



Role of vitamin D in the pathogenesis of type 1 Diabetes Mellitus



Palomer et al, Diabetes, Obesity and Metabolism, 2008

Vitamin D & Type 1 diabetes - Seasonal and geographical variation

- Some evidence for north-south gradient
  - **exceptions (e.g. Sardinia)**
  - **association diluted by variations in genetic susceptibility?**

- Little evidence for seasonal variation by time of birth in diabetic cases or according to season of the onset of the disease
  - **multifactorial disease, latency may be long**
  - **confounded by use of vitamin D supplements, recommended during the dark seasons of the year**

Vitamin D & Type 1 diabetes

-Studies in animals and humans

- **Type 1 diabetes prevented by 1,25-$(OH)_2$D in animal models**
- **Some evidence for protective effect in humans**
  - **only a few studies published to date**

Vitamin D & Type 1 diabetes
- Relevant time window?

- Pregnancy
  - **mothers cod liver oil consumption ⇨ diabetes risk ⇩**
- Infancy
  - **any vitamin D supplementation ⇨ diabetes risk ⇩**
  - **dose of supplementation ⇧ ⇨ diabetes risk ⇩**
  - **vitamin D deficiency ⇨ diabetes risk ⇧**
- Childhood ? Adolescence? Adulthood?

Intake of vitamin D and risk of type 1 diabetes: a birth cohort study

Elina Hyppönen, Esa Läärä, Antti Reunanen,
Marjo-Riitta Järvelin, Suvi Virtanen

Lancet 2001;358:1500-1503

Northern Finland 1966 Cohort Study

- All pregnant mothers in the two northernmost provinces of Finland (Oulu and Lapland) with expected date of delivery in 1966 invited to participate -> 12,058 live births

- Information on vitamin D intake/status collected at 1 year of age (n=10, 366)

- Follow-up for type 1 diabetes up to December 1997

Hyppönen et al. Lancet 2001;358:1500-1503

Incidence of type 1 diabetes by use of vitamin D supplements in infancy

	Cases	Incidence /100,000 years at risk	Crude RR (95% CI)	Adjusted* RR (95% CI)
Use of vitamin D supplements				
Not at all	2	204	1 (reference)	1 (reference)
Irregularly	12	33	0. 16 (0.04-0.72)	0.16 (0.04-0.74)
Regularly	67	24	0.12 (0.03-0.47)	0.12 (0.03-0.51)

* Adjusted for neonatal, social and anthropometric factors.

Hyppönen et al. Lancet 2001;358:1500-1503

Incidence of type 1 diabetes by dose of vitamin D supplementation

	Cases	Incidence /100,000 years at risk	Crude RR (95% CI)	Adjusted* RR (95% CI)
Dose of Vitamin D†				
Low	2	96	1 (reference)	1 (reference)
Recommended	63	24	0.20 (0.05-0.84)	0.21 (0.05-0.88)
High	2	15	0.14 (0.02-0.97)	0.14 (0.02-1.01)

* Adjusted for neonatal, social and anthropometric factors.

† Dose has been presented for infants receiving vitamin D regularly

Hyppönen et al. Lancet 2001;358:1500-1503

Incidence of type 1 diabetes by suspected rickets in infancy

	Cases	Incidence /100,000 years at risk	Crude RR (95% CI)	Adjusted* RR (95% CI)
Suspected rickets				
No	77	25	1(reference)	1 (reference)
Yes	4	62	2.6 (1.0-7.2)	3.0 (1.0-9.0)

* Adjusted for neonatal, social and anthropometric factors.

Hyppönen et al. Lancet 2001;358:1500-1503

Associated temporal changes?
(in Finland)

- Increasing incidence of type 1 diabetes

AND

- Dose reduction in infant vitamin D recommendations
  - 1956: 4000-5000 IU
  - 1964: -> 2000 IU
  - 1975: -> 1000 IU
  - 1992: -> 400 IU
- Changes in the compliance of giving vitamin D?
- Increase in the incidence of rickets during 1980s

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2009; 25: 411–416.
Published online 1 June 2009 in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/dmrr.977

RESEARCH ARTICLE

Protective effects of 1-α-hydroxyvitamin D3 on residual β-cell function in patients with adult-onset latent autoimmune diabetes (LADA)

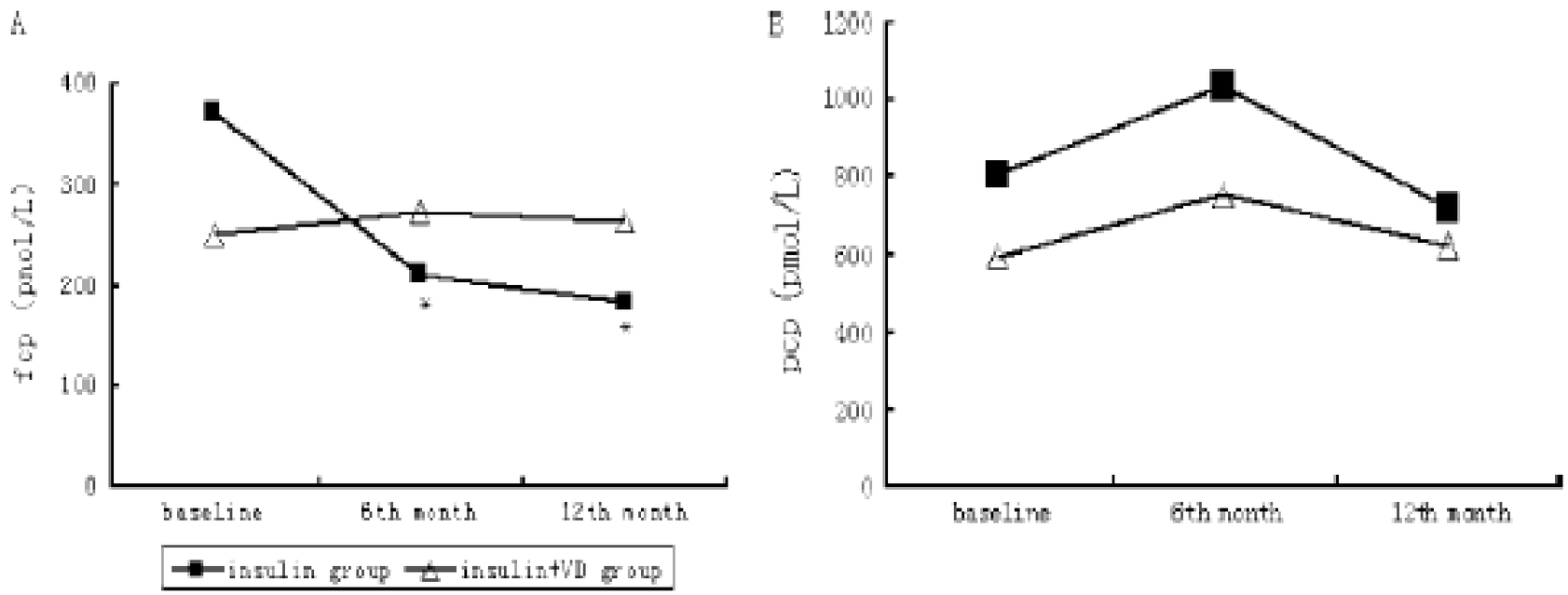


Figure 1. Changes of fasting and postprandial C-peptide levels during the treatment period. Data are shown as median. (A) Changes of fasting C-peptide; (B) Changes of postprandial C-peptide levels. * When compared with baseline, $P < 0.05$. Fasting C-peptide levels in insulin alone group decreased from 368 pmol/L at entry to 208 pmol/L at 6th month ($P = 0.02$), and to 179 pmol/L at 12th month ($P = 0.006$). No significant changes were found in the group treated with insulin plus vitamin D

Endocrinology, Diabetes & Metabolism CASE REPORTS

E Rapti and others | LADA treatment with sitagliptin and Vitamin D

ID: 15-0136; May 2016
DOI: 10.1530/EDM-15-0136

Combined treatment with sitagliptin and vitamin D in a patient with latent autoimmune diabetes in adults

E Rapti[1], S Karras[1], M Grammatiki[1], A Mousiolis[1], X Tsekmekidou[1], E Potolidis[1], P Zebekakis[1], M Daniilidis[2] and K Kotsa[1]

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kalmanthou@yahoo.gr

ΣΔ 1 και βιταμίνη D

- **Η πλειοψηφία των μελετών παρατήρησης στηρίζει τη δράση της βιταμίνης D**
- **Ωστόσο, κάποιες μελέτες ήταν ουδέτερες**
- **Χρειάζονται μελέτες παρέμβασης (σχεδιασμός;)**

The BIG public health question

IF the association between vitamin D and type 1 diabetes is shown to be causal, is it because...

...the intake is too low only to prevent the destructive autoimmune reaction in susceptible individuals ?

OR

...the intake is too low to prevent human immune system from developing/working optimally ?

Κυριότερες αμφιβολίες-ασάφειες

- Προβλήματα στο σχεδιασμό των μελετών
- Σχέσεις 25(OH)D με 1,25 (OH)2D και PTH
- Σχέση 25(OH)D με άλλες παραμέτρους (BMI, σωματική άσκηση)
- Γενετικοί παράγοντες (SNPs DBP)
- Τοπική παραγωγή 1,25(OH)2D σε σχέση με συγκέντρωση στο αίμα

PLOS | ONE

August 26, 2015

RESEARCH ARTICLE

1,25-Dihydroxyvitamin D to PTH(1–84) Ratios Strongly Predict Cardiovascular Death in Heart Failure

Damien Gruson[1,2]*, Benjamin Ferracin[1], Sylvie A. Ahn[3], Claudia Zierold[4], Frank Blocki[4], Douglas M. Hawkins[5], Fabrizio Bonelli[4], Michel F. Rousseau[3]

1 Pôle de recherche en Endocrinologie, Diabète et Nutrition, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium, **2** Department of Laboratory Medicine, Cliniques Universitaires St-Luc and Université Catholique de Louvain, Brussels, Belgium, **3** Division of Cardiology, Cliniques Universitaires St-Luc and Pôle de recherche cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium, **4** DiaSorin Inc, 1951 Northwestern Avenue, Stillwater, Minnesota, 55082, United States of America, **5** School of Statistics, University of Minnesota, Minneapolis, Minnesota, 55455, United States of America

The combined effect of vitamin D and parathyroid hormone concentrations on glucose homeostasis in older patients with prediabetes: a cross-sectional study

Spyridon N. Karras [1], Panagiotis Anagnostis [2], Vasiliki Antonopoulou [1], Xanthipi Tsekmekidou [1], Theocharis Koufakis [1], Dimitrios G. Goulis [2], Pantelis Zebekakis [1], Kalliopi Kotsa [1]

•Division of Endocrinology and Metabolism, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece
•Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece

The aim of this study was to examine the role of PTH / Vit_D_axis on glucose homeostasis in elderly persons with prediabetes (preDM).

Subjects / Methods: Patients with preDM (n = 144) and healthy age-matched controls (n = 81) with normal fasting glucose were included in this cross-sectional study. Study parameters included anthropometric characteristics, morning fasting glucose (FPG), insulin (FPI), PTH, 25-hydroxyvitamin D [25(OH)D], Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Homeostasis Model Assessment of β-cell function (HOMA-β). Both groups were stratified into subgroups according to Vit_D status and tertiles of PTH.

Accepted for publication 9/2017 in Diabetes and Vascular Disease Research

Table 2: Impact of vitamin D status on insulin resistance and insulin secretion indices in both PreDM and NFG groups.

Variable	Group	25(OH)D status		
		Deficient [a]	Sufficient [a]	p-value
FPI (μU/mL)	NFG	9.8 ± 0.7	8.4 ± 1.1	0.280
	PreDM	10.9 ± 0.6	11.5 ± 0.8	0.571
HOMA-IR	NFG	2.26 ± 0.19	2.16 ± 0.27	0.764
	PreDM	2.81 ± 0.18	2.90 ± 0.21	0.749
FPG (mg/dl)	NFG	93.5 (91.5 - 95.5)	93.8 (91.8 - 95.8)	0.937
	PreDM	100.7 (98.7 - 102.7)	101.4 (99.4 - 103.4)	0.716
HOMA-β	NFG	96.38 (94.20 - 98.57)	91.00 (88.7 - 93.27)	0.766
	PreDM	93.97 (91.84 - 96.11)	98.63 (96.46 - 100.79)	0.725

[a] Vitamin D status is defined by 25(OH)D levels. Vitamin D deficient is defined as 25(OH)D < 20ng/ml and sufficient as 25(OH)D > 20ng/ml.

Abbreviations: HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β-cell function; FPI: Fasting Plasma Insulin; FPG: Fasting Plasma Glucose; NFG: Normal Fasting Glucose; PreDM: Prediabetes Mellitus; 25(OH)D: 25-hydroxyvitamin D.

Vit D deficiency was prevalent in both groups. Eighty-two participants (57%) in the preDM group, and 56 in NFG group (69%) were 25(OH)D deficient (p = 0.451). Participants, with vit D deficiency, did not differ according to FPG and FPI as well as HOMA-IR and HOMA-β, compared with those who were vit D sufficient, for both PreDM and NFG groups.

Table 3: Impact of PTH status on glycemic status (FPG), insulin resistance (Fasting Insulin and HOMA-IR) and insulin secretion (HOMA-β) for PreDM and NFG diagnosis group separately.

		PTH status (pg/ml)			
Variable	**Group**	**≤ 20-40 (A)**	**20-40 (B)**	**≥ 40 (C)**	**p-value [a]**
FPI	NFG	9.9 ± 0.9	9.4 ± 1.2	8.8 ± 1.0	0.747
(μU/mL)	PreDM	9.3 ± 0.9	12.1 ± 0.8	11.6 ± 0.9	0.051
HOMA-IR	NFG	2.26 ± 0.24	2.31 ± 0.32	2.12 ± 0.28	0.900
	PreDM	2.37 ± 0.24	3.06 ± 0.21	3.06 ± 0.24	0.065
FPG	NFG	92.9	93.8	94.2	0.885
(mg/dl)		(90.9 - 94.9)	(91.8 - 95.8)	(92.2 - 96.2)	
	PreDM [b]	96.8	103.3	106.8	0.011
		(94.8 - 98.8)	(101.3 - 105.3)	(100.8 - 109.8)	
HOMA-β	NFG	96.61	93.54	92.47	0.978
		(94.35 - 98.86)	(91.19 - 95.89)	(90.17 - 94.77)	
	PreDM	92.68	91.83	103.20	0.650
		(90.47 - 94.90)	(89.66 - 94.00)	(101.89 - 105.22)	

[a] p-value refers to comparisons across all groups; [b] A vs B p=0.013, A vs C p=0.006, B vs C p=0.039.

PTH subgroups did not differ in relation to HOMA-IR, HOMA-β and insulin, concentrations, after accounting for the demographic covariates for NFG group. However, in the PreDM group, FPG differed significantly across PTH tertiles, increasing from the 1st to 2nd to 3rd tertile (p = 0.011, across all groups), after adjusting for age, gender, BMI and season of sampling. No differences in parameters of glycemic homeostasis were observed among other subgroups of PTH tertiles.

Table 4: Impact of the combination of Vitamin D (Vit D) and PTH status on glucose homeostasis and insulin secretion for the PreDM group.

Variable	Vit D sufficient + PTH 1st-2nd tertile (n=22) (A)	Vit D deficient + PTH 1st-2nd tertile (n=20) (B)	Vit D sufficient + PTH 3rd tertile (n=40) (C)	Vit D deficient + PTH 3rd tertile (n=62) (D)	p-value [a]
FPI (μU/mL)	9.5 ± 1.3	9.1 ± 1.2	11.5 ± 0.7 [b]	12.0 ± 0.9	0.031
FPG (mg/dl)	97.3 (95.3 - 99.3)	96.2 (94.2 - 98.2)	102.8 [c, d] (100.8 - 104.8)	103.5 (101.5 - 107.5)	0.027
HOMA-IR	2.33 ± 0.36	2.42 ± 0.32	3.00 ± 0.21*	3.56 ± 0.25	0.039
HOMA-β	95.06 (92.71 - 97.41)	94.78 (92.47 - 96.10)	103.20 (101.89 - 105.22)	100.00 (97.79 - 102.21)	0.971

[a] p-value refers to comparisons between group D and all other groups; [b] C vs A, p=0.015 [c] C vs A, p=0.024 [d] C vs B, p=0.018 * C vs A, p=0.038.

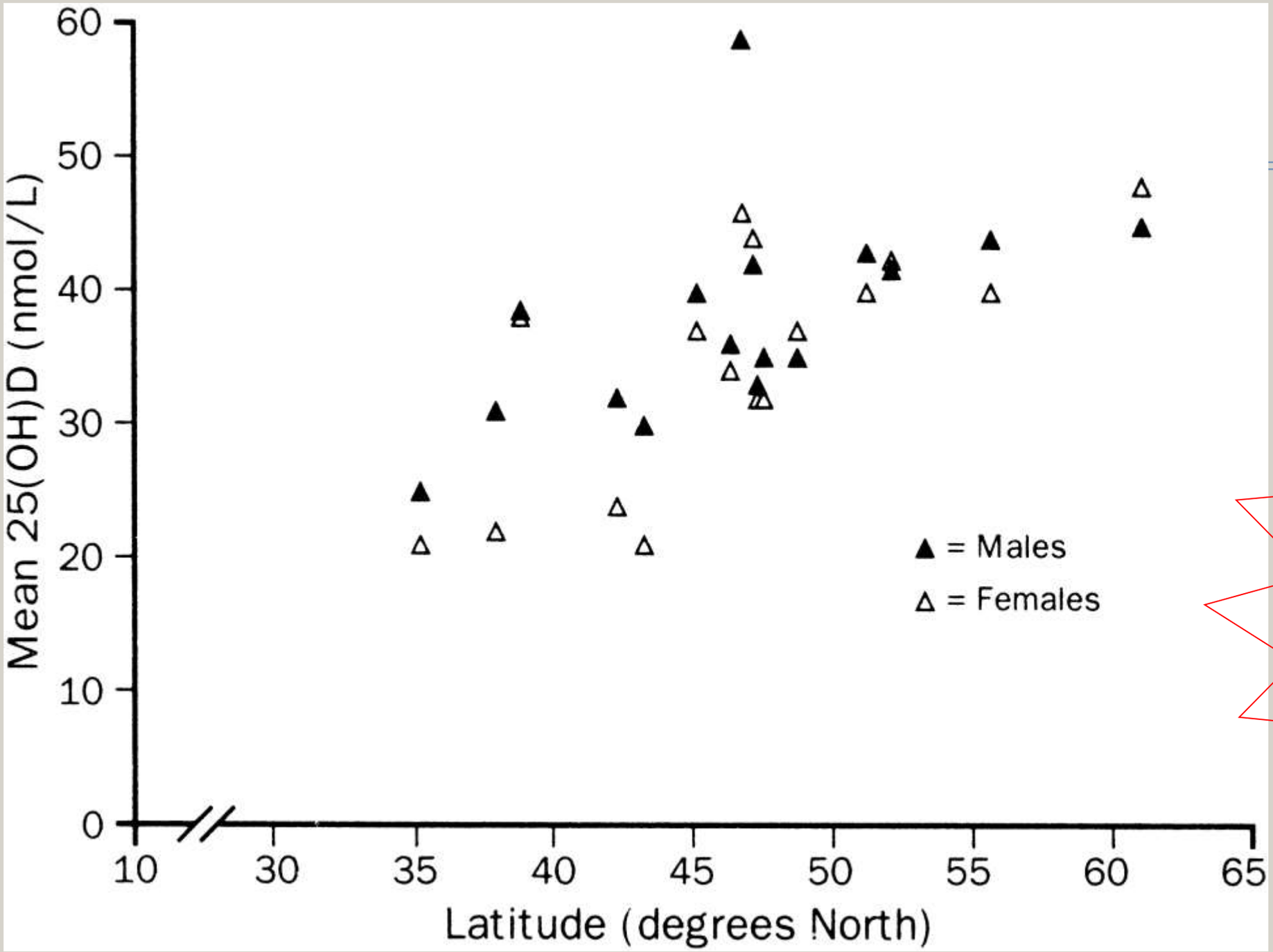
There was an increasing trend for both FPI and FPG according to PTH tertiles, which resulted in significantly higher concentrations in participants classified as vit D deficiency / PTH 3rd tertile compared to all other groups (p = 0.031 and 0.027, respectively). Participants with vit D sufficiency / PTH 3rd tertile demonstrated increased FPI concentrations (p = 0.015), compared with those with vit D sufficiency / PTH 1st - 2nd tertile, after adjustment for age, gender, BMI and season of sampling. Participants with vit D sufficiency / PTH 3rd tertile had increased FPG compared with those with vit D sufficiency / PTH 1st - 2nd tertile (p =_0.024) and those with vit D deficiency / PTH 1st - 2nd tertile (p = 0.018). HOMA-IR was significantly higher in PreDM group in the vit D deficiency / PTH 3rd tertile (p = 0.039) compared to all other groups. These results were also evident (p = 0.038) for participants with vit D sufficiency / PTH 3rd tertile, compared with participants with vit D sufficiency / PTH 1st -2nd tertile. No statistical differences for HOMA-β were observed among groups.

NEW EMERGING CALCIOTROPIC HORMONES NORMS FOR METABOLIC COMPLICATIONS?

- Or in other words……

- the Vitamin D metabolic system needs its ……”TSH” in analogy with the thyroid hormone system to accurately and finely tune and estimate levels and therapeutic results!!!!!!

Serum 25(OH)D measured in elderly people in 16 European centers participating in the Euronut SENECA Study.



The lowest values were found in Greece, Spain, and Italy

Lips, P. Endocr Rev 2001;22:477-501

ENDOCRINE REVIEWS

Eur J Nutr
DOI 10.1007/s00394-017-1415-1

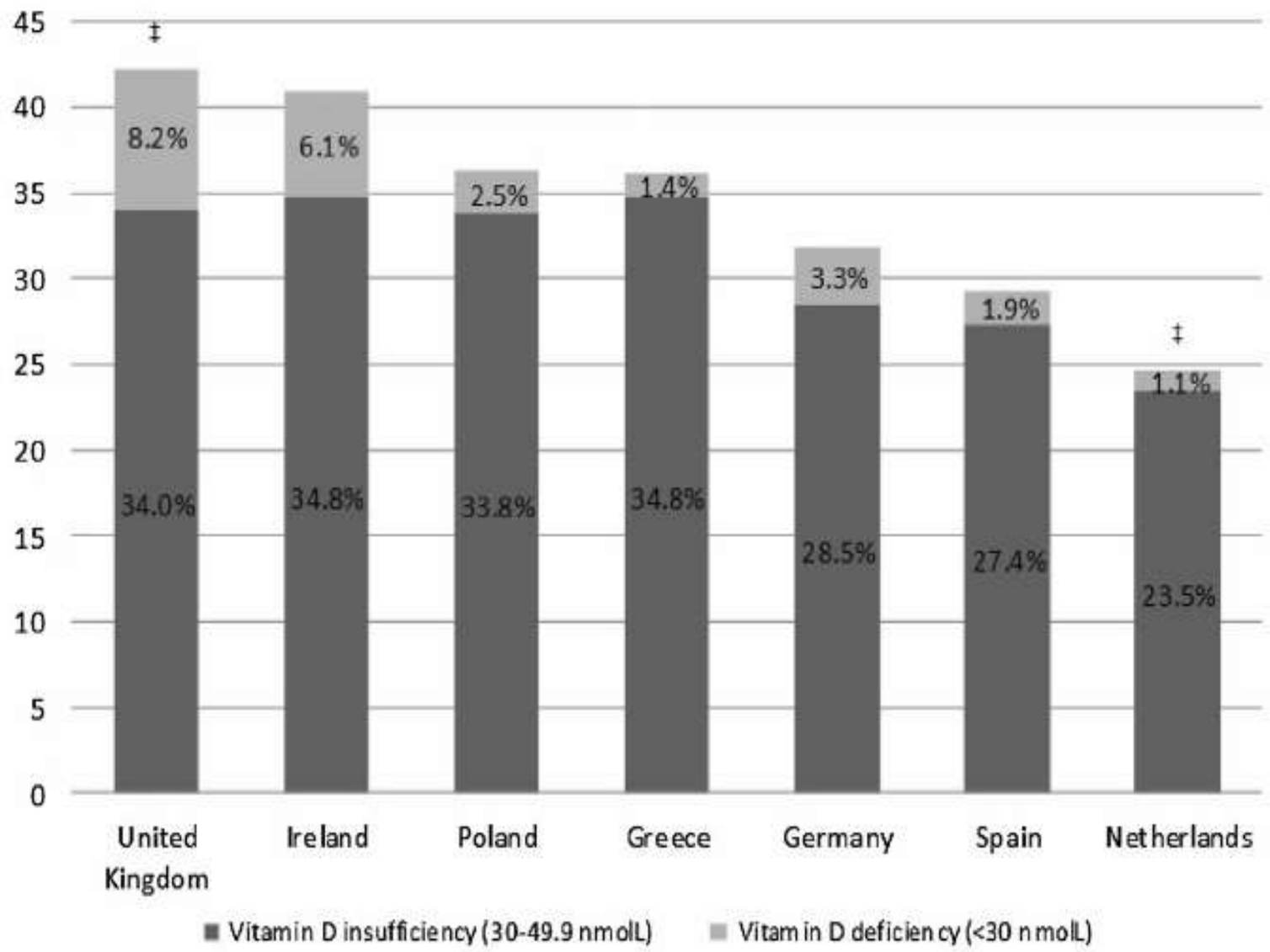
ORIGINAL CONTRIBUTION

Associations of vitamin D status with dietary intakes and physical activity levels among adults from seven European countries: the Food4Me study

Yannis Manios[1,14] · George Moschonis[1] · Christina P. Lambrinou[1] · Christina Mavrogianni[1] · Lydia Tsirigoti[1] · Ulrich Hoeller[2] · Franz F. Roos[2] · Igor Bendik[2] · Manfred Eggersdorfer[2] · Carlos Celis-Morales[3] · Katherine M. Livingstone[3] · Cyril F. M. Marsaux[4] · Anna L. Macready[5] · Rosalind Fallaize[5] · Clare B. O'Donovan[6] · Clara Woolhead[6] · Hannah Forster[6] · Marianne C. Walsh[6] · Santiago Navas-Carretero[7] · Rodrigo San-Cristobal[7] · Silvia Kolossa[8] · Jacqueline Hallmann[8] · Mirosław Jarosz[9] · Agnieszka Surwiłło[9] · Iwona Traczyk[9] · Christian A. Drevon[10] · Ben van Ommen[11] · Keith Grimaldi[12] · John N. S. Matthews[13] · Hannelore Daniel[8] · J. Alfredo Martinez[7] · Julie A. Lovegrove[5] · Eileen R. Gibney[6] · Lorraine Brennan[6] · Wim H. M. Saris[4] · Mike Gibney[6] · John C. Mathers[3] · on behalf of the Food4Me Study

Received: 11 May 2016 / Accepted: 19 February 2017

Fig. 1 Prevalence of vitamin D insufficiency and deficiency by country. ‡$P < 0.05$ for the differences in the prevalence of vitamin D deficiency (25-OHD_3 < 30 nmol/L) between countries sharing the same symbol



International Journal of Endocrinology
Volume 2015, Article ID 710363, 5 pages
http://dx.doi.org/10.1155/2015/710363

Research Article

Thyroid Autoimmunity in the Context of Type 2 Diabetes Mellitus: Implications for Vitamin D

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Received 21 October 2014; Accepted 29 December 2014

Table 1: Descriptive characteristics of the study population.

	Normal	Type 2 diabetes mellitus	*P*
N	234	264	
Male gender (female)	89 (38)	109 (41)	NS
Age (years)	72.2 (6.5)	67.6 (9.7)	0.0001
Body mass index (kg/m^2)	30.6 (4.9)	31.6 (5.7)	0.032
Type 2 diabetes mellitus duration (years)	N/A	10.0 (8.4)	
Glycated haemoglobin (%)	4.7 (0.5)	7.1 (1.5)	0.0001
25-Hydroxy-vitamin D (ng/mL)	22.6 (12.6)	16.5 (10.4)	0.0001
Presence of vitamin D deficiency/insufficiency	172 (73.5%)	215 (81.4)	0.04
Thyroid peroxidase Ab (IU/mL)	60 (156)	90 (200)	0.005
Thyroglobulin Ab (IU/mL)	44 (131)	54 (136)	NS
Thyroid autoimmunity	18 (7.7)	38 (14.4)	0.018
Thyroid stimulating hormone (μIU/mL)	1.95 (1.60)	2.25 (3.64)	NS
Hypothyroidism	8 (3.4)	11 (4.2)	NS

Data presented as mean (standard deviation) or *N* (%). *P* values refer to Mann-Whitney test or Pearson chi-square. NS: nonsignificant at the level of 0.05. Abs: autoantibodies.

Σε ποιούς μετράμε επίπεδα βιτD;

- Σε όλους
- Σε κανέναν - απλώς δίνουμε υποκατάσταση σε όλους
- Σε ομάδες υψηλού κινδύνου

What are the optimal 25-(OH)-D levels?

Defficiency: <10 ng/mL

Insufficiency: ≥10 and <20 ng/mL

Partial Insufficiency: ≥20 to <30 ng/mL

Recommendation:

The target level should be greater than 50 nmol/L at the end of winter. Each laboratory should be encouraged to report the same decision limits.

Most adults will eventually need vitamin D supplements due to insufficient sun exposure and dietary habits that do not support 25-(OH)-D level ≥30 ng/mL all year through

800 IU/day vitD_3 seems to be adequate to support ADEQUATE levels

Adequate levels are???

Συμπεράσματα

Vitamin D actions in pancreatic and immune cells suggest a possible protective or/and adjunctive role in T2DM prevention and treatment

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There optimal cut-off sed (for now….

Risk as

Combining vitamin D values with other parameters (i.e.PTH) may help in the future.

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CrossMark

Vitamin D and diabetes mellitus: Causal or casual association?

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