Il ruolo immunomodulante della vitamina D e le nuove evidenze cliniche

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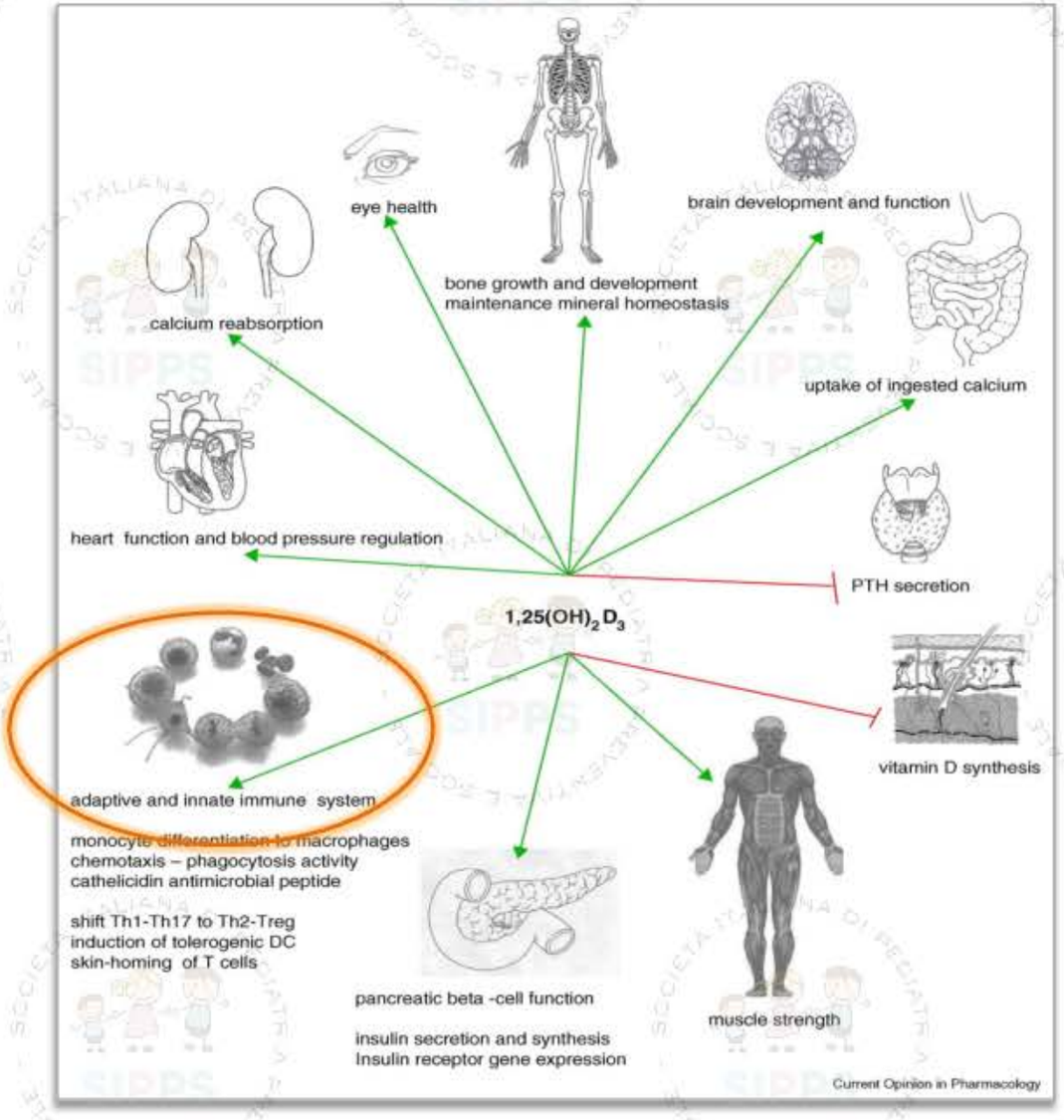
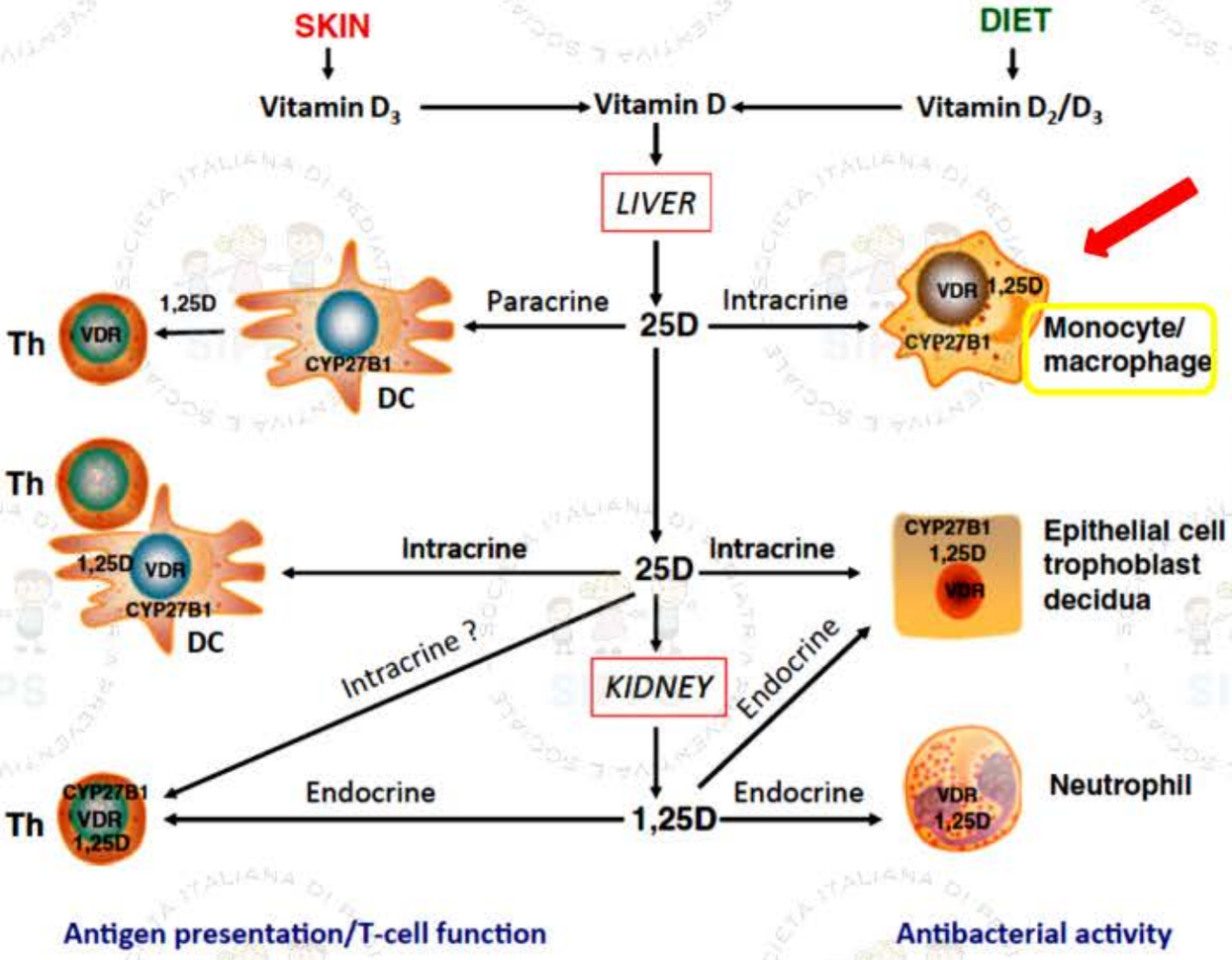
→ Vitamina D: il ruolo immunomodulante

Vitamin D works on many organs and peripheral tissues

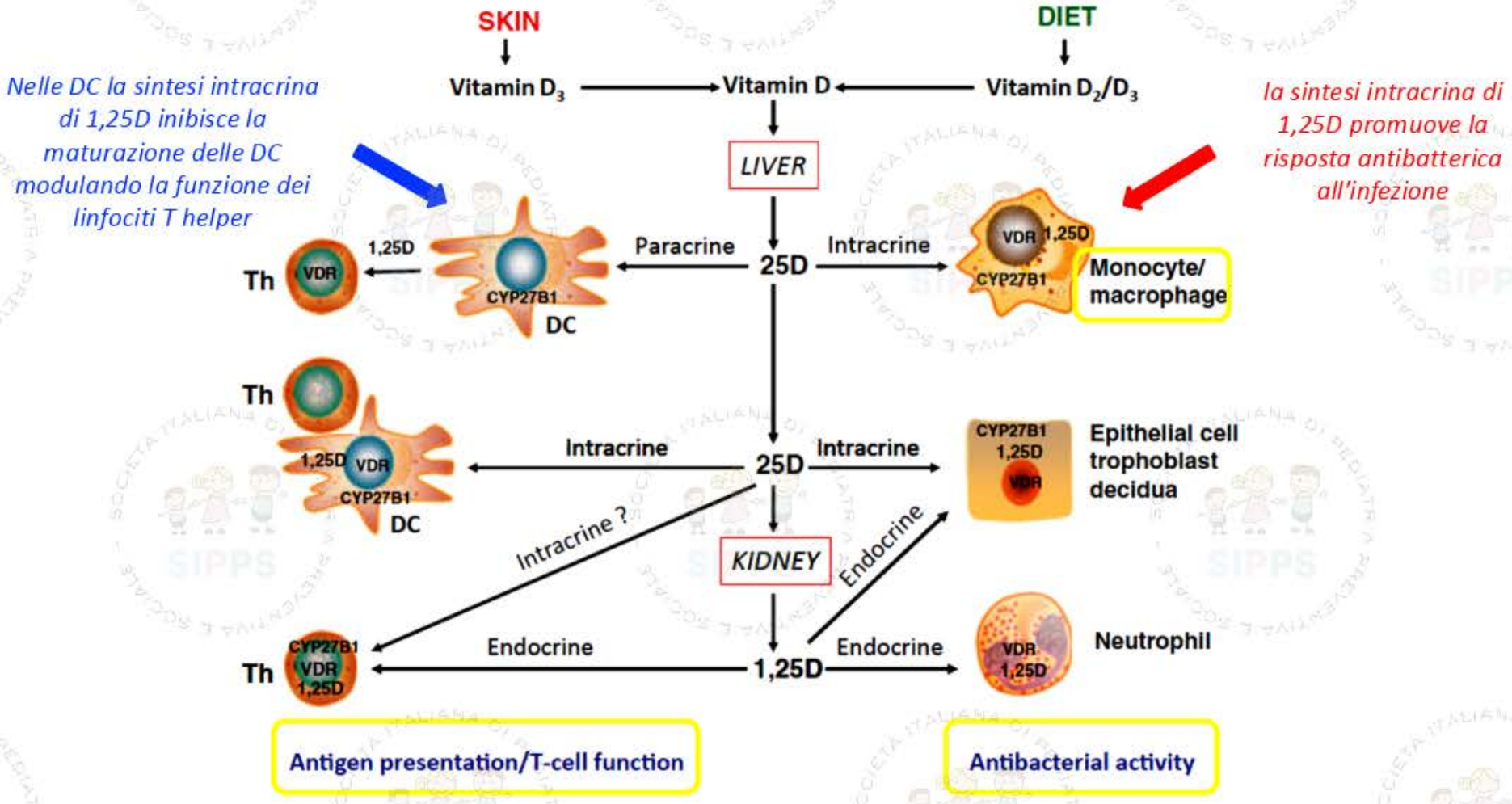


Vitamin D and immune function: an overview

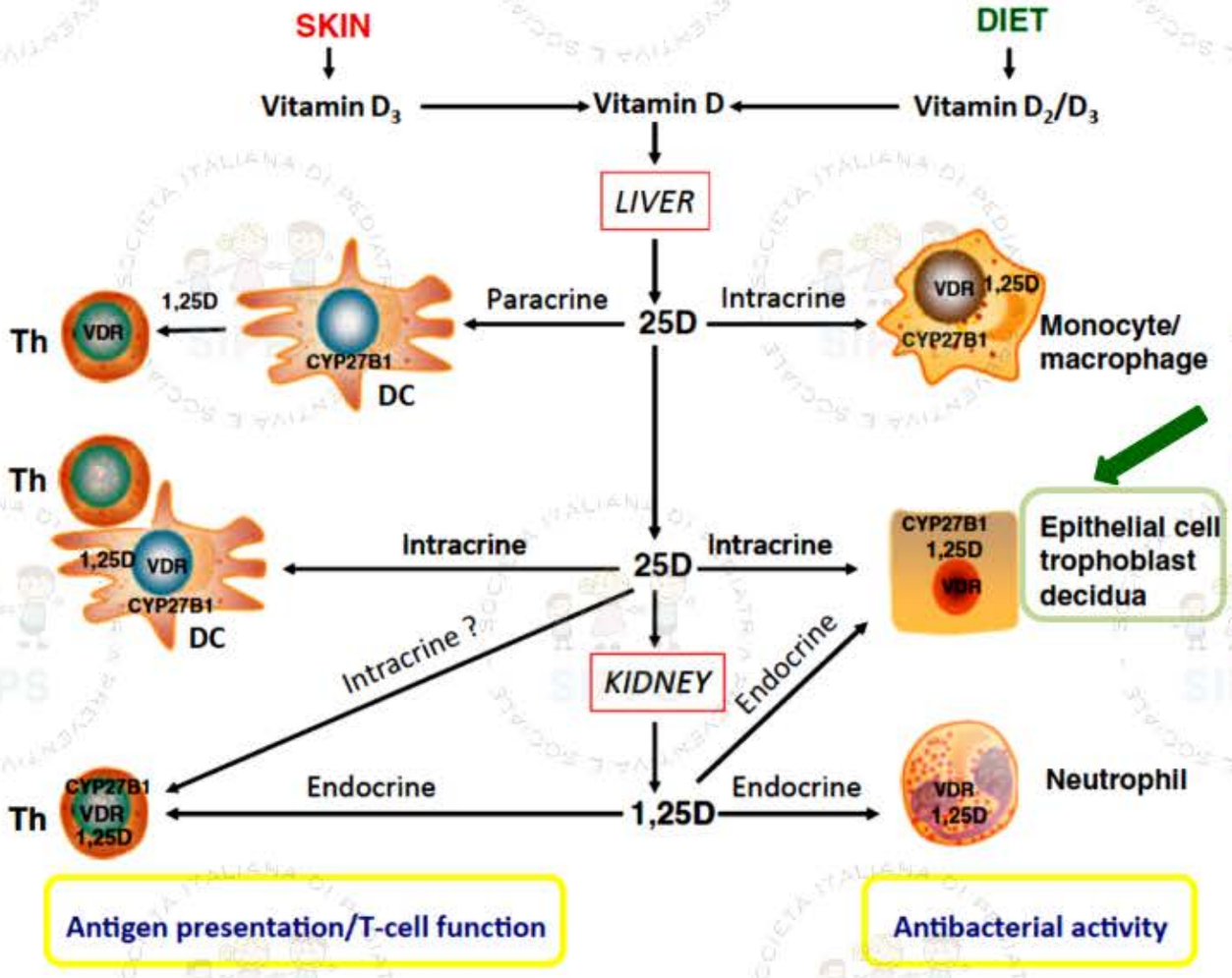


esprimono l'enzima di attivazione della vit. D CYP27B1 e il recettore della vitamina D (VDR) possono quindi utilizzare 25D per le risposte intracrine tramite la conversione localizzata in vit. D attiva (1, 25D).

Vitamin D and immune function: an overview

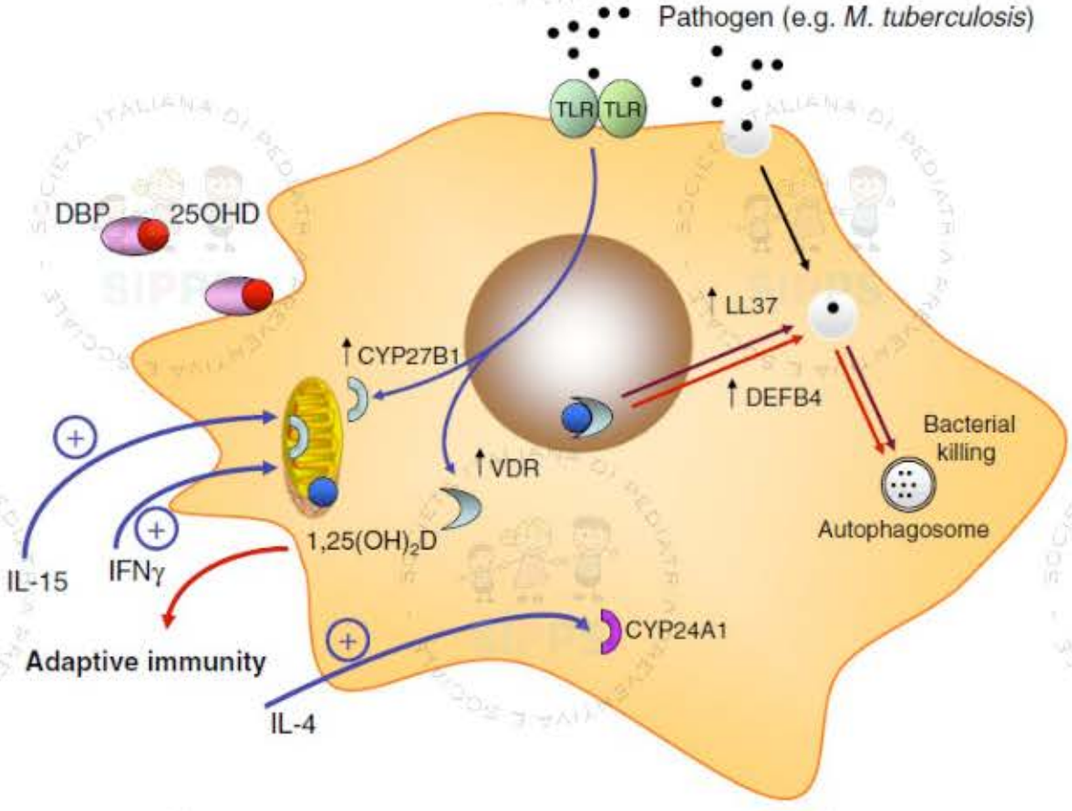


Vitamin D and immune function: an overview



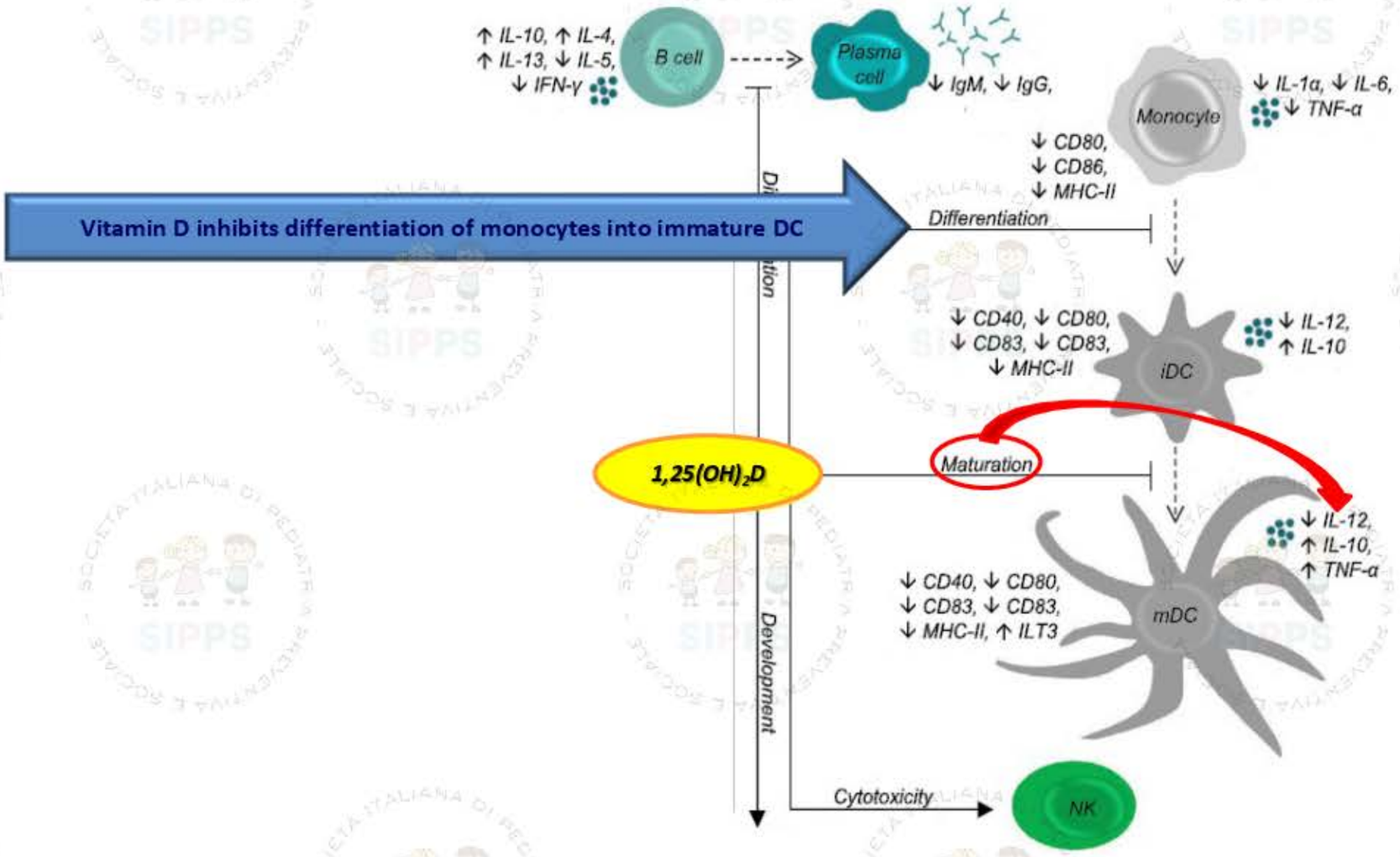
sono tutte in grado di rispondere in modo intracrino alla 25D, ma possono anche rispondere alla 1,25D sistemica per promuovere risposte antibatteriche.

Vitamin D and immune function: an overview

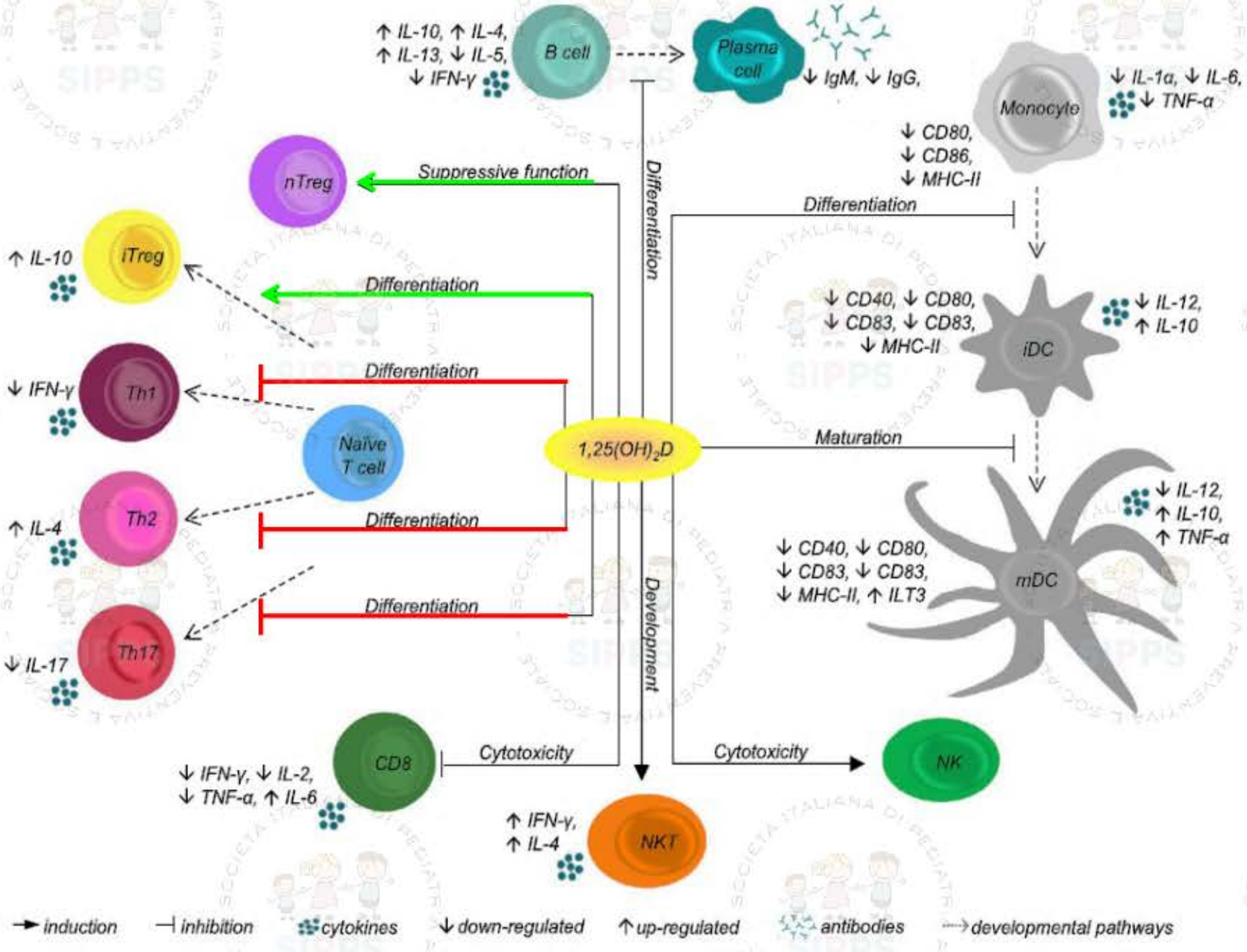


Vitamin D and monocyte antibacterial activity. Circulating 25-hydroxyvitamin D (25OHD) bound to serum vitamin D binding protein (DBP) enters monocytes and is converted to 1,25-dihydroxyvitamin D (1,25(OH)$_2$D) by mitochondrial CYP27B1. VDR-bound 1,25(OH)$_2$D is then able to act as a transcriptional factor, inducing expression of **cathelicidin (LL-37) and ß-defensin 2 (DEFB4). 1,25(OH)$_2$D-induced LL-37 promotes autophagy**

Martin Hewison Martin Hewison Proceedings of the Nutrition Society



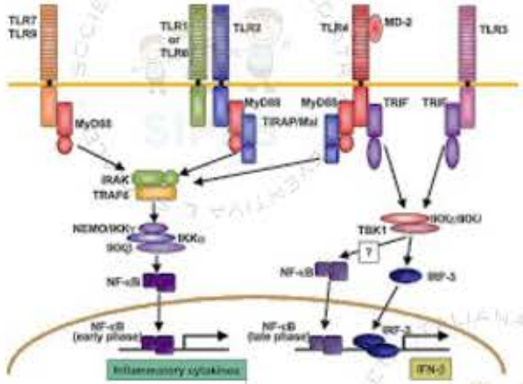
Peelen E. Autoimmunity Reviews 2011

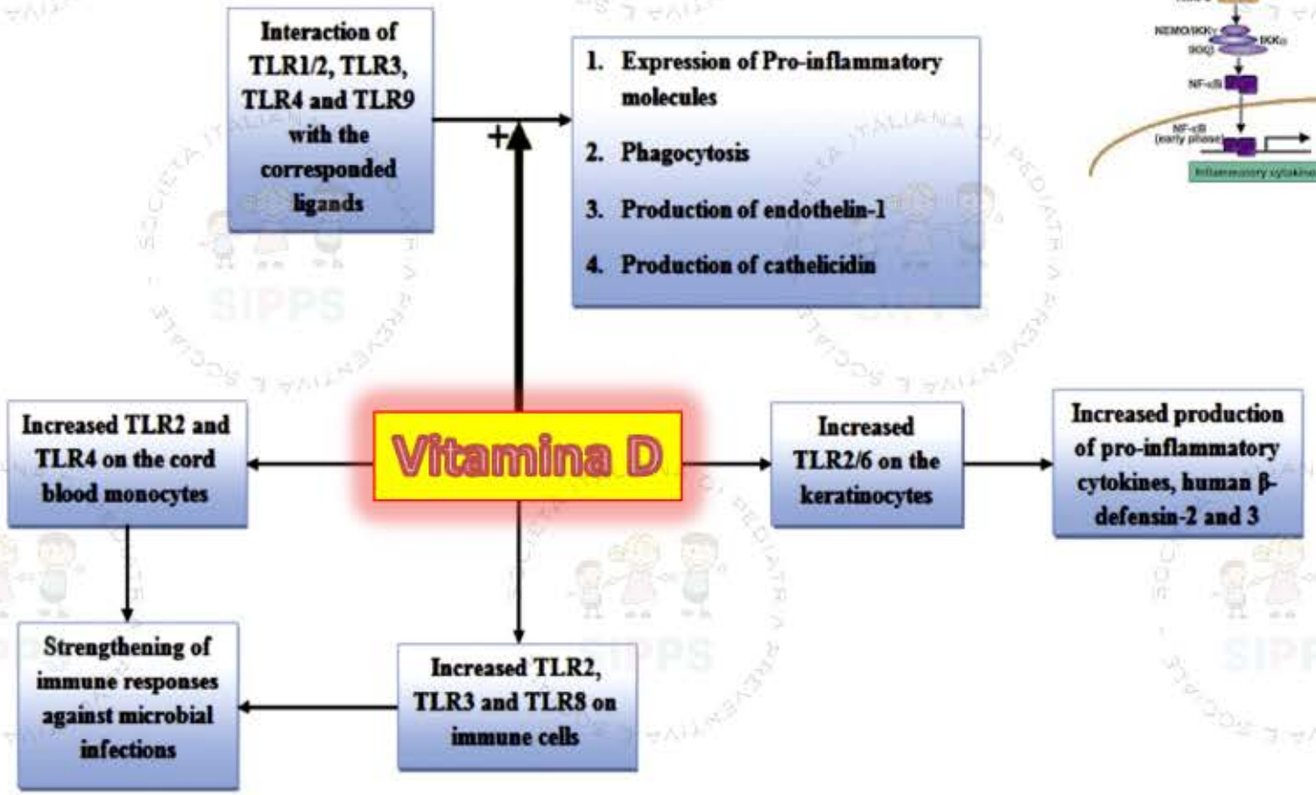


Peelen E. Autoimmunity Reviews 2011

Vitamin D and toll like receptors

Abababadi MK et al Life Sciences 2018; 203: 105–111



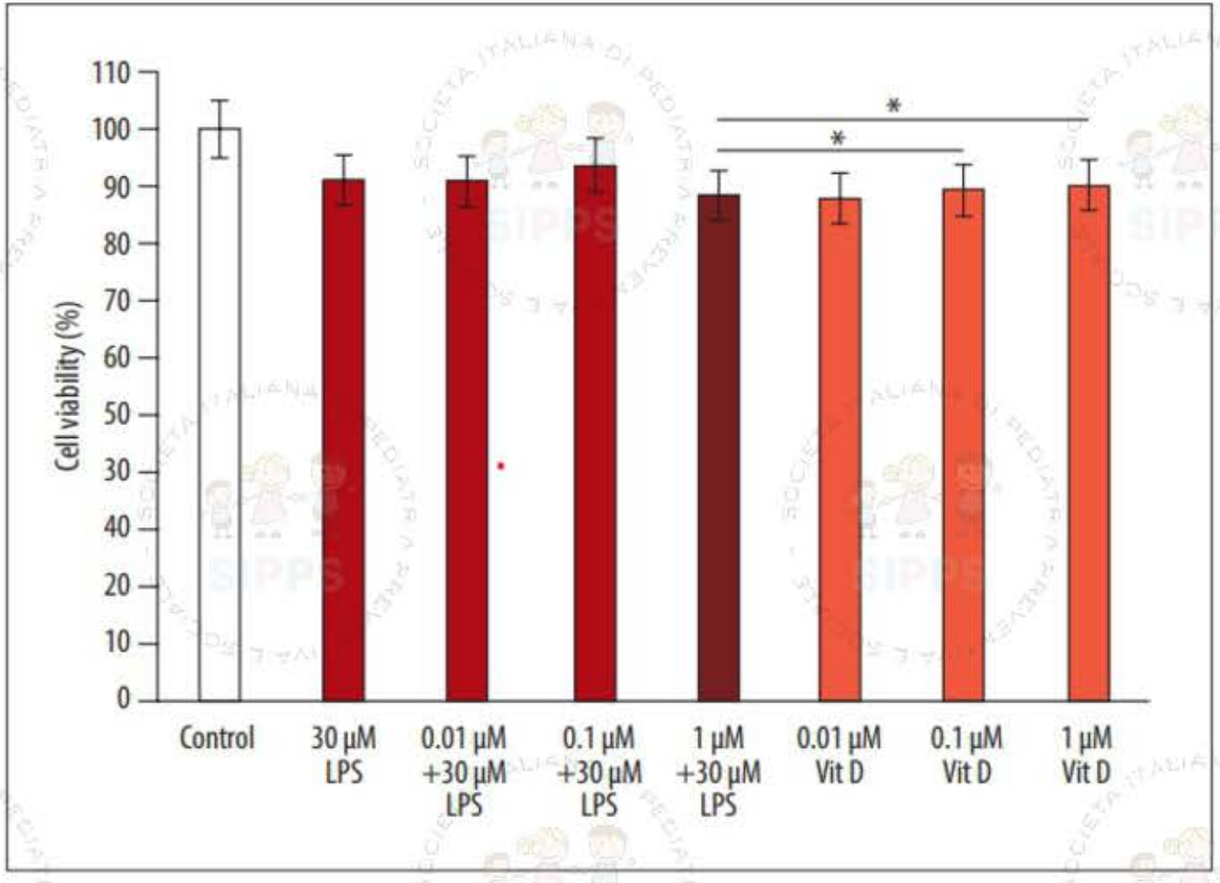


Gli effetti della vitamina D (VD) sull'espressione dei TLR durante le malattie infettive.
La VD aumenta la risposta immune in neonati attraverso l'up-regulation di TLR2 e TLR4 sui monociti del sangue del cordone ombelicale. VD aumenta l'espressione di TLR2, TLR3 e TLR8 sulle cellule immunitarie adulte con azione antimicrobica. La vitamina up-regola TLR2 / 6 sui cheratinociti con aumento della produzione di β-defensina.

Vitamin D Inhibits Lipopolysaccharide (LPS)-Induced Inflammation in A549 Cells by Downregulating Inflammatory Cytokines *Gatera VA et al Med Sci Monit Basic Res, 2021; 27: e931481*

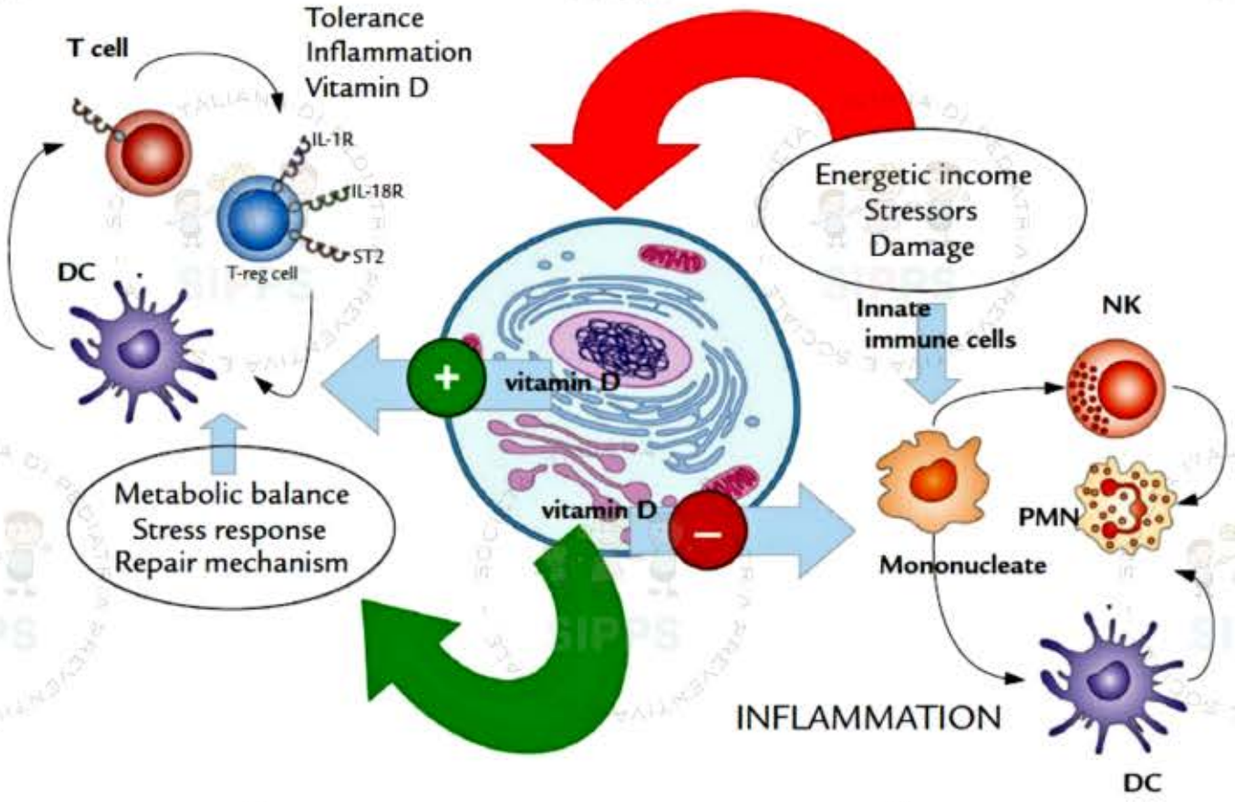
I nostri risultati hanno indicato che la vitamina D ha favorito la sopravvivenza cellulare dopo infiammazione indotta da LPS sopprimendo l' NFK delle cellule B attivate, il TNF-alfa, IL-1b, IL-6 e IL- 12.

Conclusioni: questi risultati hanno indicato che la vitamina D ha il potenziale per gestire l'infiammazione polmonare



The Role of Vitamin D in the Immune System as a Pro-survival Molecule

Chirumbolo S et al Clinical Therapeutics 2017; 39



I segnali di *stress* (**freccia rossa**) entrano nella cellula e provocano **l'attivazione della vitamina D** contro la risposta allo stress e una **risposta antinfiammatoria** (**freccia verde**) di tipo T-helper 2 e di tipo T regolatorio (T-reg).

La Vit. D agisce sincronizzando i segnali oscillatori del calcio per consentire l'autofagia cellulare o l'apoptosi durante la risposta allo stress

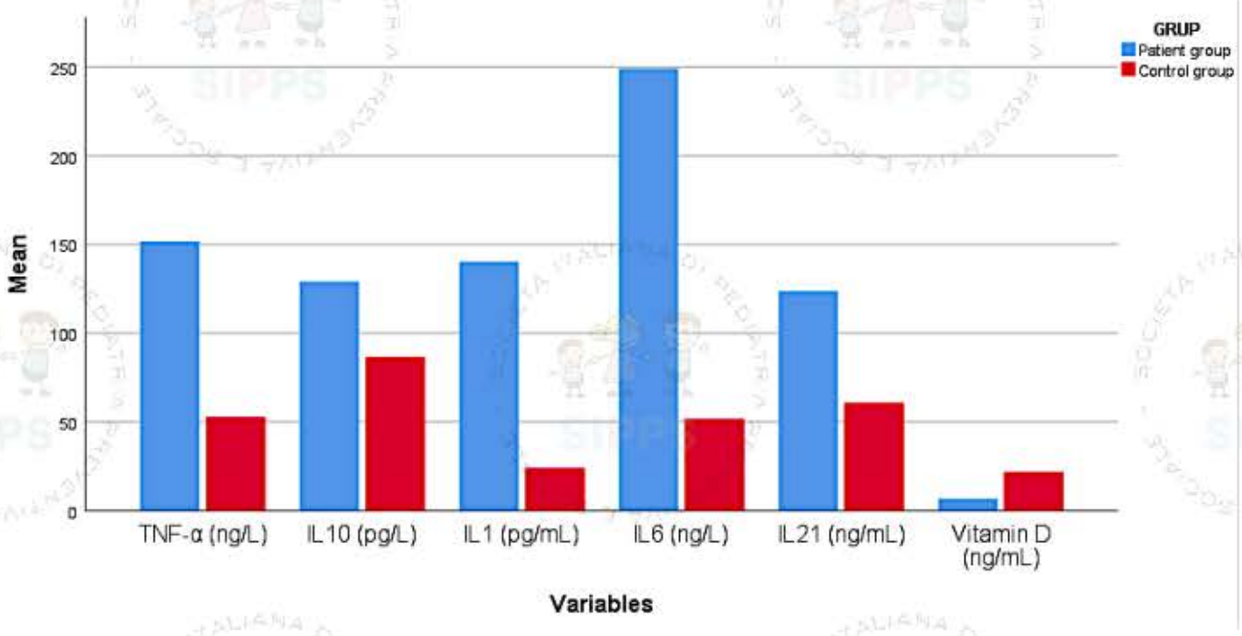
Il ruolo immunomodulante della vitamina D e le nuove evidenze cliniche

Vitamina D: Il ruolo immunomodulante

→ Vitamina D e COVID 19

Analysis of serum cytokine and protective vitamin D levels in severe cases of COVID-19 *Bayraktar N et al J Med Virol. 2021 Aug 24.*

74 Patients were divided into two groups. Patients with the COVID-19 group (n = 31), and individuals without a history of serious illness or infection used as the control group (n = 43). The serum concentrations of interleukin-1 (IL-1), IL-6, IL-10, IL-21, and TNF-α were measured by enzyme-linked immunosorbent assays (ELISA). Levels of serum vitamin D were detected



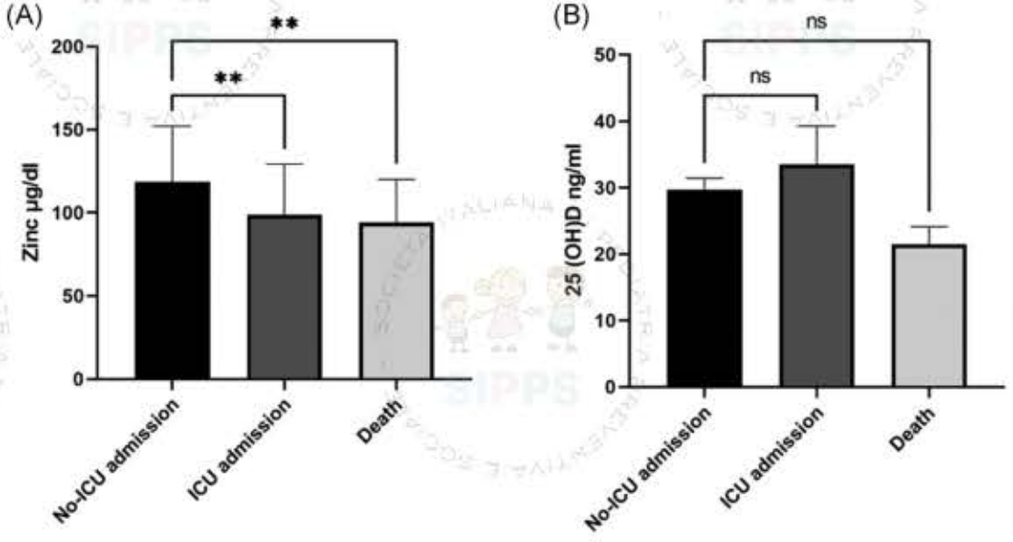
The serum cytokine levels in COVID-19 pateint group were significantly higher (151.59 ± 56.50, 140.37 ± 64.32, 249.02± 62.84, 129.04 ±31.64, and 123.58± 24.49, respectively) from control groups. Serum vitamin D was also significantly low (6.82 ± 3.29) in patients with the COVID-19 group than the controls (21.96 ± 5.39).

Evaluation of the relationship between serum levels of zinc, vitamin B12, vitamin D, and clinical outcomes in patients with COVID-19

Shakeri *et al J Med Virol. 2021 1-6.*

JOURNAL OF MEDICAL VIROLOGY

We measured serum levels of zinc, **25(OH)D**, and vitamin B12 within 3 days of admission. Of the 293 hospitalized, the median age was 53 years. Thirty-seven patients (12.62%) were admitted to the intensive care unit (ICU), and forty-two (14.32%) died. We found that the serum levels of zinc, vitamin B12, and **25(OH)D** were lower in patients who died than those who were admitted to ICU or non-ICU and survived; however, these differences were not statistically significant for vitamin B12 and 25(OH)D ($p > 0.05$)



Variable	Length of hospital stay			Intubation		
	< 7 day	≥ 7 days	*p* value	Need	No-Need	*p* value
Zinc	114.9 ± 34.17	115.4 ± 34.17	0.92	122.5 ± 29.18	114.4 ± 33.92	0.37
25(OH)D	26.38 ± 19.11	32.30 ± 19.64	0.13	15.01 ± 13.27	30.29 ± 19.42	0.006
Vitamin B12	426.6 ± 45.13	532.5 ± 51.86	0.06	443.8 ± 68.08	490.9 ± 40.75	0.71

Note: Data are the mean ± *SD*. *$p < 0.05$ was considered statistically significant.

The Relationship Between Vitamin D Levels and Severity in Illness in COVID-19 Patients: A Cross- Sectional Study *Nimavat N et al. Cureus March 14, 2022*

A cross-sectional study was conducted at a tertiary care hospital in India.
The aim was to quantify Vitamin D among COVID-19 patients. The study compared Vitamin D deficiency and insufficiency among different groups, i.e., age, sex, BMI, comorbidity, etc. Diabetes and hypertension **were evaluated as risk factors for mortality.**

Results: A total of 225 patients were investigated. Of these, 13.6% had Vitamin D deficiency and 38.9% had insufficiency. **Vitamin D level was statistically significant among different age groups, sex, and smokers.**
Patients aged >60 years were 23 times more likely to have a severe illness (adjusted OR (aOR) 23.53, 95%CI 4.67-118.61), whereas those aged 40 to 60 years were 11 times more likely to have a severe illness (aOR 10.86, 95%CI 2.39-49.31). Patients with many comorbidities, on the other hand, had a tenfold greater chance of severe COVID-19 (aOR 9.94, 95%CI 2.47-39.88). **A deficiency of vitamin D increased the chance of a serious illness by nearly five times** (aOR 4.72, 95%CI 1.31-17.03).

Conclusion: Vitamin D level was associated with severity of illness; it can be used to estimate the prognosis of COIVD-19 patients and aid in the modification of treatment protocols.

Characteristics	Disease severity		p-value	Disease mortality		p-value
	Non-severe	Severe		No	Yes	
Age (year), Mean (SD)	43.0 (15.4)	59.8 (15.0)	0.206	43.3 (15.4)	62.8 (14.5)	<0.001
Age category (years)						
<40	94 (96.9)	3 (3.1)	<0.001	95 (97.9)	2 (2.1)	<0.001
41-60	73 (83.9)	14 (16.1)		79 (90.8)	8 (9.2)	
>60	25 (61.0)	16 (39.0)		26 (63.4)	15 (36.6)	
Sex						
Male	125 (81.7)	28 (18.3)	0.025	131 (85.6)	22 (14.4)	0.023
Female	67 (93.1)	5 (6.9)		69 (95.8)	3 (4.2)	
BMI (kg/m2), Mean (SD)	24.4 (4.3)	25.3 (4.2)	0.715	24.5 (4.3)	25.4 (4.8)	0.321
BMI						
Obese	18 (78.3)	5 (21.7)	0.107	19 (82.6)	4 (17.4)	0.202
Overweight	60 (78.9)	16 (21.1)		64 (84.2)	12 (15.8)	
Normal	102 (90.3)	11 (9.7)		105 (92.9)	8 (7.1)	
Underweight	12 (92.3)	1 (7.7)		12 (92.3)	1 (7.7)	
Alcohol intake						
No	147 (86.0)	24 (14.0)	0.634	152 (88.9)	19 (11.1)	1.000
Yes	45 (83.3)	9 (16.7)		48 (88.9)	6 (11.1)	
Smoking						
No	153 (88.4)	20 (11.6)	0.016	158 (91.3)	15 (8.7)	0.034
Yes	39 (75.00	13 (25.0)		42 (80.8)	10 (19.2)	
Comorbidity						
Multiple	6 (35.3)	11 (64.7)	<0.001	10 (58.8)	7 (41.2)	<0.001
Single	31 (79.5)	8 (20.5)		32 (82.1)	7 (17.9)	
No comorbidity	155 (91.7)	14 (8.3)		158 (93.5)	11 (6.5)	
Vitamin D level (ng/ml), Mean (SD)	21.7 (10.2)	18.1 (14.7)	0.030	21.6 (10.9)	17.5 (11.3)	0.084
Vitamin D status						
Deficient	19 (63.3)	11 (36.7)	<0.001	23 (76.7)	7 (23.3)	0.050
Insufficient	77 (87.5)	11 (12.5)		78 (88.6)	10 (11.4)	
Optimal	96 (89.7)	11 (10.3)		99 (92.5)	8 (7.5)	

Association of vitamin D and severity of COVID-19 in children

Karimian P et al. Eur J Transl Myol 32 (2): 10453, 2022

This cross-sectional study was performed on 101 COVID 19 infected children from September 2020 to October 2021. The average of children was 2.85 ± 0.85 years.

RESULTS:

Low oxygen saturation was observed in 35.3% of infected children.

Clinical signs in cases with deficient vitamin D levels were more severe in terms of tachypnea and tachycardia (p = 0.01) and children with vitamin D lower than 10 ng/ml showed more frequency (p = 0.02).

Vitamin D levels were associated with levels of involvement, tachycardia, tachypnea, clinical signs, gastrointestinal problems, and O2 levels.

Statistical correlation findings demonstrated **that vitamin D levels were considerably related with disease severity (p < 0.01).** .

Table 2. Distribution of Levels of vitamin D by age group

	Vitamin D levels (ng/mL)					p-value
Age	Less than 10	10-20	21-30	More than 30	Total	
Under two years	45.0%	47.7%	46.0%	53.7%	47.4%	0.20
More than two years	55.0%	52.3%	54.0%	46.3%	52.6%	
Total	100%	100%	100%	100%	100%	

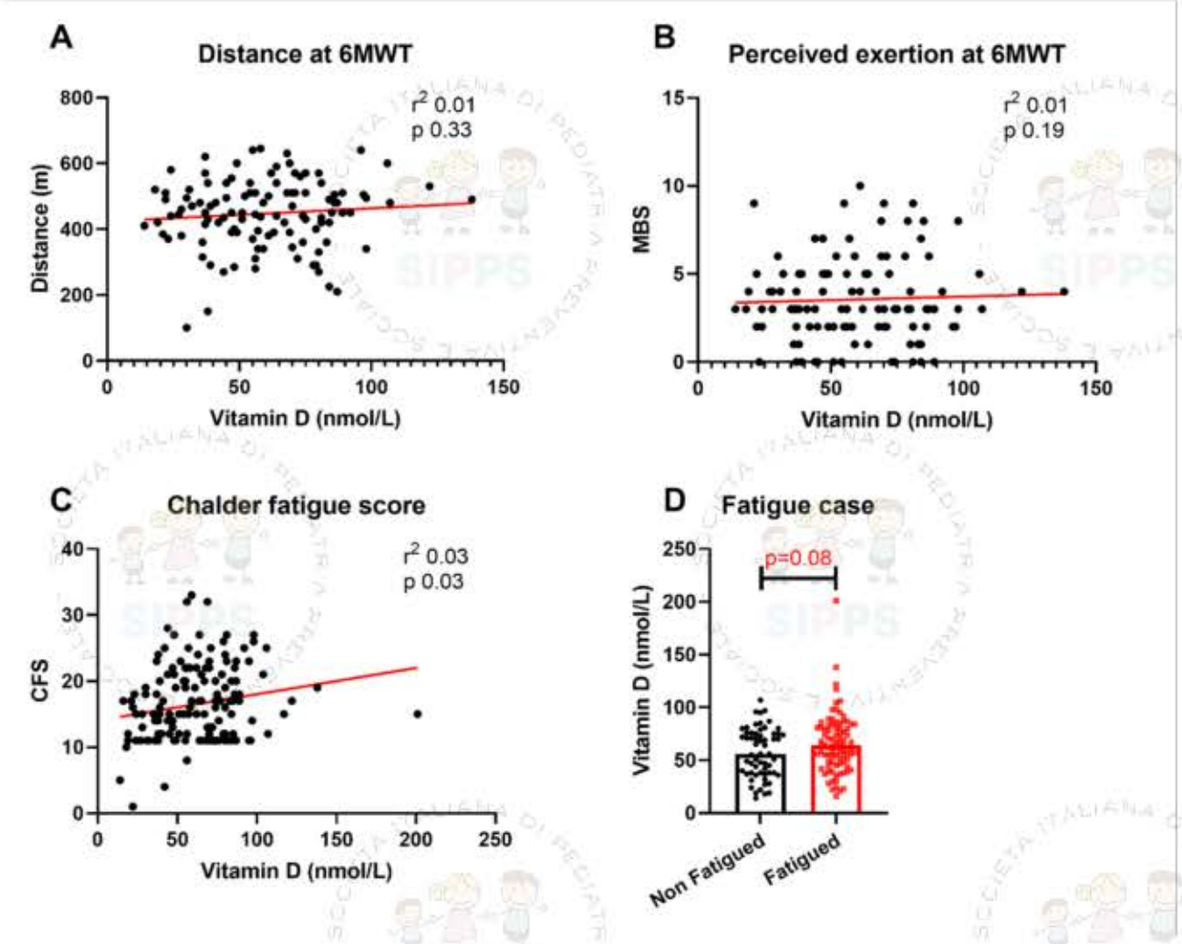
Table 4. Association among vitamin D levels and disease severity based on clinical findings

	Disease severity based on clinical findings			p-value
	Outpatient (mild)	Hospitalization (moderate)	ICU hospitalization (severe)	0.000
Vitamin levels less than 10	0.0%	25.0%	75.0%	
Vitamin levels between 10-20	0.0%	50.0%	50.0%	
Vitamin levels between 21-30	4.2%	70.8%	25.0%	
Vitamin levels more than 30	32.0%	62.0%	6.0%	
Total	17.7%	60.4%	21.9%	

Investigating the Relationship between Vitamin D and Persistent Symptoms Following SARS-CoV-2 Infection

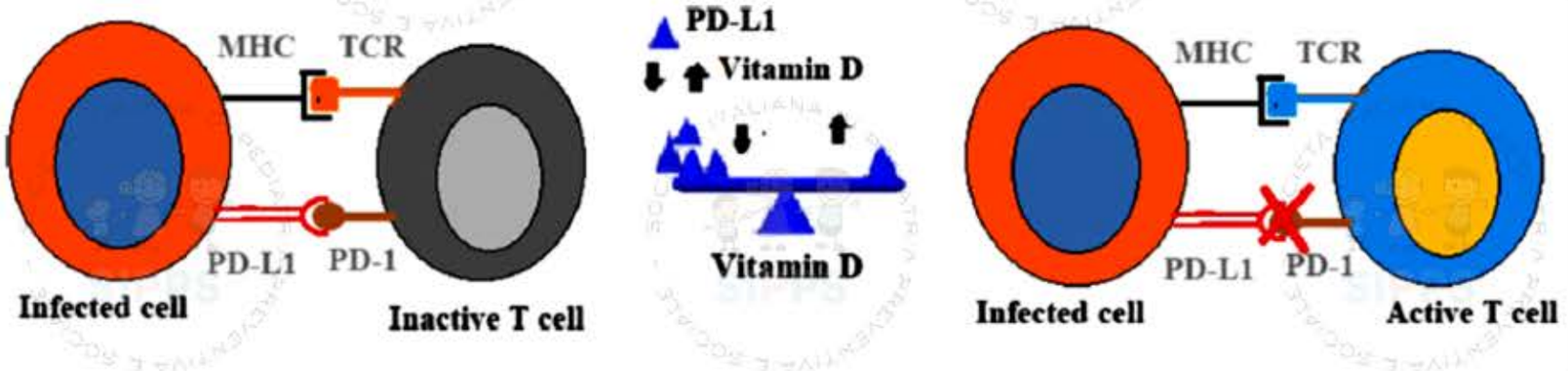
Townsend L et al Nutrients 2021, 13, 2430.

The persistent symptoms following SARS-CoV-2 infection, known as **long COVID.** The cardinal features are fatigue and reduced exercise tolerance. We hypothesize that vitamin D levels are associated with persistent symptoms following COVID-19. Herein, we investigate the relationship between vitamin D and fatigue and reduced exercise tolerance, assessed by the six-minute walk test. Multivariable linear and logistic regressionnmodels were used to evaluate the relationships. A total of **149 patients were recruited at a median of 79 days after COVID-19 illness**. The median vitamin D level was 62 nmol/L, with n = 36 (24%) having levels 30–49 nmol/L and n = 14 (9%) with levels <30 nmol/L. Fatigue was common, with n = 86 (58%) meeting the case definition. **RESULTS: These results suggest that persistent fatigue and reduced exercise tolerance following COVID-19 are independent of vitamin D.**



Vitamin D can reduce severity in COVID-19 through regulation of PD-L1 *Aygun H . Archives of Pharmacology (2022) 395:487–494*

La caratteristica tipica di COVID-19 è la deplezione dei linfociti, in particolare dei linfociti T. Nelle infezioni da COVID-19, esiste l'aumentata espressione delle **molecole del checkpoint immunitario inibitorio (PD-1/PD-L1) sulle superfici dei linfociti T**. È stato dimostrato che i livelli di PD-1/PD-L1 aumentano negli individui gravemente infetti da COVID-19.



Dopo il legame di PD-1 PD-L1, le cellule T diventano inattive e vanno in apoptosi e si sviluppa immunosoppressione. La vitamina D mantiene i livelli di PD-L1 in equilibrio. Quindi l'effetto immunosoppessivo di PD-L1 sul sistema immunitario scompare

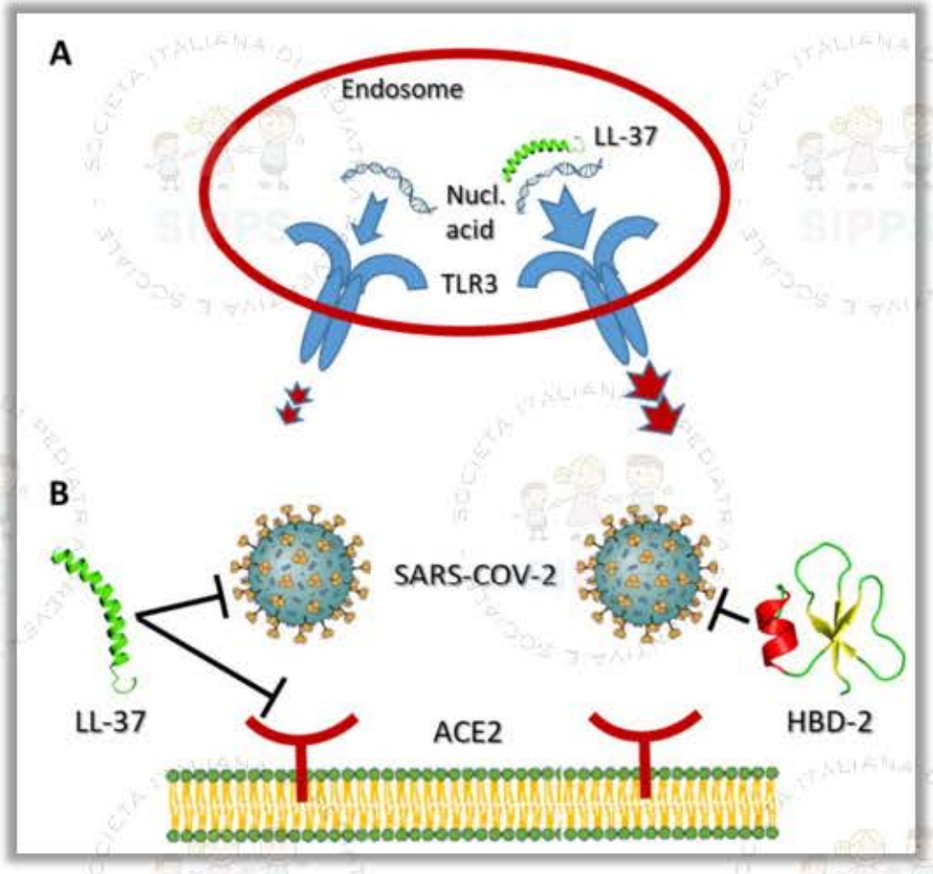
programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1

Emerging Roles of Vitamin D-Induced Antimicrobial Peptides in Antiviral Innate Immunity *White JH Nutrients 2022, 14, 284*

Contributions of vitamin D-induced AMPs to antiviral immunity.

(A) Interaction of the positively charged **LL-37 (catelicidina)** with nucleic acid augments binding and signaling through nucleic acid sensing TLRs.

(B) **Interactions of LL-37 and HBD-2 with SARS-COV-2 spike protein and/or cell surface receptor ACE2 block viral entry**



I BAMBINI CHE VANNO AL MARE SI AMMALANO DI MENO

Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis *Martineau AR et al Health Technology Assessment 2019;2:23*

INCLUDED STUDIES

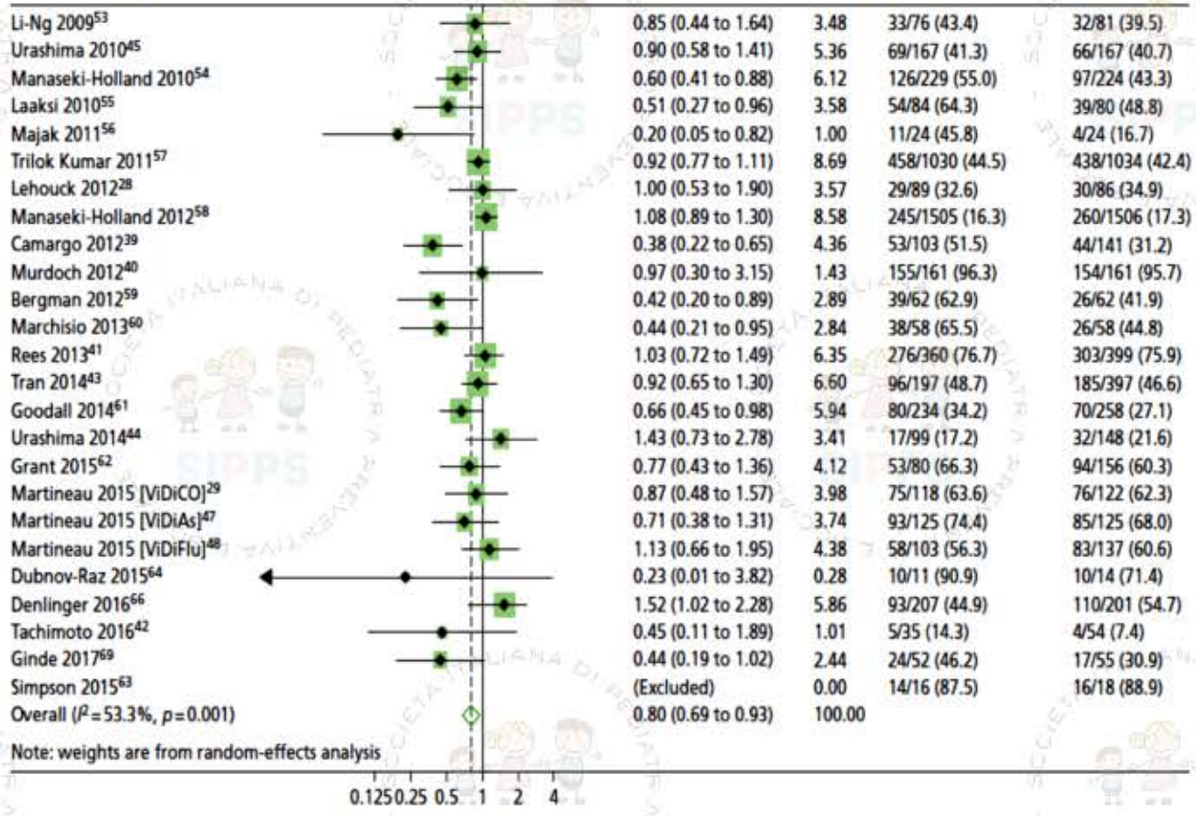
10,933 people from 25 trials conducted in 15 countries. All of the studies compared vitamin D with placebo (dummy medication), which is the gold standard trial design.

KEY RESULTS

Overall, vitamin D supplements reduced the risk of having at least one ARI from 42% to 39%. We also showed that **vitamin D had greater protective effects when it was given daily or weekly to people with the lowest vitamin D levels: the risk of having at least one ARI was reduced from 60% to 32% in these individuals.**

CONCLUSION

Taking a vitamin D supplement can protect against ARIs. The strongest effects are seen when a daily or weekly supplement is given to people with the lowest vitamin D levels.



First author and year	aOR (95% CI)	% weight	Proportion with ≥1 ARI, subgroup (%) Control	Intervention
Li-Ng 2009[53]	0.85 (0.44 to 1.64)	3.48	33/76 (43.4)	32/81 (39.5)
Urashima 2010[45]	0.90 (0.58 to 1.41)	5.36	69/167 (41.3)	66/167 (40.7)
Manaseki-Holland 2010[54]	0.60 (0.41 to 0.88)	6.12	126/229 (55.0)	97/224 (43.3)
Laaksi 2010[55]	0.51 (0.27 to 0.96)	3.58	54/84 (64.3)	39/80 (48.8)
Majak 2011[56]	0.20 (0.05 to 0.82)	1.00	11/24 (45.8)	4/24 (16.7)
Trilok Kumar 2011[57]	0.92 (0.77 to 1.11)	8.69	458/1030 (44.5)	438/1034 (42.4)
Lehouck 2012[28]	1.00 (0.53 to 1.90)	3.57	29/89 (32.6)	30/86 (34.9)
Manaseki-Holland 2012[58]	1.08 (0.89 to 1.30)	8.58	245/1505 (16.3)	260/1506 (17.3)
Camargo 2012[39]	0.38 (0.22 to 0.65)	4.36	53/103 (51.5)	44/141 (31.2)
Murdoch 2012[40]	0.97 (0.30 to 3.15)	1.43	155/161 (96.3)	154/161 (95.7)
Bergman 2012[59]	0.42 (0.20 to 0.89)	2.89	39/62 (62.9)	26/62 (41.9)
Marchisio 2013[60]	0.44 (0.21 to 0.95)	2.84	38/58 (65.5)	26/58 (44.8)
Rees 2013[41]	1.03 (0.72 to 1.49)	6.35	276/360 (76.7)	303/399 (75.9)
Tran 2014[43]	0.92 (0.65 to 1.30)	6.60	96/197 (48.7)	185/397 (46.6)
Goodall 2014[61]	0.66 (0.45 to 0.98)	5.94	80/234 (34.2)	70/258 (27.1)
Urashima 2014[44]	1.43 (0.73 to 2.78)	3.41	17/99 (17.2)	32/148 (21.6)
Grant 2015[62]	0.77 (0.43 to 1.36)	4.12	53/80 (66.3)	94/156 (60.3)
Martineau 2015 [ViDiCO][29]	0.87 (0.48 to 1.57)	3.98	75/118 (63.6)	76/122 (62.3)
Martineau 2015 [ViDiAs][47]	0.71 (0.38 to 1.31)	3.74	93/125 (74.4)	85/125 (68.0)
Martineau 2015 [ViDiFlu][48]	1.13 (0.66 to 1.95)	4.38	58/103 (56.3)	83/137 (60.6)
Dubnov-Raz 2015[64]	0.23 (0.01 to 3.82)	0.28	10/11 (90.9)	10/14 (71.4)
Denlinger 2016[66]	1.52 (1.02 to 2.28)	5.86	93/207 (44.9)	110/201 (54.7)
Tachimoto 2016[42]	0.45 (0.11 to 1.89)	1.01	5/35 (14.3)	4/54 (7.4)
Ginde 2017[69]	0.44 (0.19 to 1.02)	2.44	24/52 (46.2)	17/55 (30.9)
Simpson 2015[63]	(Excluded)	0.00	14/16 (87.5)	16/18 (88.9)
Overall (I^2=53.3%, p=0.001)	0.80 (0.69 to 0.93)	100.00		

Note: weights are from random-effects analysis

Two-step IPD meta-analysis, proportion of participants experiencing at least one ARI. Data from the trial by Simpson et al.63 were not included in this two-step meta-analysis, as an estimate for the effect of the intervention in the study could not be obtained in the regression model because of the small sample size.

GRAZIE

Quando dosare la vitamina D?

- Sospetto deficit sintomatico/rachitismo carenziale.
- Sospetto deficit grave di vit. D (fattori di rischio multipli) tale da richiedere trattamento.
- Sospetta patologia del metabolismo calcio-fosforo (es. "osteoporosi").
- Patologie croniche e/o farmaci interferenti con il metabolismo della vit. D.

Casi particolari (da individualizzare)

- Asma grave, steroido-resistente (prevenzione esacerbazioni).
- Infezioni respiratorie ricorrenti (prevenzione).
- Dermatite atopica grave non responsiva a tp convenzionale (score).

+ Sospetto deficit grave di vit. D

Quando NON dosare la vitamina D?

- Nel bambino "altrimenti sano".
- Nel bambino con scarsa esposizione alla luce solare.
- Nel bambino di colore "altrimenti sano".
- Nel bambino obeso "altrimenti sano".

Stile di vita

PROFILASSI

Vitamina D profilassi 1 - 18 anni

- Valutare lo stile di vita di bambini ed adolescenti e soprattutto l'esposizione solare.
- Nei soggetti a rischio di deficit, la profilassi con vitamina D può essere effettuata mediante la somministrazione giornaliera di 600-1.000 UI/die.
- I **principali fattori di rischio per deficit di vit. D**, quali ridotta esposizione alla luce solare (per stile di vita, cute iperpigmentata, copertura del corpo per motivi culturali o religiosi, eccessivo uso di filtri solari, residenza a latitudini elevate) oppure in presenza di condizioni patologiche o terapie interferenti con il metabolismo della vit. D come malassorbimento intestinale (celiachia alla diagnosi, fibrosi cistica, MICI), obesità, terapia croniche con farmaci antiepilettici, corticosteroidi sistemici, antiretrovirali o antifungini.
- L'Endocrine Society e l'AAP raccomandano che i **bambini obesi** o in terapia con questi farmaci ricevano dosi di vit. D almeno 2-3 volte superiori a quelle raccomandate per età

Vitamina D: Trattamento

- Per i bambini e gli adolescenti con deficit di **vitamina D, livelli di 25(OH)D < 20 ng/ml, si consiglia un trattamento con 2.000 UI/die o 50.000 UI/settimana di vitamina D3 per 6 settimane nei bambini e per 8 settimane negli adolescenti allo scopo di ottenere livelli di 25(OH)D > 30 ng/ml**
- Al termine di tale trattamento si consiglia una **terapia di mantenimento:** 400-1.000 UI/die di vitamina D per i soggetti entro il primo anno di vita e 600-1.000 UI/die di vitamina D per i soggetti tra 1 e 18 anni.

Da Consensus vitamina D -SIPPS

Vitamina D: Trattamento

- Per i bambini e gli adolescenti con **insufficienza di vitamina D**, [livelli di 25(OH)D compresi **tra 20 e 29 ng/ml,** si consiglia la profilassi con vitamina D 600-1.000 UI/die.
- Si può utilizzare la profilassi con dosi settimanali o mensili, per una dose cumulativa mensile di 18.000-30.000 UI di vit. D, nei casi di scarsa compliance, a partire dal 5°- 6° anno e in particolare nell'adolescente.

Da Consensus vitamina D -SIPPS

Vitamina D: Trattamento

- Per quanto riguarda la durata della profilassi, in caso di scarsa esposizione solare durante l'estate, **la vit. D può essere somministrata da ottobre a maggio e se vi sono fattori di rischio permanenti durante tutto l'anno.**

Da Consensus vitamina D -SIPPS