Vitamin D in pregnancy and early life
-implications for the mother and child

Elina Hyppönen, MSc, MPH, PhD
Reader in Epidemiology and Public Health

UCL Institute of Child Health, London, UK
Correspondence to: e.hypponen@ich.ucl.ac.uk

MRC | Centre of Epidemiology for Child Health

The child first and always

BBC

Vitamin D 'reduces risk of diabetes'

November, 2001

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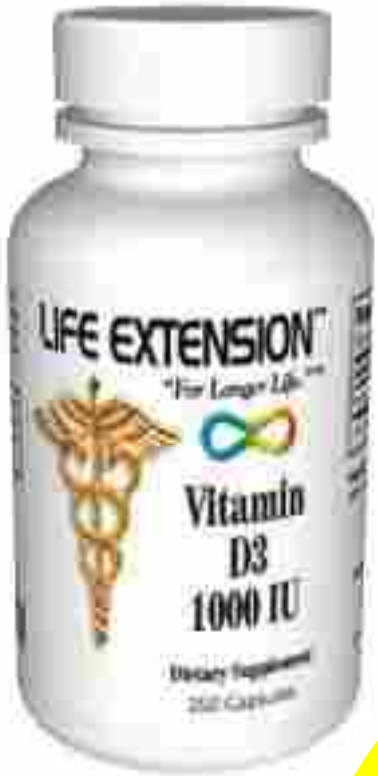

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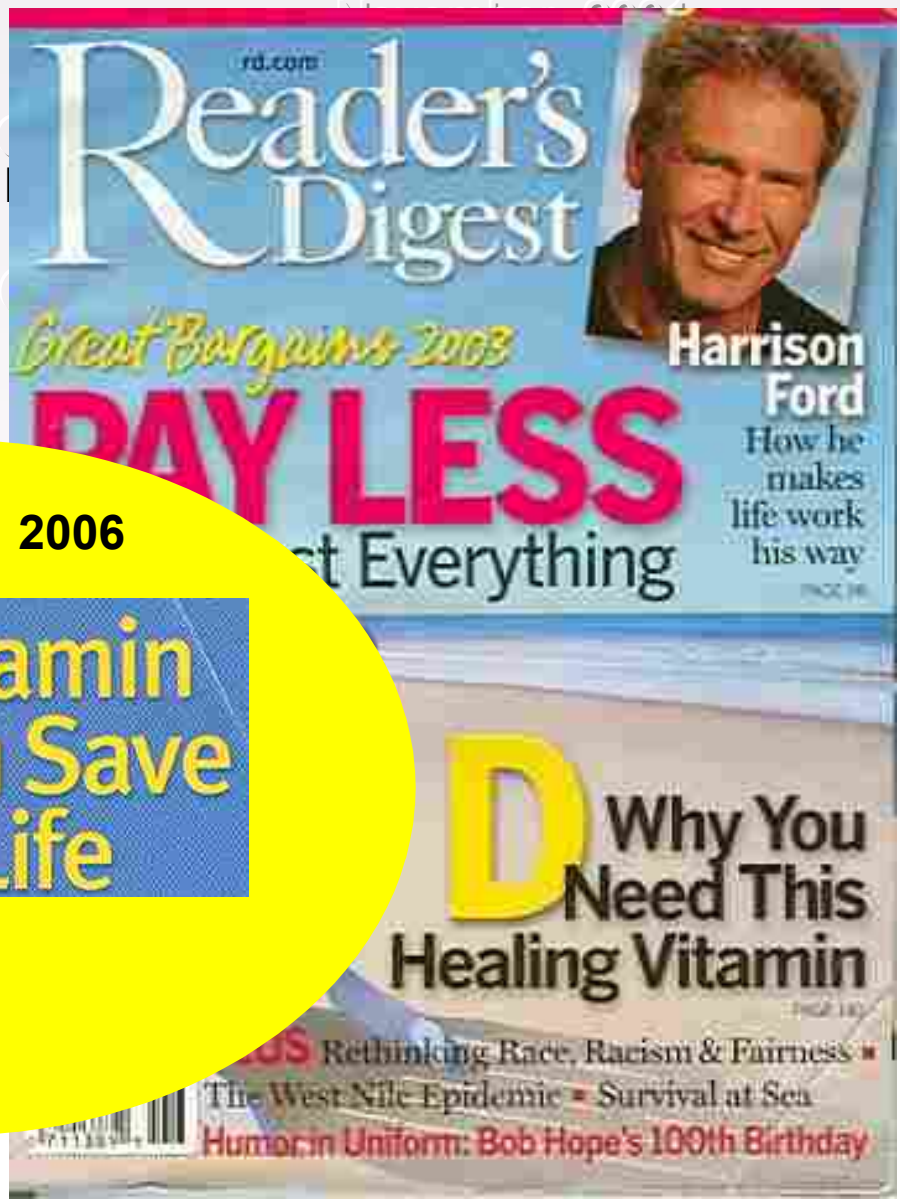
2006

One Vitamin That Can Save Your Life



Vitamin D

- Nutrient and pro-hormone

- Vitamin D receptors found from most tissues and organs of the body
  - Bone
  - Brain
  - Breast
  - Decidua
  - Heart
  - Immune cells
  - Placenta
  - Pancreas
  - Prostate
  - Etc.

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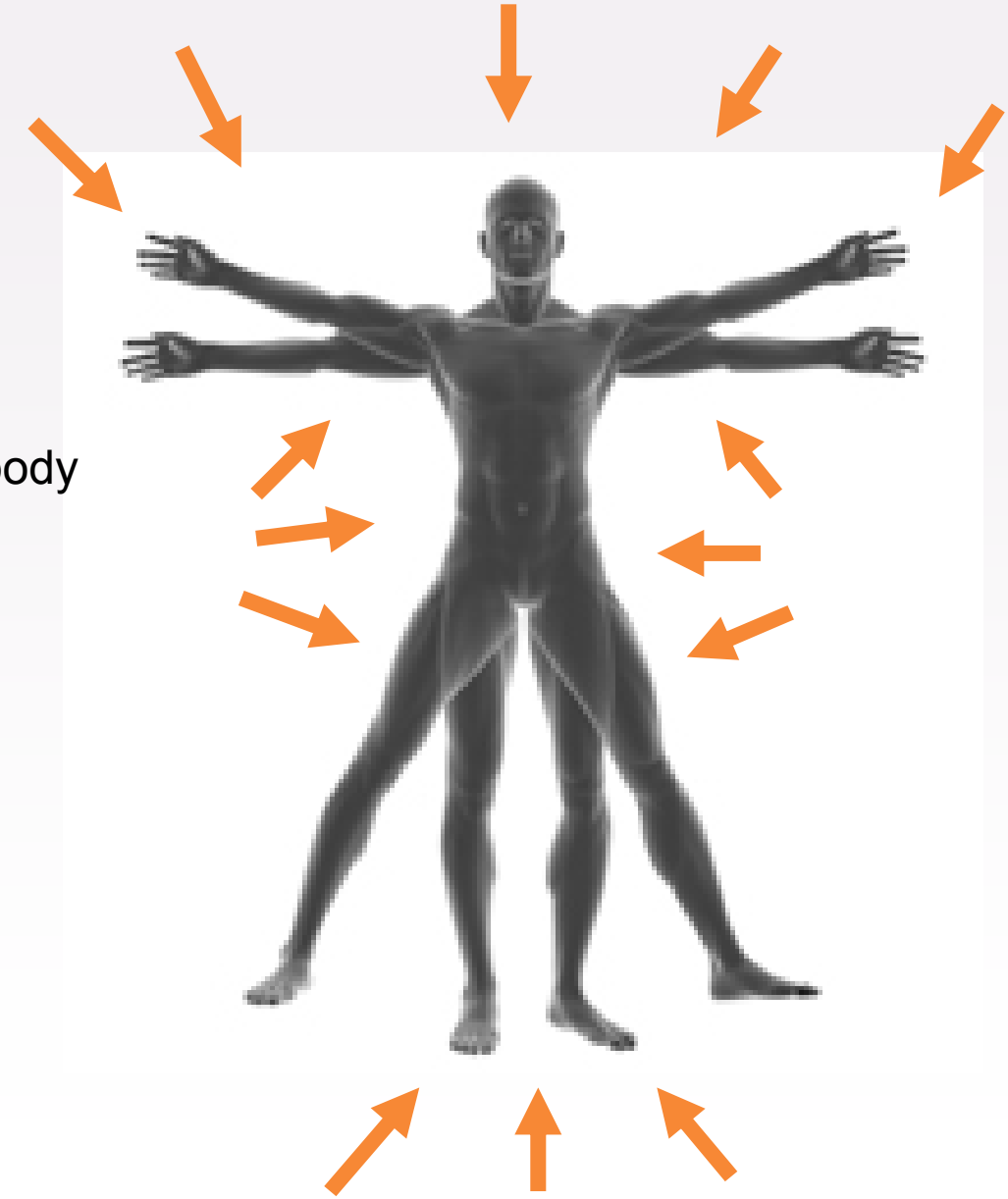


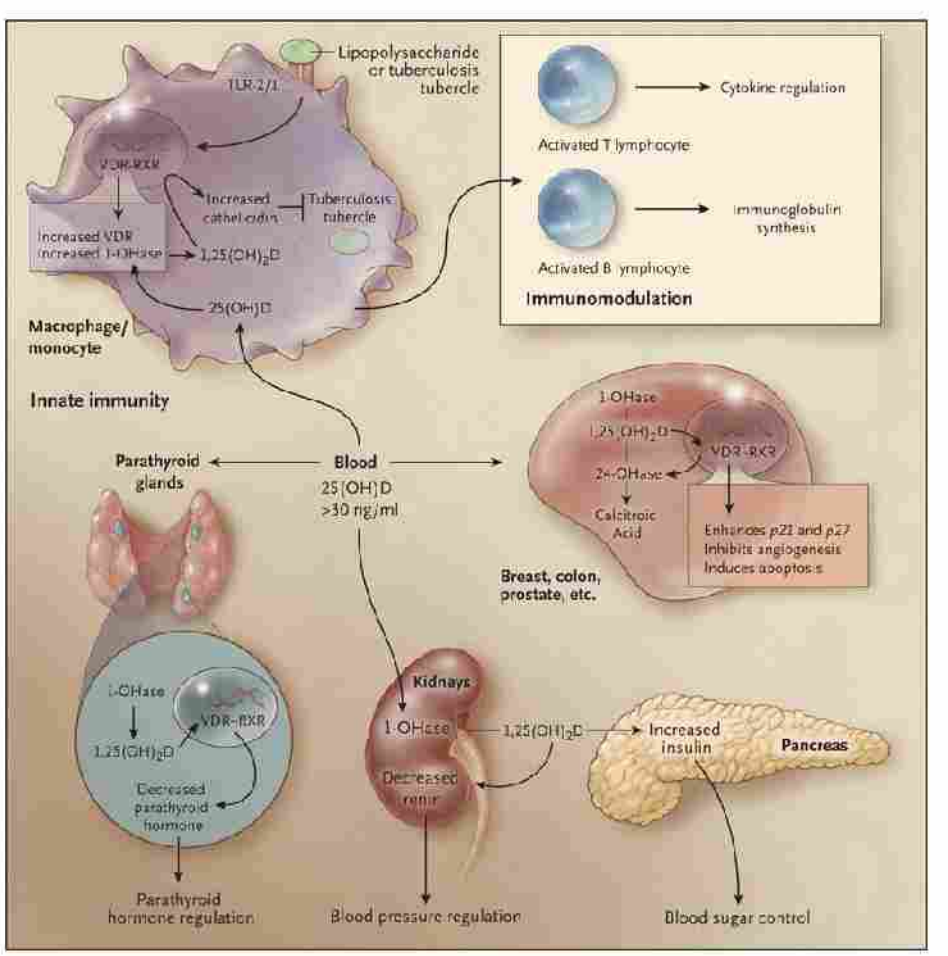
Proposed health effects of vitamin D

Regulation of calcium metabolism
Rickets, Osteomalacia
Osteoporosis
Fractures

Immunomodulatory effects
Type 1 diabetes
Multiple Sclerosis
Psoriasis
Arthritis
Inflammatory Bowel disease
Pre-eclampsia
Allergic diseases

Cardiovascular effects
Hypertension
Metabolic syndrome
CVD
Heart failure

Cell growth and regulation
Cancer risk
(prostate, colon, breast etc.)



Holick M. NEJM 2007

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UCL

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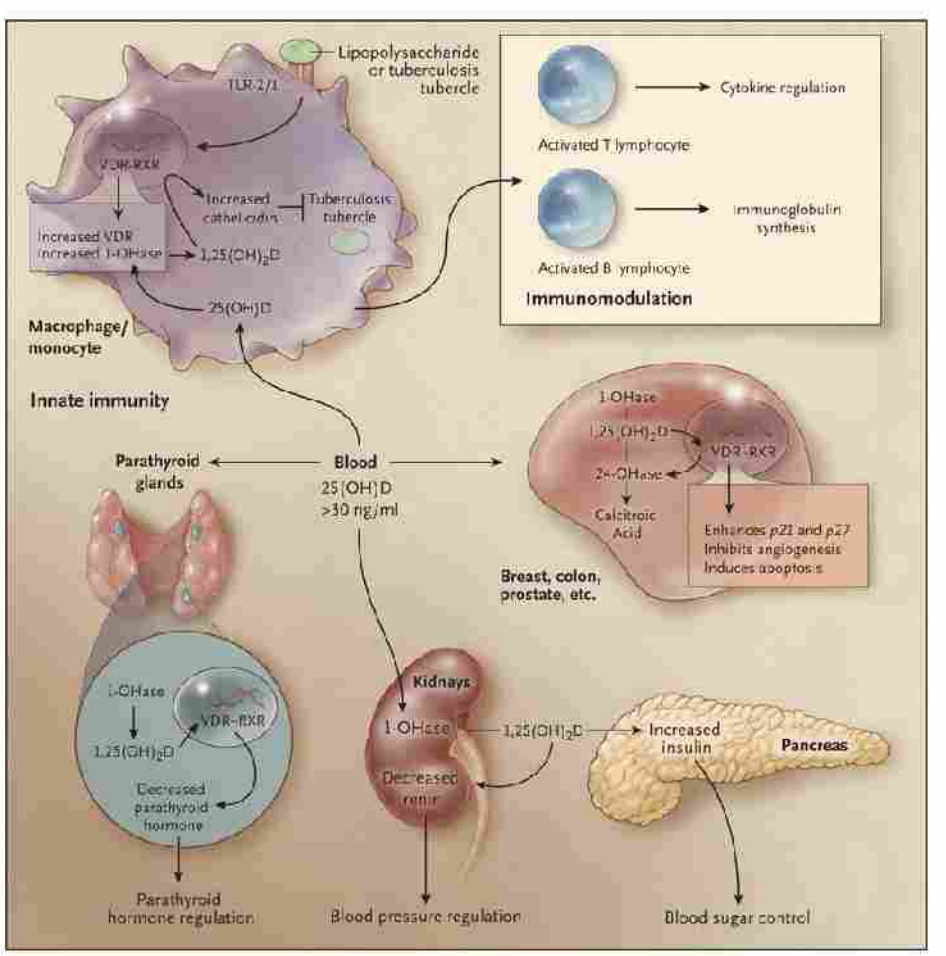


Holick M. NEJM 2007

Immunological link between vitamin D and miscarriage/pregnancy complications?

Pregnancy as an immunological challenge

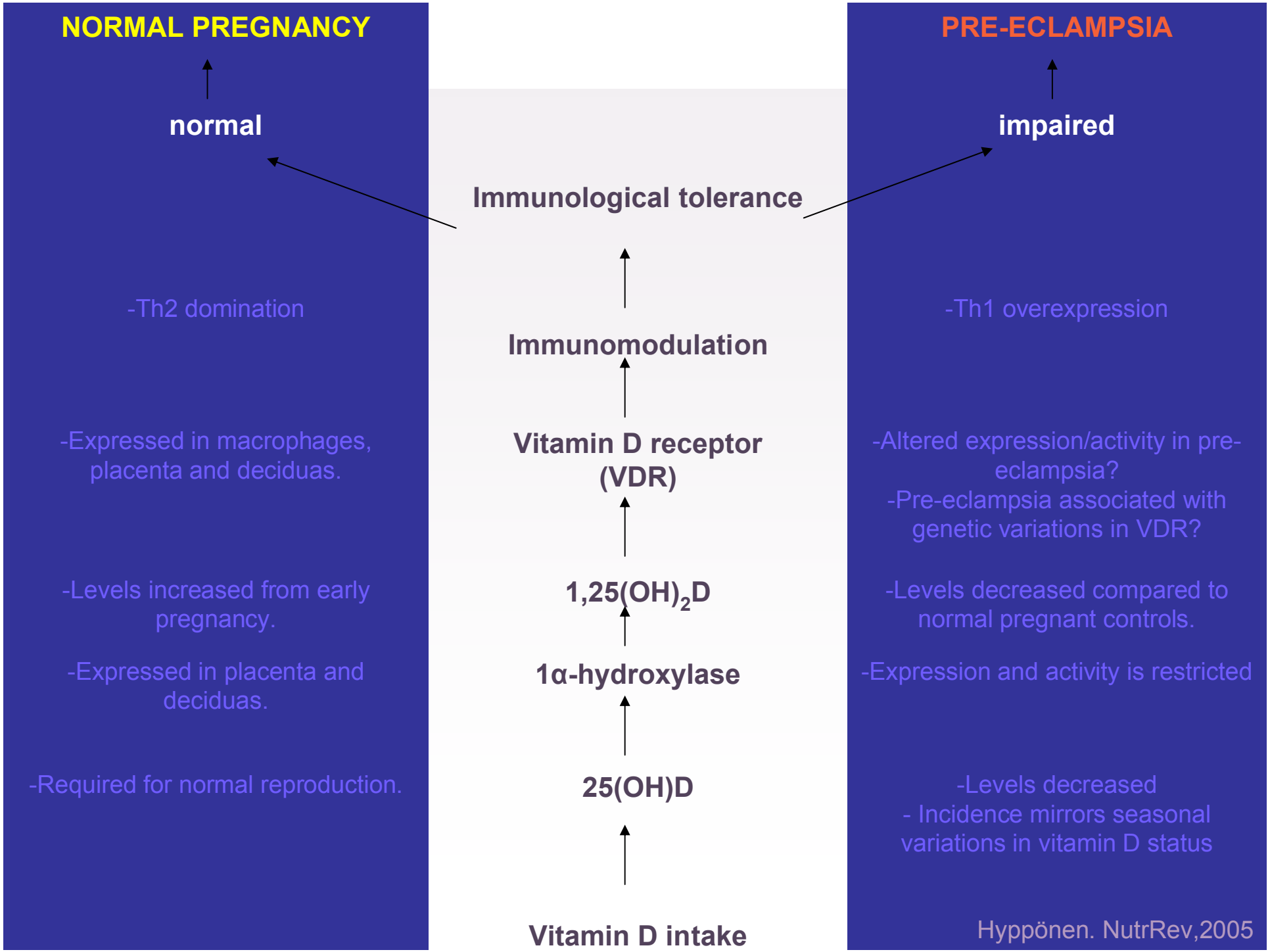
- Fetus is an allogenic tissue graft carrying paternally derived antigens.
- Immunological adaptation by a sift towards a domination by the T helper type 2 (Th2) cytokine response required for the maintenance of normal pregnancy
  - Th1 type reaction in the placenta correlated with spontaneous preterm delivery and miscarriage, possible role in pre-eclampsia

Vitamin D - Immunomodulatory properties

- Active vitamin D attenuates Th1-mediated immune response
  - Reduces secretion of INF-γ, IL-2, IL-12
- Affects dendritic cell maturation
- Affects regulatory T-cell activity

Vitamin D may be able to prevent the immune maladaptation and loss of tolerance in pre-eclampsia / miscarriage ?

Hyppönen. NutrRev,2005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Immunomodulation
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1,25(OH)2D
1α-hydroxylase
25(OH)D
Vitamin D intake
PRE-ECLAMPSIA
impaired
-Th1 overexpression
-Altered expression/activity in pre-eclampsia?
-Pre-eclampsia associated with genetic variations in VDR?
-Levels decreased compared to normal pregnant controls.
-Expression and activity is restricted
-Levels decreased
- Incidence mirrors seasonal variations in vitamin D status
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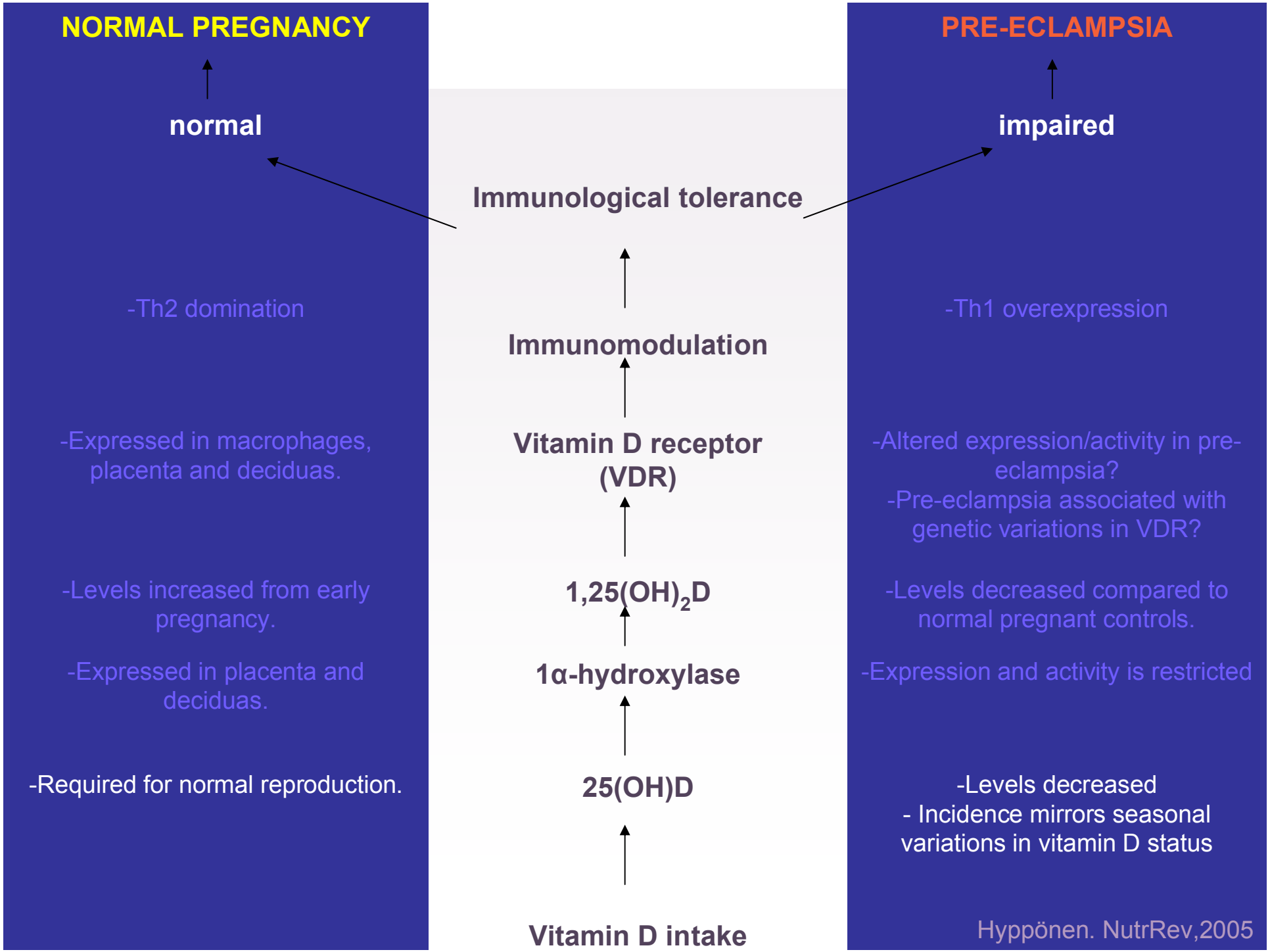
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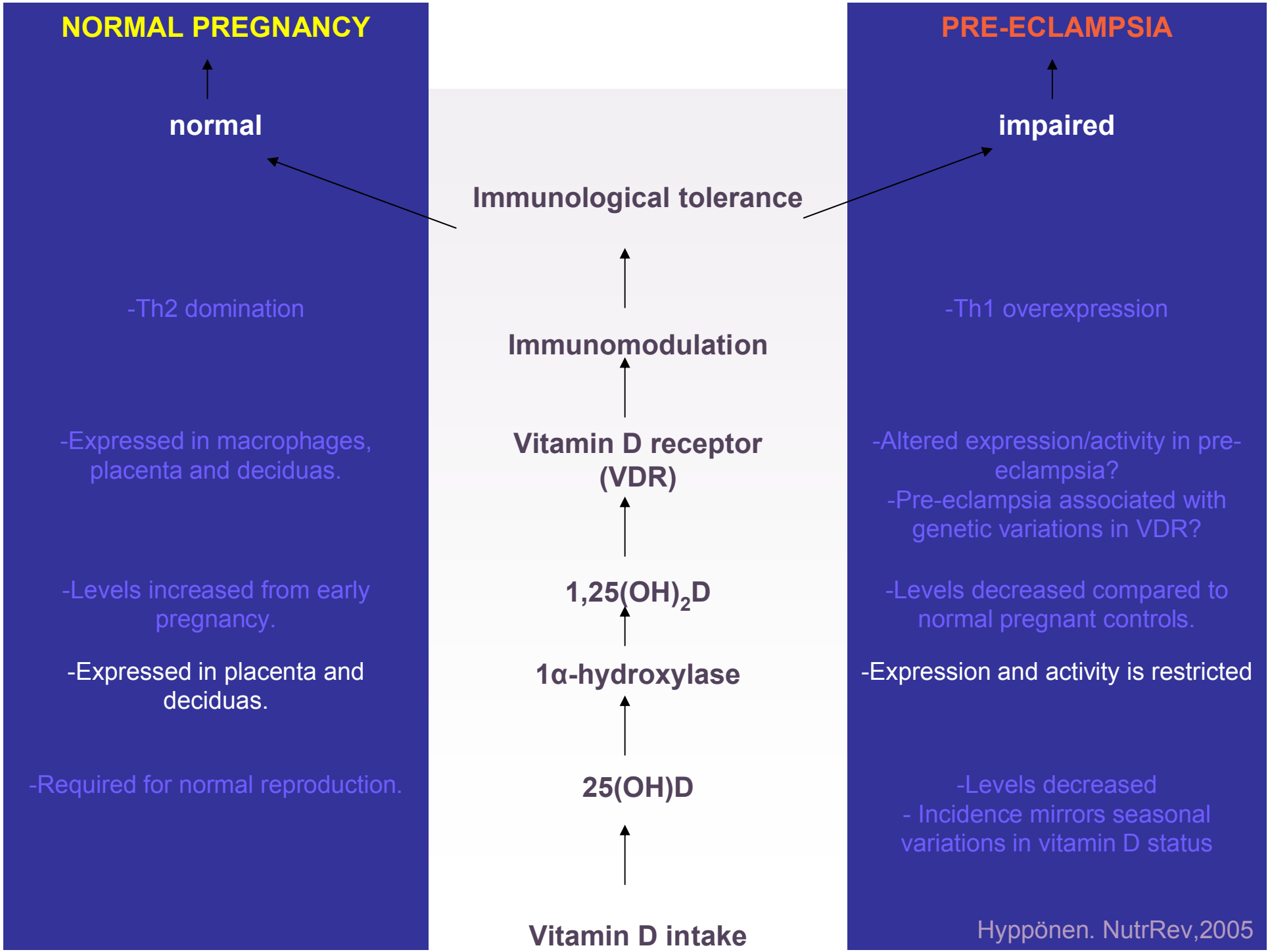
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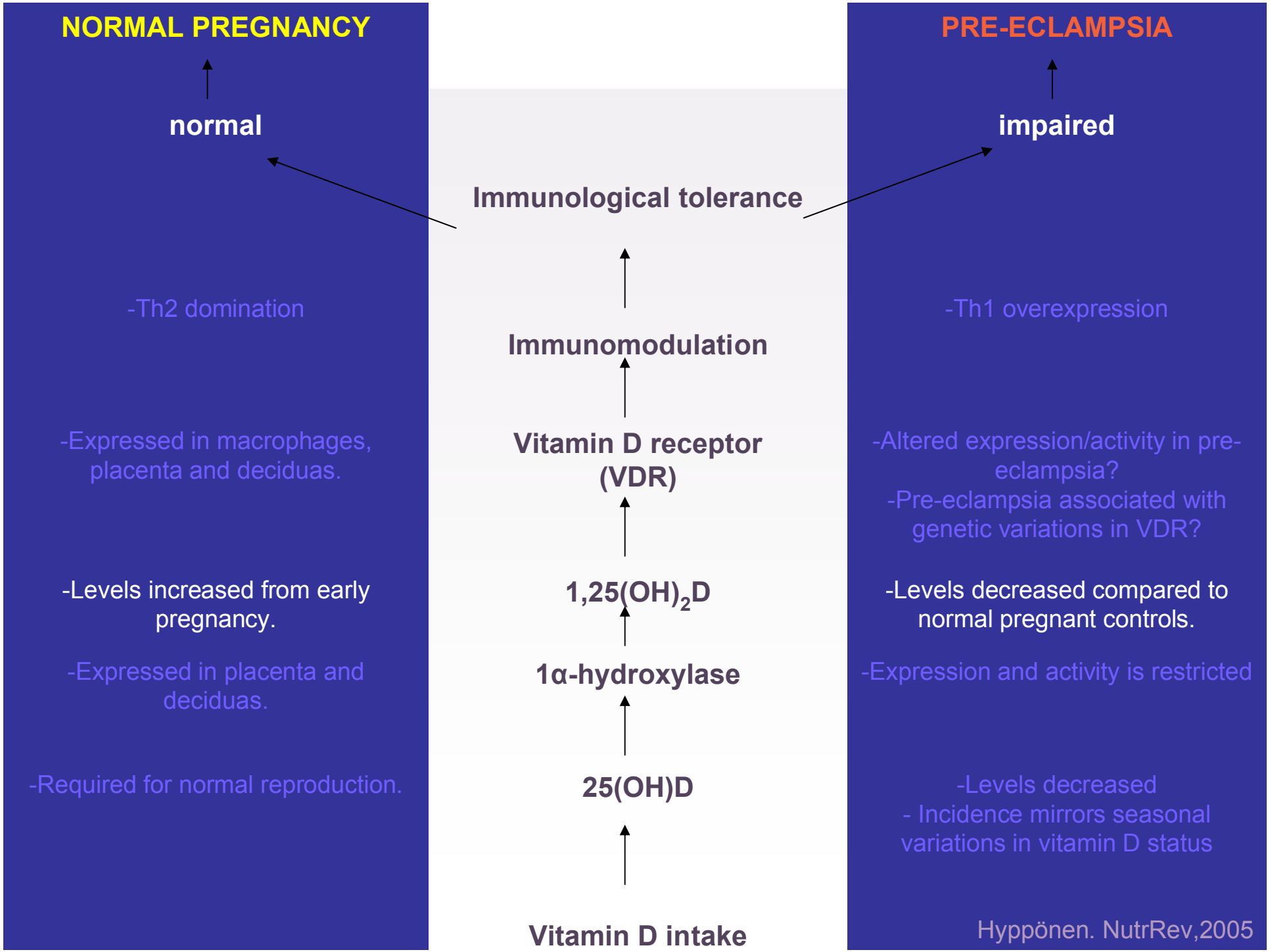
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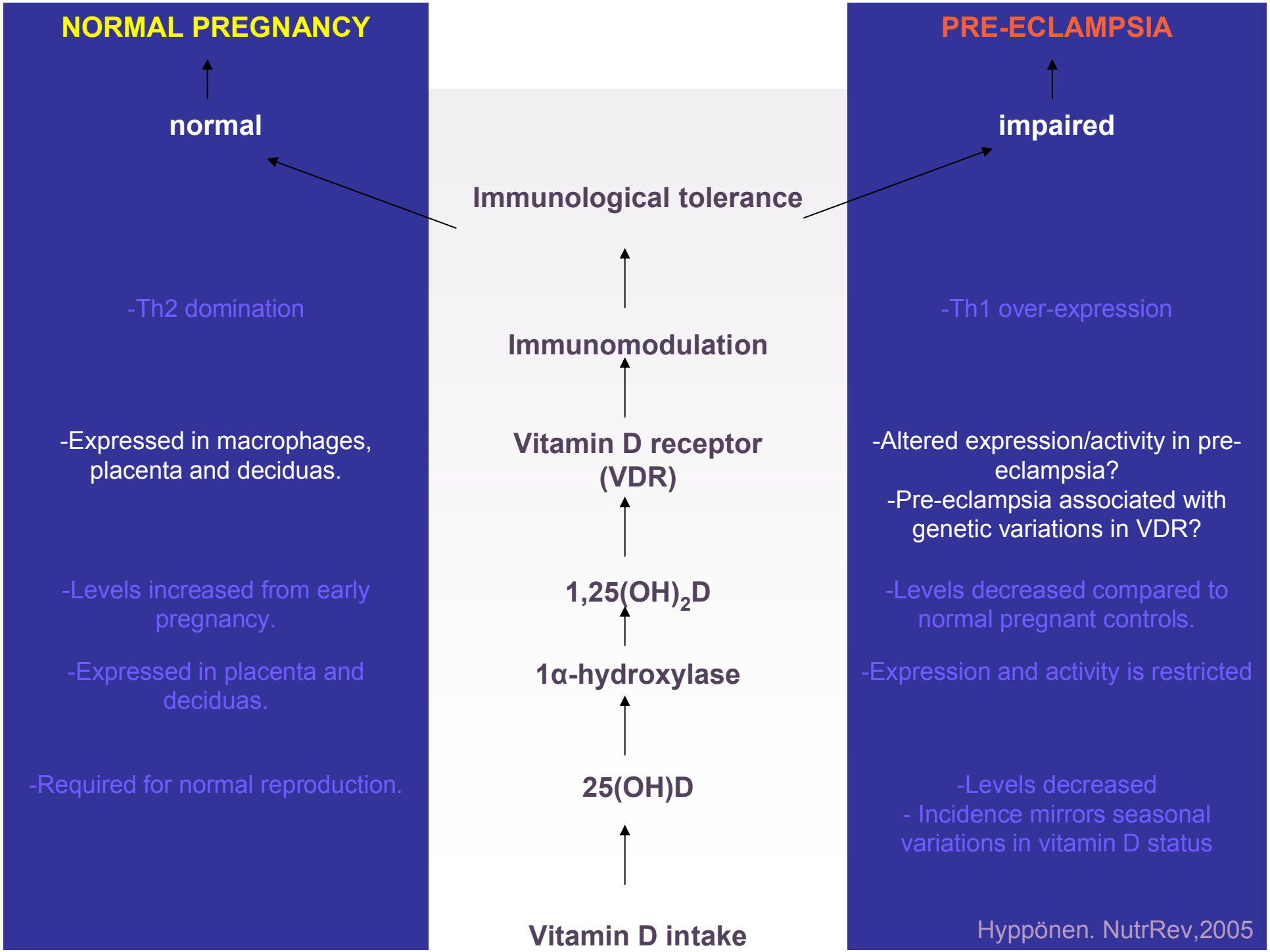
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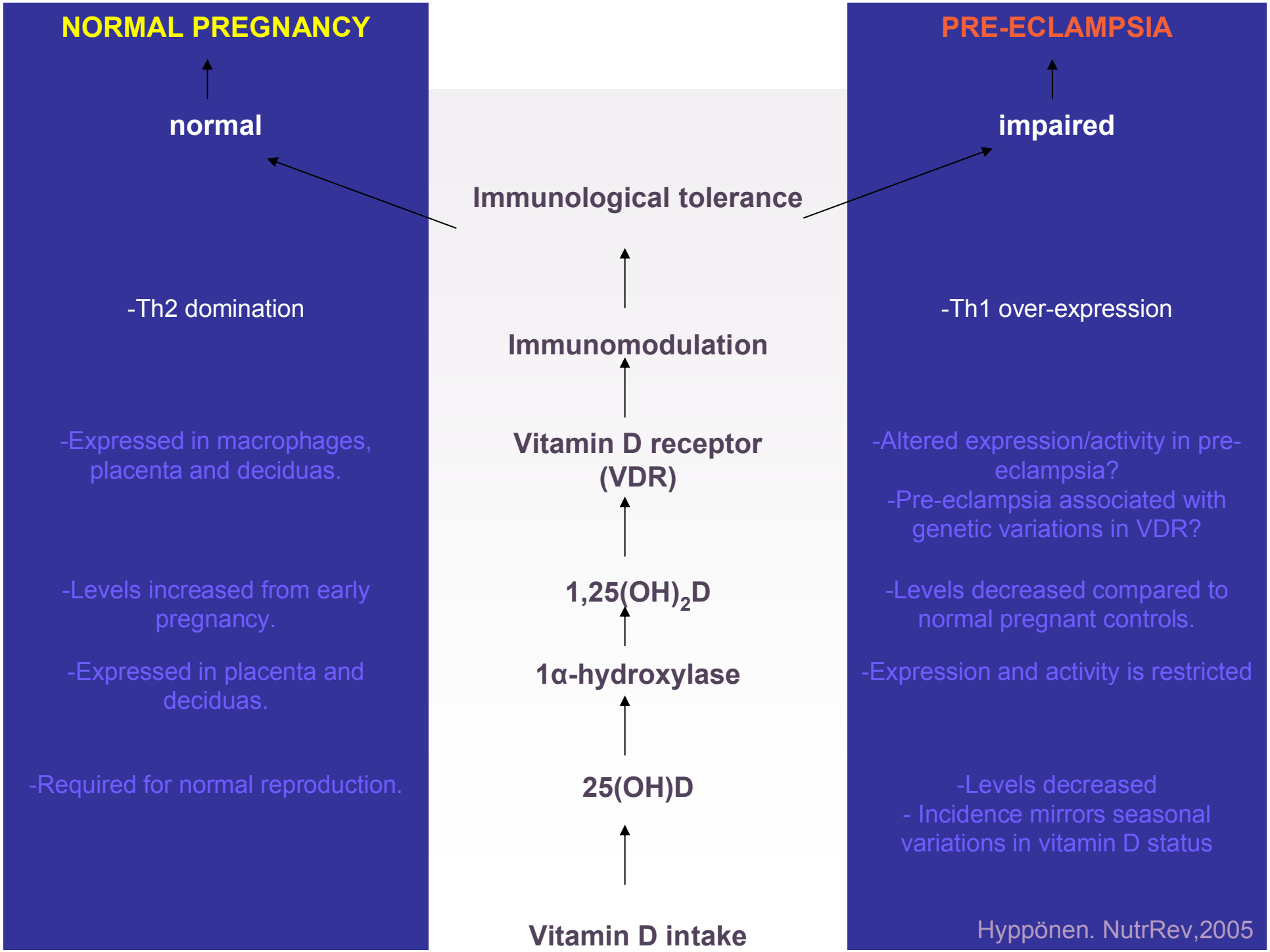
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Vitamin D and pre-eclampsia

Bodnar et al. Maternal vitamin D deficiency increases the risk of preeclampsia. JCEM 2007

- Nested case-control study with 55 cases and 219 controls
- 25(OH)D concentrations measured by 16wk, pre-eclampsia onset after 20wks.
  - **25(OH)D concentrations lower in pre-eclamptic women compared to controls (45nmol/l vs. 53nmol/l. p=0.01)**
  - **2-fold increase in pre-eclampsia risk for 50nmol/l increase in 25(OH)D**
  - **25(OH)D concentrations lower in the offspring to pre-eclamptic women compared to offspring of controls (39nmol/l vs. 50 nmol/l, p=0.001)**

Haugen et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology 2009

- Norwegian Mother and Child Cohort, 23,423 nulliparous pregnant women (1267 with preeclampsia)
- Questionnaire Information vitamin D supplementation (week 15) and dietary intake (week 22)
- Pregnancy outcomes were obtained from the Medical Birth Registry.
  - **Total vitamin D intake (15-20 µg/d vs. <5µg/d) associated with reduced pre-eclampsia risk**
  - **(OR 0.76, 95%CI 0.60-0.95).**
  - **Vitamin D supplementation (vs. no supplements) associated with reduced pre-eclampsia risk (OR 0.73, 95%CI 0.58-0.92).**
  - **No association between vitamin D intake from food and preeclampsia**

Does early-life vitamin D status or intake have long-term influences on immunological diseases ?

- Programming of the immune system, in particular related to tolerance development, starts before birth and stays under close control of the maternal immune system
  - Pre- and postnatal period important ‘window of opportunity’ for immune programming
  - Controlled by gene-environment interaction, epigenetic mechanisms

- Evidence for epigenetic regulation of genes in the vitamin D pathway
  - Placenta specific methylation of 24-hydroxylase
  - Transcriptional regulation of the CYP27B1 gene mediated by epigenetic modifications

Vitamin D and type 1 diabetes

TYPE 1 DIABETES

- Chronic autoimmune disease, multifactorial etiology with both genetic predisposition and exposure to environmental risk factors required
- Long latency from initiation to disease onset
- Insulin secreting beta cells destroyed in a T-cell dependent process
- polarization towards Th1 up-regulation is believed central to the pathogenesis

Vitamin D may be able to disrupt both the initiation and progression of the T-cell mediated pathogenesis of Type 1 diabetes?

Stene et al. Diabetologia, 2000

- Norwegian case-control study, 85 cases / 1071 control children
  - Maternal cod liver oil supplementation during pregnancy associated with a reduced diabetes risk in the offspring (OR 0.30, 95%CI 0.12-0.75)
  - Results inconclusive on the effect of infants cod liver oil intake or vitamin D supplementation

Fronzak et al. Diabetes Care 2003

- 233 children followed up for 4y, 16 developed insulin autoantibodies
  - Maternal intake of vitamin D via food associated with decreased risk of IA antibodies (HR 0.37, 95%CI 0.17, 0.78)

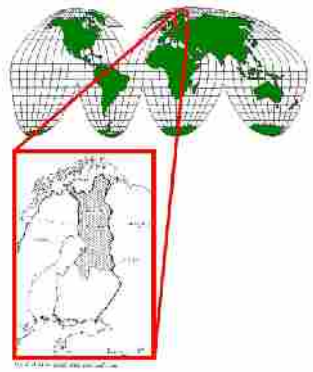
Brekke and Ludviggson, Pediatr Diabetes 2007

- Follow-up of 8695 children up to 1y for seroconversion to positivity for diabetes specific autoantibodies (n=774). (For 2.5y, 7766 and 774, respectively)

  → Use of vitamin-D supplements during pregnancy associated with reduced diabetes-related autoimmunity at 1y (OR 0.71, 95%CI 0.52-0.96) but not at 2.5y.

Northern Finland Birth Cohort 1966

* **All pregnant mothers with expected date of delivery in 1966 in two most northern provinces of Finland (n=12,058)**



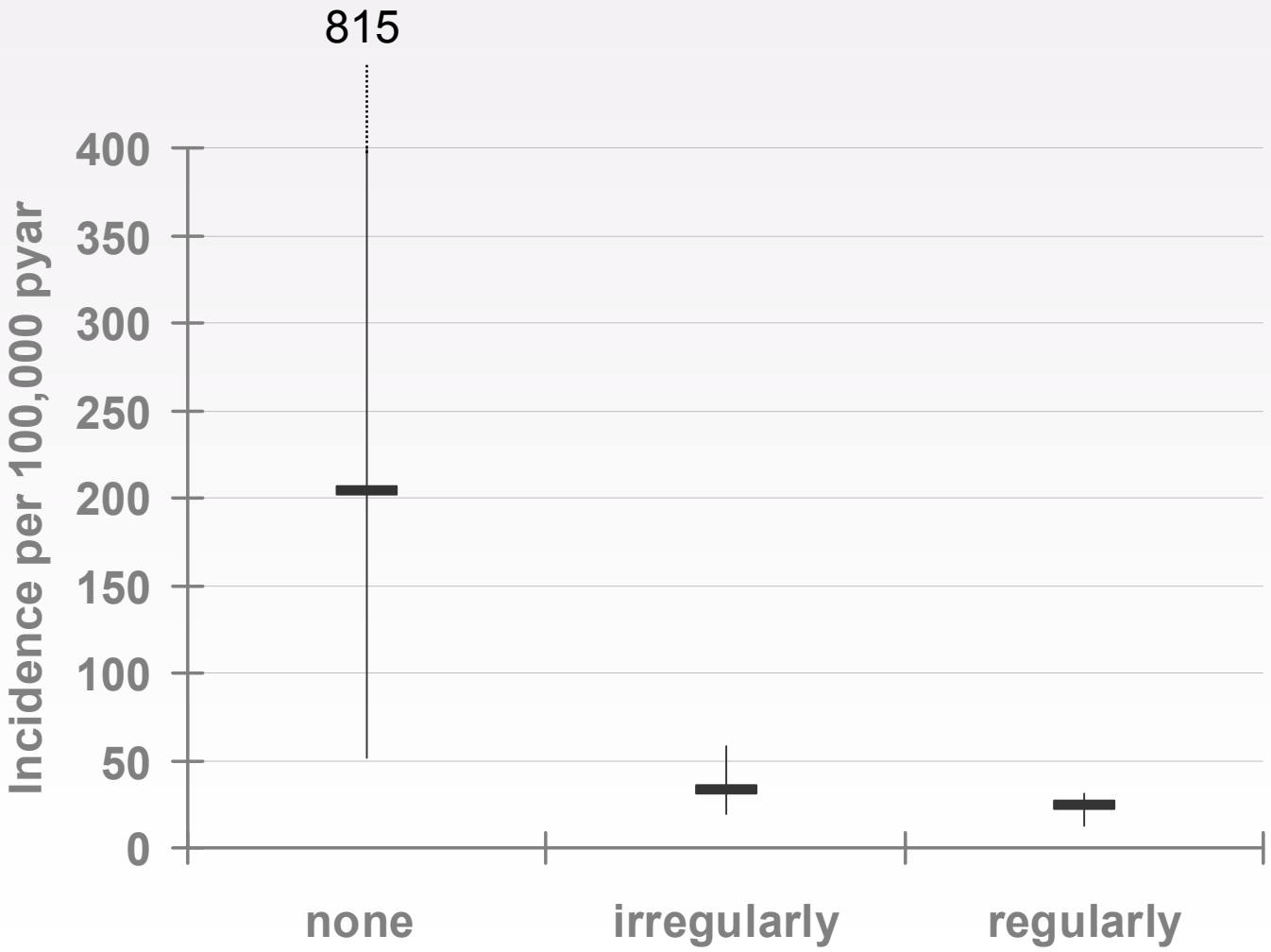
* **Information on vitamin D supplementation (frequency, dose) and suspected rickets collected at 1 year of age (n=10,366)**

*****Dose recommendation 2000 IU/day (50µg/day)*****

- **Follow-up for Type 1 diabetes to age 31 through linkage** to Central Drug Register with further ascertainment of cases diagnosed at age 20 or older using hospital discharge register and/or medical files
  - 81 cases (total n=10,366)

Hyppönen et al. Lancet, 2001

Incidence of Type 1 diabetes by FREQUENCY of vitamin D supplementation



Adjusted for:
sex, neonatal, social and anthropometrica indicators

Hyppönen et al. Lancet, 2001

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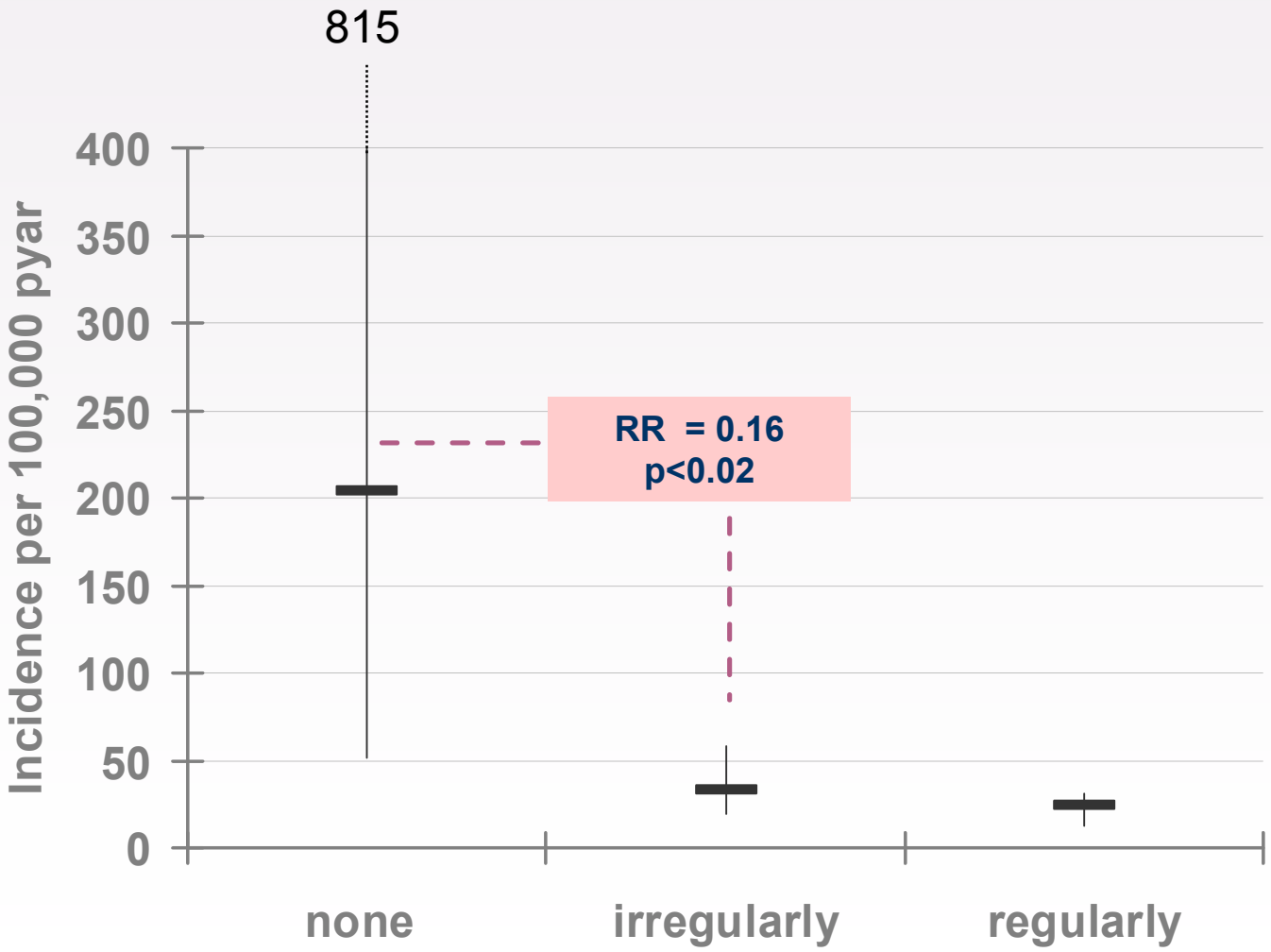

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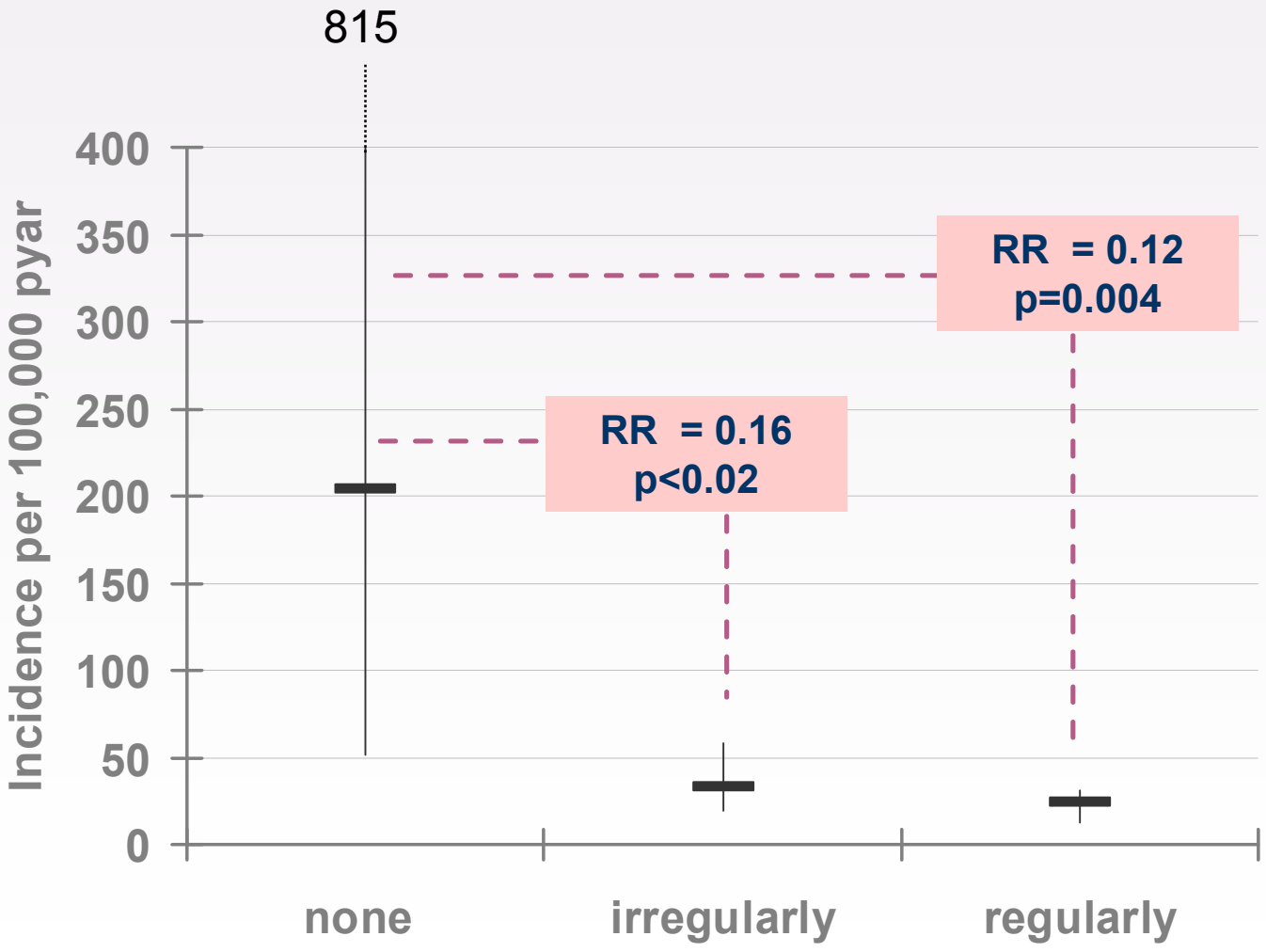

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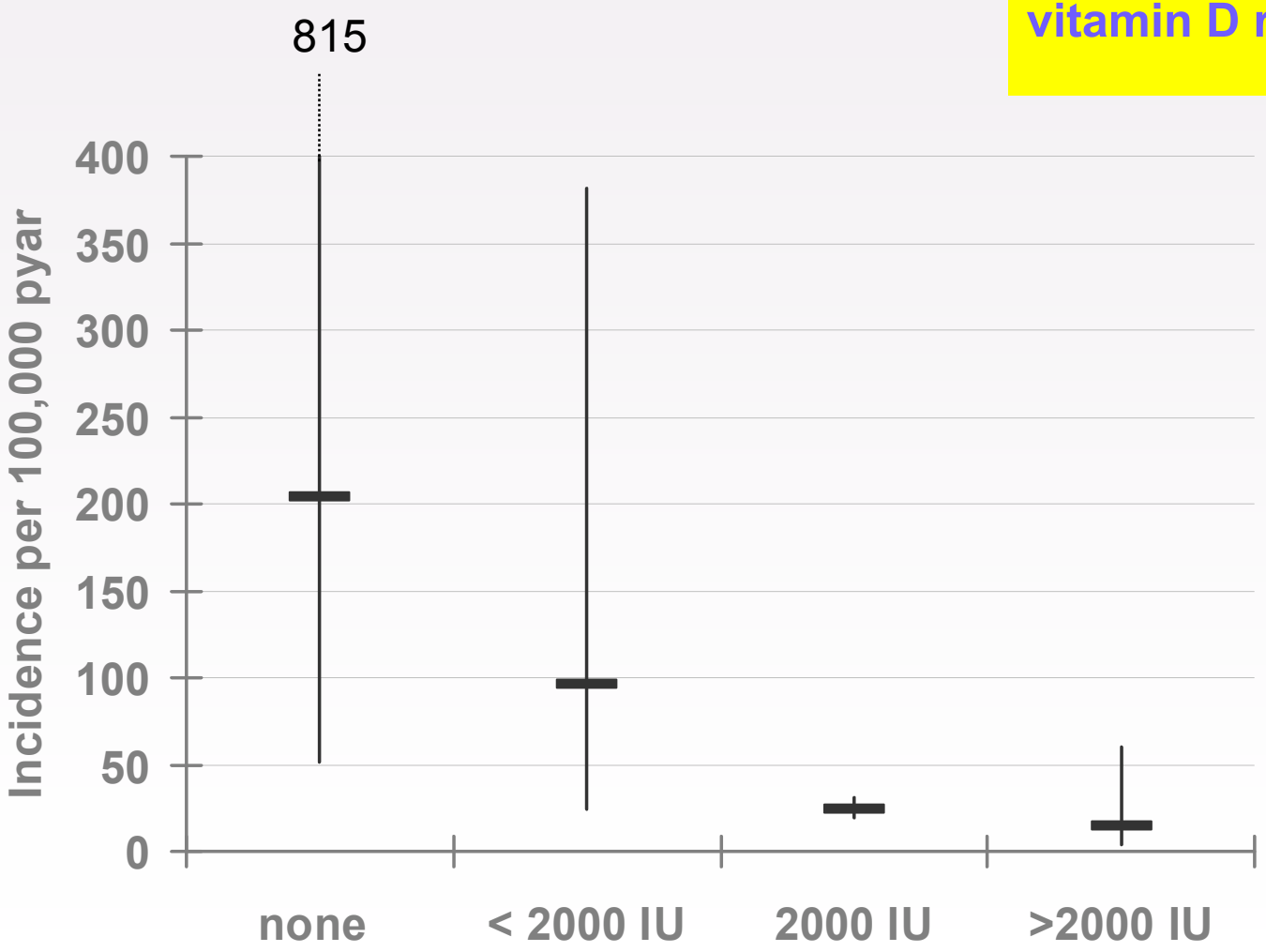
Hyppönen et al. Lancet, 2001

Incidence of Type 1 diabetes by DOSE of vitamin D supplementation

Restricted to children receiving vitamin D regularly



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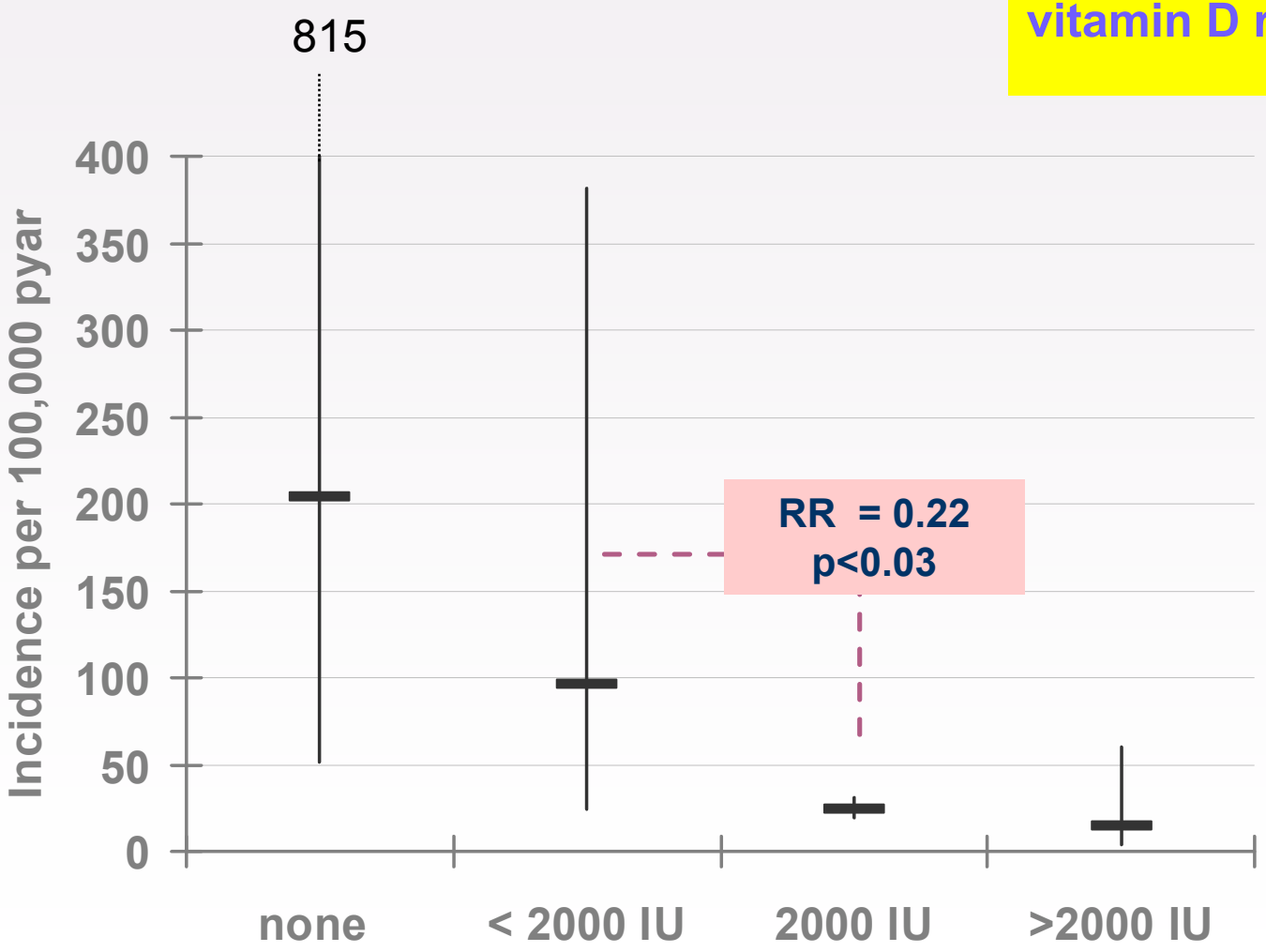

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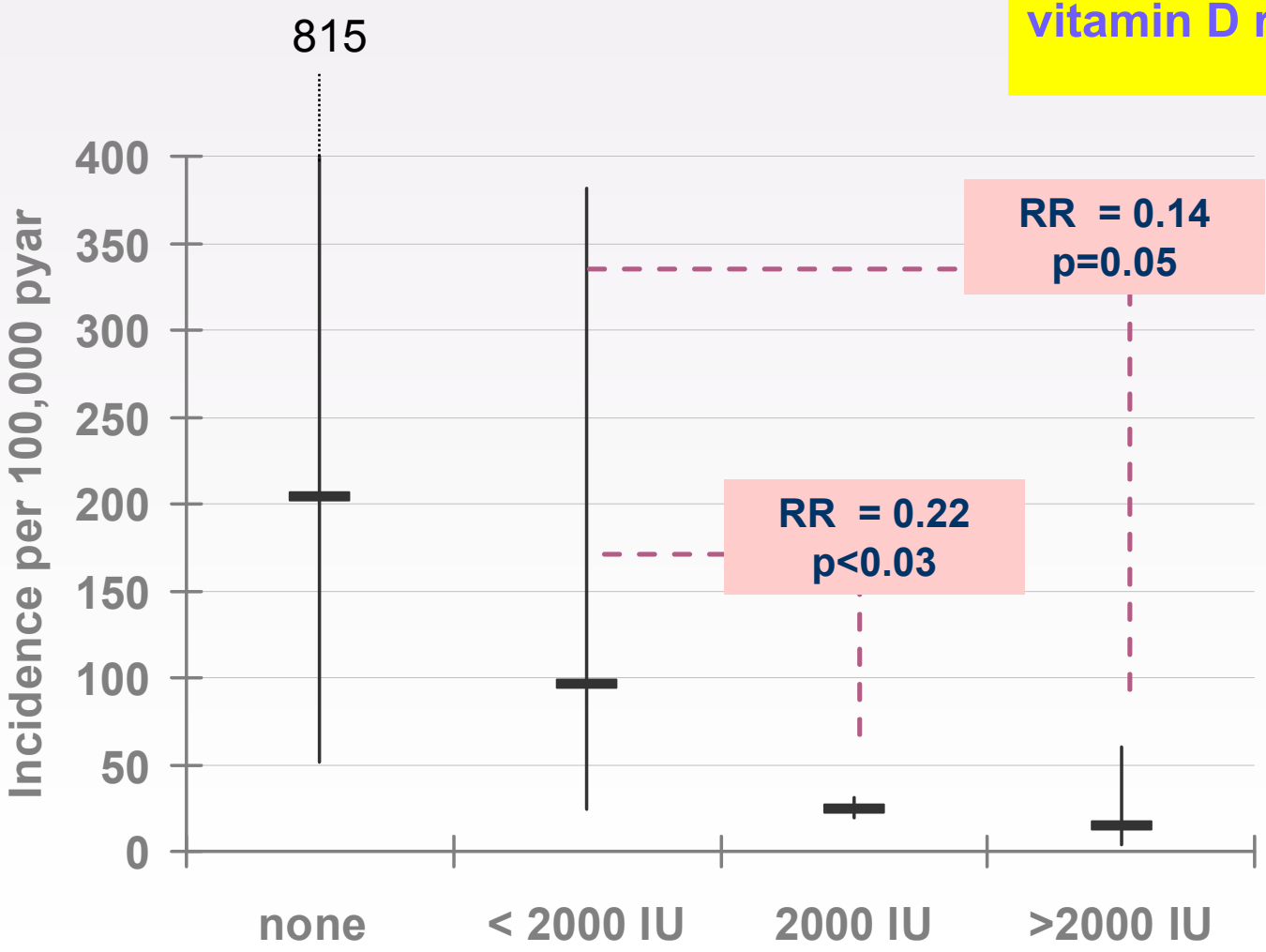

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Hyppönen et al. Lancet, 2001

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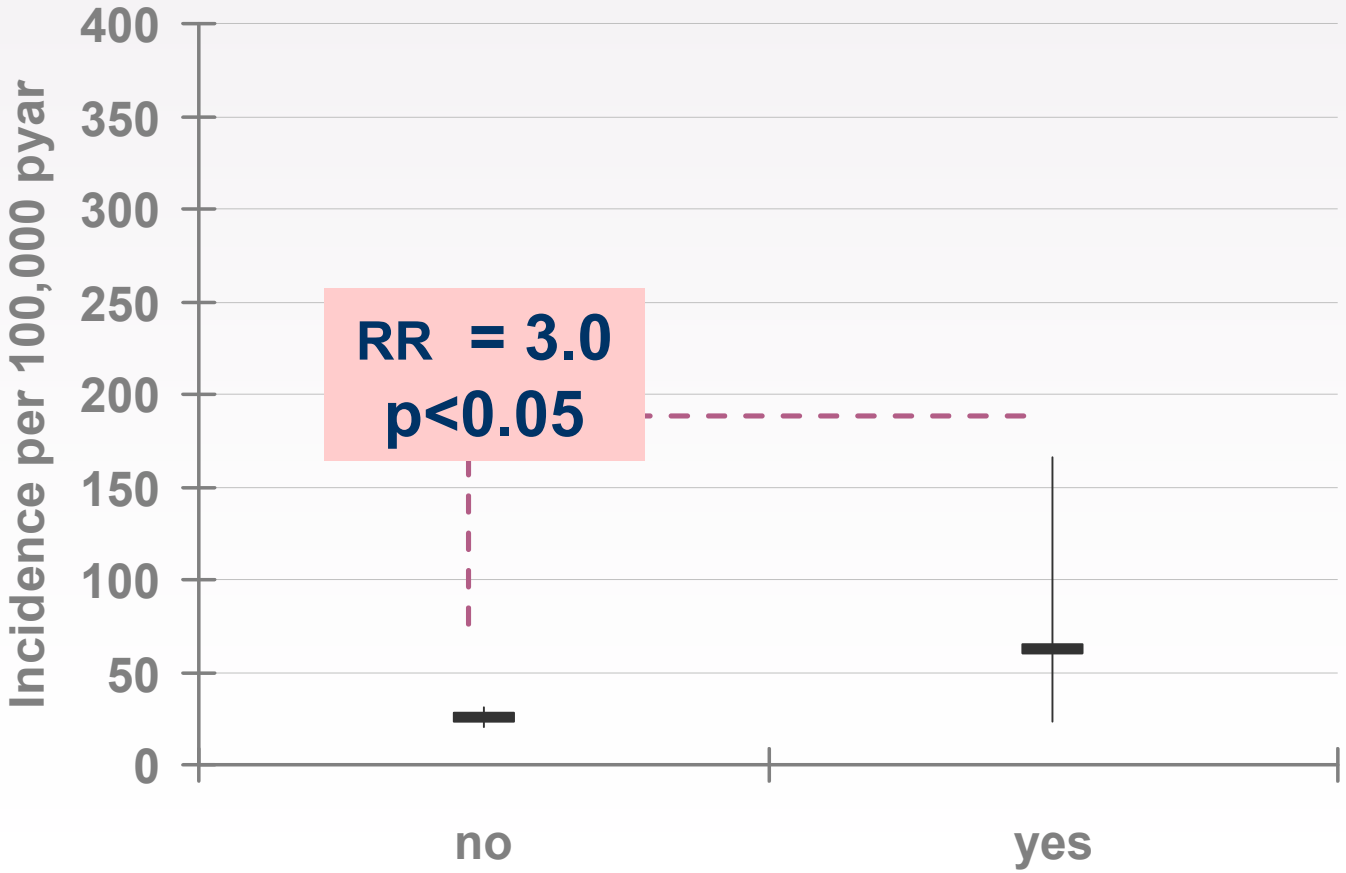

Adjusted for:
increased dose, sex
neonatal, social,
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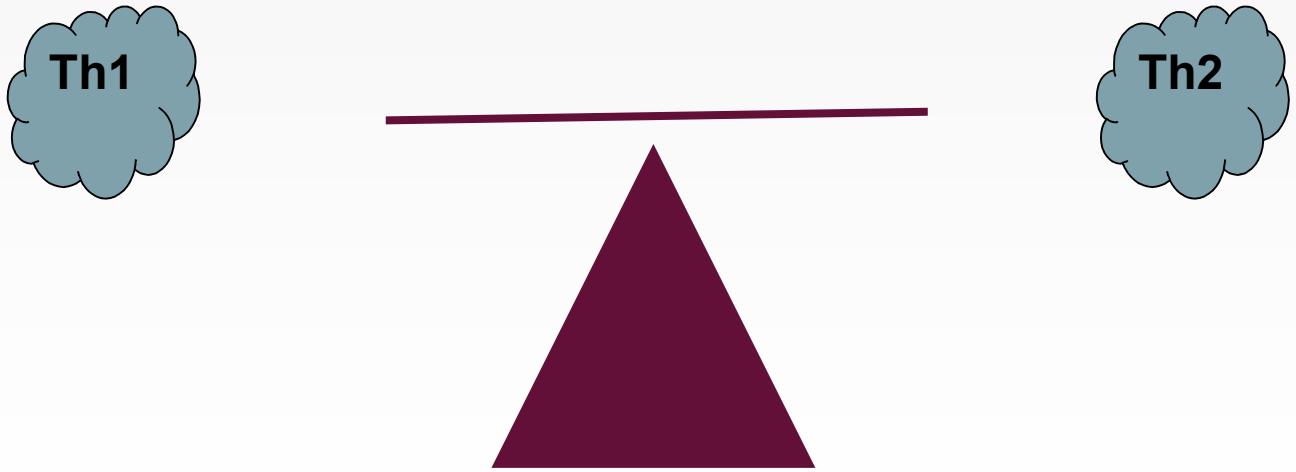
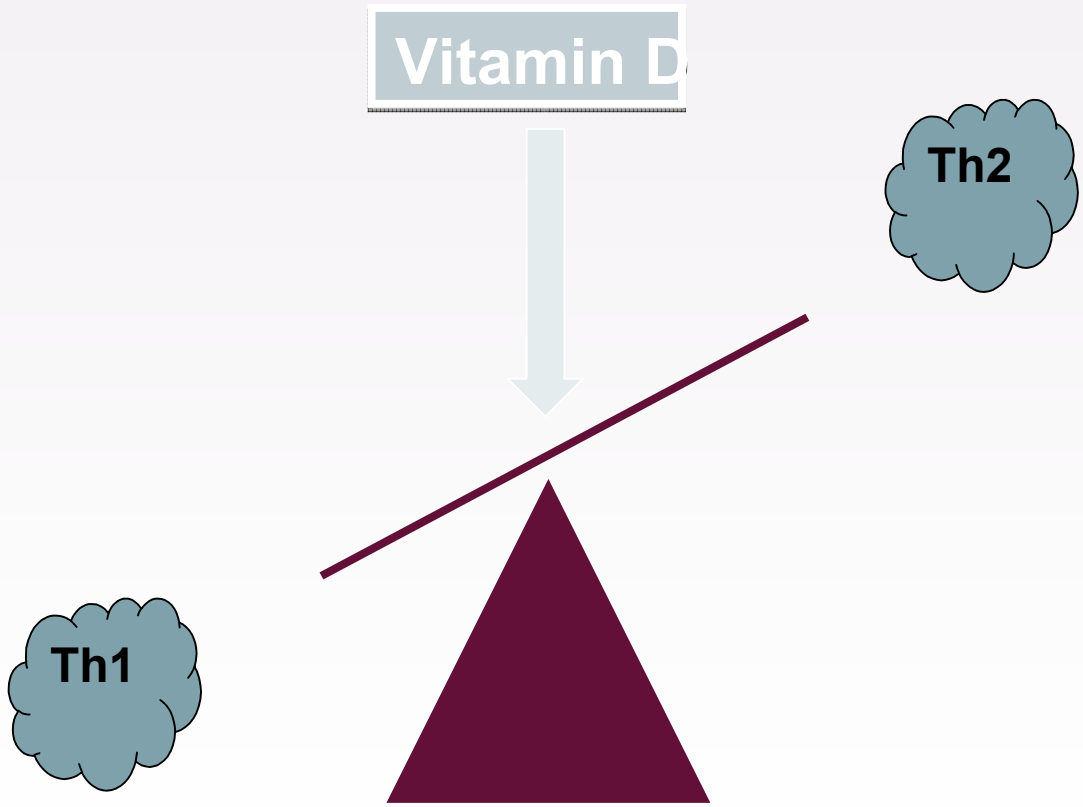
Hyppönen et al. Lancet, 2001

Supplementation on the risk of immune mediated diseases:
Th1/Th2 paradigm



Long-term effects of infant vitamin D

Supplementation on the risk of immune mediated diseases: Th1/Th2 paradigm



Type 1 diabetes ↓

Pre-eclampsia ↓

Vitamin D and Pre-eclampsia

Prevalence and risk of pre-eclampsia by **vitamin D supplementation in infancy**
-Northern Finland Birth Cohort 1966

	number	%(cases)	OR (95% CI)	Adjusted [a] OR (95% CI)
Frequency of vitamin D supplementation				
Irregularly/none	339	3.8 (13)	Reference	Reference
Regularly	2630	2.1 (55)	0.54 (0.29, 0.99)	0.49 (0.26,0.92)
Dose of vitamin D[b]				
2000 IU per day	2499	2.1 (53)	Reference	Reference
> 2000 IU per day	120	1.7 (2)	0.78 (0.19,3.26)	0.81 (0.18,3.55)

Hyppönen et al.EJCN 2007

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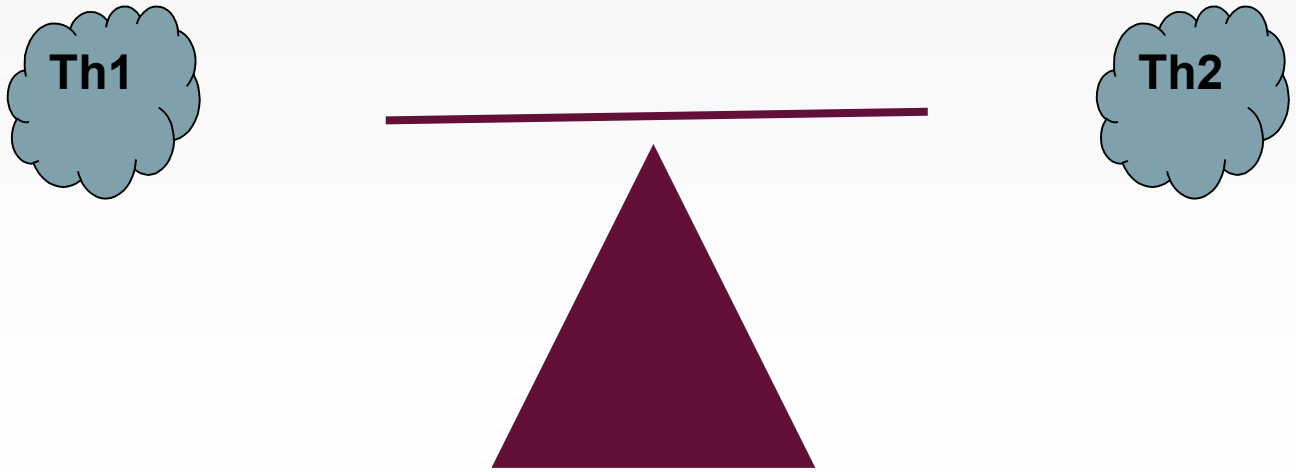

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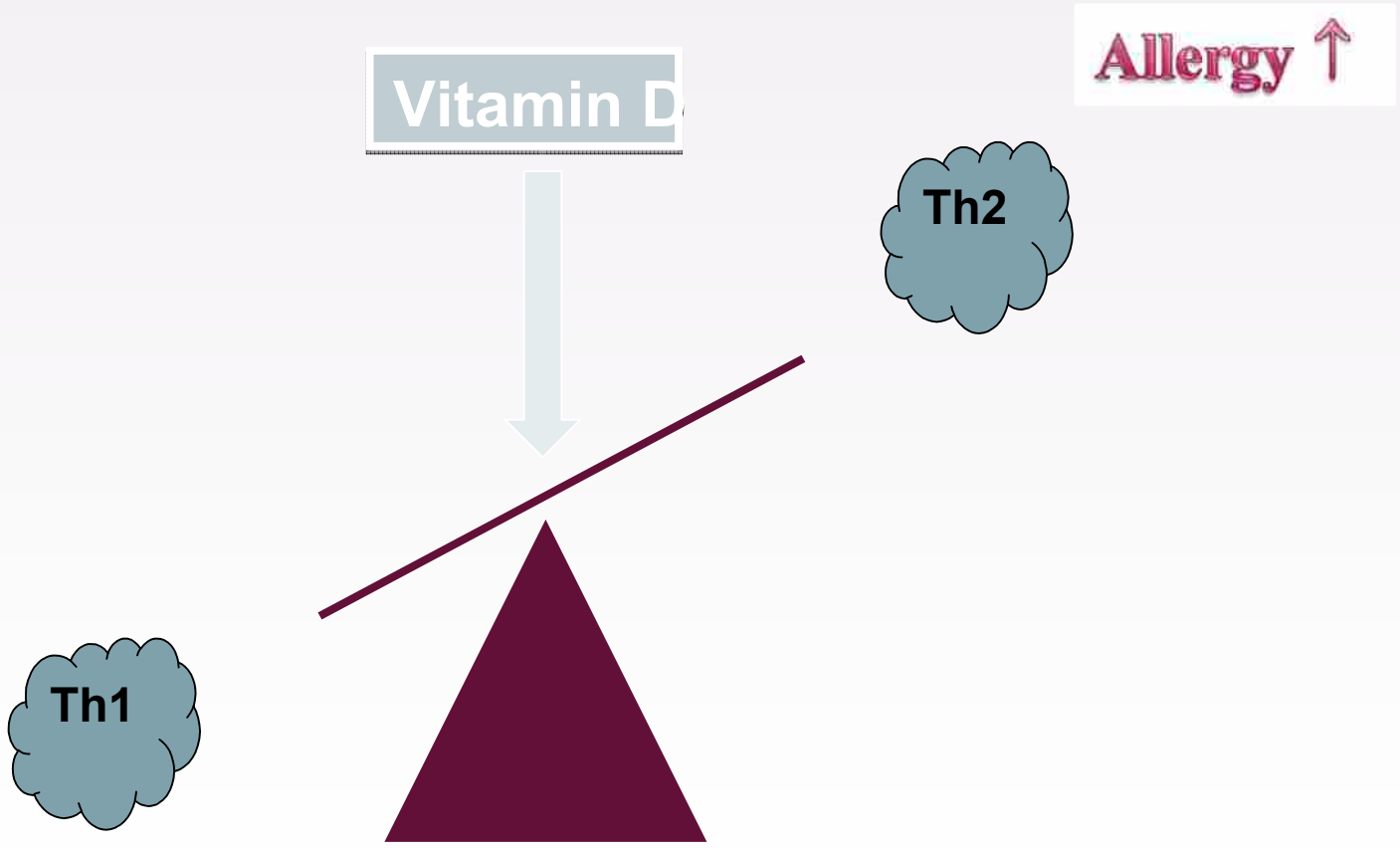
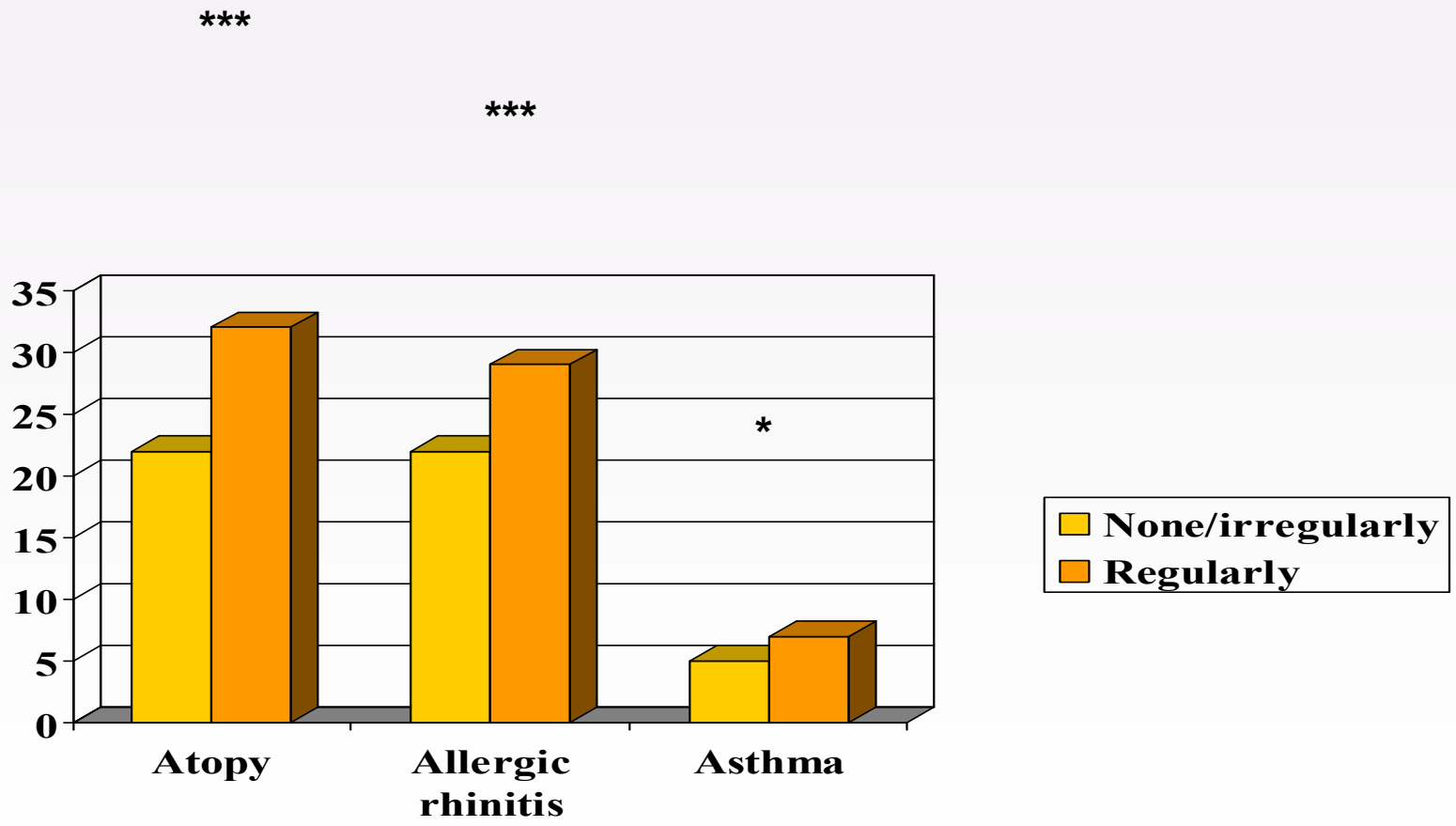


Prevalence of allergic conditions by FREQUENCY of vitamin D supplementation



*** p<0.001, * p=0.05

Hyppönen et al. ANYAS, 2004

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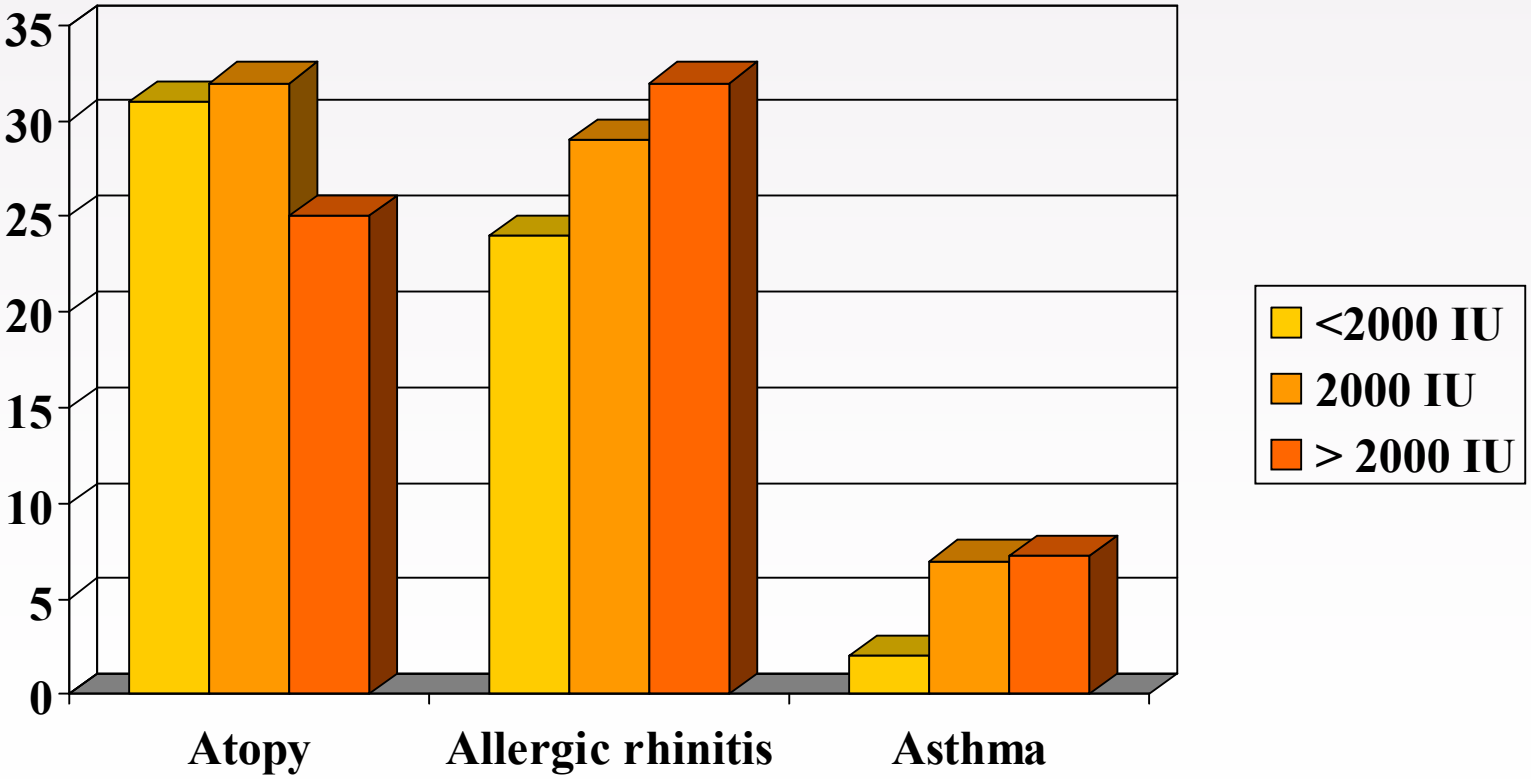


*** Restricted to infants receiving vitamin D regularly**

Hyppönen et al. ANYAS, 2004

Support for increases in allergy/asthma by vitamin D...

Gale et al. EJCN 2007

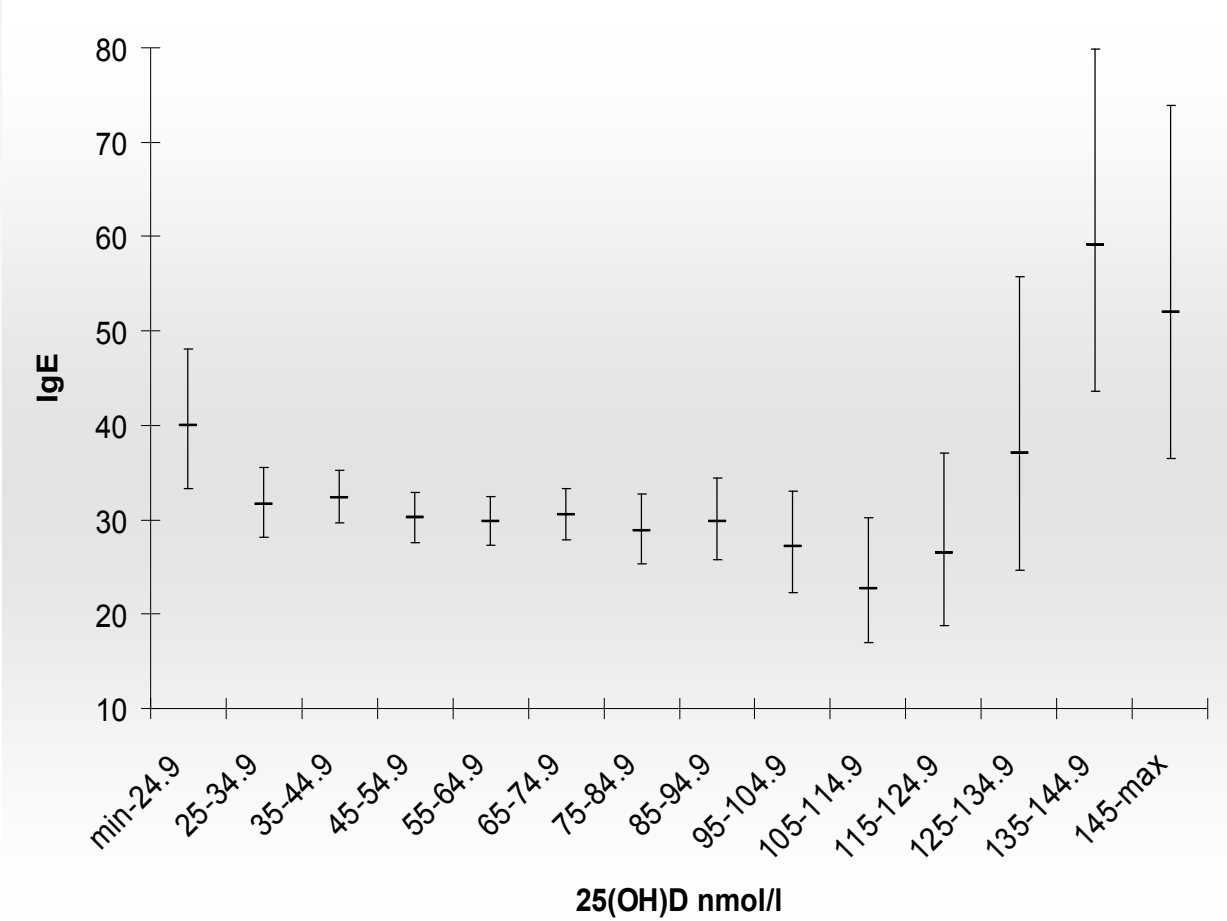
Higher maternal vitamin D status during pregnancy associated with...
...3-fold risk (95%CI 1.2-9) of visible eczema at 9 months
...over 5-fold risk (95%CI 1.1-27) of reported asthma at 9 years

Hughes et al. Pediatr Allergy & Immunol 2010

In an Australian study...
..cod liver oil supplementation in childood associated with hayfever/asthma
..greater wintertime sun exposure in childood associated with hayfever

Serum IgE by variations in 25(OH)D

-geometric mean, standardized by sex and season



Hyppönen et al. Allergy, 2009

… but what about all this??

Is vitamin D deficiency to blame for the asthma epidemic?

Litonjua & Weiss, J Allergy Clin Immunol 2007

"..using data from the two birth cohorts with maternal vitamin D assessments, we estimate that the population attributable **risk for asthma incidence caused by vitamin D deficiency in pregnancy** is about 40% of all cases."

Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Camargo et al. AJCN 2007

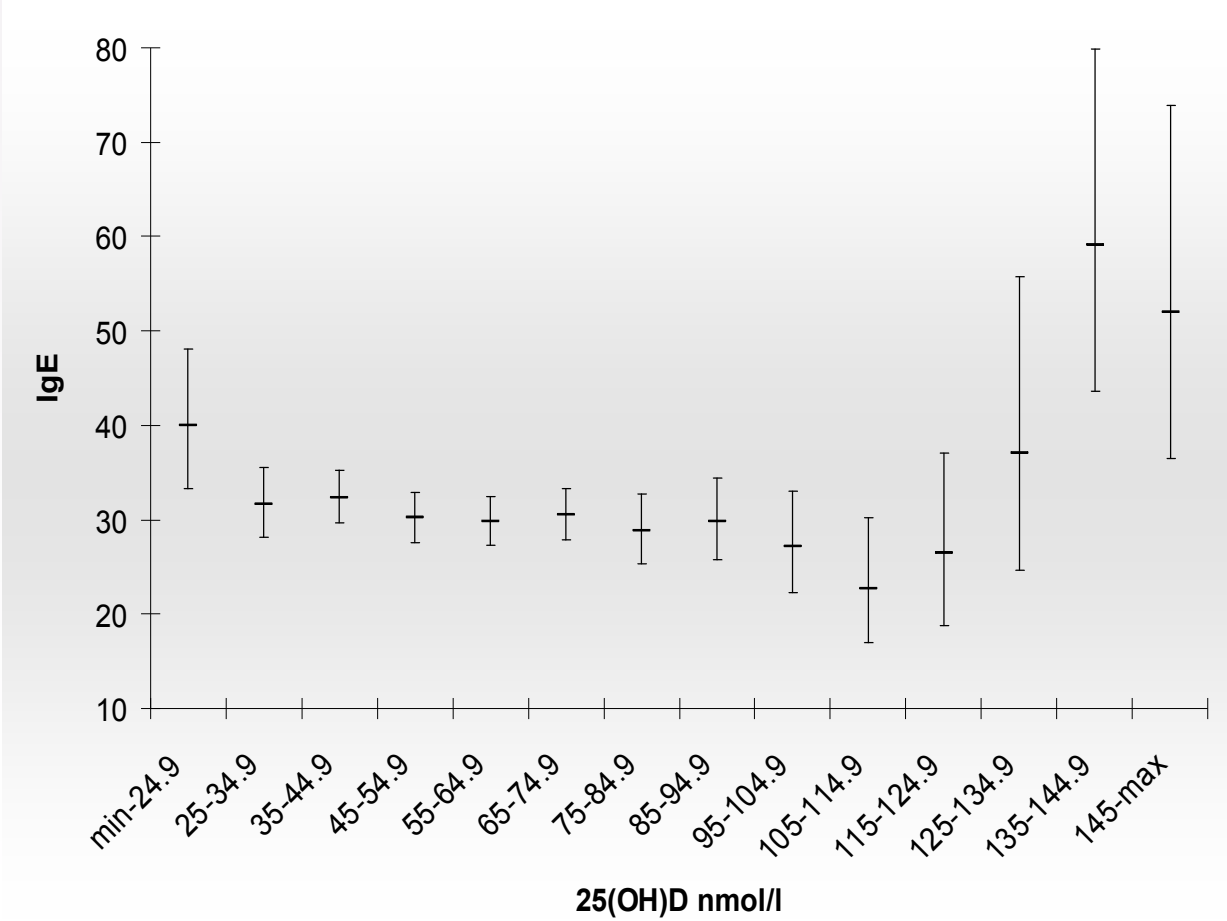
1194 mother-child pairs: Compared with mothers in the lowest quartile of daily intake (median: 356 IU), those in the highest quartile (724 IU) had a lower risk of having a child with recurrent wheeze [OR: 0.39; 95% CI: 0.25, 0.62; P for trend < 0.001].

Maternal vitamin D intake during pregnancy and early childhood wheezing. Devereux G, et al. Am J Clin Nutr. 2007 Mar;85(3):853-9.

1212 children: maternal total vitamin D intake (highest: 275IU/day vs lowest: 77IU/day quintiles) conferred lower risks for ever wheeze [OR: 0.48; 95% CI: 0.25, 0.91], wheeze in the previous year (OR: 0.35; 95% CI: 0.15, 0.83), and persistent wheeze (OR: 0.33; 95% CI: 0.11, 0.98) in child at 5y.

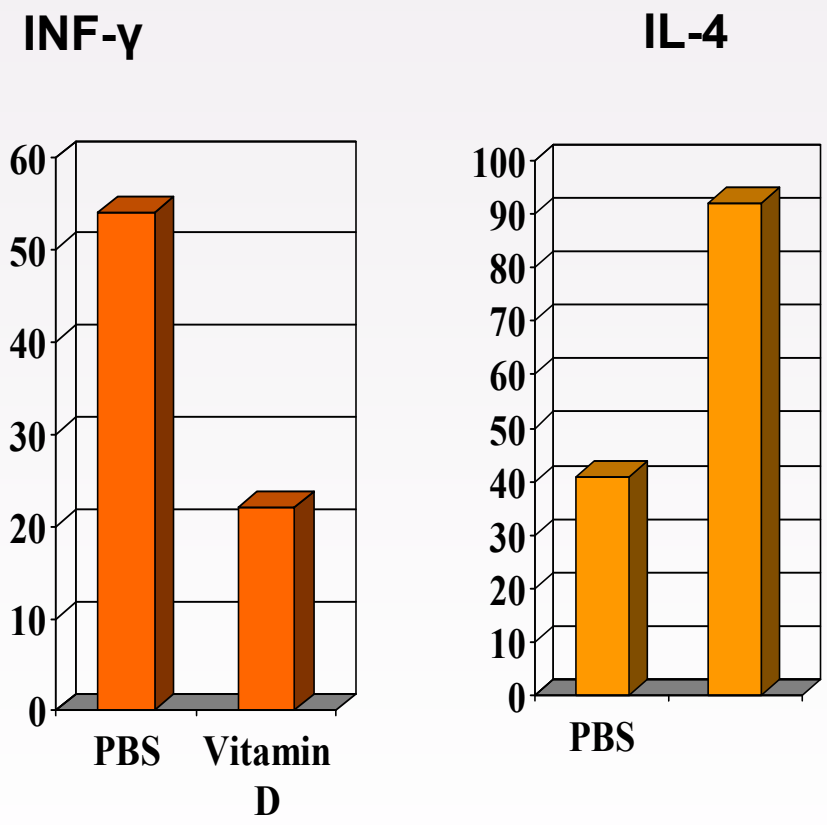
Serum IgE by variations in 25(OH)D

- geometric mean, standardized by sex and season



Hyppönen et al. Allergy, 2009

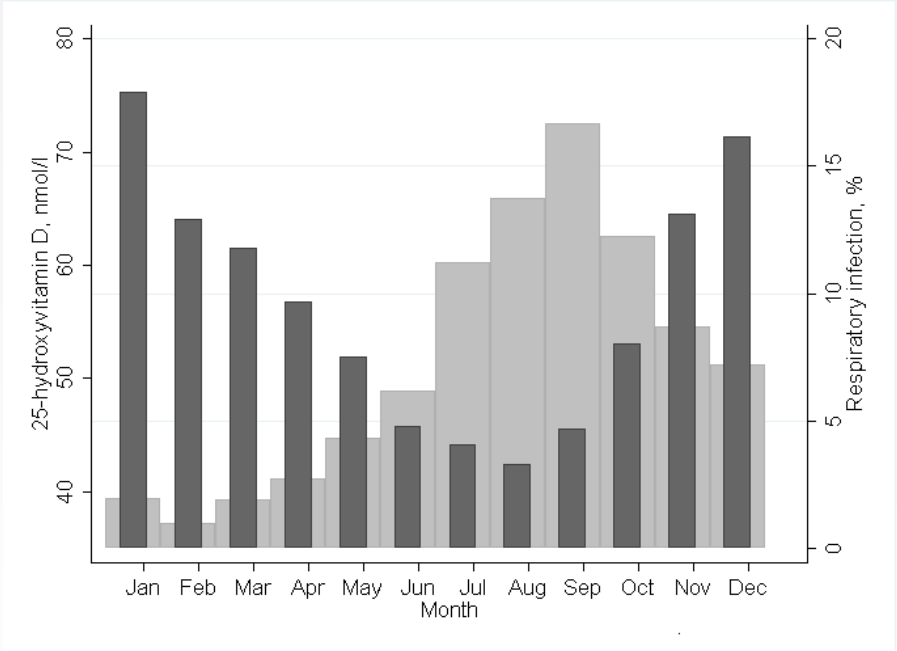
Allergen induced cytokine secretion in vitamin D treated animals

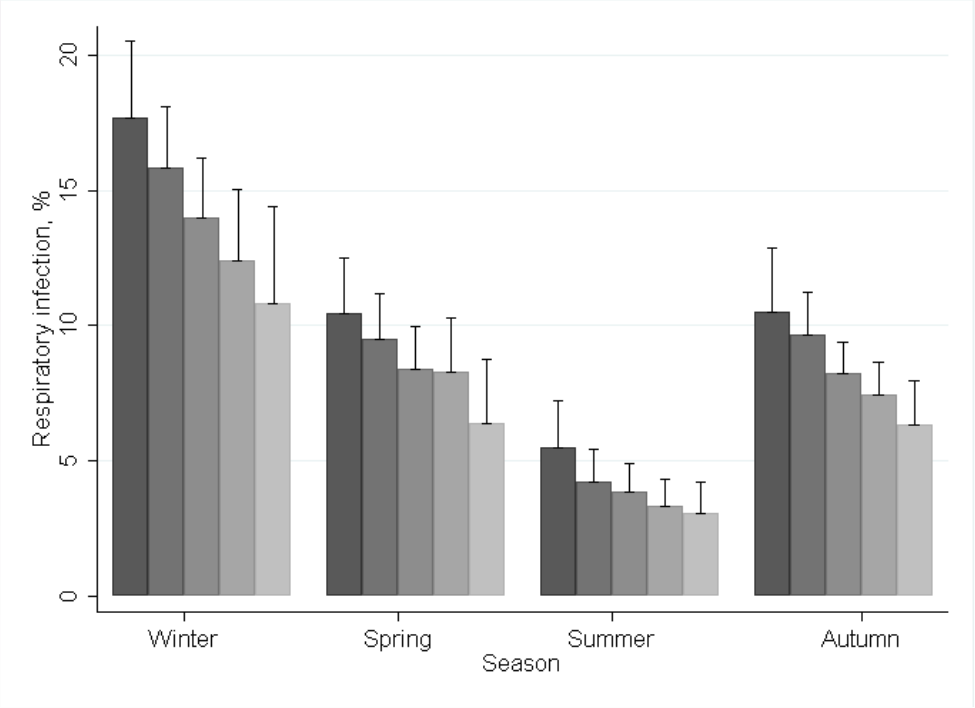


Airway eosinophilia -a key pathophysiological feature of asthma- was also reduced, possibly suggesting beneficial
Influences through a reduced inflammatory response

Matheu et al. J Allergy Clin Immunol 2003

Vitamin D status and prevalence of respiratory infections in the 1958BC





Berry et al. BJN 2011, in press

Multiple effects on immune function…

Active vitamin D (i.e. $1,25(OH)_2D$)…

- leads to a general reduction in inflammation, which together with direct anti-proliferative effects in human airway smooth muscle cells (through inhibition of matrix metallo-proteinases) is believed to be instrumental for explaining the observed reductions in asthma risk
- influences barrier integrity, which could protect against the direct influence of harmful pathogens.
- reduces MHC II antigen expression on the cell membrane surface and induces macrophages and epithelial cells to produce cathelicidin, a peptide involved in antimicrobial action.

…in addition to affecting regulatory T cell activity, and the balance between Th1 and Th2 type immunological responses

Summary

- Vitamin D is a powerful immunomodulator, which can have long term influences on immunological disease such as diabetes and allergy risk

  - Evidence accumulating for beneficial effects in infections/inflammation

- Hypovitaminosis D short of deficiency may have important implications for
  - the maintenance of normal pregnancy
  - long-term implications for offspring health.


Public health message:
Avoid vitamin D deficiency!