Irene Cetin

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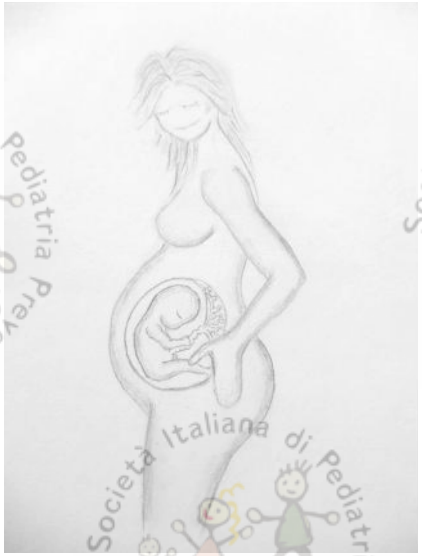
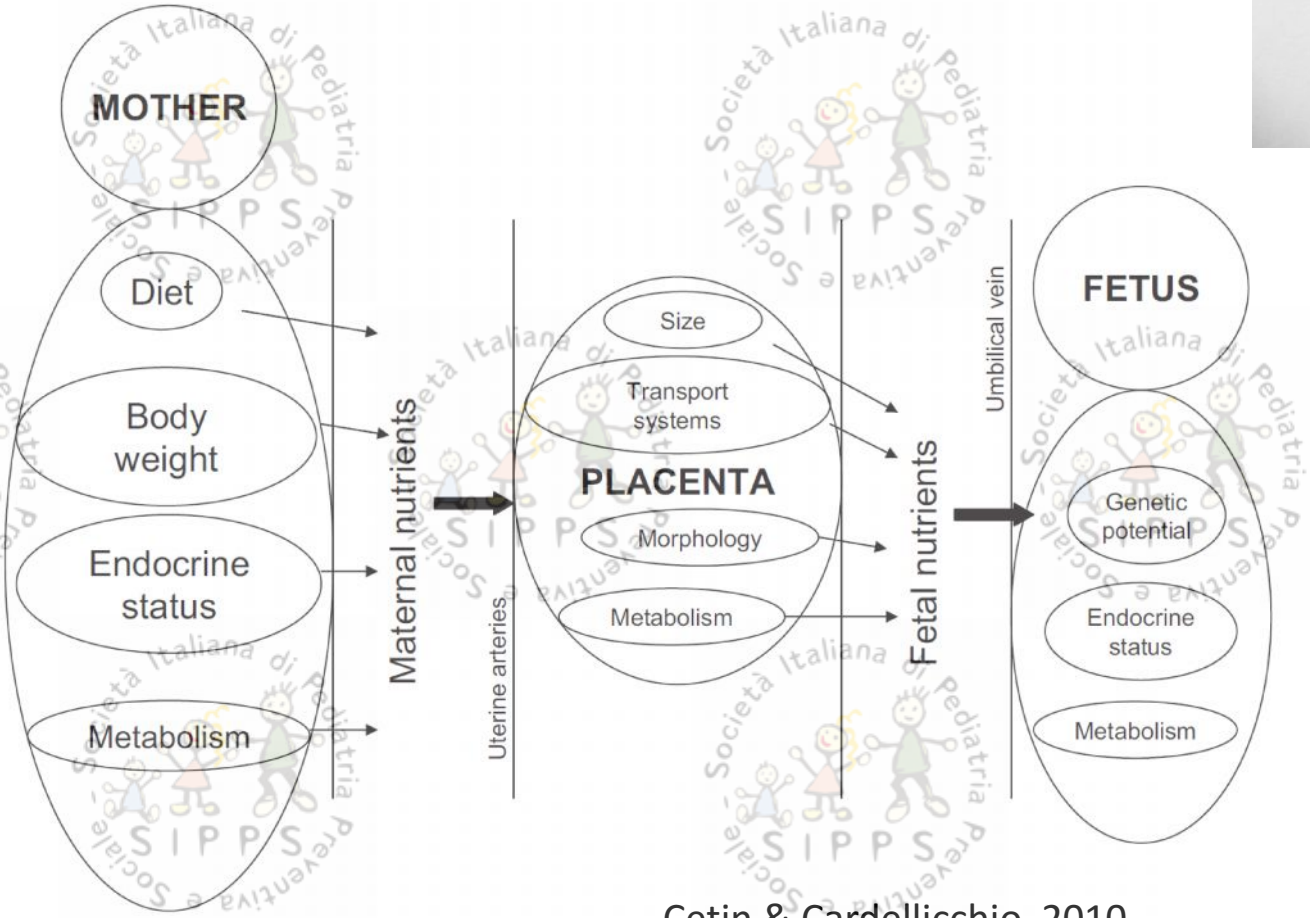
La Vita-Ormone D in gravidanza e allattamento

Napule è...

PEDIATRIA PREVENTIVA E SOCIALE

GRAVIDANZA = 3 compartimenti





Cetin & Cardellicchio, 2010

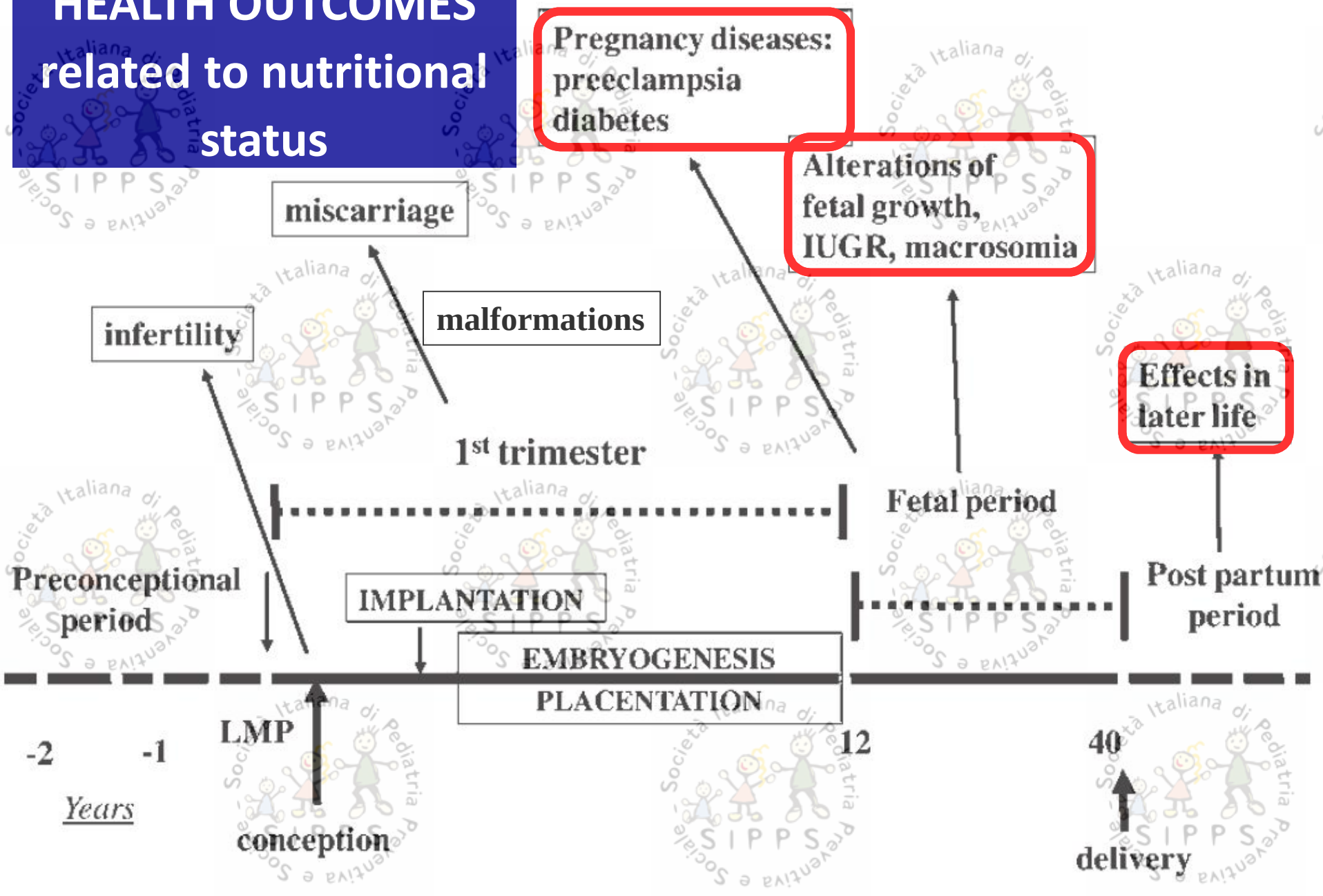
Nutrient needs in pregnancy

- **Energy (macronutrients) needs** increase only slightly during the course of pregnancy. Energy needs during the final months of pregnancy are about **10% higher** than before pregnancy

- The needs for certain **vitamins and minerals** (micronutrients) in pregnancy show a **much greater increase**

Therefore, pregnant women should pay special attention to the quality of their diet

HEALTH OUTCOMES related to nutritional status



Cetin et al, Hum Reprod Update 2010

intake - health

Poor adherence of the woman to a Mediterranean preconception diet

Mediterranean

POOR ADHERENCE

Intra Uterine Growth Restriction ↑↑

OR 2.8 (1.6 - 4.8)

Generation R Study - Rotterdam

Timmermans et al., 2009

BMJ

BMJ 2014;348:g1446 doi: 10.1136/bmj.g1446 (Published 4 March 2014)

Maternal dietary patterns and preterm delivery: results from large prospective cohort study

66000 women, FFQ in the first 4-5 mts of pregnancy

Linda Englund-Ögge *medical doctor*[1], Anne Lise Brantsæter *senior scientist*[2], Verena Sengpiel *medical doctor*[1], Margareta Haugen *senior scientist*[2], Bryndis Eva Birgisdottir *associate professor*[2 3], Ronny Myhre *senior scientist*[4], Helle Margrete Meltzer *professor*[2], Bo Jacobsson *professor*[1 4]

- ↓ high scores on the "prudent" dietary pattern were associated with significantly **reduced risk of preterm delivery** hazard ratio (0.88, 95% confidence interval 0.80 to 0.97).
- → dietary advice to eat a balanced diet including **vegetables**, **fruit**, **whole grains**, and **fish** and to drink **water**.

Courtesy of Helle Margrete Meltzer – Norwegian mother and Child Cohort Study

Maternal diet and birth size

Favourable associations

High New Nordic Diet score:
regular meals, Nordic fruits, vegetables, milk, berries and fish

Seafood, particularly lean fish

Adverse associations

Caffeine

Benzo(a)pyrene
Acrylamide

PCBs and Dioxins

Mercury

on going large prospective cohort study
FFQ in the first 4-5 mts of pregnancy

Maternal micronutrient status in pregnancy: current knowledge

Micronutrient deficiencies are very common even in developed countries

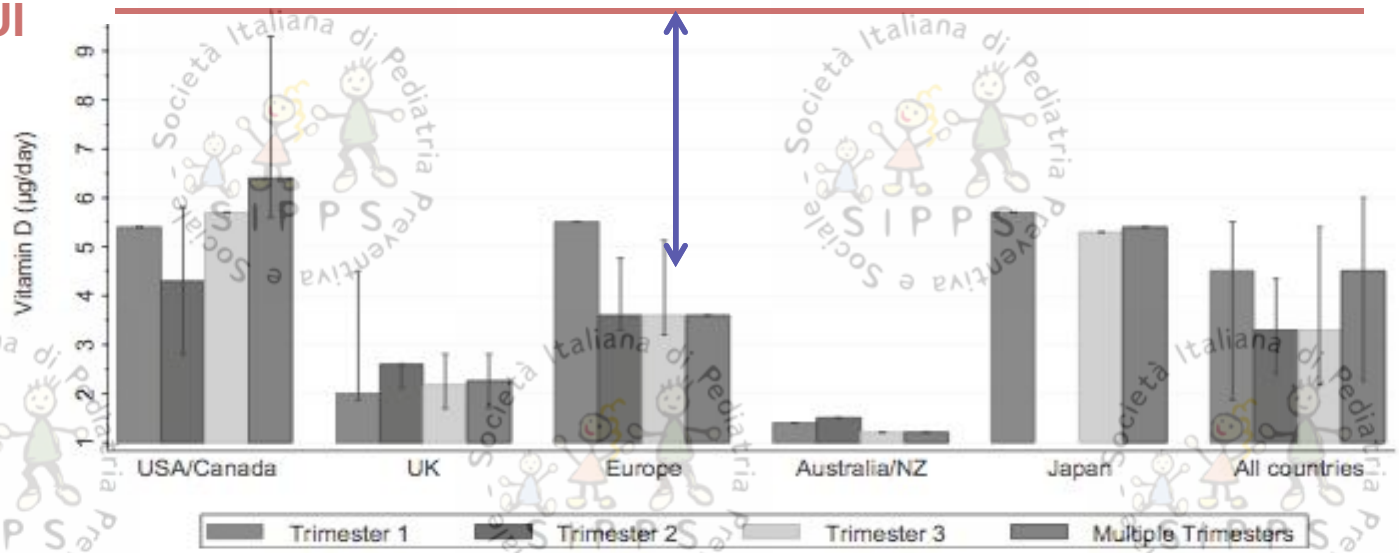
most prevalent (known) are iron, vitamin D, folate, iodine

Parisi F, Laoreti A, Cetin I, Ann Nutr Metab. 2014

vitamin D intake

10 µg
400 UI

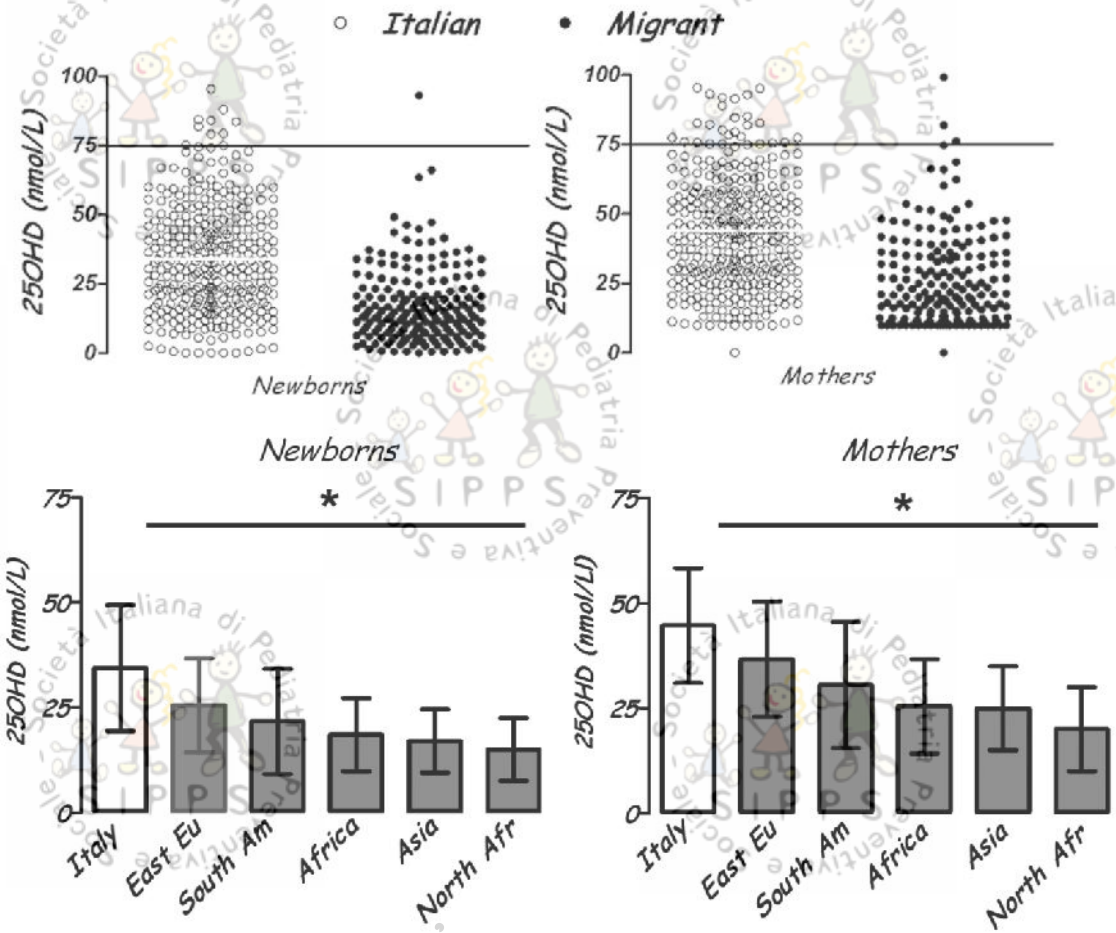
USA/EUR



Intakes were below recommendations for all regions

Blumfield M et al, Nutr Rev 2013

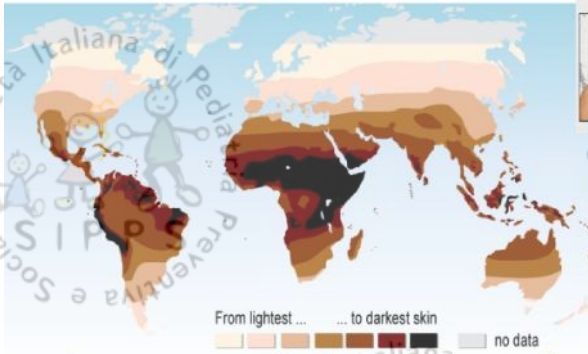
High Prevalence of Vitamin D Deficiency in Native *versus* Migrant Mothers and Newborns in the North of Italy: A Call to Act with a Stronger Prevention Program



Cadario F et al PlosOne 2015

What determines **vitamin D** status?

- Sunlight exposure
  - Degree of skin pigmentation
  - Use of sunscreen
  - Latitude
  - Season
  - Time spent outdoors
  - Protective clothing: type of clothing and degree of body covered
- Body mass and percentage body fat
- Diet
  - intake of fish oil, oily fish,
  - foods with vitamin D fortification
  - Vitamin D supplements



vitamin D in pregnancy

✓**support maternal and fetal bone health**

increased vitamin D status during pregnancy may enhance bone mineralization in the offspring *Bischoff-Ferrari HA 2011*

✓**enable the maternal immunological adaptation required to mantain a normal pregnancy**

observational and intervention studies have suggested that vitamin D supplementation benefits immune function and the loss of tolerance of preeclampsia

Hypponen E 2011

increased levels are associated with long-term protection against immunological diseases (allergies, type 1 diabetes, asthma)

Bischoff-Ferrari HA 2011

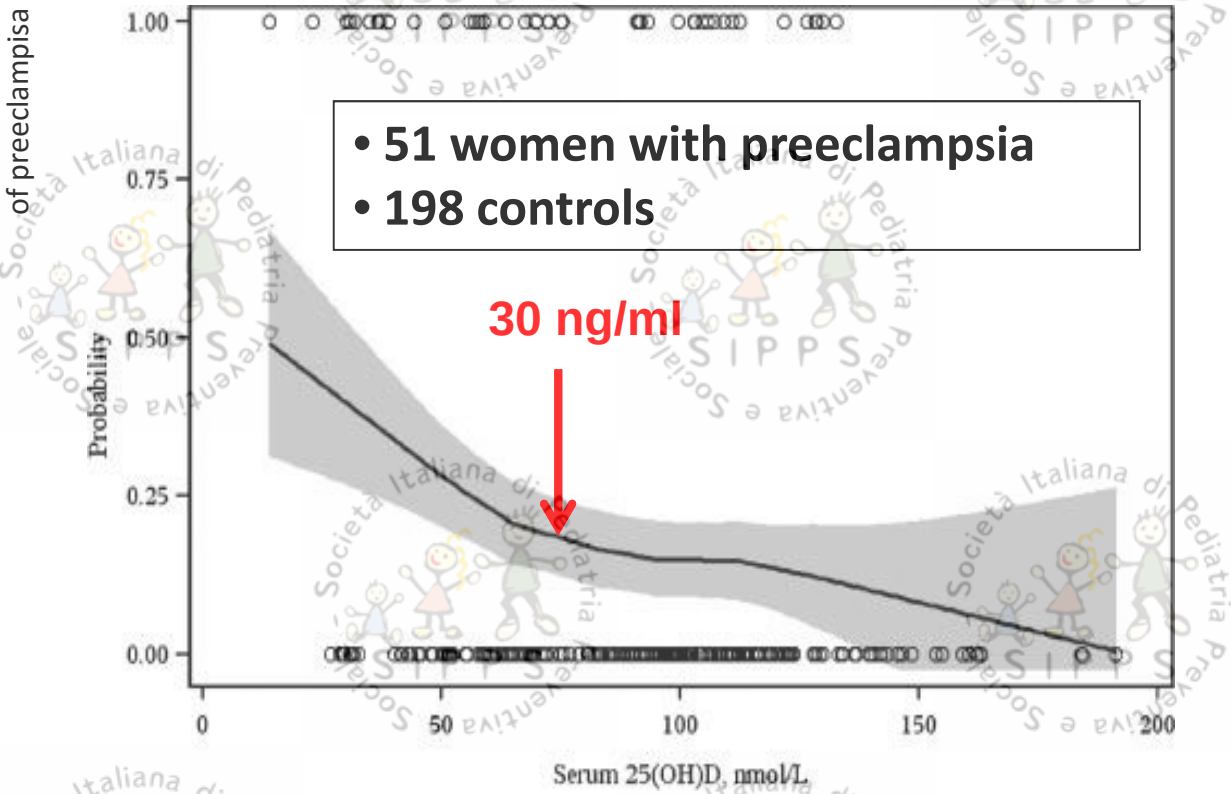
Vitamin D in pregnancy

Health implications

Stage	Serum 25(OH)D, ng/mL	Maternal adverse effects	Newborn infant adverse effects
Severe deficiency	<10	Increased risk of preeclampsia, calcium malabsorption, bone loss, poor weight gain, myopathy, higher parathyroid hormone levels	Small for gestational age, neonatal hypocalcemia, hypocalcemic seizures, infantile heart failure, enamel defects, large fontanelle, congenital rickets, rickets of infancy if breastfed
Insufficiency	11-32	Bone loss, subclinical myopathy	Neonatal hypocalcemia, reduced bone mineral density, rickets of infancy if breastfed
Adequacy	32-100	Adequate calcium balance, parathyroid hormone levels	None, unless exclusively breastfed

(Mulligan ML et al. Am J Obstet Gynecol May 2010)

Midgestation (15-20 wk) vitamin D deficiency and risk of severe preeclampsia



- **Maternal midgestation vitamin D deficiency was associated with increased risk of severe preeclampsia.**
- **Vitamin D deficiency may be a modifiable risk factor for severe preeclampsia.**

(Baker AM et al. JCEM 2010)

Plasma 25-Hydroxyvitamin D during pregnancy and Small for Gestational Age (SGA) birth in black and white infants

- N = 1.067 white and 236 black mother-child pairs.
- 25(OH)D levels assessed in 2nd trimester maternal blood

Participant characteristics	Second trimester plasma 25(OH)D (n = 1113*)			
	Severe deficiency	Deficiency	Insufficiency	Sufficiency
	<25 nmol/L (n = 47)	25 to <50 nmol/L (n = 314)	50 to <75 nmol/L (n = 543)	≥75 nmol/L (n = 229)
	n (column %)			
Race				
Black	34 (72.3)	78 (24.8)	55 (10.1)	19 (8.3)
White	13 (27.6)	236 (75.2)	488 (89.9)	210 (91.7)
Category of birthweight-for-gestational age				
SGA	7 (14.9)	18 (5.7)	22 (4.1)	6 (2.6)
Appropriate-for-gestational age	34 (72.3)	245 (78.0)	438 (80.7)	195 (85.2)
Large-for-gestational age	6 (12.8)	51 (16.2)	83 (15.3)	28 (12.2)

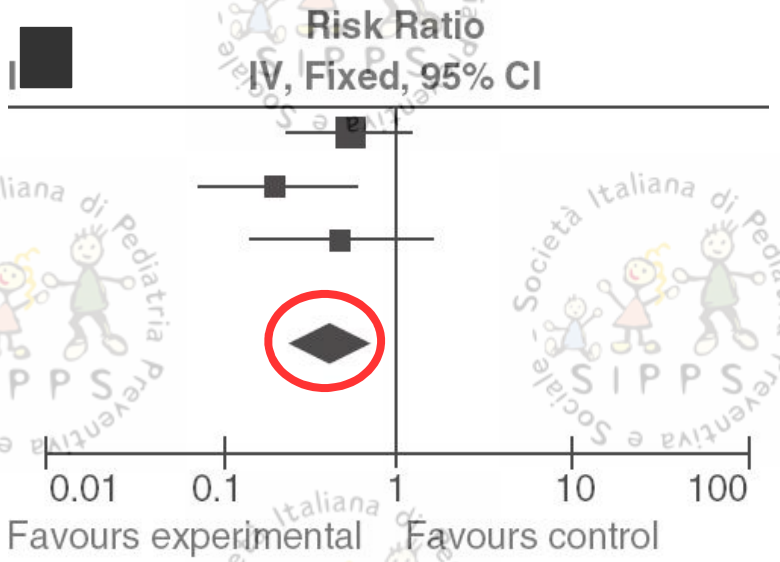
2nd trimester 25(OH)D levels < 25 nmol/L (10 ng/ml) were associated with higher prevalence of SGA in comparison with 25(OH)D levels ≥ 25 nmol/L

(Burris H et al. Annals of epidemiology, June 2012)

Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis

Daily or bolus vitamin D supplementation and risk of low birthweight

- **3 studies (cases = 279; controls = 228)**
- OR: 0.40 (I.C. 0.23-0.71)



- **Vitamin D supplementation reduces the risk of low birthweight.**
- **No effect of daily supplementation on SGA (2 trials) and preterm delivery (2 trials).**
- **Little evidence from trials exists to evaluate the effect of vitamin D supplementation during pregnancy on maternal, perinatal or infant health outcomes.**

(Thorne-Lyman A, Fawzi WW. Pediatric and Perinatal Epidemiology July 2012)

Vitamin D supplementation for women during pregnancy

(6 studies; n = 1.023 women)

Intervention: supplementation with vitamin D alone
Comparison: placebo/no intervention (no vitamins or minerals)

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Pre-eclampsia	Not estimable	0 (0 studies)	No trial assessed this outcome
Gestational diabetes	Not estimable	0 (0 studies)	No trial assessed this outcome
Maternal vitamin D status at term (25-hydroxyvitamin D in nmol/L)	MD 47.08 (23.76, 70.39)	414 (4 studies)	⊕⊕◯◯ low [1,2,3]
Preterm birth	Not estimable	0 (0 studies)	No trial assessed this outcome
Low birthweight	0.48 (0.23 to 1.01)	463 (3 studies)	⊕⊕◯◯ low [1,2,3]

- ***Vitamin D supplementation during pregnancy improves women's vitamin D levels at term and seems to protect against low birthweight.***
- ***However, there is no evidence that it prevents preeclampsia, gestational diabetes or preterm birth.***

(De-Regil LM et al. Feb 2012)

calcium-vitamin D co-supplementation and glycaemic control, inflammation and oxidative stress in gestational diabetes

A randomised placebo-controlled trial. 51 pregnant women with gestational diabetes (Iran). **Placebo vs supplemented** (5.000 UI vit D/twice during the study + 1.000 mg calcium per day). **Six weeks of intervention**.

Table 3 Metabolic profiles, inflammation and biomarkers of oxidative stress at study baseline and after a 6-week intervention in pregnant women with GDM who received either calcium plus vitamin D supplements or placebo

Variable	Placebo group[a] (n=28)			Calcium plus vitamin D group[b] (n=28)			p value[c]
	Week 0	Week 6	Change	Week 0	Week 6	Change	
Calcium (mmol/l)	2.03±0.32[d]	2.00±0.38	−0.03±0.34	2.03±0.44	2.20±0.34	0.17±0.48	0.08
Vitamin D (nmol/l)	49.05±34.30	50.80±35.48	1.75±15.36	43.11±28.17	91.30±54.60*	48.19±46.64	<0.001
FPG (mmol/l)	4.42±0.59	4.68±1.06	0.26±0.92	5.14±0.71	4.25±0.64*	−0.89±0.69	<0.001
Insulin (pmol/l)	88.39±50.13	97.56±64.43	9.17±38.50	77.87±36.51	64.32±28.73	−13.55±35.25	0.02
HOMA-IR	2.93±1.66	3.56±2.69	0.63±2.01	2.93±1.34	2.02±0.89*	−0.91±1.18	0.001
HOMA-B	63.32±39.94	65.29±44.84	1.97±28.51	48.45±26.87	47.68±23.87	−0.77±29.66	0.63
QUICKI	0.33±0.03	0.33±0.05	−0.002±0.02	0.33±0.01	0.35±0.03*	0.02±0.03	0.003
Total cholesterol (mmol/l)	5.11±1.20	5.33±1.47	0.22±0.96	5.10±1.01	5.06±1.20	−0.04±1.01	0.33
Triacylglycerol (mmol/l)	2.09±0.69	2.05±0.68	−0.04±0.63	2.02±0.78	2.14±0.84	0.12±0.58	0.36
LDL-cholesterol (mmol/l)	2.79±0.88	3.05±1.08	0.26±0.74	2.94±0.81	2.71±0.87	−0.23±0.79	0.02
HDL-cholesterol (mmol/l)	1.36±0.44	1.34±0.44	−0.02±0.24	1.22±0.27	1.37±0.33*	0.15±0.25	0.01
Total:HDL-cholesterol ratio	3.93±0.86	4.11±0.80*	0.18±0.37	4.32±1.21	3.83±0.96*	−0.49±1.09	0.003
hs-CRP (ng/ml)	6,451.03±3,924.81	6,244.83±4,192.56	−206.20±4,006.65	7,391.83±4,693.09	7,384.93±3,692.78	−6.90±4005.65	0.83
NO (μmol/l)	54.04±28.65	51.69±28.40	−2.35±28.65	60.39±32.56	66.48±29.41	6.09±34.07	0.32
TAC (mmol/l)	724.71±176.51	789.39±176.47*	64.68±128.19	702.08±190.66	751.34±129.29	49.26±140.80	0.67
GSH (μmol/l)	761.69±383.11	714.42±365.83	−47.27±203.63	570.91±97.73	622.05±127.85	51.14±131.64	0.03
MDA (μmol/l)	2.69±1.42	3.62±1.83*	0.93±2.00	2.99±0.53	3.05±0.72	0.06±0.66	0.03

[a] Received placebos for calcium daily and for vitamin D twice during the study: at study baseline and on day 21 of intervention

[b] Received 1,000 mg calcium carbonate daily plus 50,000 U vitamin D_3 twice during the study: at study baseline and on day 21 of intervention

[c] Obtained from repeated measures ANOVA

[d] All values are mean ± SD. Baseline values of FPG, HOMA-B, QUICKI, GSH and MDA were significantly different between the two groups

*Different from Week 0, $p<0.05$

Reduction of **fasting plasma glucose (FPG)** ($p < 0,001$), **serum insulin levels** ($p = 0,02$) and **HOMA-IR** ($p = 0,001$) compared with placebo.

(Asemi Z. June 2014, Diabetologia)

Vitamin D supplementation in pregnancy: A systematic review

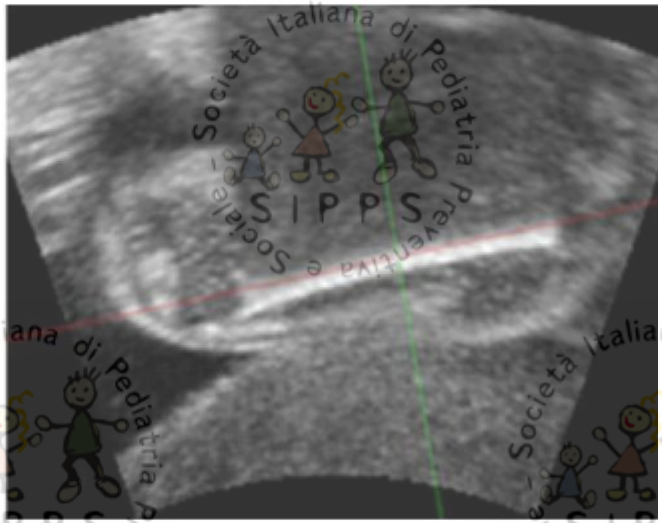
Nicholas C Harvey[1,2,*], Christopher Holroyd[1,*], Georgia Ntani[1], Kassim Javaid[3], Philip Cooper[1], Rebecca Moon[1], Zoe Cole[1], Tannaze Tinati[1], Keith Godfrey[1,2], Elaine Dennison[1], Nicholas J Bishop[4], Janis Baird[1], and Cyrus Cooper[1,2,3]

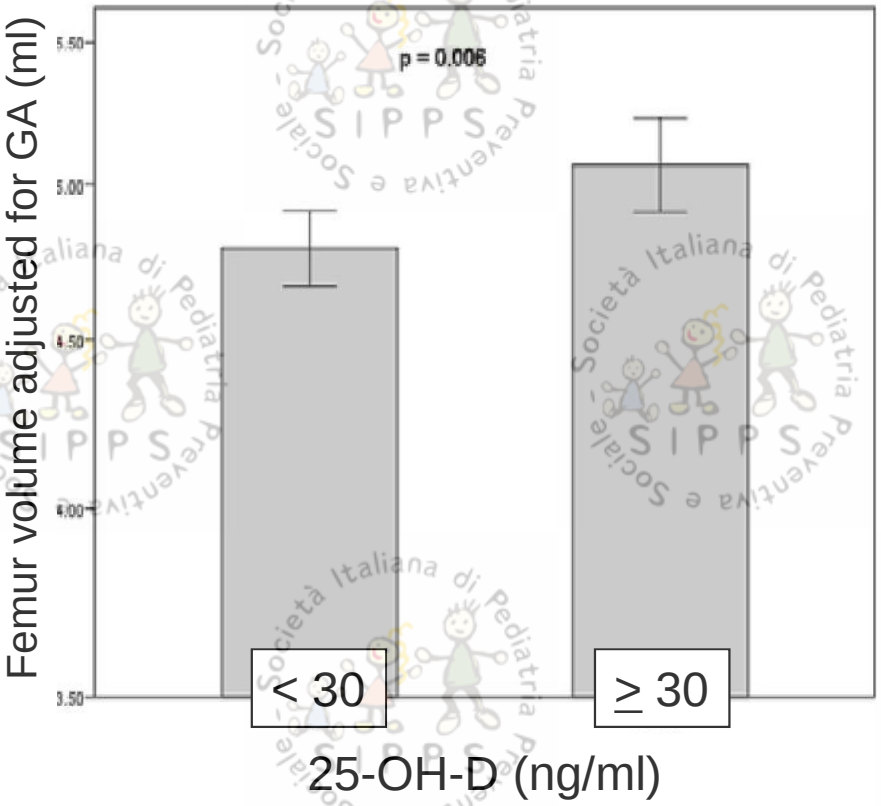
- *Five of the eight observational studies relating maternal 25(OH)-vitamin D status to **offspring bone outcomes** demonstrated positive associations. The one small intervention study identified did not, but the methodology is unclear and a statistically significant result is unlikely based on the sample size.*
- *Thus observational studies suggest that maternal 25(OH)-vitamin D status may influence offspring bone development, but do not allow public health recommendations to be made. Further high-quality intervention studies are required here, such as the ongoing MAVIDOS Maternal Vitamin D Osteoporosis Study*

Health Technol Assess. 2014 July ; 18(45): 1–190.

The effect of maternal vitamin D concentration on fetal bone

- n. 357 pregnant women
- fetal 3D ultrasound and maternal 25-OH-D levels assessed at 34 wk





- **Fetus from vitamin D sufficient mothers have higher femur volume.**
- **Maternal vitamin D concentrations are significant predictors of femoral volume.**

(Ioannou C et al. JCEM Nov 2012)

Maternal 25-hydroxyvitamin D level and fetal bone growth assessed by ultrasound

A systematic review

750 pubblications , 5 selected for inclusion in final review

Parameters studied:
humerus length (HL) and femour length (FL) and their Z-scores, femoral volume, femoral distal metaphyseal cross-sectional area (CSA), femoral proximal methaphyseal diameter (PMD), femoral mid-shaft diameter and crown-rump lenght.

Low maternal 25(OH)D levels may affect fetal bone growth (FL, HL Z-scores), especially in cases of simultaneous low calcium intake.

(Galthen M. et al. 2014 Ultrasound Obstet Gynecol)

Prenatal Vitamin D and Dental Caries in Infants

UK: 207 pregnant mothers in 2° trim

33% were vitamin D deficient

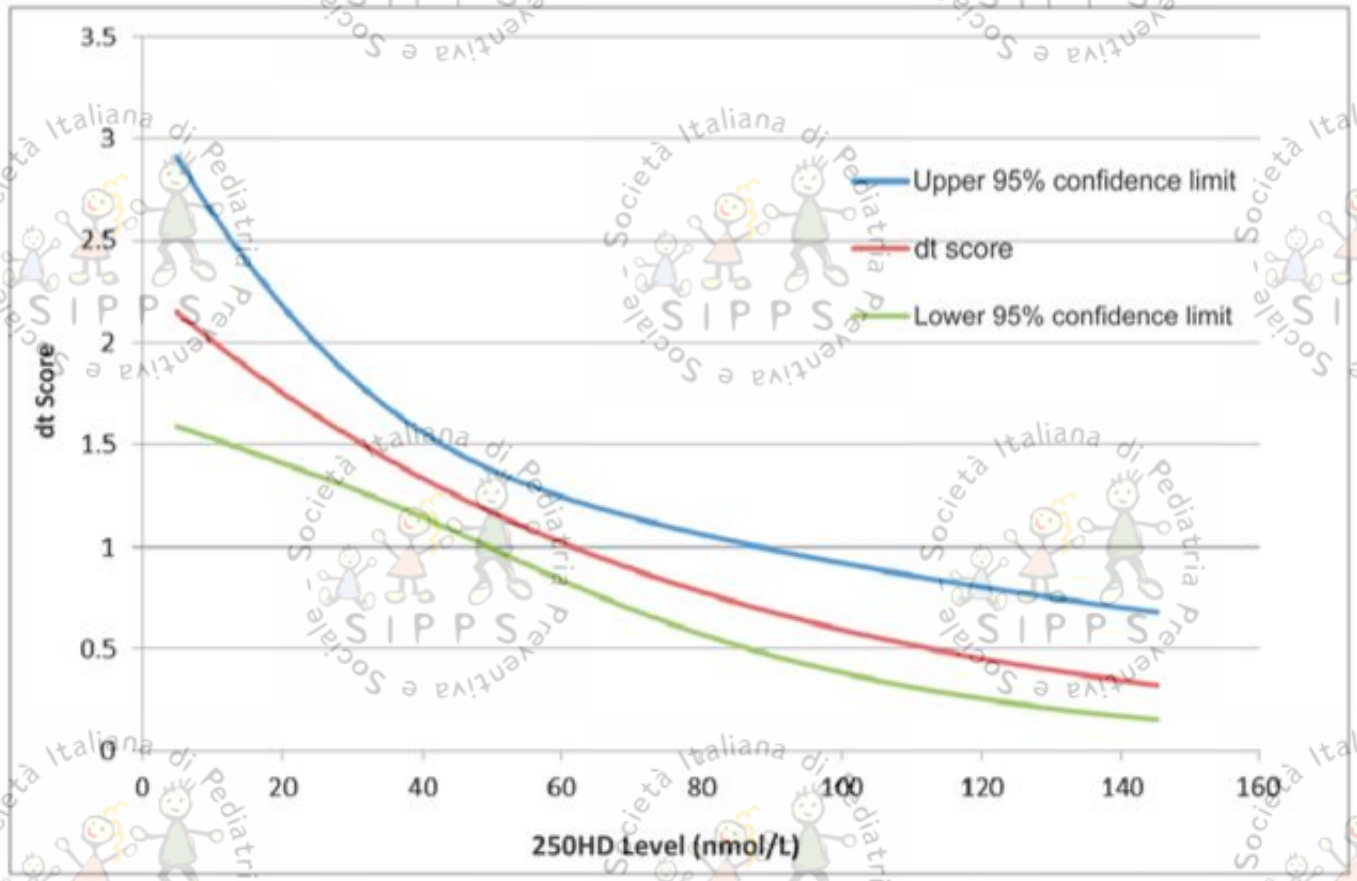


FIGURE 1
Predicted number of decayed primary teeth (dt score) according to 250HD level.

PEDIATRICS Volume 133, Number 5, May 2014

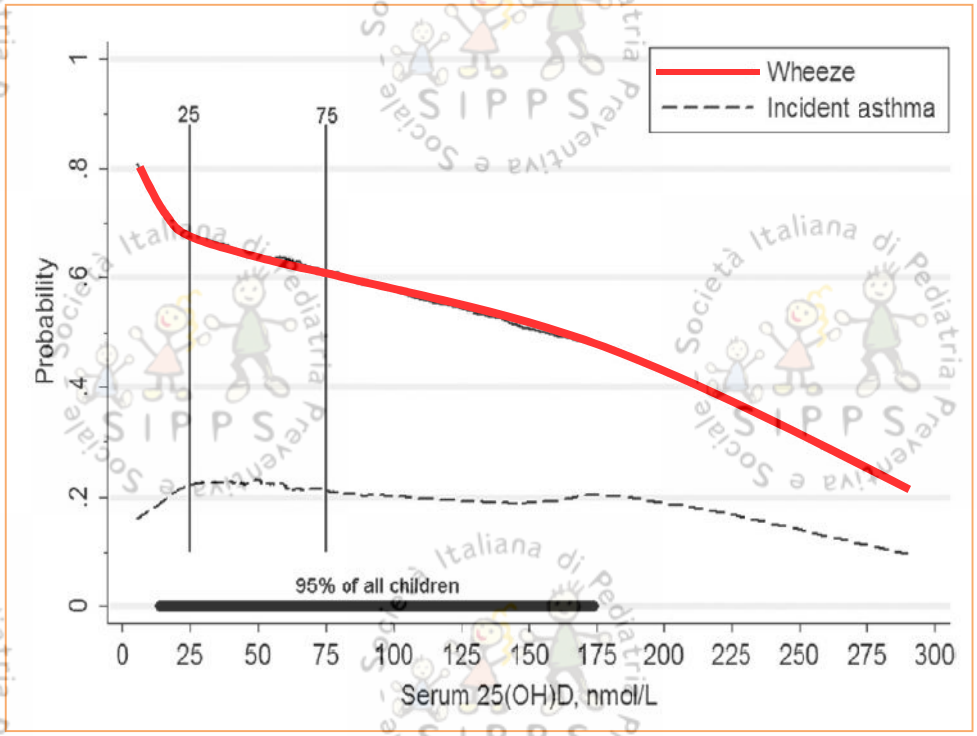
Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma by the age of 3 months until 5 years

- **N = 922 newborns**
- **Follow-up at 3 months, until 5 yr**
- Median cord-blood 25-OHD = 17.6 ng/ml

  25-OHD > 30 ng/ml = 27.2 %

  25-OHD: 10-30 ng/ml = 53.2 %

  25-OHD < 10 ng/ml = 19.6 %



Low cord-blood levels of 25-OHD were common in newborns and were associated with higher risk of respiratory infections by the age of 3 months.

Cord blood 25-OHD levels were inversely associated with wheeze throughout early childhood but had no association with incident asthma.

(Camargo CA et al. Pediatrics Jan 2011)

Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing

Cohort study of children (0-5 years). Vitamin D supplement and wheezing data were available for **2.478 children**, and blood samples were available for 1.275 children.

Vitamin D supplementation during pregnancy was associated with reduced odds of wheezing (aOR=0.65; 95% CI: 0.46-0.93), but child vitamin D supplementation and childhood 25(OH)D were not associated with reduced wheezing.

The timing of exposure may be important in understanding the association between vitamin D and childhood wheezing.

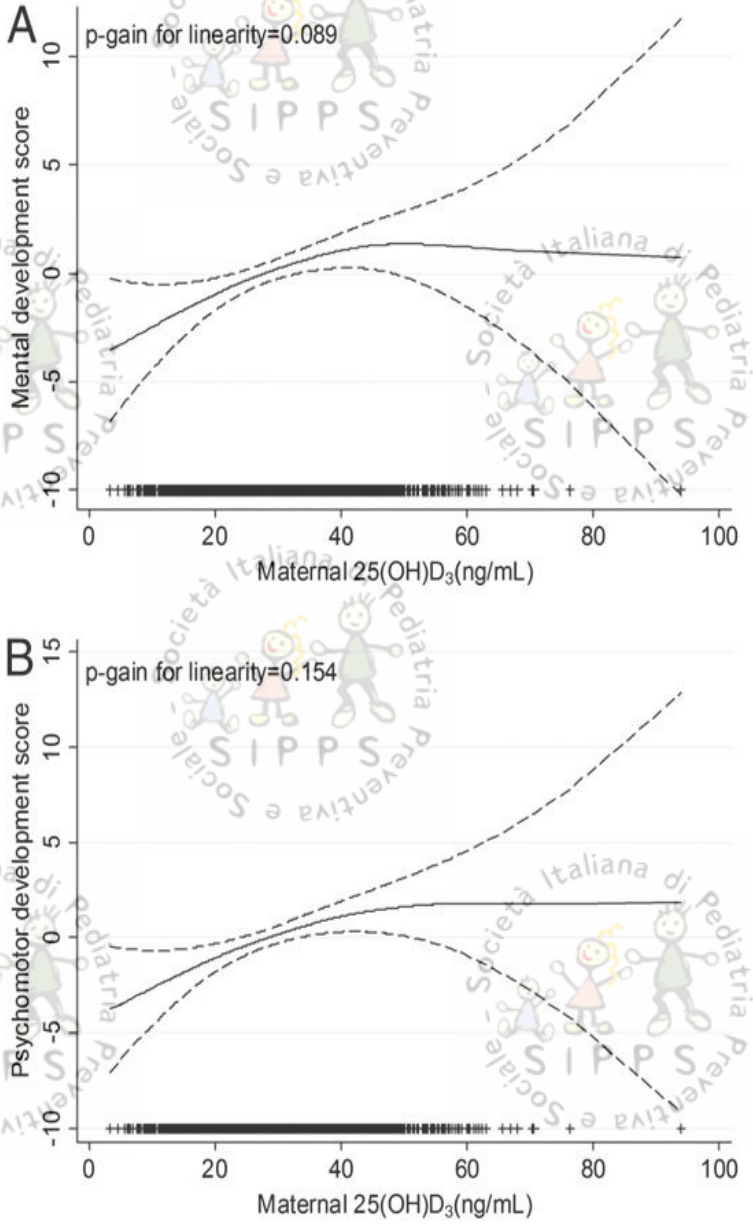
Anderson LN et al
Dev Orig Health Dis 2015

Circulating 25-hydroxyvitamin D_3 in pregnancy and infant neuropsychological development

- **n. 1.820 mother-infant pairs.**
- 25-OH-D levels assessed during 1st trimester (13.5 ± 2.1 wk).
- Offspring mental and psychomotor scores were assessed at age 14 months by using the Bayley Scales of Infant Development.

Higher circulating concentrations of maternal 25(OH)D_3 in pregnancy were associated with improved mental and psychomotor development in infants at 14 months.

(Morales et al. Pediatrics Oct 2012)



Vitamin D in Fetal Development: Findings From a Birth Cohort Study

Hart PH. et al. 2015

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

- **Cohort of 901 mother-offspring pairs** (Western Australia)
- Relationships between **maternal vitamin D deficiency at 18 weeks** (36% of the pregnant woman, 323 of 901) and **long term health outcomes** in the offspring were examined

Vitamin D deficiency was associated with: **impaired development of fetal lung** in 6 years old offspring, **neurocognitive difficulties** at age 10, increased risk of **eating disorders** in adolescence, and **lower peak bone mass** at 20 years.

TABLE 1 Summary of the Associations of Organ Development of the Offspring With Maternal Serum 25(OH)D Levels From 5 Separate Studies (N = 901)

Organ	Measure	Age at Measure	n	Association
Lung	Z scores[6] FVC	6 y	260	Positive
Brain	Language scores[7]	5, 10 y	743	Positive
	Eating disorder risk[8]	14, 17, 20 y	526	Negative
	Autism-Spectrum Quotient[9]	Early adulthood	406	Negative
Bone	Peak bone mass[10]	20 y	341	Positive

Vitamin D may have an important, multifaceted role in the development of fetal lungs, brain, and bone.

Vitamin D supplementation in pregnancy

IOM	Institute of Medicine	2011	600 UI/day for all
LARN	National Recommended Energy and Nutrient Intake Levels	2012	600 UI/day for all
FDA	Food and Drug Administration	2015	600 UI/day for all
ES	Endocrine Society	2014	600 UI/day for all (1.500-2.000 at risk)
ACOG	College of Obstetricians and Gynecologist	2011	1.500 - 2.000 UI/day only if risk factors
WHO	World Health Organization	2012	No routine supplementation
RCOG	Royal College of Obstetricians and Gynaecologists	2014	• 400 UI/day for all • 1.000 UI/day if risk factors

2015

all pregnant women: 600 UI/day

pregnant women with risk factors: 1.000-2000 UI/day

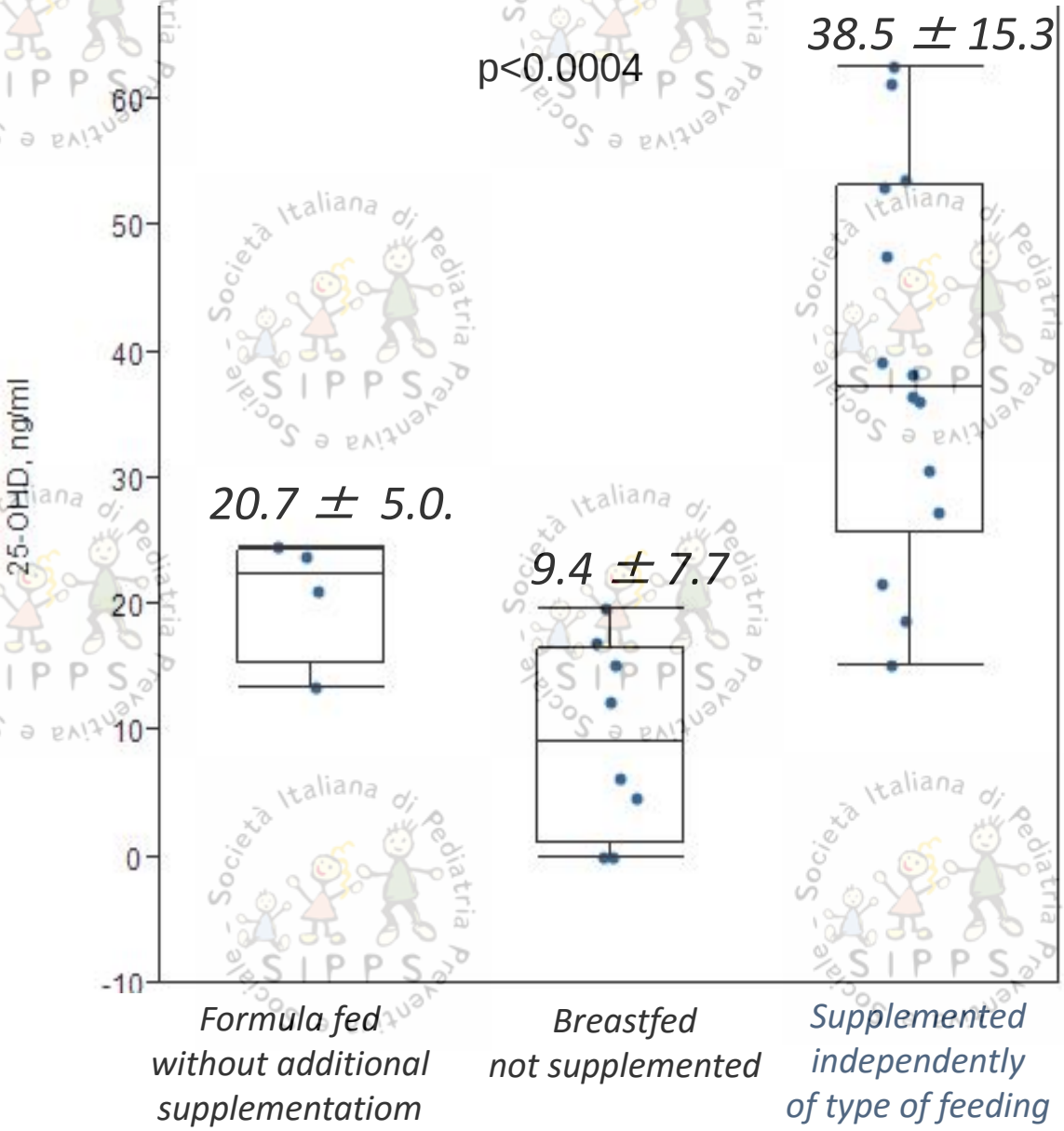
Vitamin D status: **breastfeeding** vs formula feeding

(Department of Pediatrics, University of Pisa)

46 unweaned infants

(1 – 7 months)

- *25-OH-D levels were significantly different according to supplementation and type of feeding.*
- *Exclusively breastfed infants are at higher risk of vitamin D deficiency.*



Minerva Pediatr. 2013 Jun;65(3):253-60.

Is vitamin D supplementation necessary in healthy full-term breastfed infants? A follow-up study of bone mineralization in healthy full-term infants with and without supplemental vitamin D.

Bagnoli F[1], Casucci M, Toti S, Cecchi S, Iurato C, Coriolani G, Tiezzi M, Vispi L.

METHODS:

Bone mineralization was studied by performing ultrasound scans of 73 healthy full-term subjects at the age of 3 months.

The infants were divided into three groups:

group A: breastfed without supplemental vitamin D (BF);

group B: breastfed with supplement of 400 IU/day of vitamin D(BFD);

group C: fed with formula (with and without supplemental vitamin D 400 IU/day) (FF).

RESULTS:

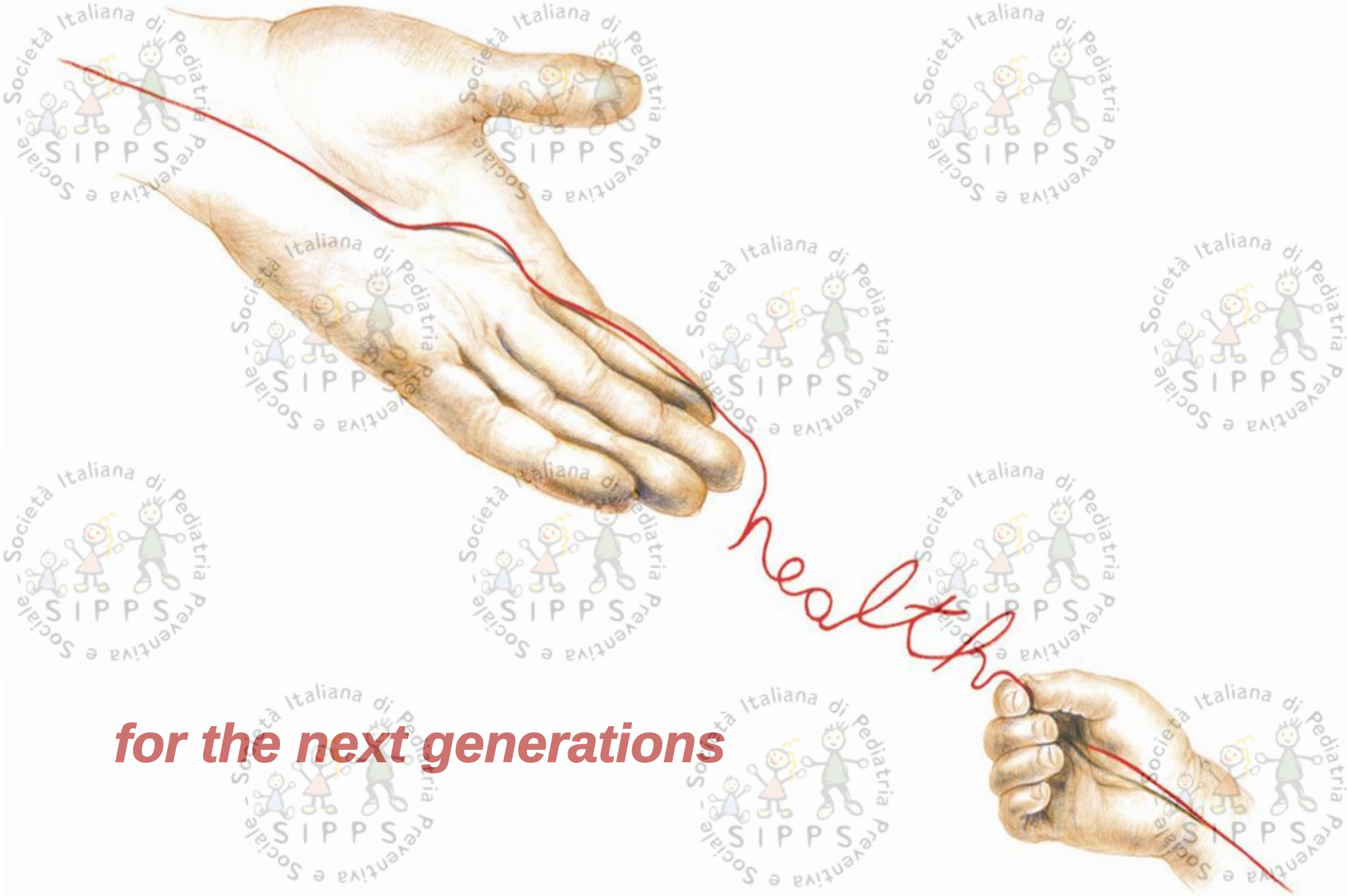
n 75% of subjects of group A mcSOS and mcBTT values were ≤ the 10th percentile, while in group B they were between the 10th and 50th percentile. In FF infants given supplemental vitamin D mcSOS and mcBTT values were between the 25th and 75th percentile

Supplementazione con Vitamina D nella nutrice

- La profilassi nella nutrice deve essere effettuata con 600 UI di vitamina D, anche se con tale dosaggio il latte materno contiene scarse quantità di vitamina D (25-78 UI/l).
- Non è consigliabile utilizzare dosi più elevate per la profilassi nella nutrice (es. 4.000 UI/die) per ottenere livelli più elevati di vitamina D nel latte.
- La profilassi del lattante deve essere attuata con la somministrazione diretta di vitamina D al lattante stesso.

Key points

- ✓ Encourage women to establish **healthy dietary practice before conception**
- ✓ Folate: routine periconceptional supplementation – *starting before conception, at least 400 µg/day*
- ✓ **vitamin D: 600 UI/day in all pregnant and lactating women**
- ✓ **Individualization of supplementation (1000-2000 UI/day of vit D; iron and iodine)**: obesity, adolescents, vegetarians, twins, celiac disease, veiling, specific pregnancy risks…….



for the next generations

Courtesy of David Barker