UNC SCHOOL OF MEDICINE

Vitamin D: 10 things your mother never told you

Folami Y. Ideraabdullah, PhD

Assistant Professor

UNC Chapel Hill

Department of Genetics

Department of Nutrition

folami@email.unc.edu,

704-250-5039

Things our mothers told us about food:

1. Veggies will make you tall/strong
2. Liver is good for you
3. Milk is good for you
4. Mushrooms are good for you
5. Soda will rot your teeth
6. Coffee will stunt your growth
7. Eat all of your food because there are children starving who would love to have it.

But…as a child did your mother ever tell you about vitamin D?

Ten things to know about vitamin D

1. What is it?
2. Where can I get some?
3. What does the body do with it? How is it used?
4. How much do I need? Am I deficient?
5. How much is too much?
6. What may be keeping me from getting enough?
7. How common is deficiency?
8. What happens if I don't have enough (deficient)?
9. What happens if I don't have enough during pregnancy?
10. Are there long term consequences of deficiency?

Ten things to know about vitamin D

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10. **Are there long term consequences of deficiency?**

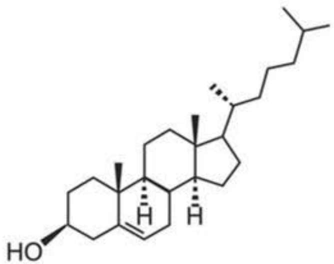
1. What is vitamin D?

Vitamin D is known as an essential “nutrient”

- At least 10 different forms of vitamin D

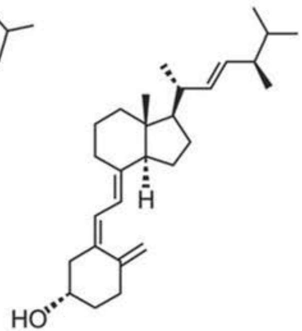
Inactive form

7-dehydrocholesterol



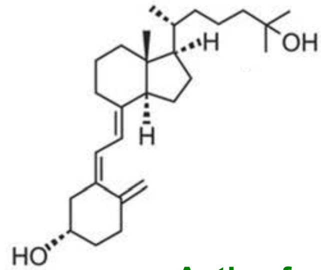
Inactive form

cholecalciferol
(vitamin D3)

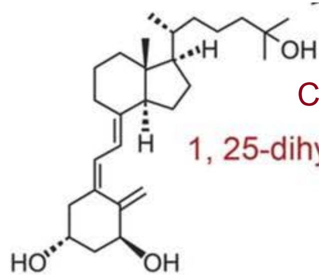


Inactive form

25-hydroxyvitamin D



Active form

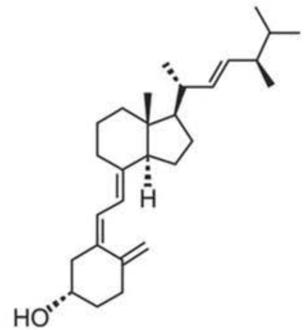


Calcitriol

1, 25-dihydroxyvitamin D_2

Inactive form

ergocalciferol
(vitamin D2)



2. Where can I get some?

Diet & supplements

Vitamin D2 (ergocalciferol):
UV-irradiated mushrooms
Oral supplements
Artificially fortified foods (e.g. milk, cereals, bread, margarine)
Vitamin D3 (cholecalciferol):
Ultraviolet B light (290-315 nm): the major source of vitamin D3
Fatty fish:
Salmon
Mackerel
Tuna
Sardines
Eel
Cod liver oil
Eggs
Oral supplements
Artificially fortified foods (e.g. milk, cereals, bread, margarine)

Kitson & Roberts 2012, Journal of hepatology

2. Where can I get some?

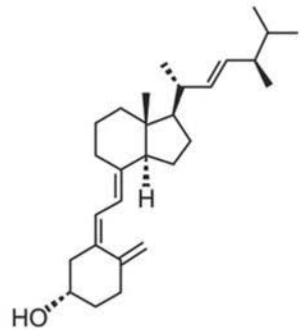
- Is vitamin D a vitamin? Is it an essential nutrient?

Dietary intake

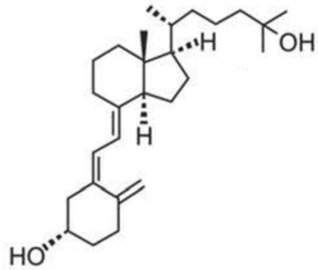
Fortified foods, supplements (D2 or D3), fish oils (D3)

Egg yolk
Liver

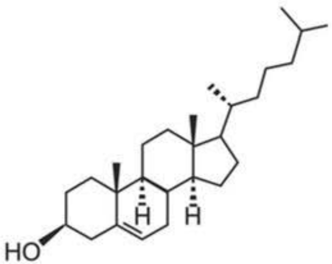
ergocalciferol (vitamin D2)



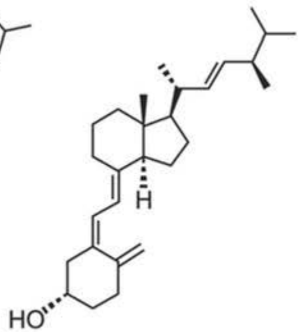
25-hydroxyvitamin D

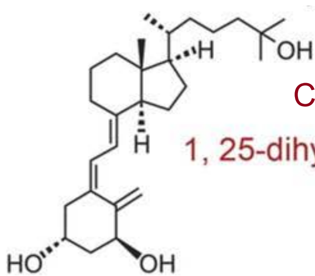


7-dehydrocholesterol



cholecalciferol (vitamin D3)



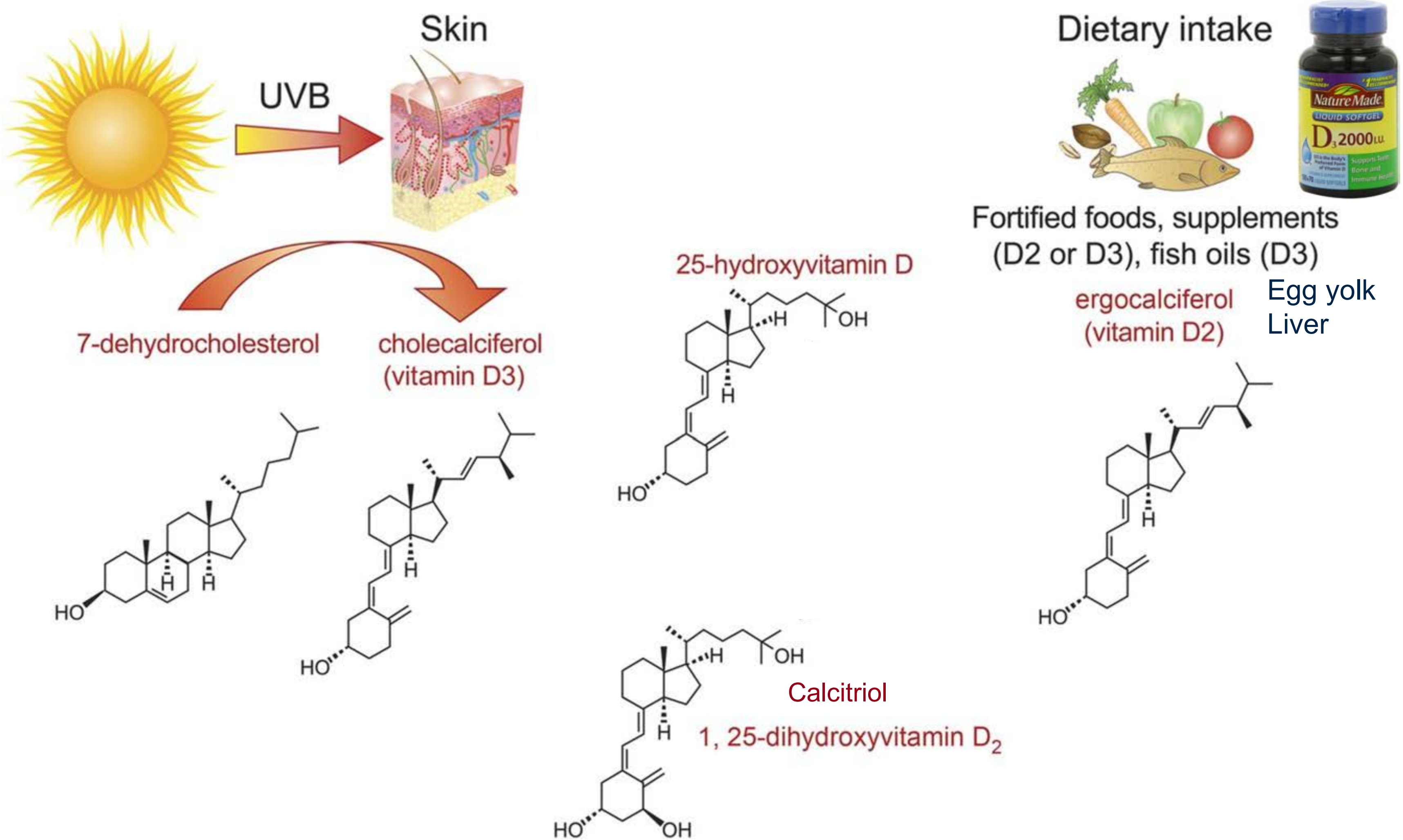


Calcitriol

1, 25-dihydroxyvitamin D_2

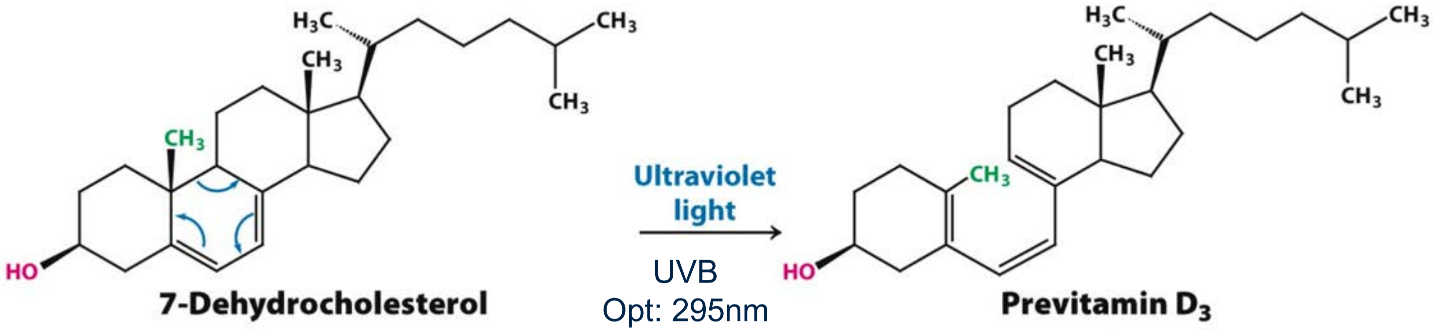
2. Where can I get some?

- Sun exposure



2. Where can I get some?

- Synthesis of vitamin D in the skin (epidermis)
- Is vitamin D a vitamin? Is it an <u>essential</u> nutrient?



UVB
Opt: 295nm
270-315nm

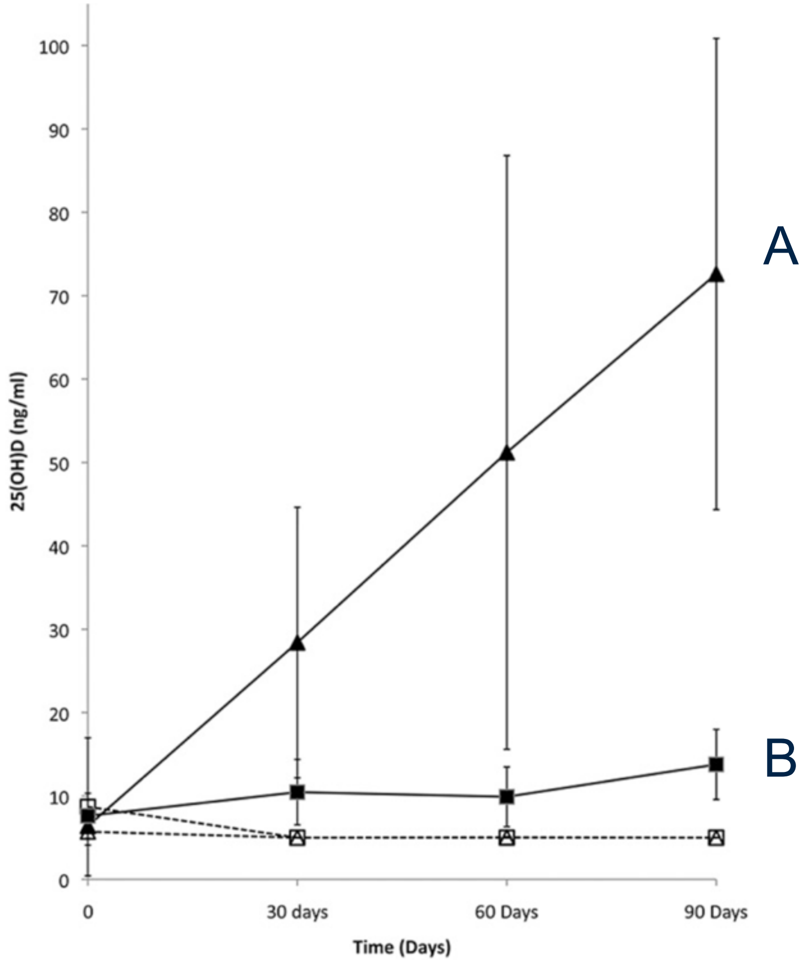
Figure 26.32
***Biochemistry*, Seventh Edition**

2. Where can I get some?

- What about nocturnal animals?
- Species differ in how much they need

A. *Rousettus aegyptiacus:*
   - caves, tombs, and buildings

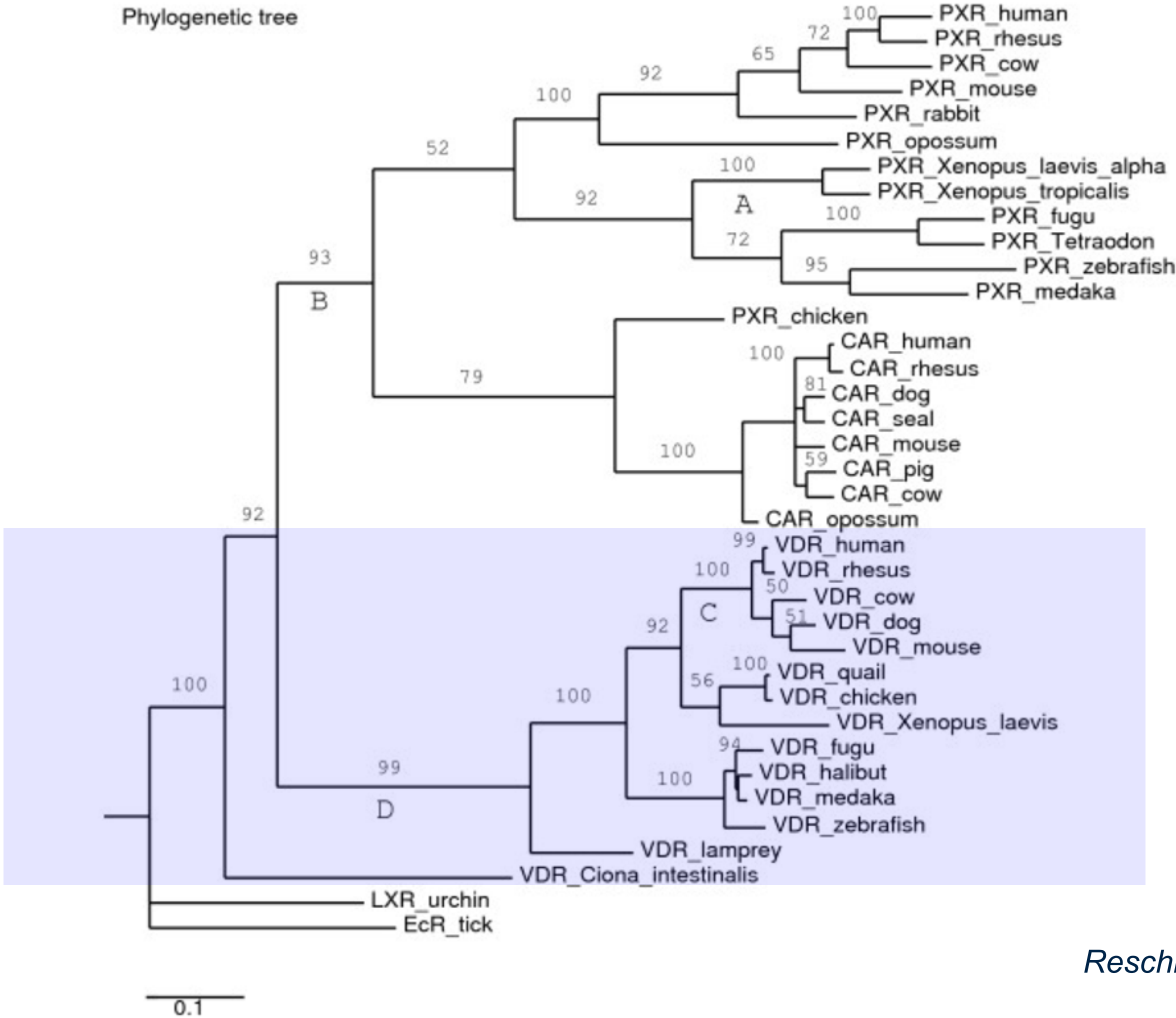
B. *Pteropus hypomelanus:*
   - trees



Southworth L. et al 2013

3. What does the body do with it?

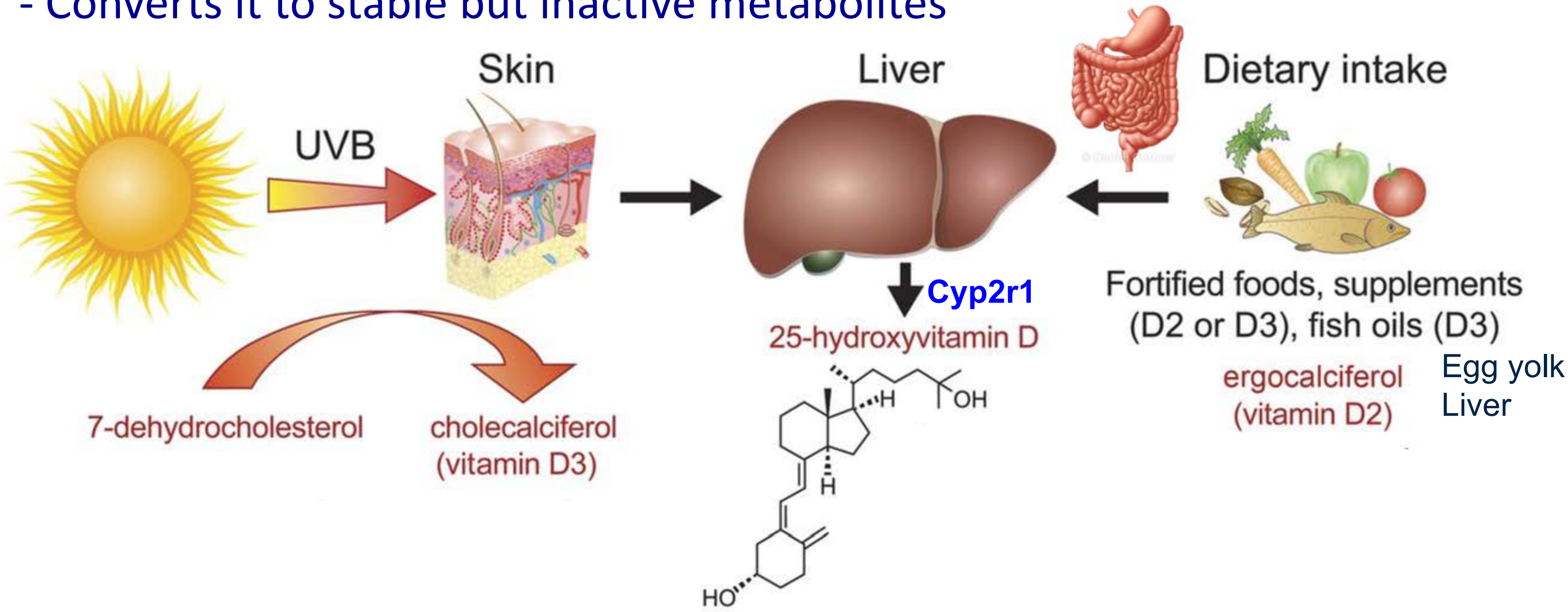
- Vertebrates and invertebrates have conserved VitD pathways
- Most get requirements from sunlight



Reschly E et al 2007

3. What does the body do with it?

- Converts it to stable but inactive metabolites



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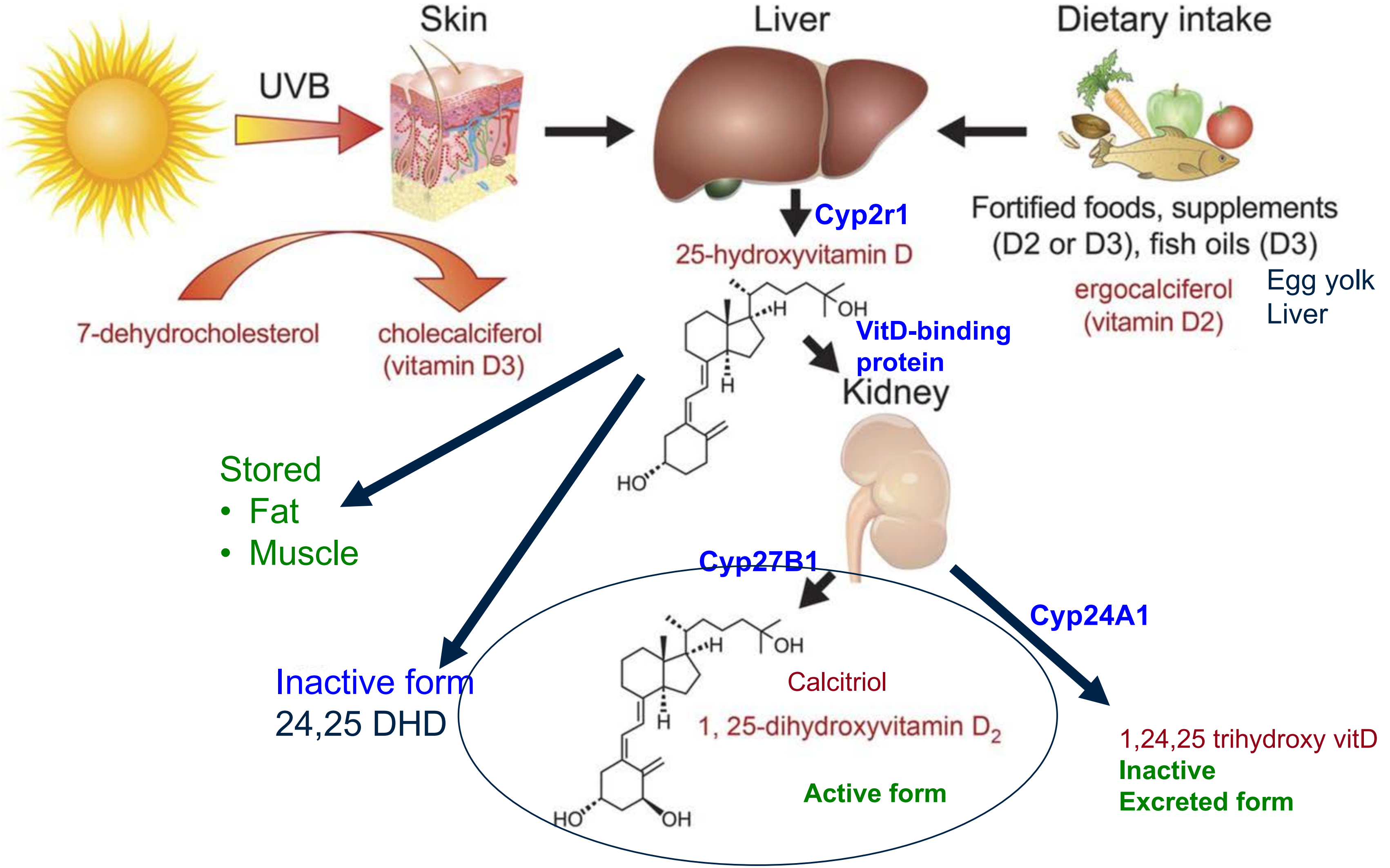
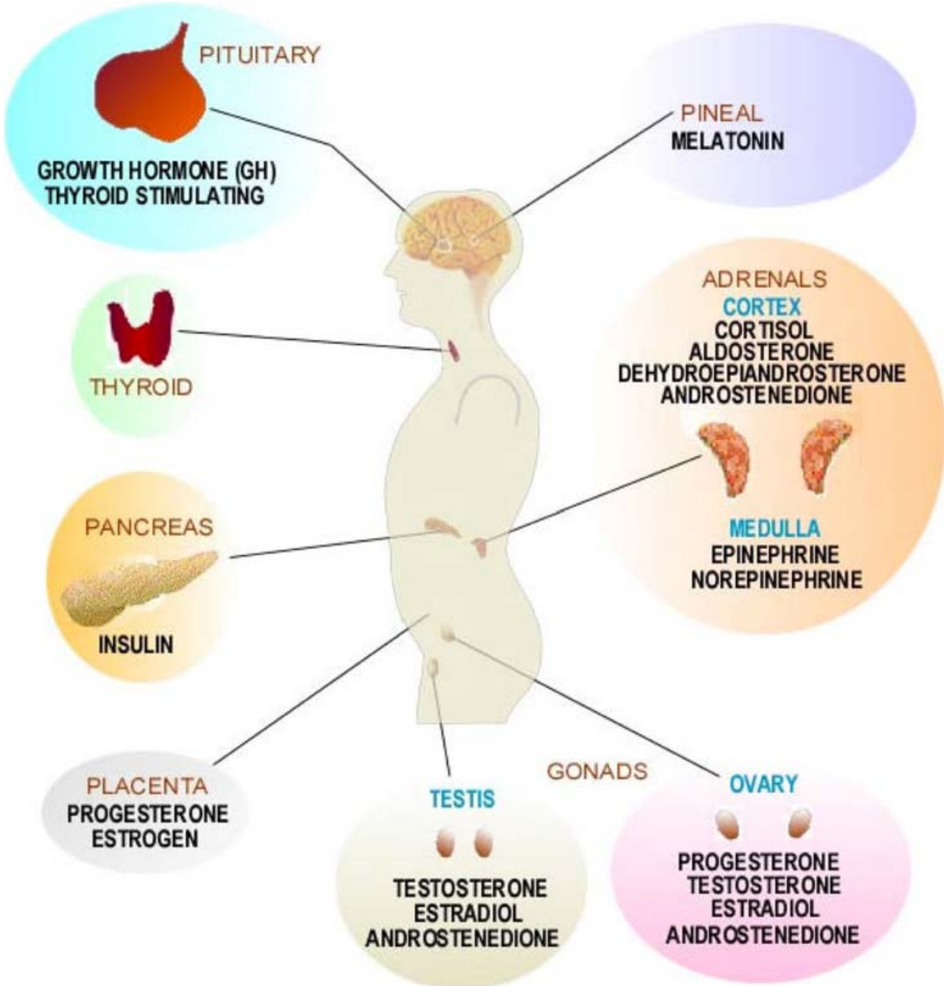


3. What does the body do with it?

- Active vitamin D (1, 25-dihydroxyvitamin D) is steroid hormone
- Circulating signaling molecule



www.centerforhealthandhealing.org

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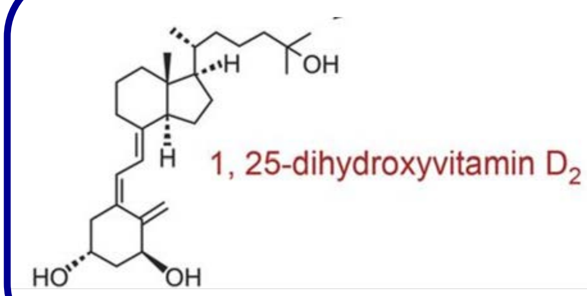
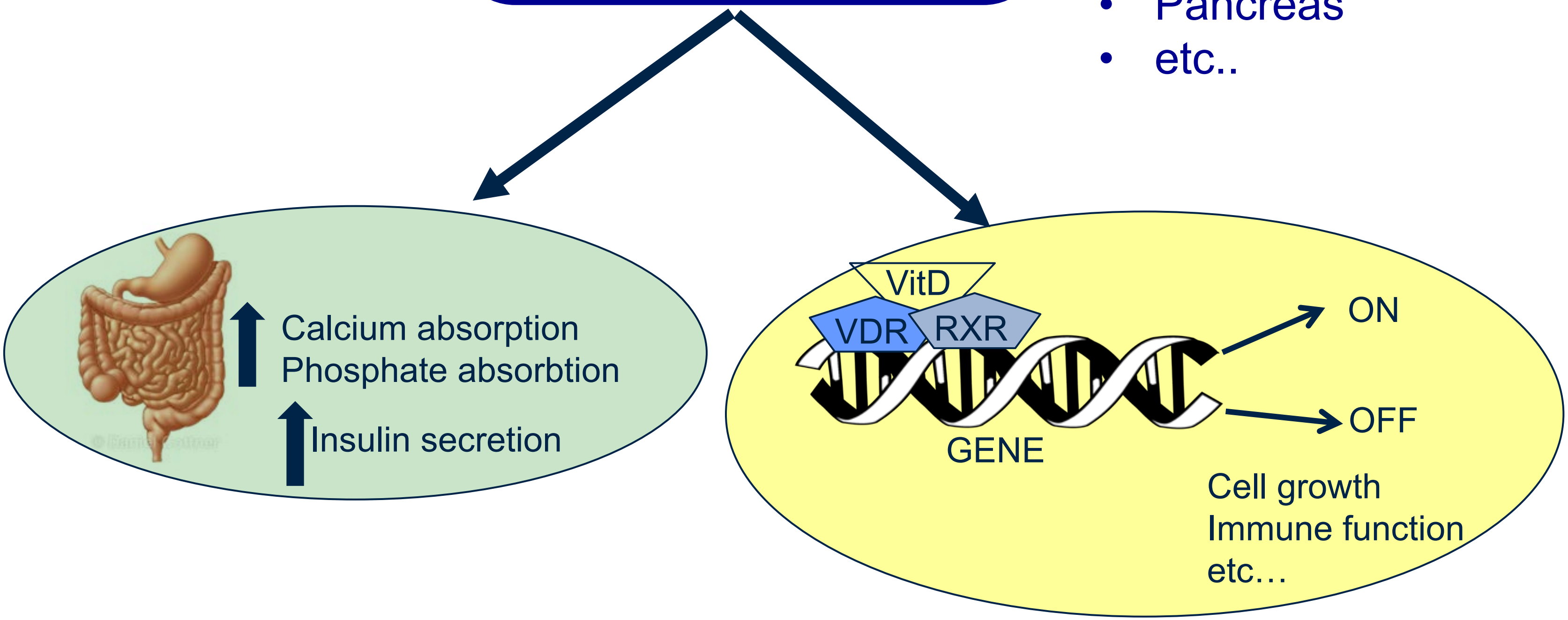


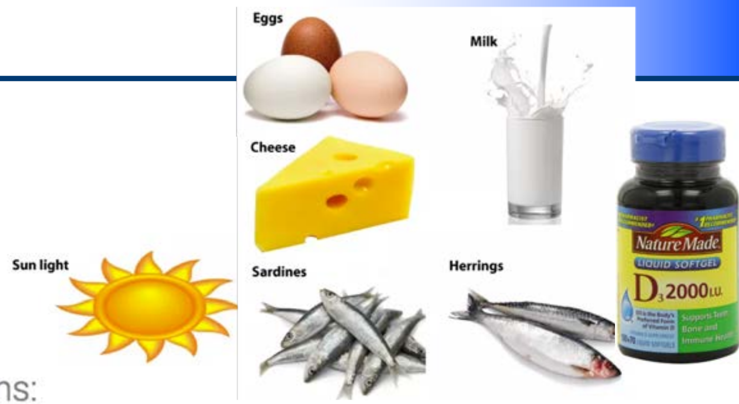
<u>Affected tissues</u>

- Brain
- Gut (intestines)
- Heart
- Muscle
- Liver
- Pancreas
- etc..



4. How much do I need?

- Still under investigation – Guidelines vary
- IOM recommends adequate levels are:
  - ≥ 50nmol/L <u>or</u> ≥ 20ng/ml



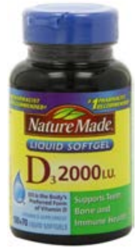
Vitamin D 25(OH)D range guidelines from various organizations:

	Vitamin D Council	Endocrine Society	Food and Nutrition Board	Testing Laboratories
Deficient	0-30 ng/ml	0-20 ng/ml	0-11 ng/ml	0-31 ng/ml
Insufficient	31-39 ng/ml	21-29 ng/ml	12-20 ng/ml	
Sufficient	40-80 ng/ml	30-100 ng/ml	>20 ng/ml	32-100 ng/ml

www.vitamindcouncil.org

5. How much is too much?

- Still under investigation
  - Toxic levels are >150ng/ml -> Hypercalcemia
  - Do not take >10,000 IU/day > 3 months



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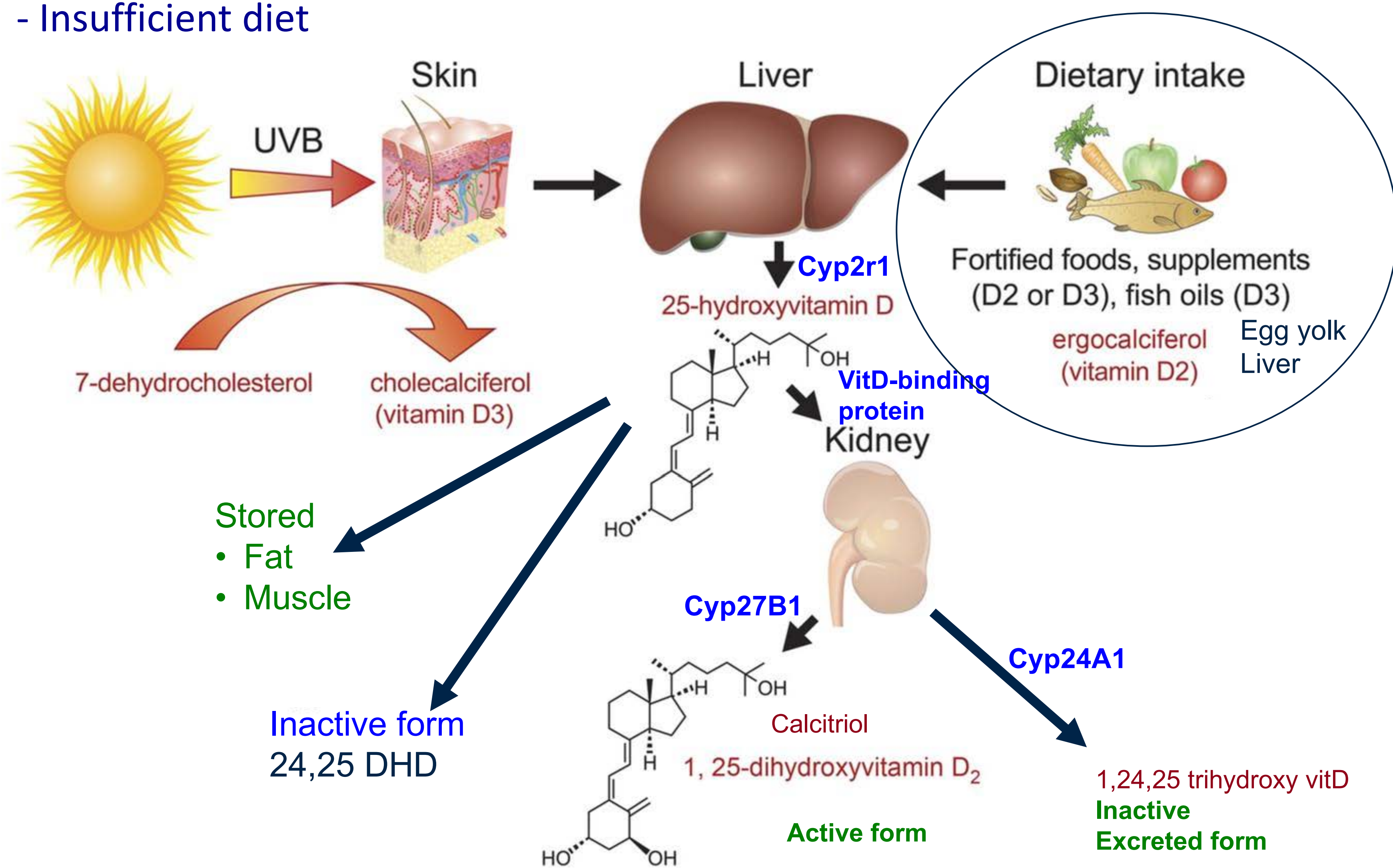
Toxic	>150 ng/ml			

www.vitamindcouncil.org

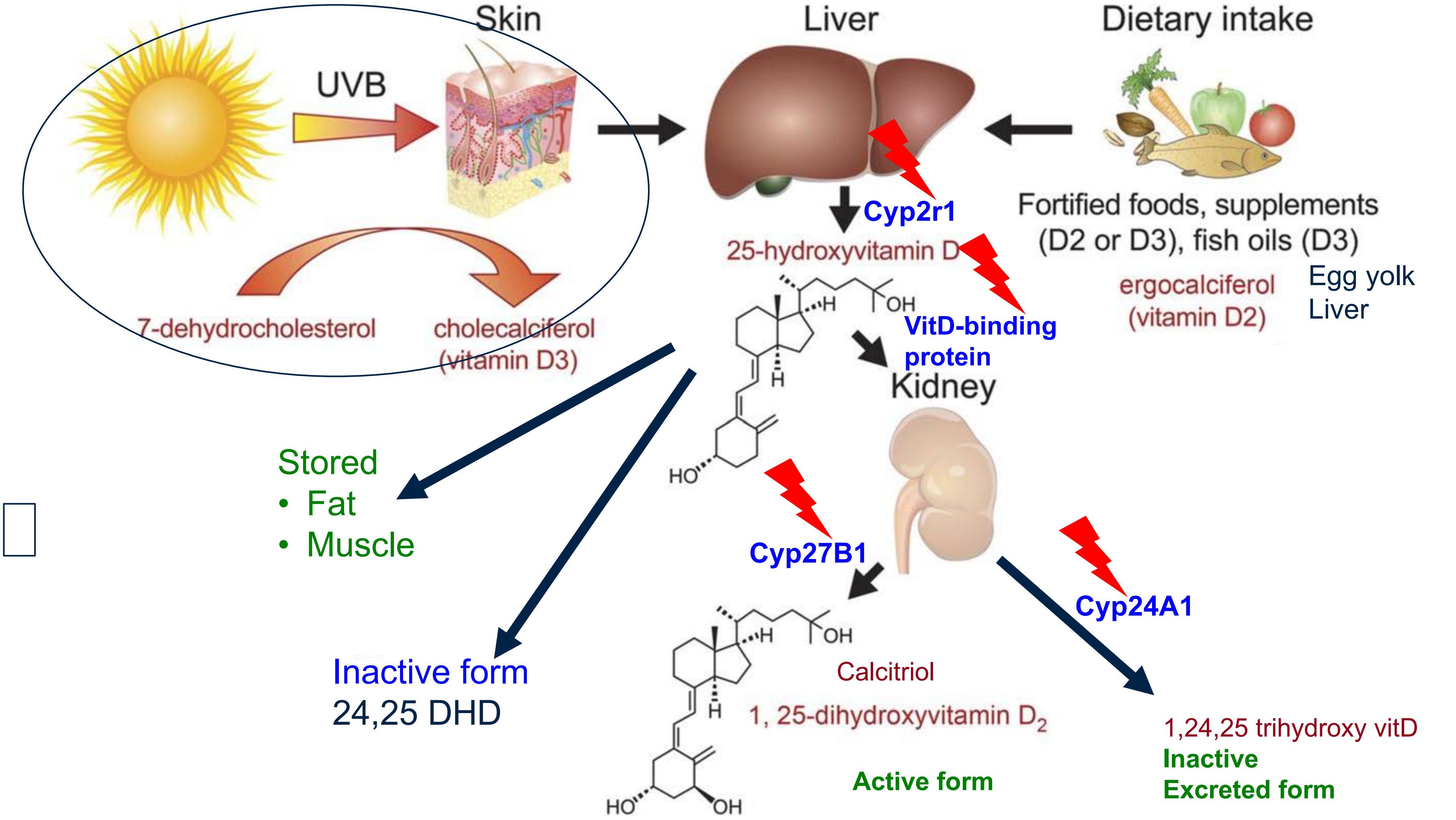
6. What keeps me from getting enough?

- Insufficient diet



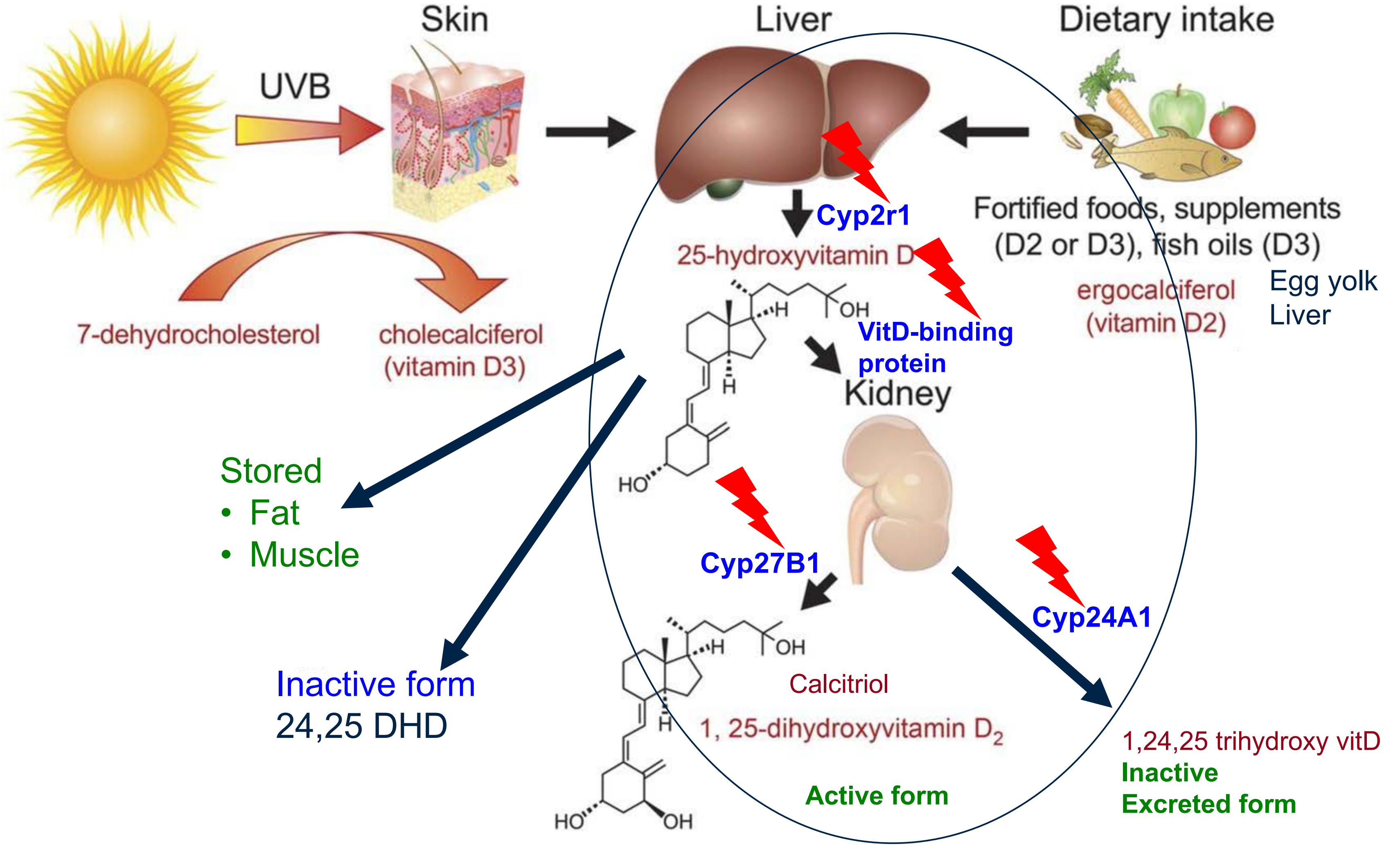
6. What keeps me from getting enough?

- Insufficient sun exposure



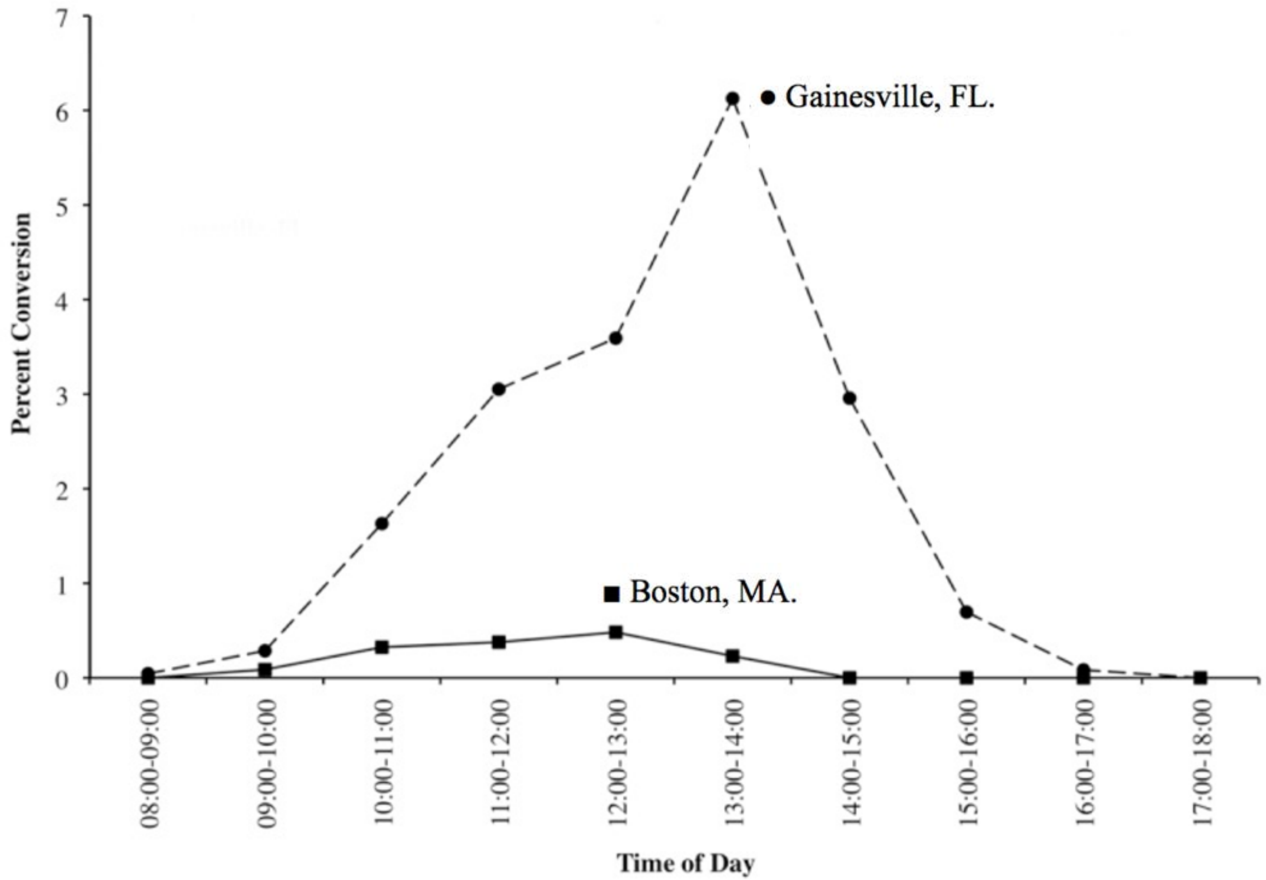
6. What keeps me from getting enough?

- Genetic differences at transport/metabolism genes



6. What keeps me from getting enough?

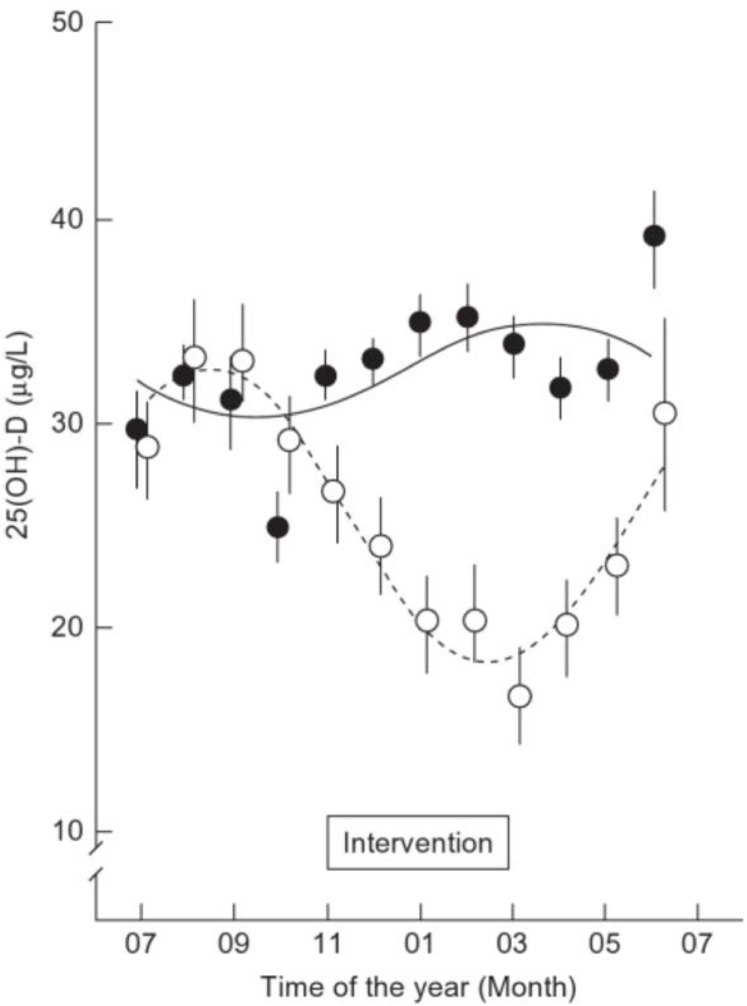
- Outside at wrong time of day



Southworth L. et al 2013

6. What keeps me from getting enough?

- Seasonal differences in exposure to sunlight



On VitD supplement (500IU)

No VitD supplement

Nutrition in the prevention and treatment of disease

6. What may be keeping me from getting enough?

- Skin pigment - melanin: competes with > 7-dehydrocholesterol
- Prolonged UVB exposure: converts previtamin D3 into inactive compounds (tachysterol and luminseterol).
- Clothing
- Window Glass
- Sun Screens that block UVB
- Too much time indoors not enough time outdoors
- Clouds
- Smog & other air pollution
- Season (Winter)
- Distance from equator
- Adiposity/obesity
- Intestinal malabsorption:
  - Disease (crohn's disease) & Pharmaceuticals
- Age
- Ethnicity (eg. genetic differences in vitamin D metabolism genes)

7. How common is “deficiency”?

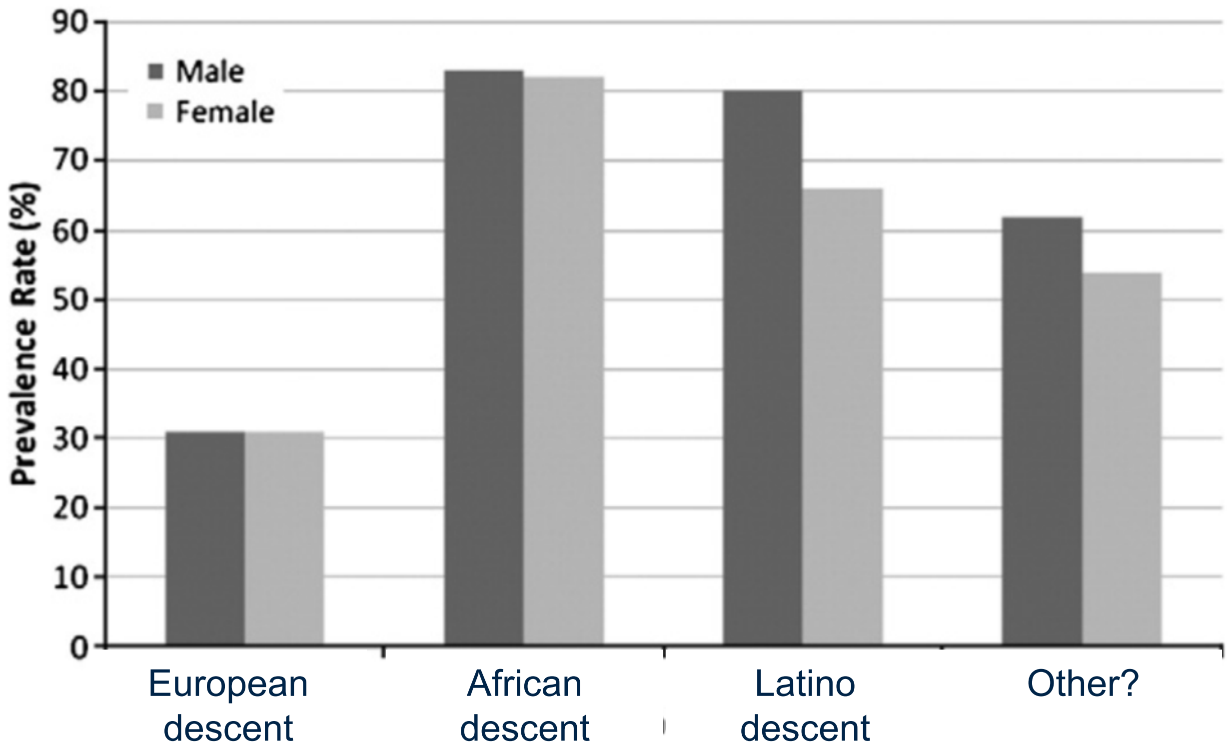
- Age & gender dependent

Sex	Age group (yrs)	Avg nmol/l	%<50nmol/l
Male	1-8	~70	10
Male	9-13	~60	21
Male	14+	~60	30-36
Female	1-8	~70	12
Female	9-13	~60	27
Female	14+	~60	34-38

NHANES 2001-2006

7. How common is "deficiency"?

- Ethnicity dependent (genetic & cultural differences)



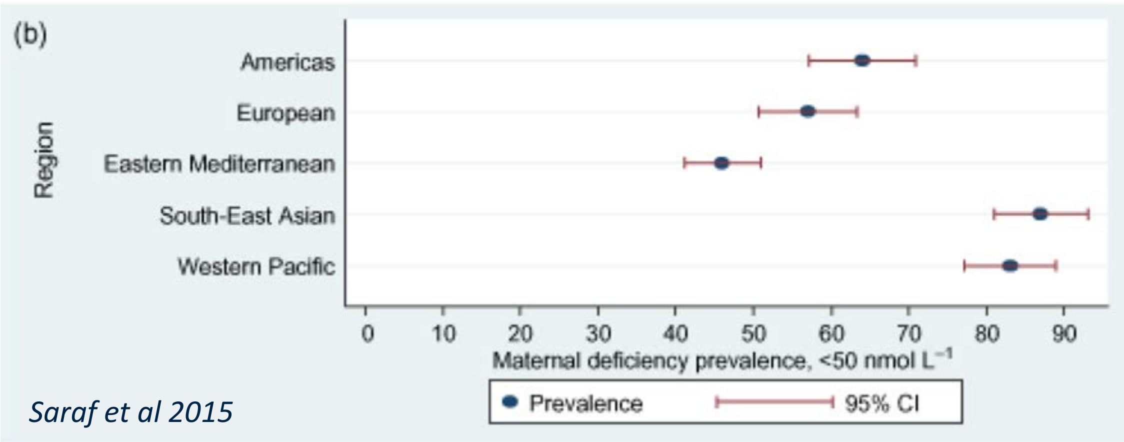
Vitamin D deficiency prevalence by ethnicity and gender

Modified Forrest K 2010, Nutr Res.

7. How common is "deficiency"?

- Geographical location dependent

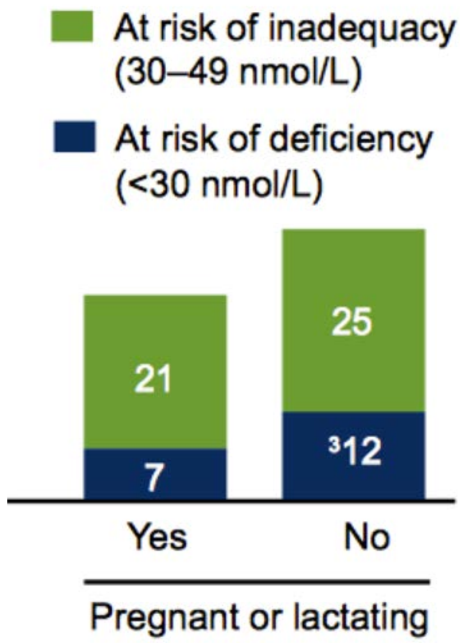
Global populations



Saraf et al 2015

US (NHANES)

- Females 12-44yrs

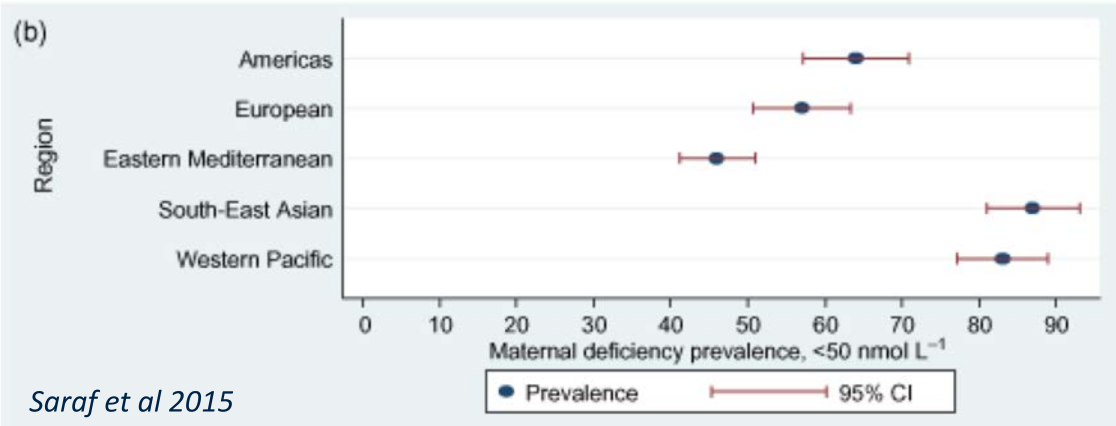


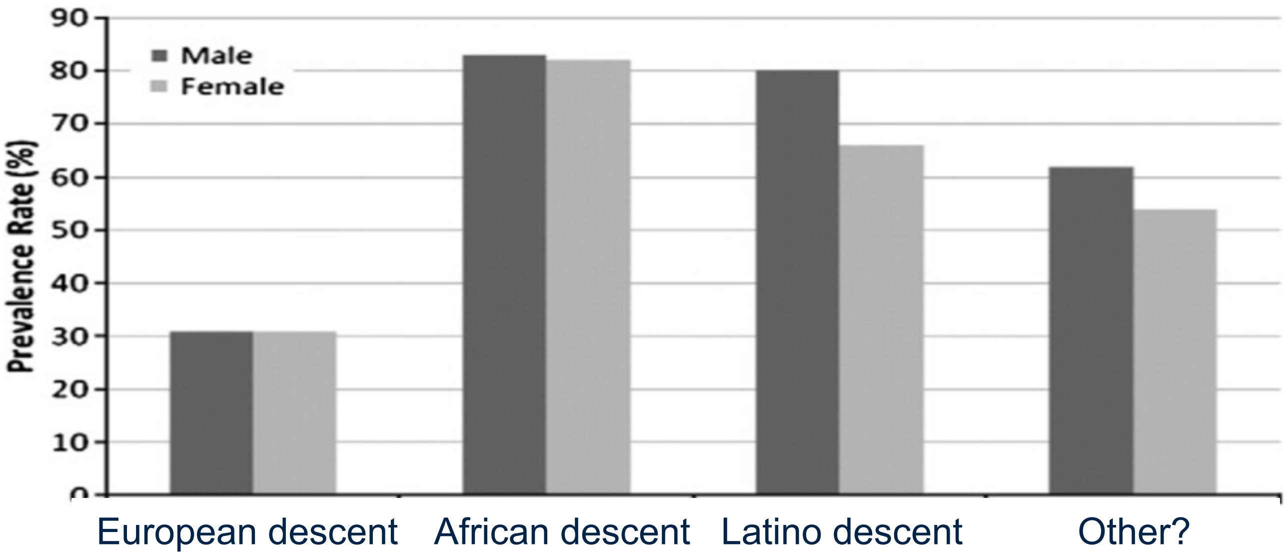
Looker et al. 2011

- No global standard of screening pregnant women
- Supplementation is widespread

4. How much do I need?

- Are all of these people really “deficient”? Should we all be on supplements?





Vitamin D deficiency prevalence by ethnicity and gender

4. How much do I need?

- Still under investigation
- Growing evidence that needs may differ by genetic differences

TABLE 2. Distributions of vitamin D status by race/ethnicity (n = 1114), BACH/Bone Survey, 2002–2005

Variable	Race/ethnicity: Black	Hispanic	White	*P* value
Mean 25(OH)D ± SD (ng/ml)	25.0 ± 14.7[a,b]	32.9 ± 13.9[b]	37.4 ± 14.0	<0.001
25(OH)D quartiles (ng/ml)				<0.001
Q1: 25(OH)D ≤ 20.8	44.4[a,b]	23.1[b]	11.4	
Q2: 20.8 < 25(OH)D ≤ 31.3	25.6	24.5	27.2	
Q3: 31.3 < 25(OH)D ≤ 42.7	18.2	30.8	28.5	
Q4: 25(OH)D > 42.7	11.7	21.6	32.9	

Means, SD, and percentages were adjusted inversely to the probability of selection. *P* values are from *F*-test for $\beta_{Black} = \beta_{Hispanic} = 0$ (continuous variables) where White men serve as the reference group or χ^2 test of independence (categorical variables). To convert 25(OH)D to nmol/liter, multiply values by 2.496.

TABLE 4. Age-, weight-, and height-adjusted partial correlation coefficients (r_p) for serum 25-hydroxyvitamin D in relation to BMD measures by race/ethnicity, BACH/Bone Survey, 2002–2005

	Black		Hispanic		White	
	r_p	*P* value	r_p	*P* value	r_p	*P* value
Hip: femoral neck	−0.03	0.653	0.07	0.360	0.12	0.044
Hip: trochanter	−0.01	0.853	0.06	0.375	0.13	0.009
Hip: total	−0.06[a]	0.387	0.07	0.301	0.11	0.034
Spine: L1–L4	−0.10[a]	0.106	−0.05[a]	0.445	0.12	0.024
Forearm: distal radius	−0.01	0.867	0.07	0.325	0.00	0.951
Forearm: ultradistal radius	−0.02	0.766	0.02	0.799	0.14	0.008

P values shown test whether the correlation between BMD outcome and 25(OH)D within each race and ethnic group is 0.

[a] $P < 0.05$ *vs.* White from an individual test comparing correlations in Black men or Hispanic men with those in White men.

Holick M.F et al 2008

8. What happens if I don't have enough?

- Increased risk for disease/disorders:

Bone health

- Rickets: bone, muscle, respiratory, impaired growth
- Osteoporosis: low bone mineral density
- Osteomalacia: muscle atrophy, bone pain and fatigue

Immune health

- Infection
- Autoimmune disorders (MS, autism)

Cardiometabolic health

- Cardiovascular disease
- Diabetes

Neurological health

- Parkinsons, Alzheimer's, epilepsy etc.

Cancer

- Colon, breast, lung, prostate

Reproductive health

- Male and female fertility

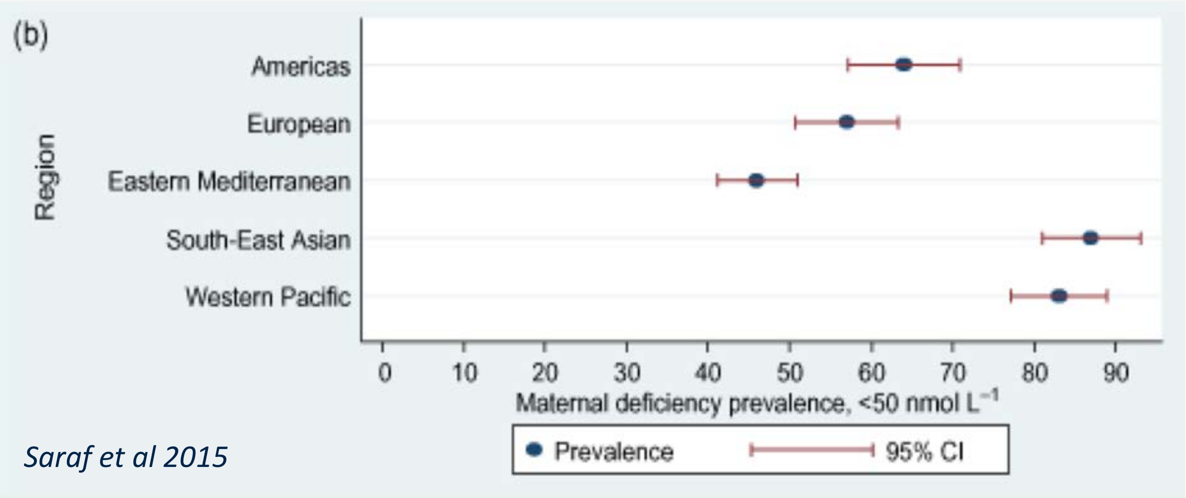
Fetal development?

9. What happens if I don’t have enough during pregnancy?

- Still under investigation

9. What happens if I don't have enough during pregnancy?

- High percent of mothers are at risk of inadequacy



Saraf et al 2015

- Low vitamin D during pregnancy = increased risk for:
  - Gestational diabetes
  - Small for gestational age (low birthsize)
  - Low birth weight
  - Preterm birth

HOW?

4. What is "enough" during pregnancy?

- Still under investigation
- Growing evidence that needs may differ between individuals

TABLE 2 Association between maternal vitamin D status and the risk of SGA by race/ethnicity

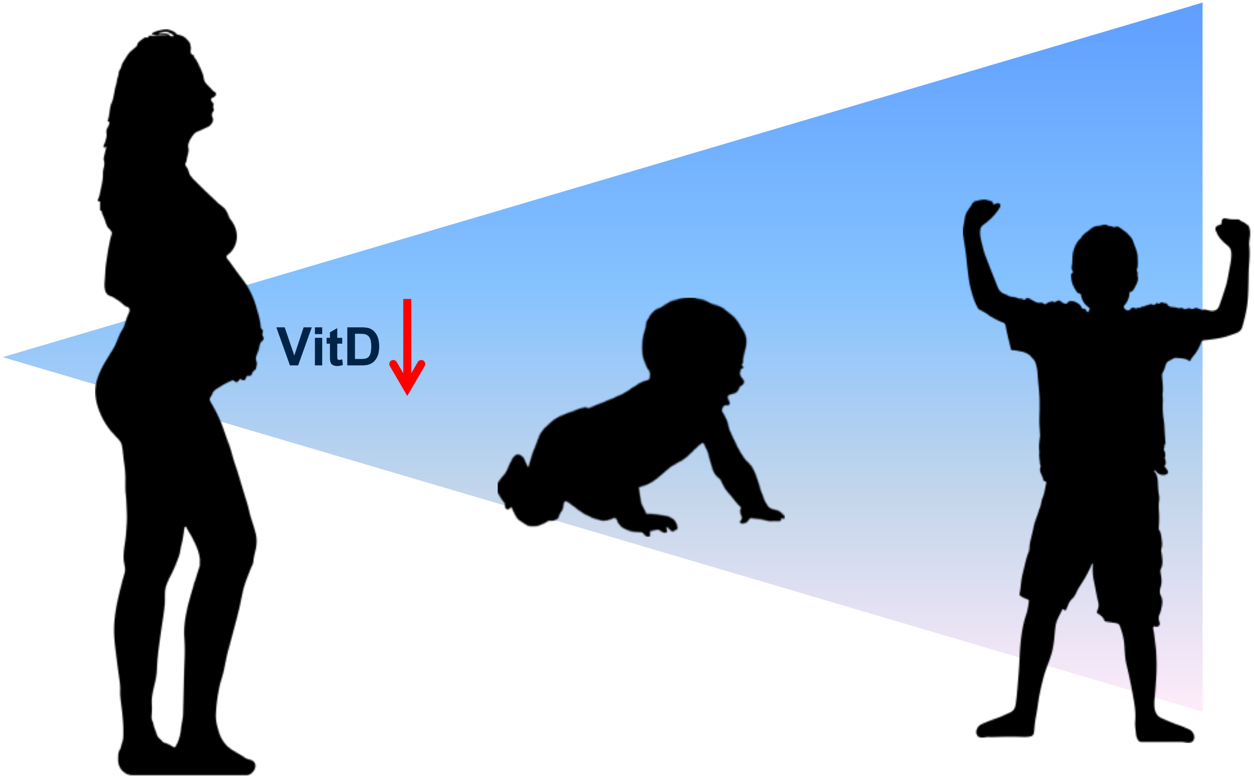
	Controls	SGA	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)
	n (%)			
White women				
Serum 25(OH)D at <22 wk[2]				
<37.5 nmol/L	3 (1.5)	8 (10.4)	10.6 (2.6, 42.5)	7.5 (1.8, 31.9)
37.5 – 75 nmol/L	107 (54.6)	27 (35.1)	1.0 (ref)	1.0 (ref)
>75 nmol/L	86 (43.9)	42 (54.5)	1.9 (1.1, 3.4)	2.1 (1.2, 3.8)
Quartile 1 [21.0–58.0 nmol/L]	49 (25.0)	25 (32.5)	3.1 (1.3, 7.6)	2.7 (1.1, 6.8)
Quartile 2 [58.1–71.4 nmol/L]	49 (25.0)	8 (10.4)	1.0 (ref)	1.0 (ref)
Quartile 3 [71.5–90.6 nmol/L]	49 (25.0)	15 (19.5)	1.9 (0.7, 4.8)	1.9 (0.7, 5.1)
Quartile 4 [90.7–245.0 nmol/L]	49 (25.0)	29 (37.6)	3.6 (1.5, 8.7)	3.9 (1.6, 9.7)
Black women				
Serum 25(OH)D at <22 wk				
<37.5 nmol/L	48 (45.7)	17 (50.0)	1.4 (0.6, 3.1)	1.5 (0.6, 3.5)
37.5–75 nmol/L	50 (47.6)	13 (38.2)	1.0 (ref)	1.0 (ref)
>75 nmol/L	7 (6.7)	4 (11.8)	2.2 (0.6, 8.7)	2.2 (0.5, 9.0)
Quartile 1 [13.8–30.0 nmol/L]	27 (25.7)	11 (32.4)	1.8 (0.6, 5.5)	1.7 (0.5, 5.5)
Quartile 2 [30.1–38.8 nmol/L]	26 (24.8)	6 (17.7)	1.0 (ref)	1.0 (ref)
Quartile 3 [40.4–49.3 nmol/L]	26 (24.8)	5 (14.7)	0.8 (0.2, 3.1)	0.8 (0.2, 3.2)
Quartile 4 [49.4–137.2 nmol/L]	26 (24.8)	12 (35.3)	2.0 (0.7, 6.1)	1.8 (0.5, 5.8)

[1] Adjusted for prepregnancy BMI, smoking during pregnancy, and SES. Additional adjustment for season, maternal age, gestational age at blood sampling, marital status, insurance status, smoking in the year before pregnancy, periconceptional multivitamin use, or preconception physical activity had no meaningful impact on the results.
[2] Distribution differs by case status, $P < 0.0001$ (Pearson chi-squared test).

Bodnar LM et al 2010

10. Are there long term consequences?

- Still under investigation



Strong evidence that diet during pregnancy affects adult health

The Dutch famine birth cohort study

- Children from pregnancies during the famine have increased disease risk
- Timing during development was important

http://www.dutchfamine.nl

Diabetes

People exposed to undernutrition in utero had more diabetes. But we found no evidence that diabetes progresses more rapidly among these people.

- More about diabetes...

Cardiovascular disease

Among people conceived during the famine, there was a 3-fold increase in coronary heart disease prevalence (angina, myocardial infarction or revascularization surgery).

- More about coronary heart disease...

Cholesterol

People conceived in famine had higher LDL/HDL cholesterol ratios compared to unexposed people.

- More about cholesterol...

Obesity

Women conceived in famine were more likely to be obese.

Pulmonary disease

People exposed to famine in mid gestation had more pulmonary disease. Their lung function was not decreased.

- More on pulmonary disease...

Renal disease

There was more microalbuminuria among those exposed in mid gestation. This was not due to excess hypertension or cardiovascular disease.

- More on renal disease...

Stress

People conceived in famine had a higher blood pressure rise under stress. We have found no evidence for HPA programming.

- More about stress...

Breastcancer

Women who were exposed to famine during gestation are more likely to develop breast cancer.

Gestational timing of undernutrion matters

Increase in coronary artery disease linked to malnutrition during early gestation only

	Born before famine	Time of exposure to famine: Late gestation	Midgestation	Early gestation	Conceived after famine
General					
No. of subjects	289	160	138	87	301
Men (%)	48	44	39	44	53
Maternal characteristics					
Maternal age (y)	29	31[1]	29	27[1]	28
Weight at the end of gestation (kg)	67	62[1]	63[1]	68	69
Weight gain in the last trimester (kg)	3.2	0.0[1]	5.0[1]	5.5[1]	4.3
Occupation of head of family, manual (%)	83	71	70	62[1]	69
Primiparous (%)	35	24[1]	34	39	39
Birth characteristics					
Birth weight (g)	3396	3183[3]	3195[3]	3437	3449
Head circumference (cm)	32.8	32.4[3]	32.1[3]	32.8	33.2
Ponderal index (kg/m^3)	26.2	26.0[3]	25.7[3]	26.0	26.7
Coronary artery disease					
No. of cases	24	12	11	11	25
Cumulative incidence (%)	8	8	8	13[4]	8
Age at onset (y)[5]	51	50	50	47[4]	49

Painter et al 2006, Am J Clin Nutr

What about before and after pregnancy?

- Multiple stages may be important

<u>Preconception</u>

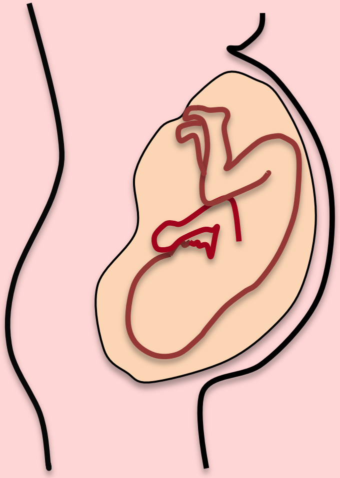
Mom Dad

Oocyte
“Egg”

Sperm

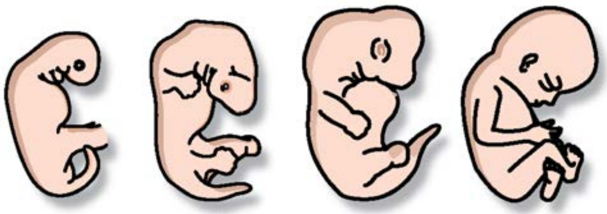
Single cell

<u>Gestation</u>



<u>Lactation</u>

Multicellular
Multi-tissue/organ



Rapid and widespread changes in cell number, function and location

What about my grandchildren?

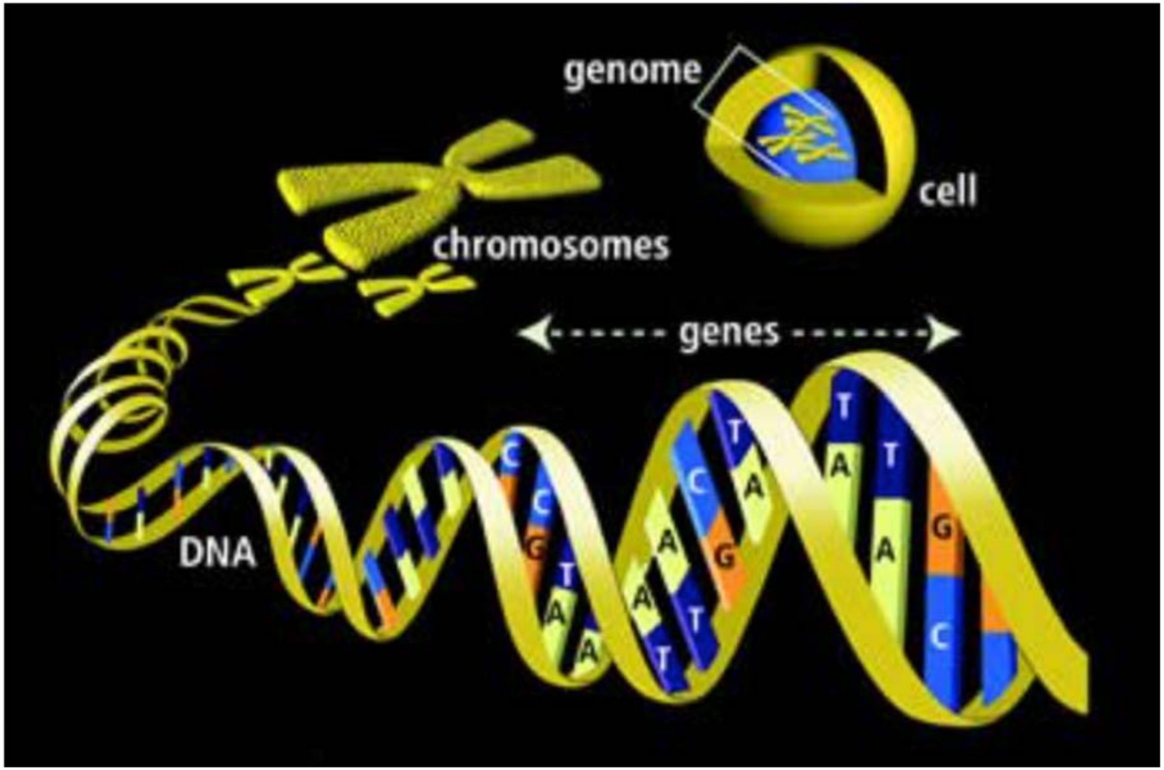
- Still under investigation

- Focus of Ideraabdullah lab research

Ideraabdullah lab studies the genome & epigenome

- Genome = DNA = code that determines how cells function

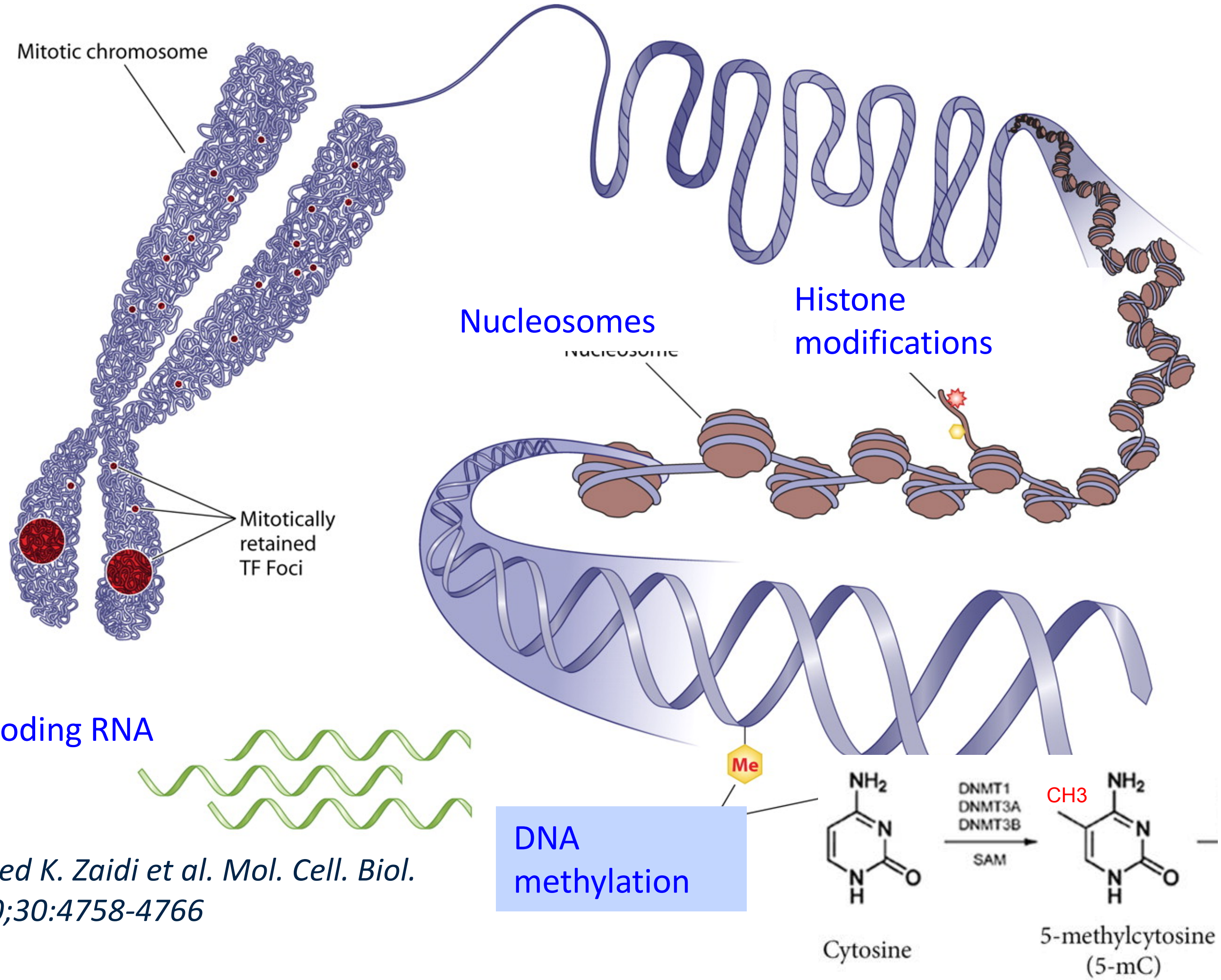
<u>Human genome</u>
46 chromosomes (23 each)
20,000+ protein coding genes



http://www.differencebetween.info

Ideraabdullah lab studies the genome & epigenome

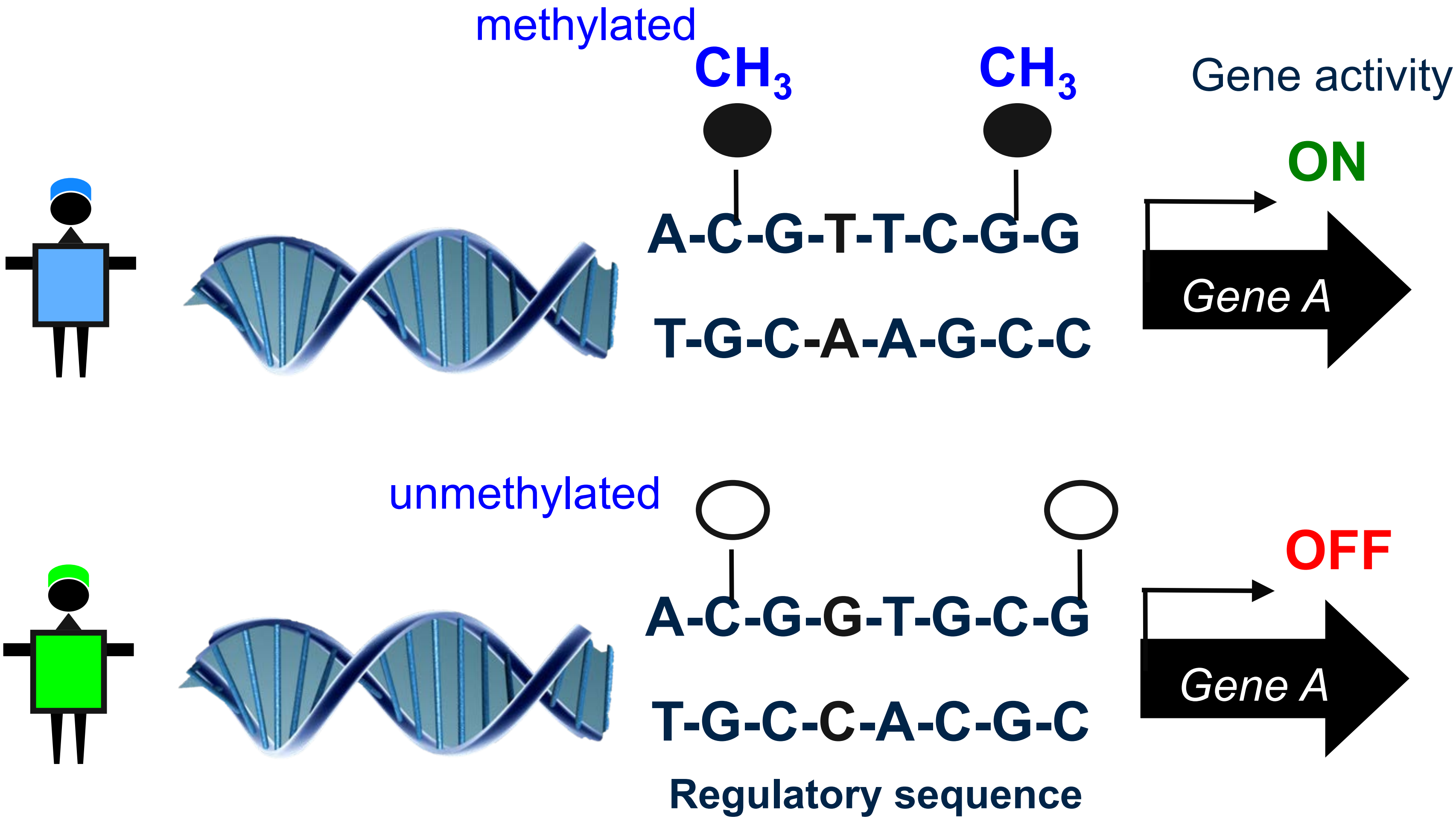
- Epigenome = Factors that regulate how the genome is interpreted



Sayyed K. Zaidi et al. Mol. Cell. Biol. 2010;30:4758-4766

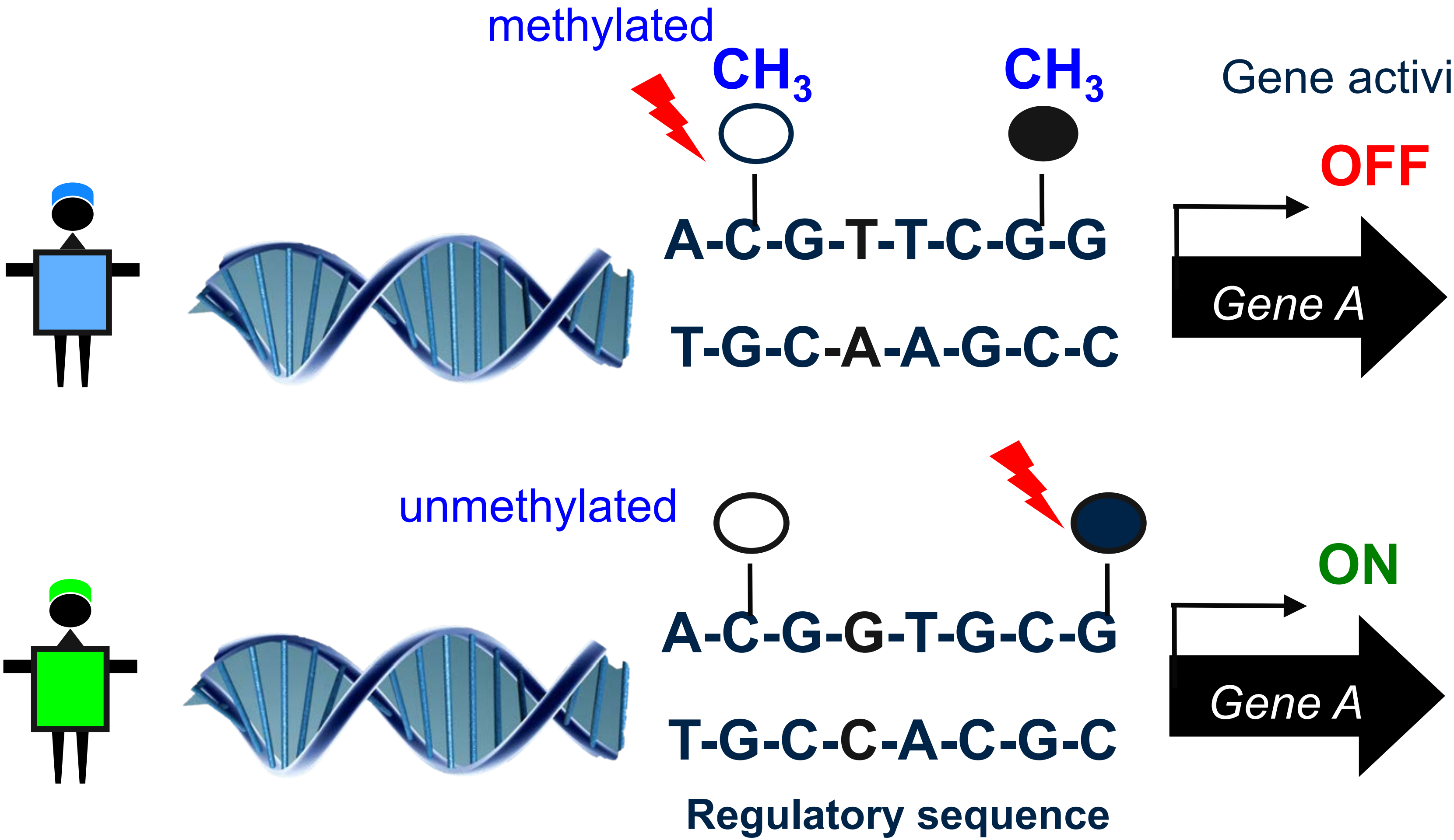
Epigenetic modifications

- DNA methylation: Feature regulates gene activity



Epigenetic modifications

- Diet-induced changes in DNA methylation and changes gene activity



Epigenome changes & disease

<u>During development:</u>

Epigenome Dysregulation/disruption

↓

Change Gene activity

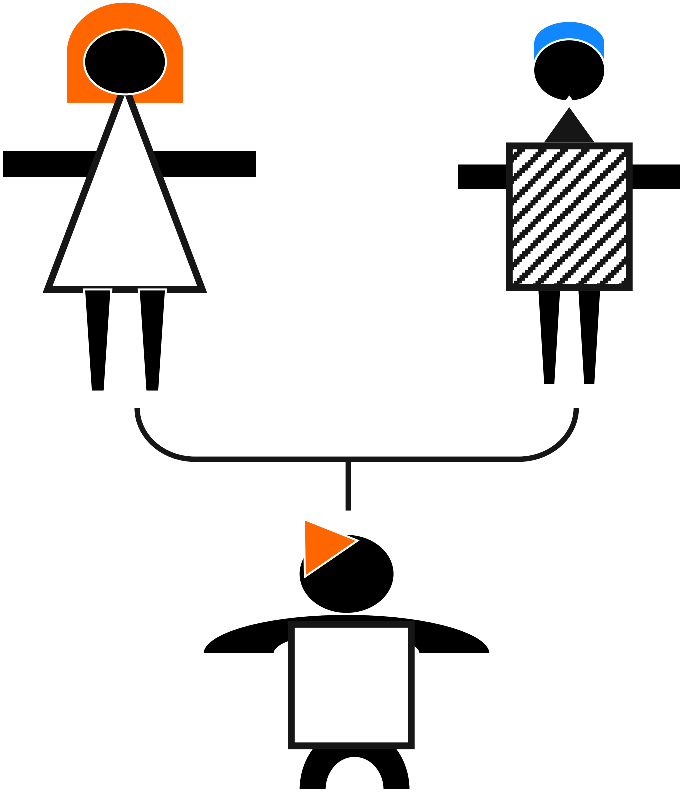
↓

Abnormal Development of different cells/tissues/organs

↓

Disease/ Susceptibility

The genome and epigenome are heritable

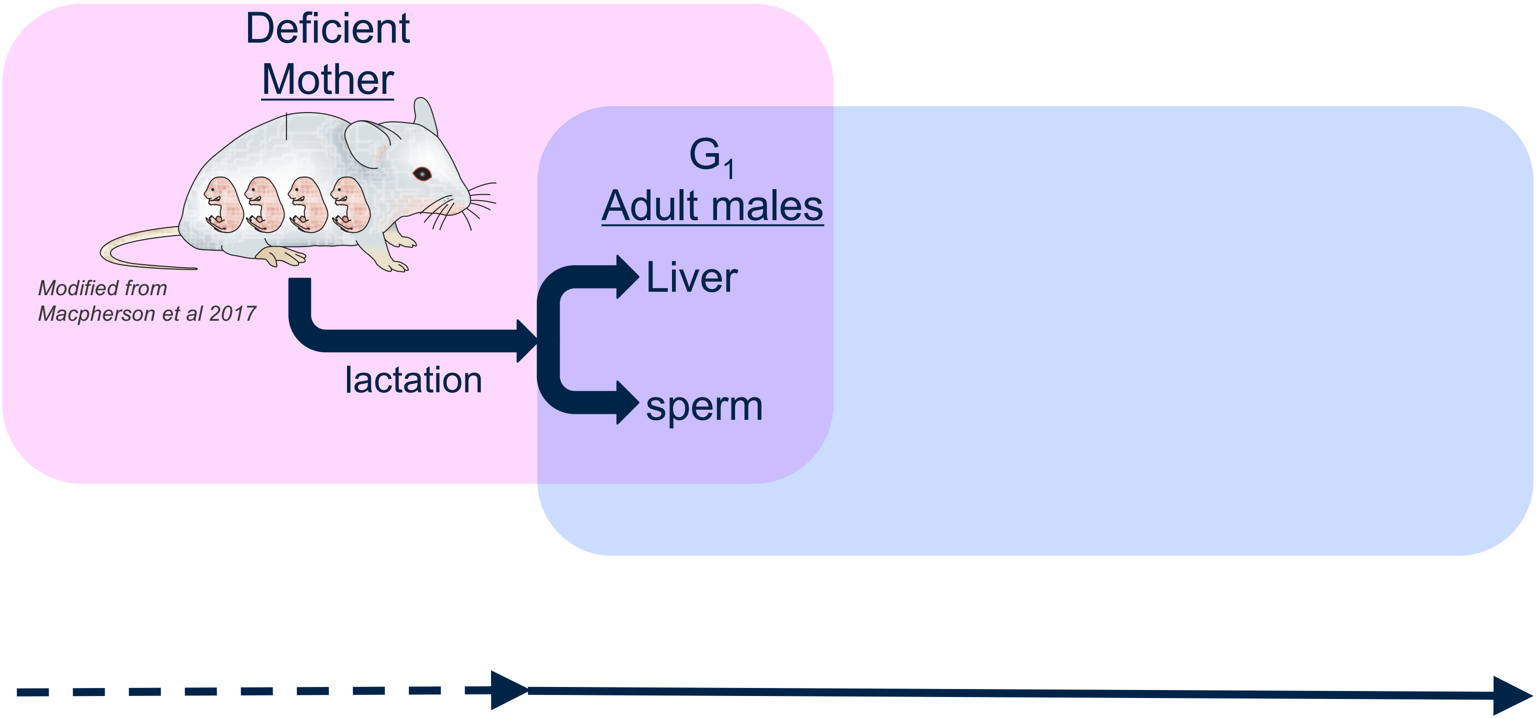


Heritable

Capable of being passed from one generation to the next.

Does vitamin D deficiency during pregnancy affect pups?

Treatments in mouse

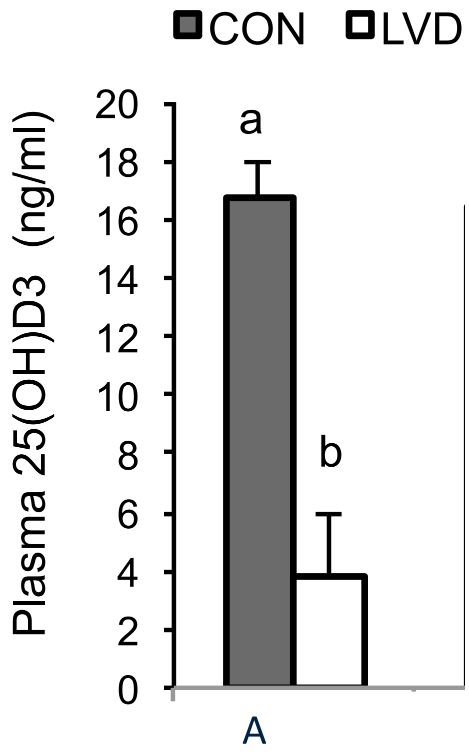


Vitamin D depleted (LVD)
Or
Vitamin D sufficient (CON)

Vitamin D sufficient

Reduction in plasma 25(OH)D levels is strain dependent

- Diet reduced level of vitamin D in blood

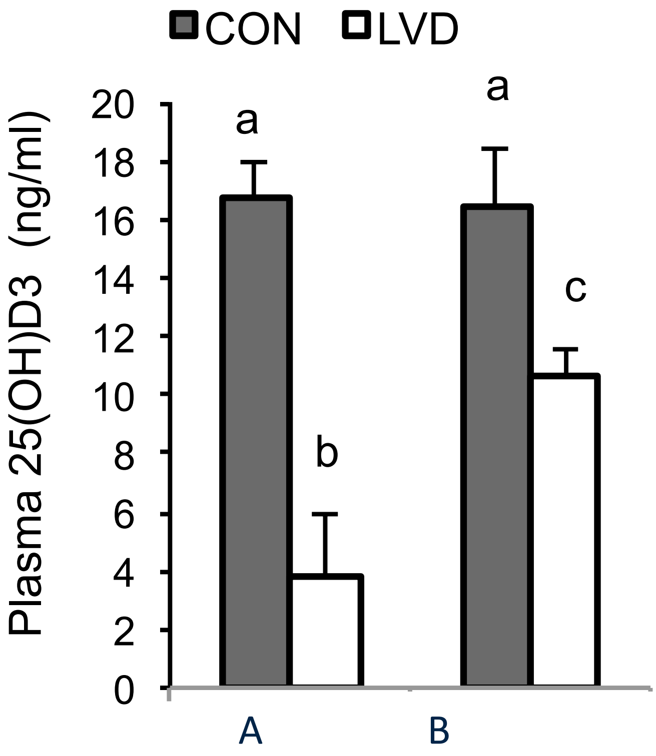


Xue J et al, Clinical Epigenetics, 2016

Reduction in plasma 25(OH)D levels is strain dependent

- Deficient diet reduced level of vitamin D in blood

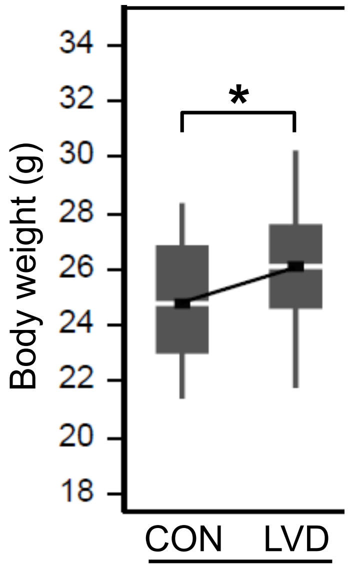
- Genetic differences in strain A & B = differences in status



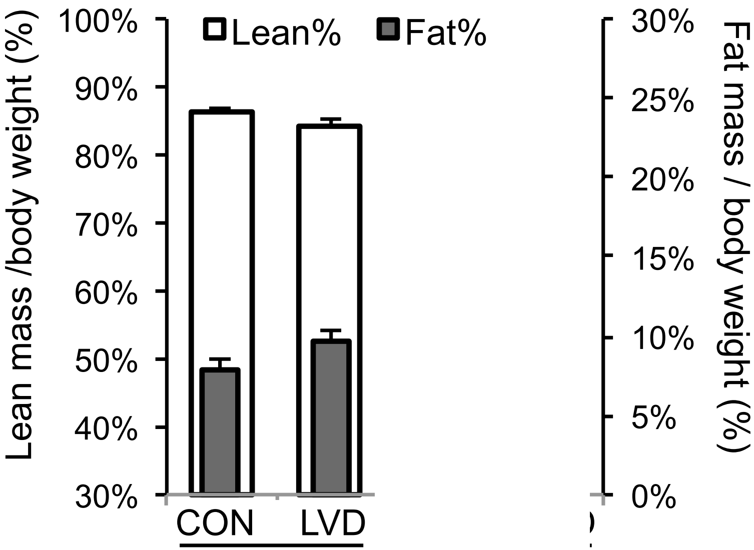
Xue J et al, Clinical Epigenetics, 2016

Increase in body weight and fat mass in adult pups

- Deficient diet = increased pup bodyweight & fat mass



A

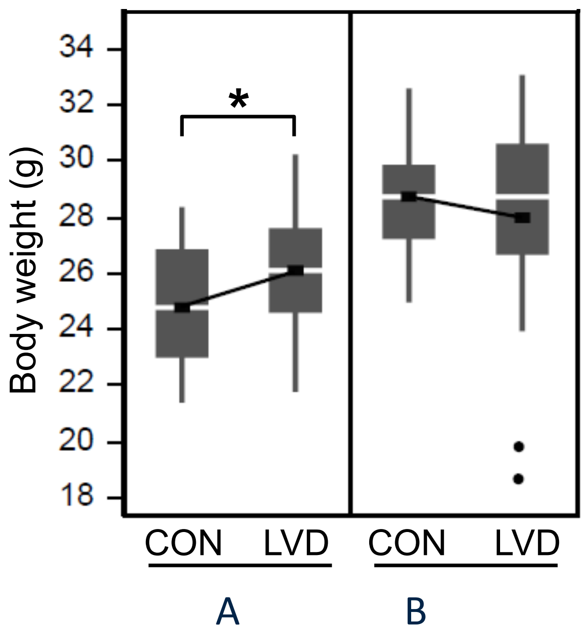


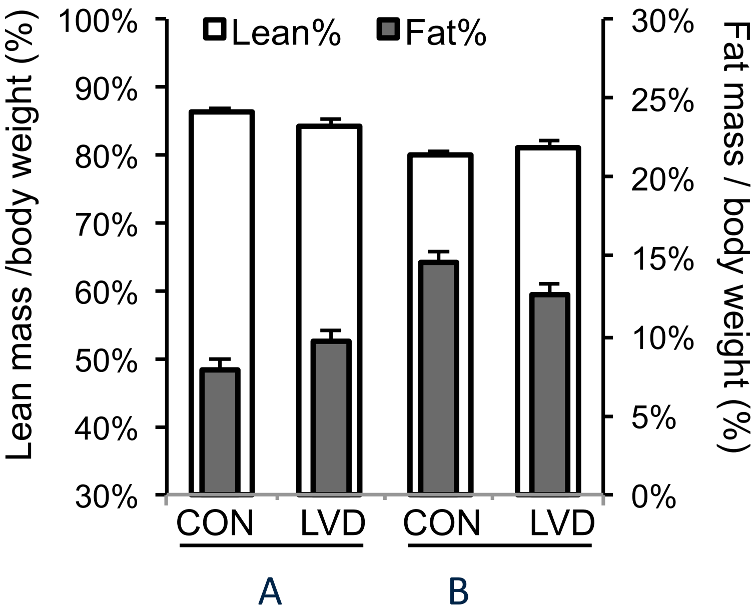
A

Xue J et al, Clinical Epigenetics, 2016

Increase in body weight and fat mass in adult pups

- Deficient diet = increased pup bodyweight & fat mass
- Genetic differences in strain A & B = differences in growth & adiposity



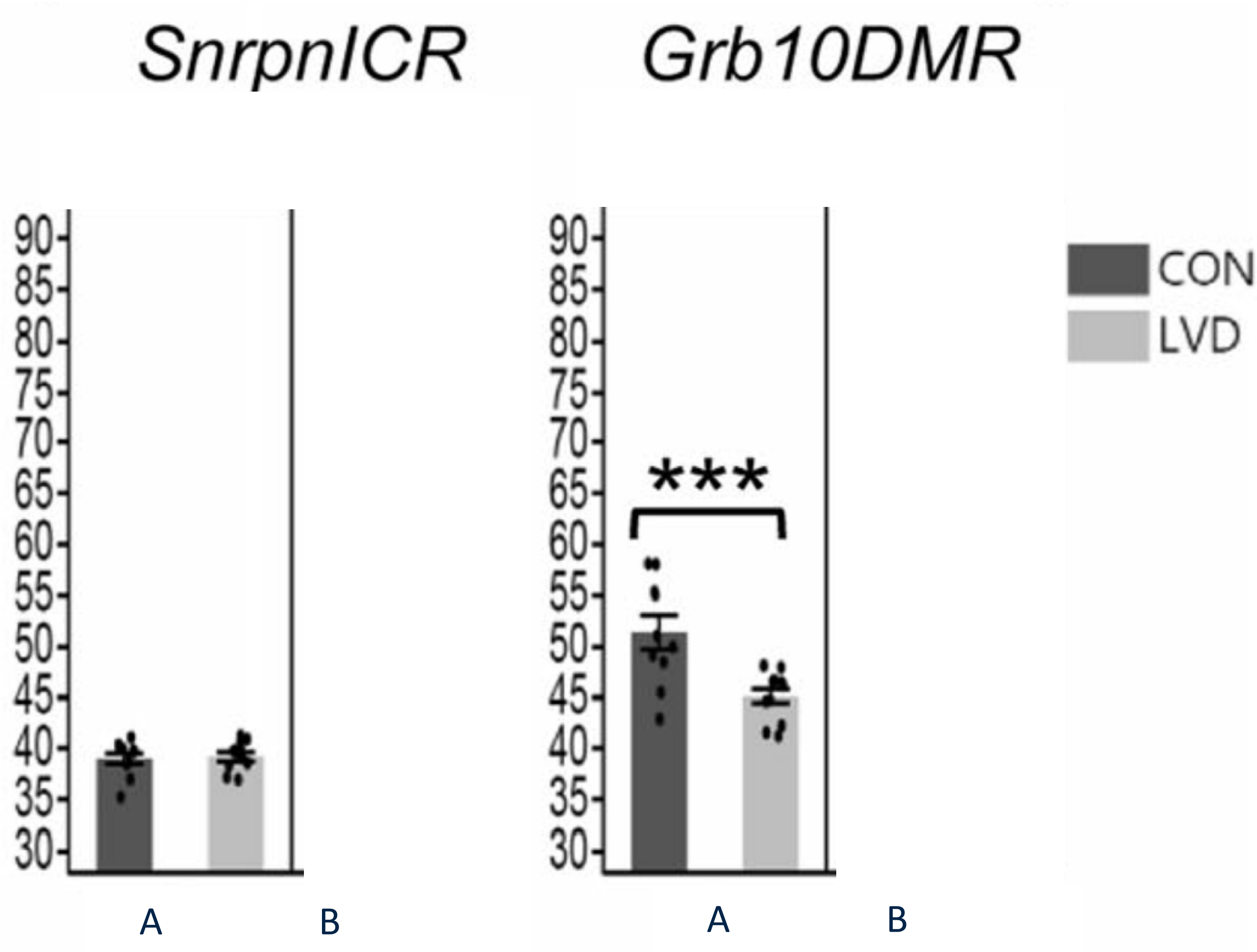


Xue J et al, Clinical Epigenetics, 2016

Decrease in DNA methylation

- Some but not all genes were changed

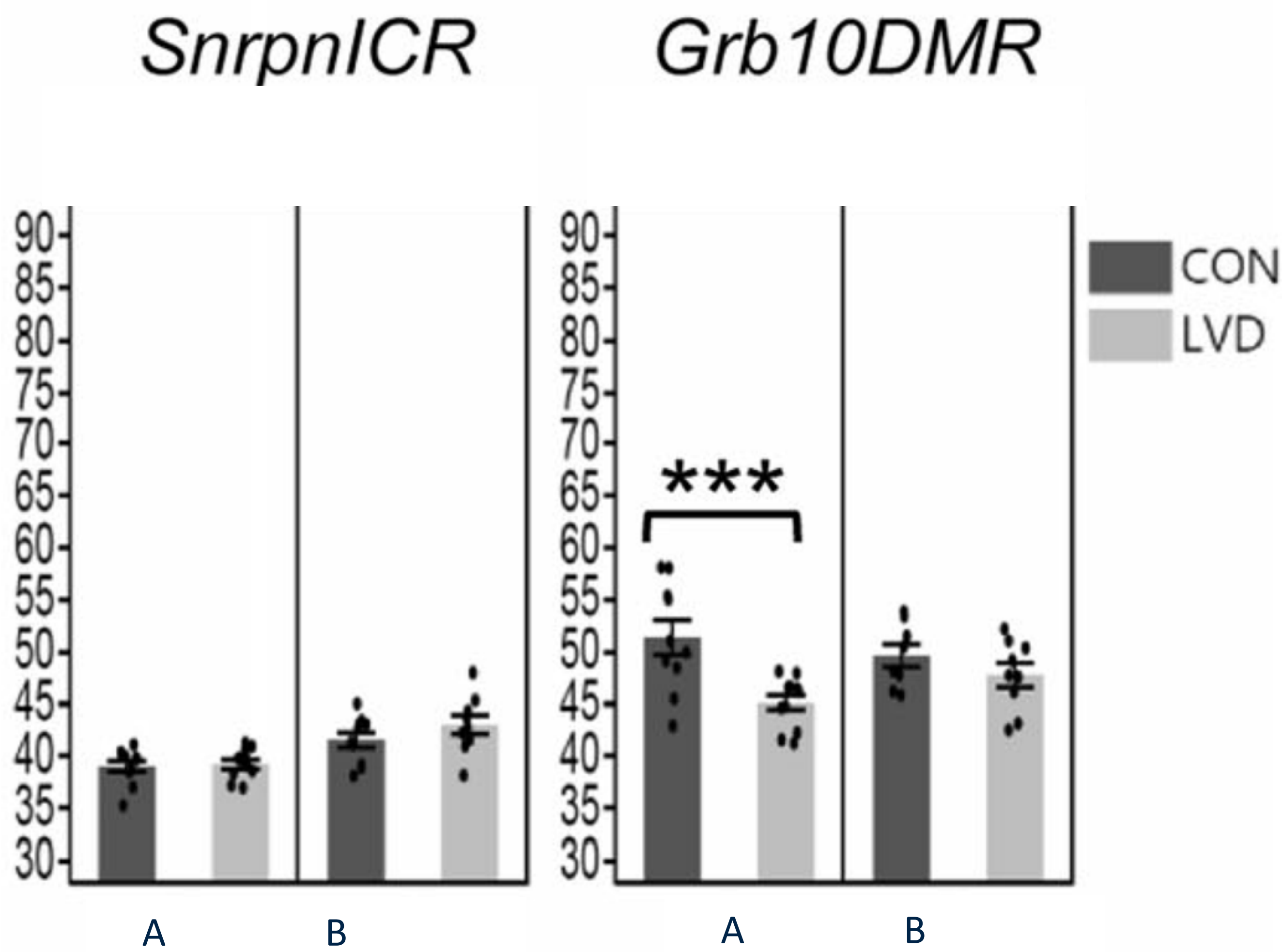
Adult Liver



Decrease in DNA methylation

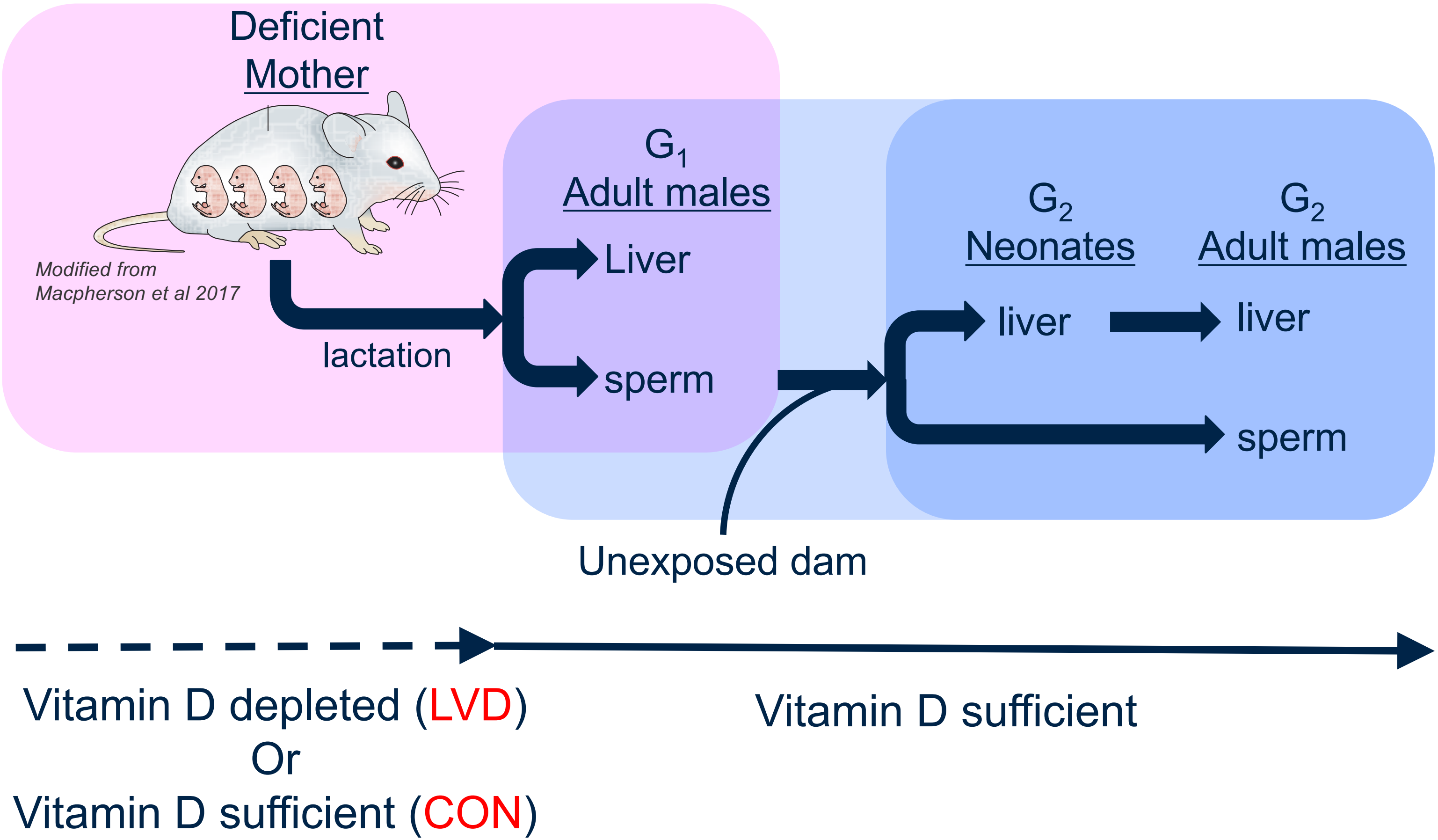
- Some but not all genes were changed
- Genetic differences in strain A & B = differences in methylation

Adult Liver



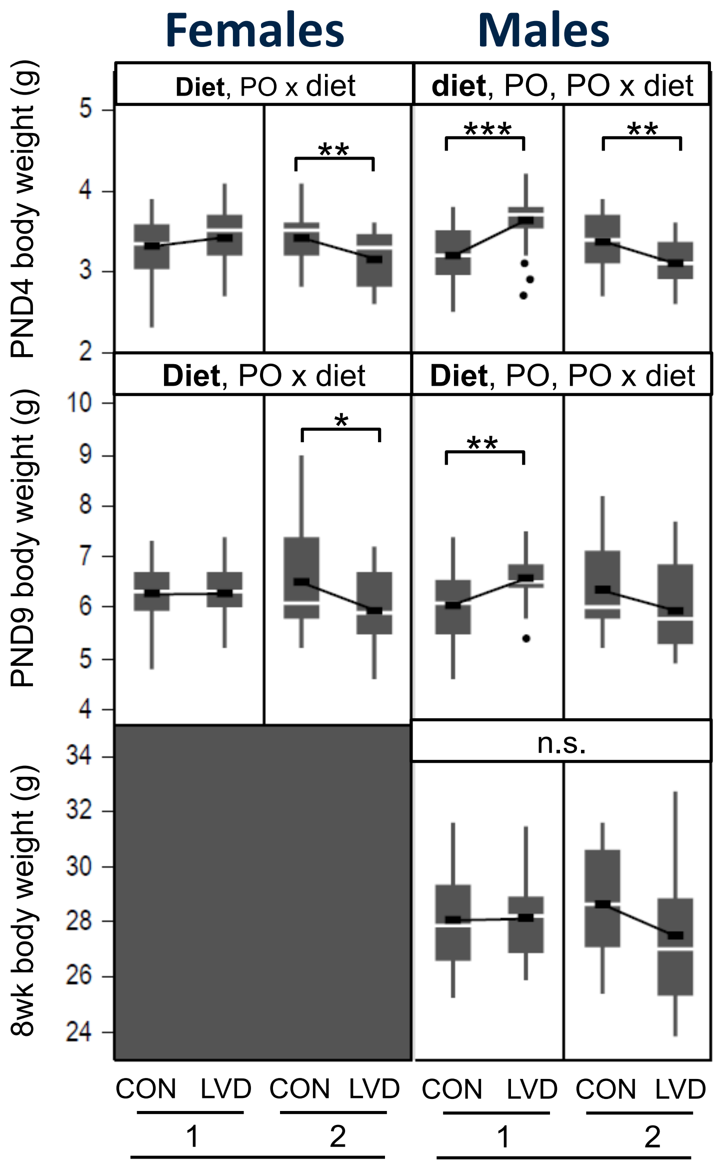
Are there multigenerational consequences?

Treatments in mouse



Grandmaternal deficiency alters neonatal bodyweight

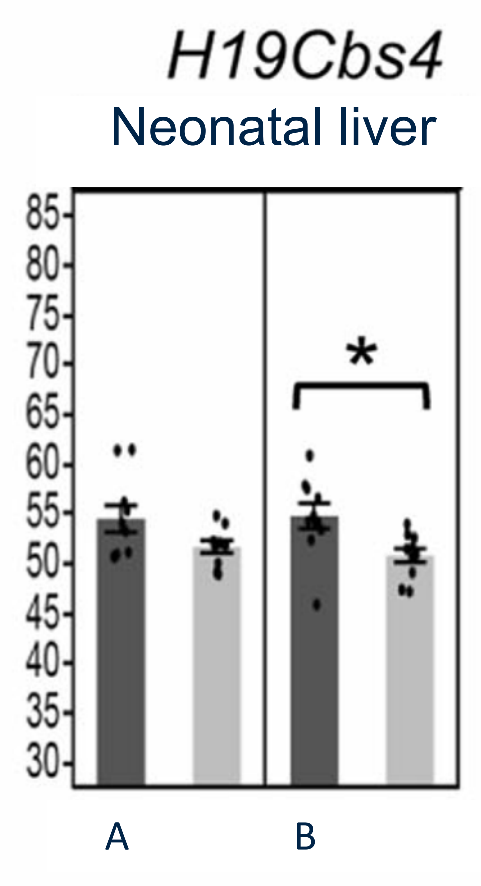
- Bodyweight changes
- Genetic strain dependent

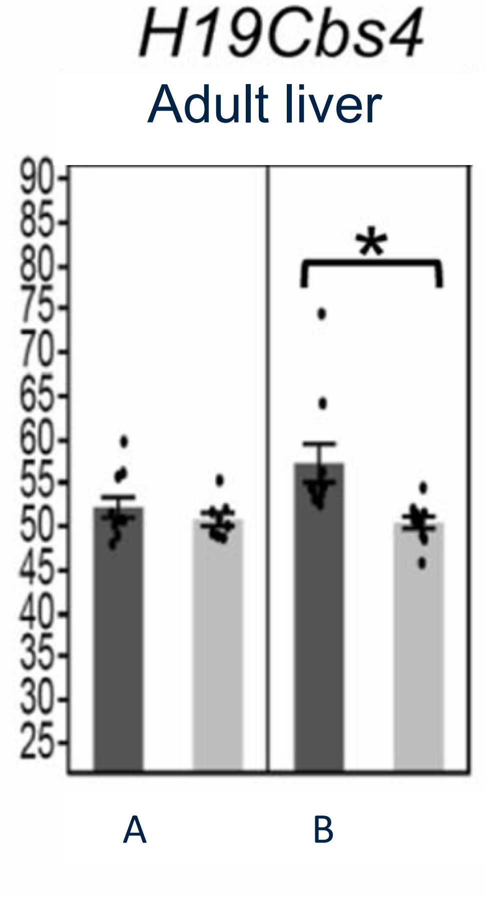


Xue J et al, Clinical Epigenetics, 2016

Grandmaternal deficiency alters neonatal & adult methylation

- Bodyweight changed
- Genetic strain differences

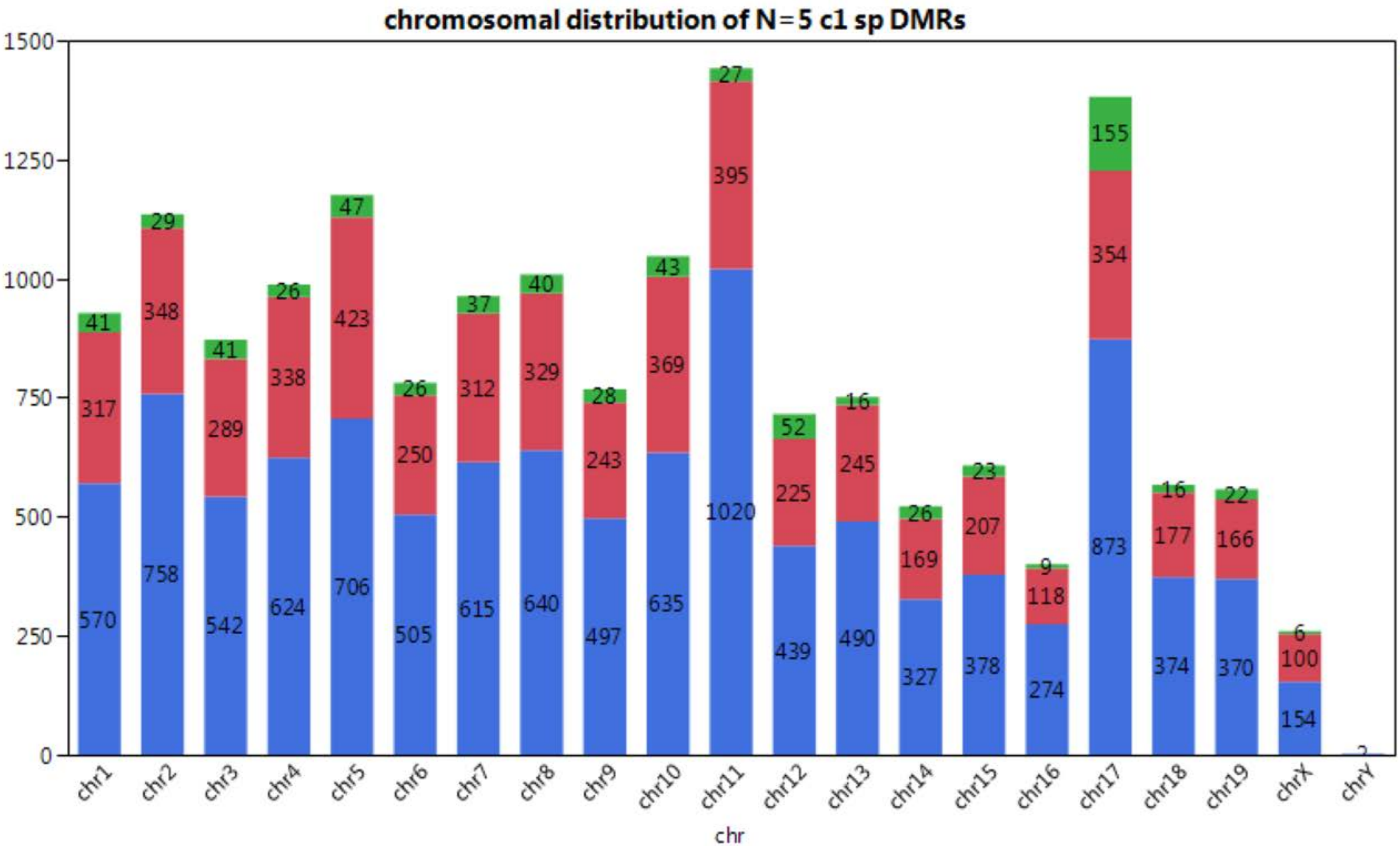




Xue J et al, Clinical Epigenetics, 2016

Ongoing studies

- Other genes in the genome are changed (all chromosomes)



Ongoing studies

- Changed genes are related to vitamin D deficiency diseases
    - Development
    - Cancer (prostate, colorectal, breast, lung, thyroid, ovarian..)
    - Reproduction
    - Embryo development
    - Dermatological disorders (ichthyosis type 1, hyperpigmentation)

Top Diseases and Bio Functions

Diseases and Disorders

Name	p-value	#Molecules
Neurological Disease	1.21E-02 - 2.87E-06	29
Organismal Injury and Abnormalities	1.19E-02 - 7.56E-05	105
Psychological Disorders	1.21E-02 - 7.56E-05	18
Hereditary Disorder	1.08E-02 - 7.70E-05	30
Skeletal and Muscular Disorders	1.19E-02 - 7.70E-05	28

Physiological System Development and Function

Name	p-value	#Molecules
Nervous System Development and Function	1.21E-02 - 4.64E-05	29
Behavior	1.08E-02 - 7.12E-05	20
Organ Morphology	1.08E-02 - 1.39E-04	18
Organismal Development	1.11E-02 - 1.39E-04	37
Reproductive System Development and Function	1.21E-02 - 2.86E-04	13

Conclusions

- Maternal vitamin D deficiency during pregnancy
  1. Differs between mice with genetic differences
  2. Changes body weight of offspring
  3. Changes fat mass of offspring
  4. Changes epigenome of offspring
  5. Can affect body weight and epigenome of multiple generations

6. Effects of maternal vitamin D deficiency on offspring differs between individuals with genetic differences
   - Genetic differences = vitamin D status = birthoutcomes

Acknowledgements

Lab members

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Laetitia Meyrieu

Collaborators

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UNC center for environmental health and susceptibility (CEHS)

Bioinformatics - UNCC

Corey Brouwer
- Raad Gharaibeh

Human studies: diet and heredity

European Journal of Human Genetics (2006) 14, 159–166

www.nature.com/ejhg

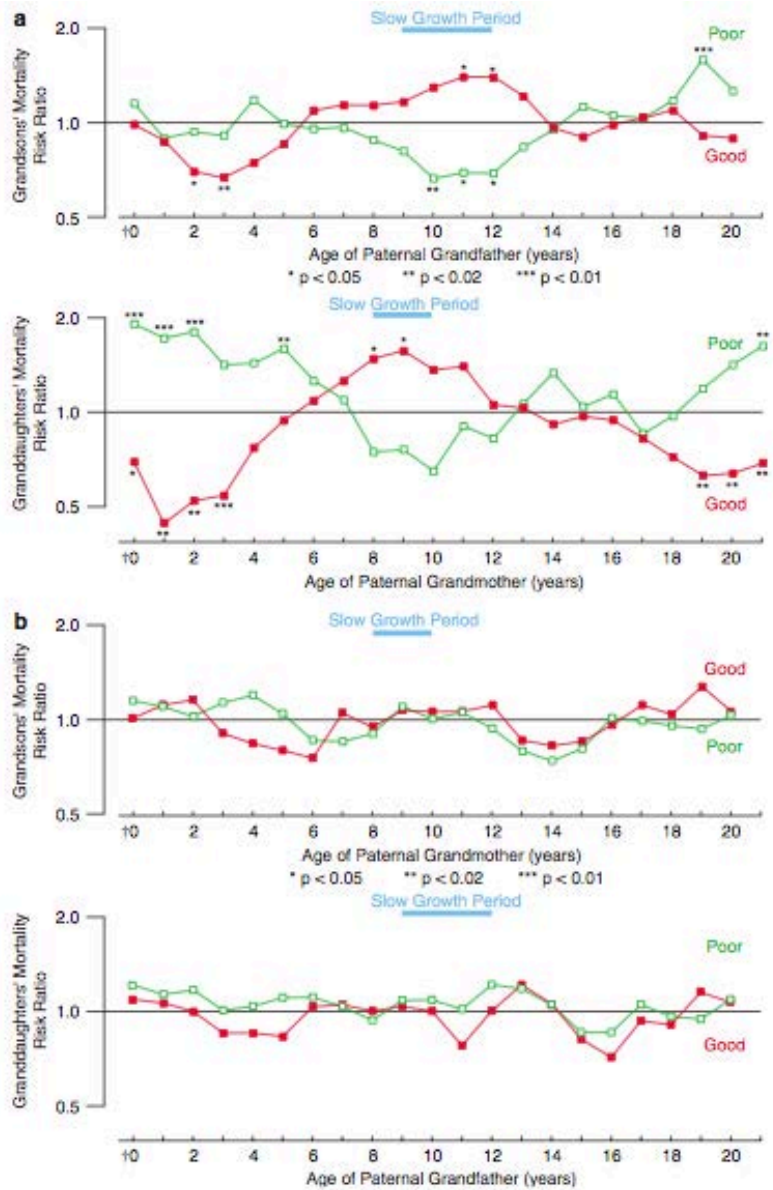
ARTICLE

Sex-specific, male-line transgenerational responses in humans

Marcus E Pembrey*[,1,2], Lars Olov Bygren[3,6], Gunnar Kaati[4], Sören Edvinsson[5], Kate Northstone[2], Michael Sjöström[6], Jean Golding[2] and The ALSPAC Study Team[2]

Effects transmitted through paternal lineage:

- Paternal grandfather food intake linked to grandson's mortality risk
- Paternal grandmother food intake linked to granddaughters mortality risk
- Paternal smoking <11yrs linked to increased BMI in sons.

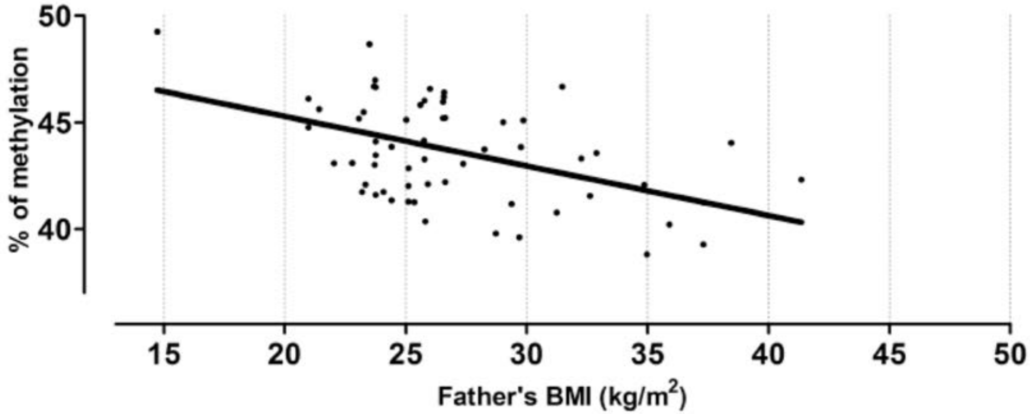


Human studies: diet and heredity

Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort

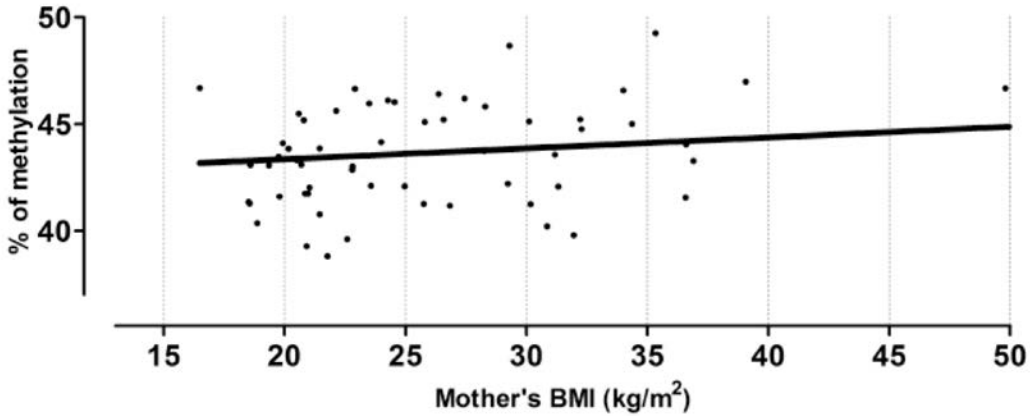
BMC Medicine 2013, **11**:29 doi:10.1186/1741-7015-11-29

Adelheid Soubry (adelheid.soubry@duke.edu)
Joellen M Schildkraut (joellen.schildkraut@dm.duke.edu)
Amy Murtha (amy.murtha@dm.duke.edu)
Frances Wang (frances.wang@dm.duke.edu)
Zhiqing Huang (zhiqing.hung@duke.edu)
Autumn Bernal (abernal3@mac.com)
Joanne Kurtzberg (joan.kurtzberg@dm.duke.edu)
Randy L Jirtle (jirtle@radonc.duke.edu)
Susan K Murphy (susan.murphy@dm.duke.edu)
Cathrine Hoyo (catherine.hoyo@dm.duke.edu)

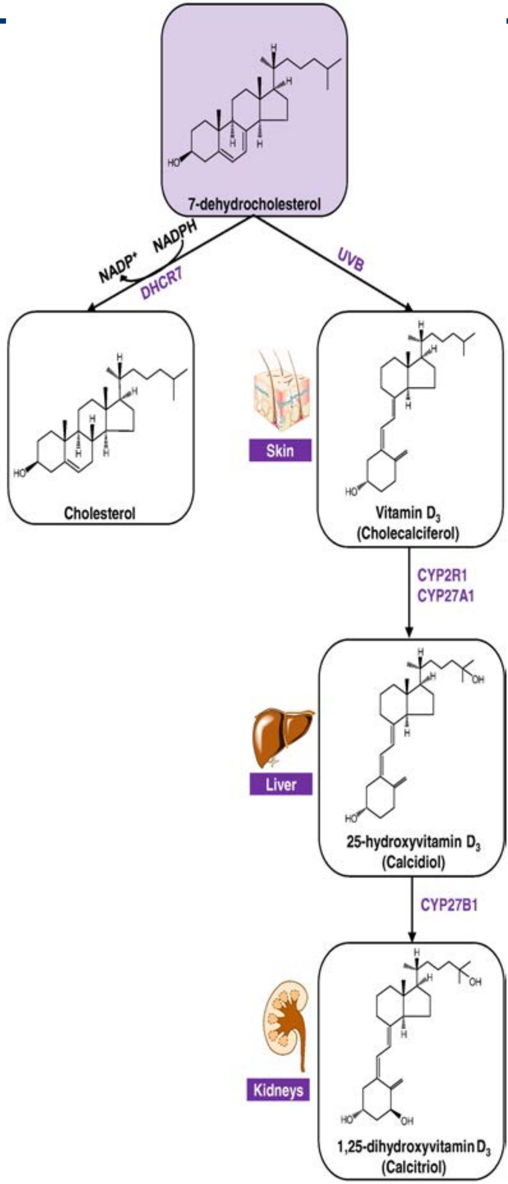


Effects transmitted through paternal lineage:

- Paternal BMI linked to decreased DNA methylation at IGF2 in cod blood



How is vitamin D metabolized in the body?
SKIN



Review

DHCR7: A vital enzyme switch between cholesterol and vitamin D production

Anika V. Prabhu[a], Winnie Luu[a], Dianfan Li[b], Laura J. Sharpe[a], Andrew J. Brown[a]

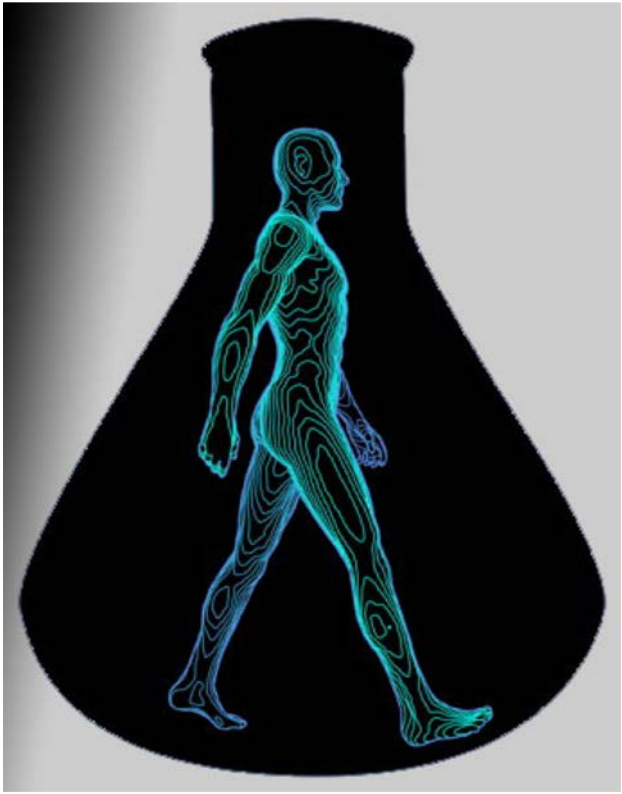
[a] School of Biotechnology and Biomolecular Sciences, The University of New South Wales, Sydney, NSW, Australia

[b] National Center for Protein Sciences, State Key Laboratory of Molecular Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

Received 18 July 2016, Revised 29 September 2016, Accepted 29 September 2016, Available online 30 September 2016

Challenges of human studies

- Limited access to multiple generations
- Cell/tissue sample collection
- Developmental timing
- Phenotypic variability
- Multiple/aggregate exposures
- Associations ≠ causal?



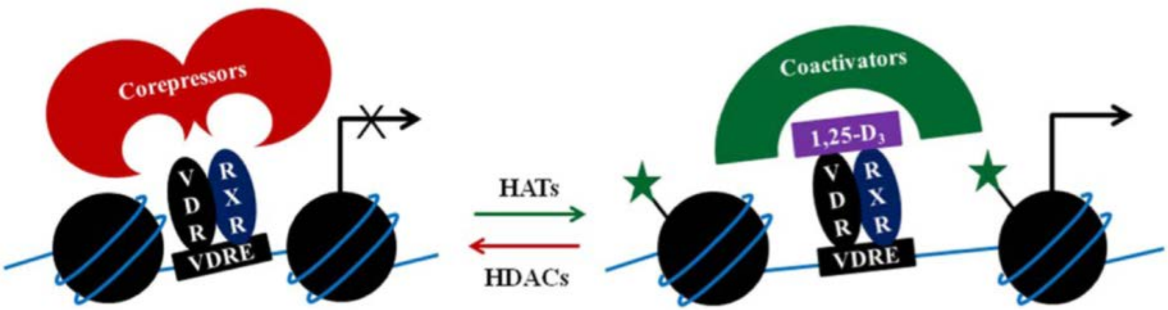
cnc.ucr.edu

Benefits of mouse models

- Fast generation time (18-21days)
- Inbred strains: genetically identical or genetically diverse
  10X genetic differences *vs.* humans (Ideraabdullah et al 2004)
- Access to any tissue/cell type
- Access to any developmental window
- Controlled exposure
- Many conserved genes
- Inducible system: test causality

Evidence for vitamin D role in epigenetic mechanisms

- Positive correlation between vitamin D status and global DNA methylation
- Targets histone demethylases (JmjC & LSD families)
- Proposed to regulate recruitment of HATs, HDACs, HMTs, and chromatin remodelers

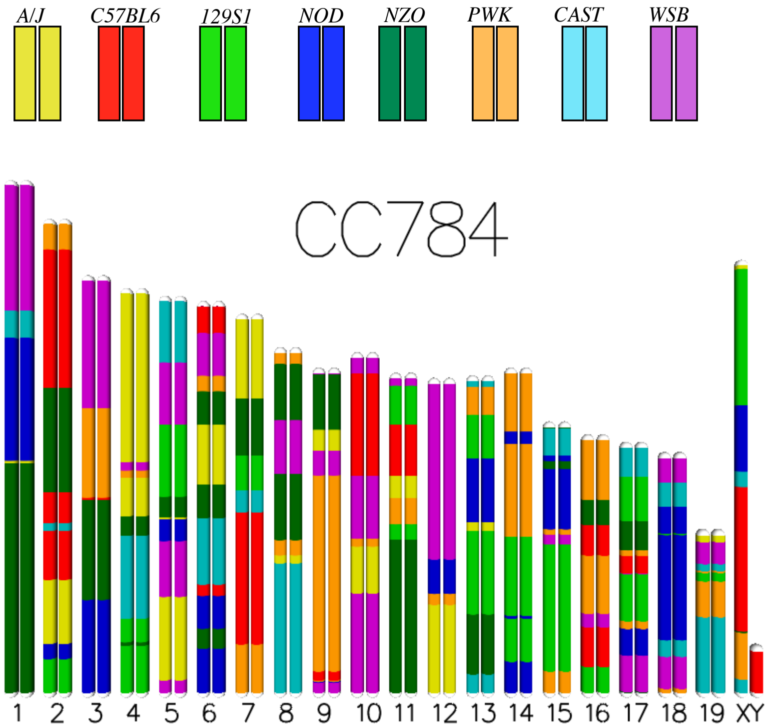


Reviewed in Fetahu 2014 frontiers in physiology

Genetic reference population

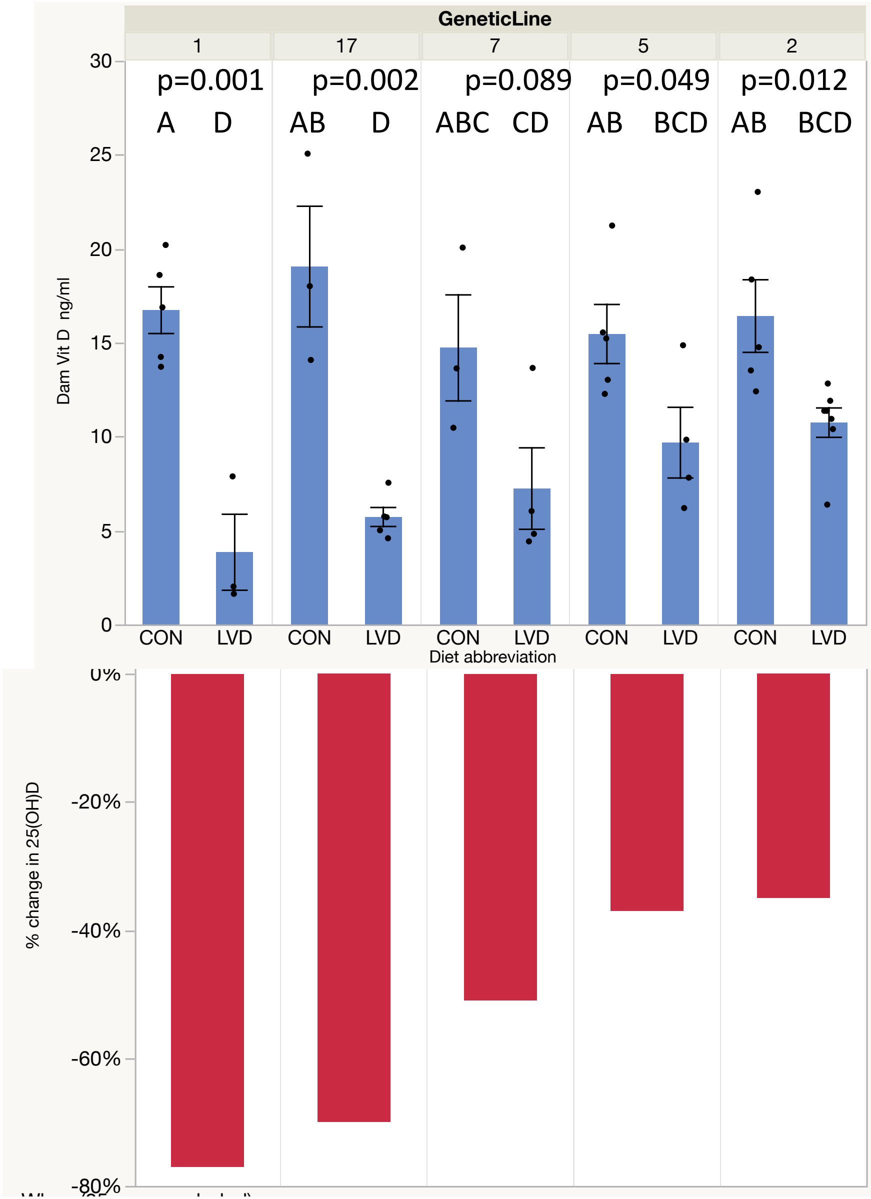
Collaborative Cross – recombinant inbred lines

- Highly genetically divergent



http://csbio.unc.edu/CCstatus/index.py

Strain dependent differences in extent of depletion



Ingenuity Pathway Analysis (IPA): Genes at VitD-DMCs >10%Δ

Liver, 164 mapped genes

Top Diseases and Bio Functions

Diseases and Disorders

Name	p-value	#Molecules
Cancer	2.09E-02 - 4.69E-09	105
Organismal Injury and Abnormalities	2.09E-02 - 4.69E-09	107
Gastrointestinal Disease	2.09E-02 - 6.72E-09	97
Dermatological Diseases and Conditions	1.05E-02 - 4.61E-07	61
Reproductive System Disease	2.09E-02 - 7.63E-07	72

Physiological System Development and Function

Name	p-value	#Molecules
Nervous System Development and Function	2.09E-02 - 7.97E-34	42
Tissue Morphology	2.09E-02 - 7.97E-34	42
Organismal Survival	1.68E-09 - 1.68E-09	45
Embryonic Development	2.09E-02 - 2.71E-04	20
Hematological System Development and Function	2.09E-02 - 2.71E-04	13

Sperm, 199 mapped genes

Top Diseases and Bio Functions

Diseases and Disorders

Name	p-value	#Molecules
Neurological Disease	1.21E-02 - 2.87E-06	29
Organismal Injury and Abnormalities	1.19E-02 - 7.56E-05	105
Psychological Disorders	1.21E-02 - 7.56E-05	18
Hereditary Disorder	1.08E-02 - 7.70E-05	30
Skeletal and Muscular Disorders	1.19E-02 - 7.70E-05	28

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Name	p-value	#Molecules
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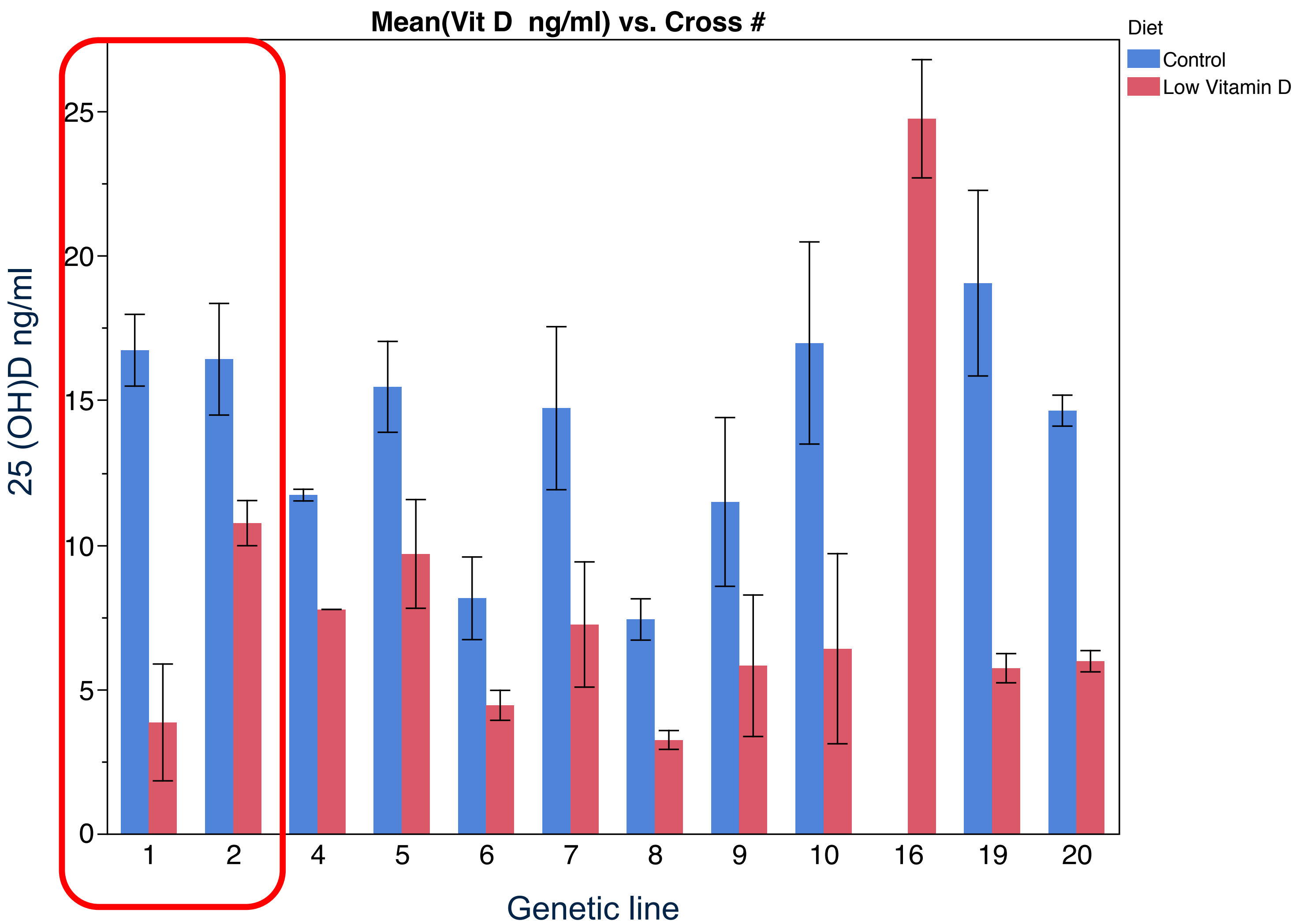
Organismal Development	1.11E-02 - 1.39E-04	37
Reproductive System Development and Function	1.21E-02 - 2.86E-04	13

Vitamin D levels influenced by genetic background

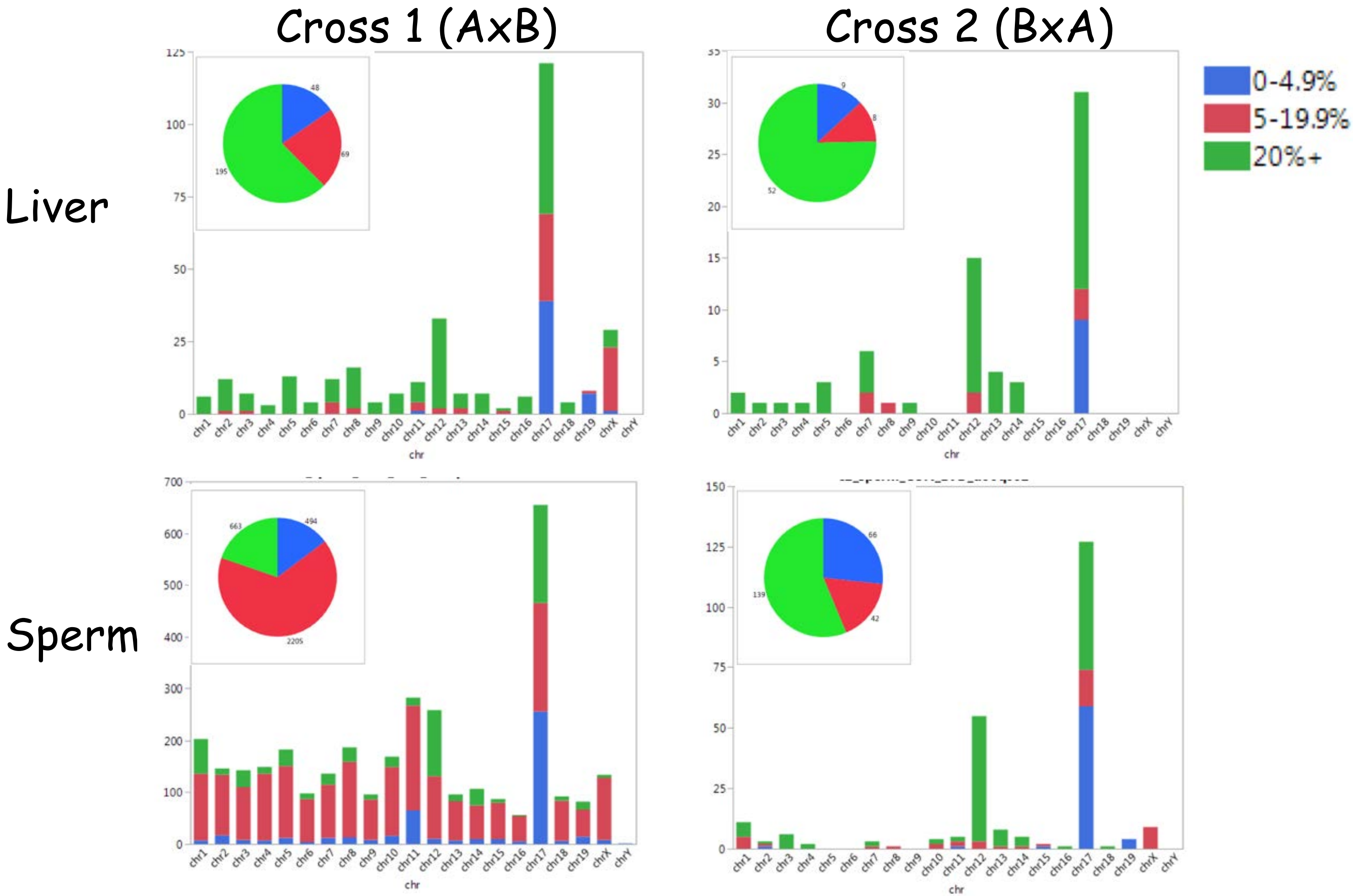
Maternal Plasma 25 (OH) D levels after 11+ weeks on diet

- Differences in extent of depletion



Vitamin D dependent differentially methylated regions

- Most of methylation changes >20% and enriched on Chr 17

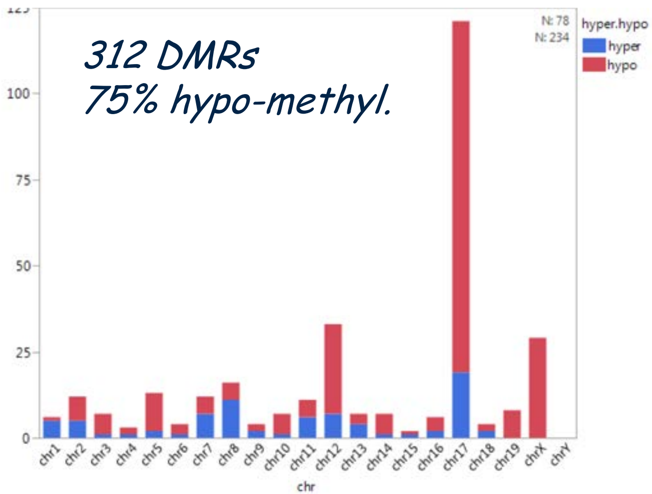


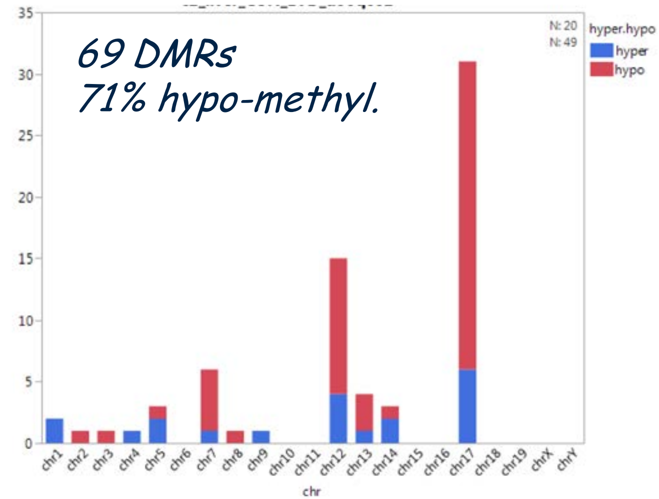
Vitamin D dependent differentially methylated regions

- Perturbation is cell type and cross dependent and mostly LOM
- - q < 0.01

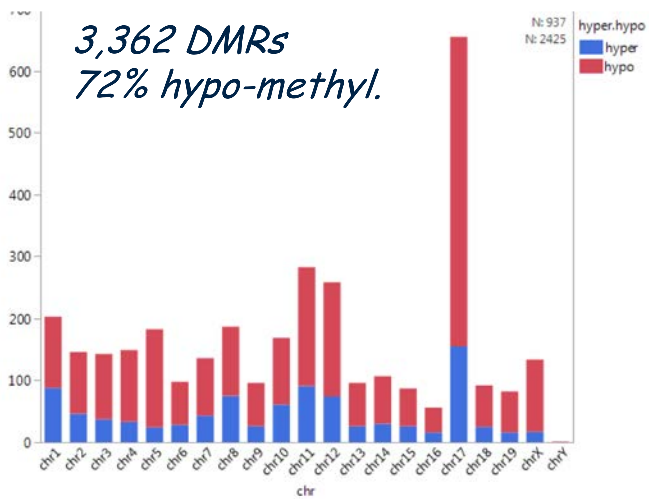
Cross 1 (AxB) | Cross 2 (BxA)

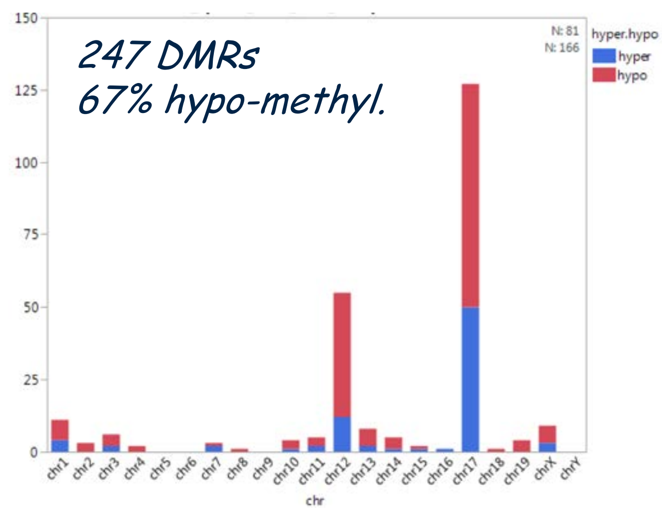
Liver





Sperm





25(OH)D levels borderline significant correlations
Standard least squares – all in model