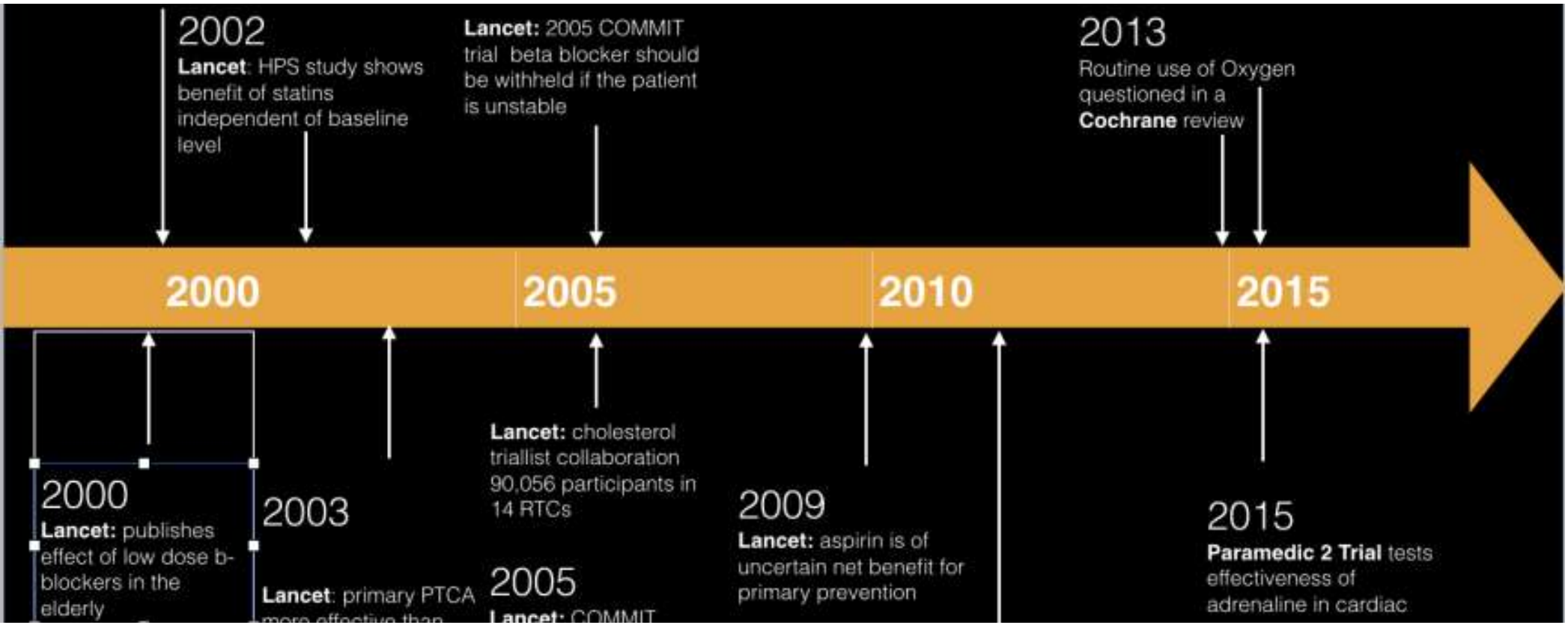
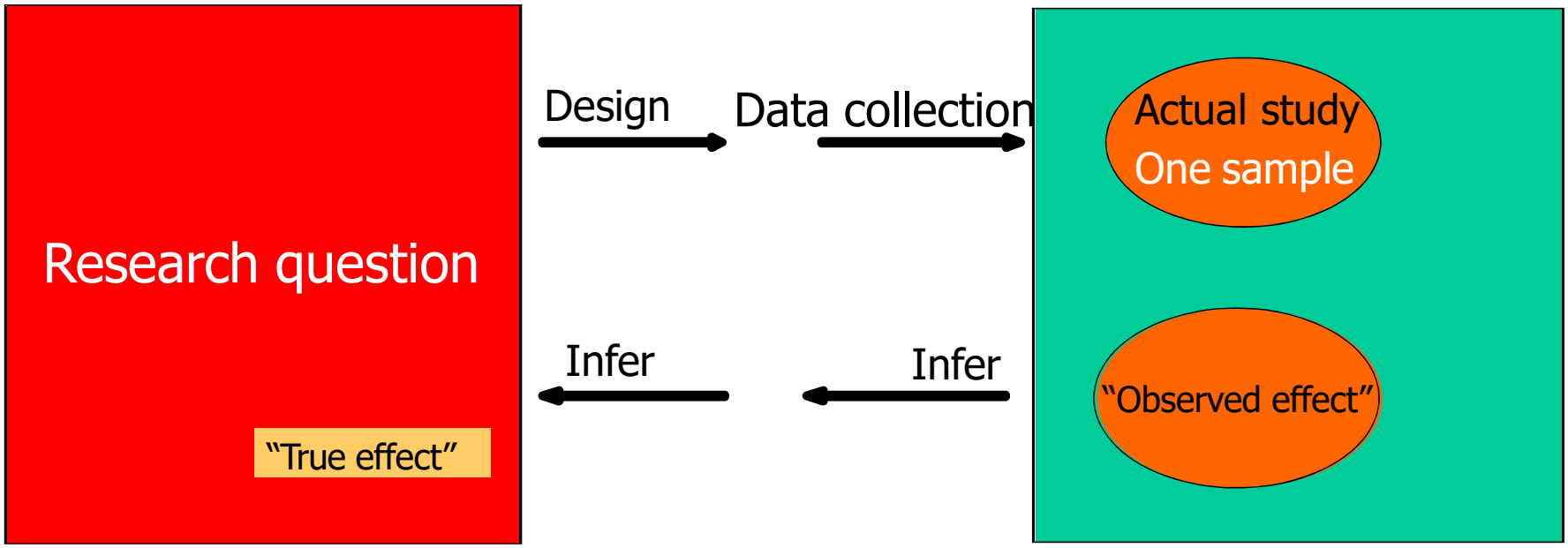
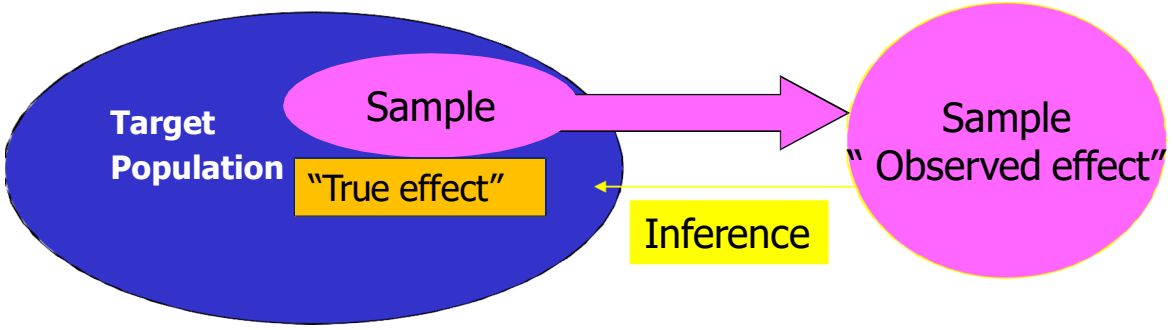
Beyond EBM & RCT's

- Asst. Prof. Mart Maiprasert.
- Department of Anti-Aging and Regenerative Medicine
- College of Integrative Medicine
- Dhurakit Pundit University

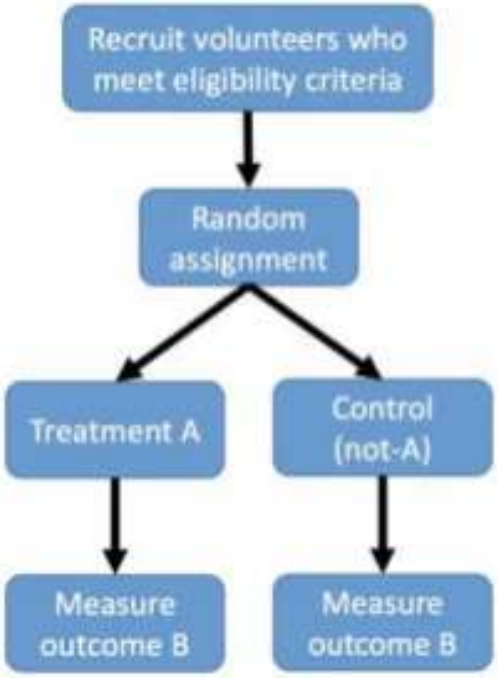
History of EBM




Research question
"True effect"
Design
Data collection
Actual study
One sample
Infer
Infer
"Observed effect"


Target
Population
Sample
"True effect"
Sample
" Observed effect"
Inference

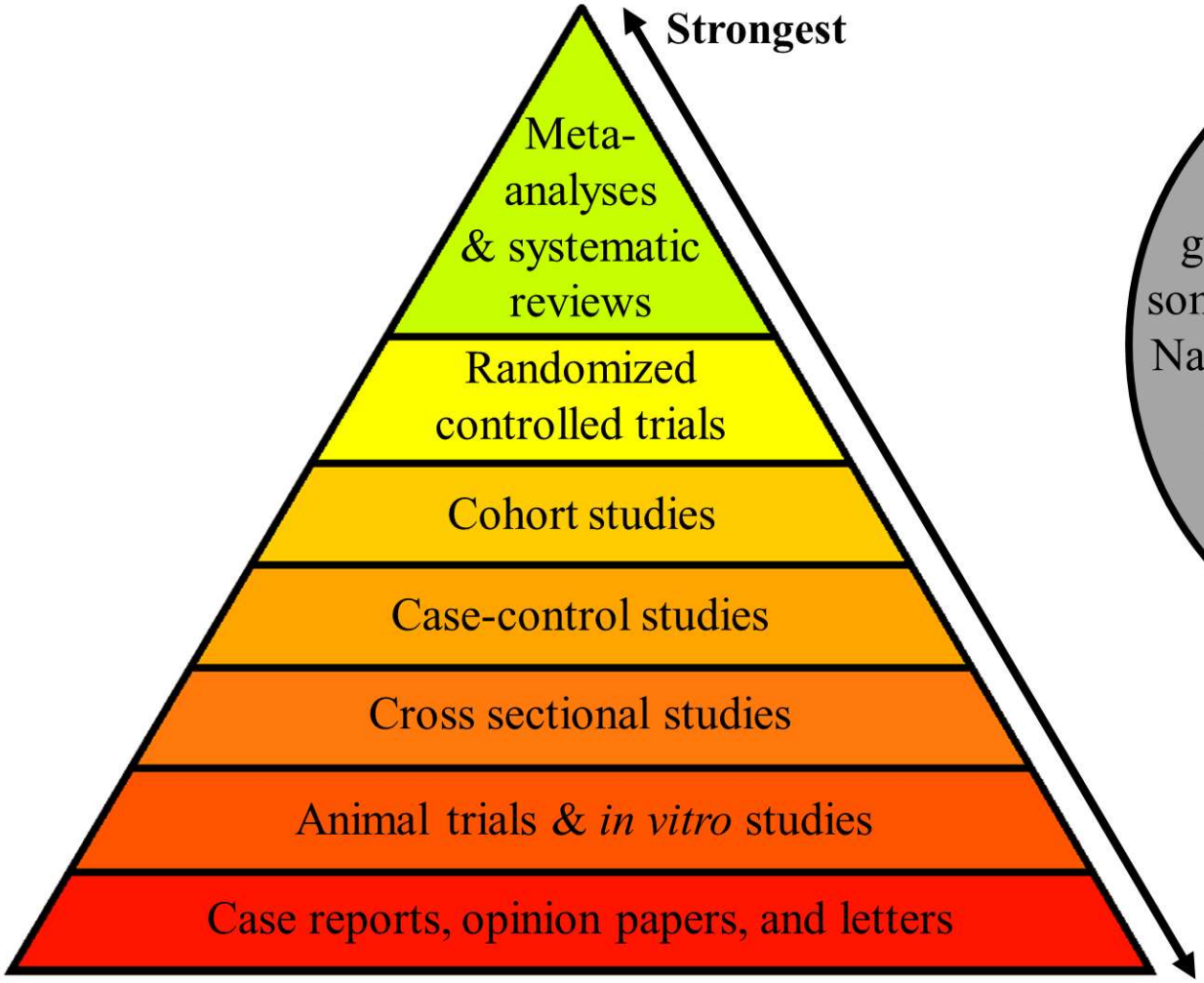
Randomized Controlled Trial (RCT)



- Medical RCTs test the efficacy of medical treatments.
- Features:
  - Control group (placebo or standard treatment)
  - Random assignment
  - Neither doctors nor patients know which group is which ("double blind")

Image credit: Ancker, Jessica S & Quynh Pham. "Beyond the RCT Evaluating innovations in the Learning Health System" AMIA 2016 Tutorial

Hierarchy of Scientific Evidence

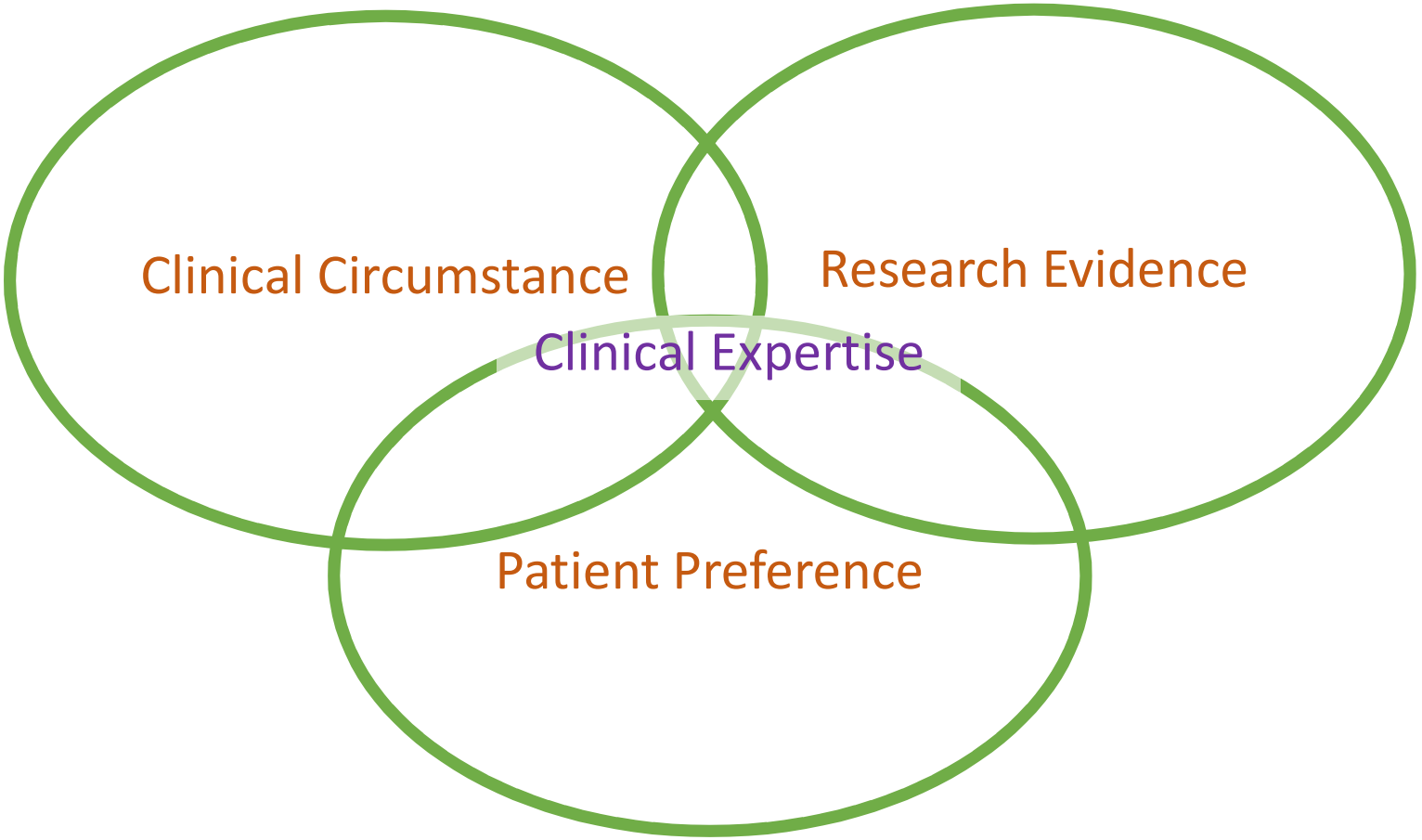


Not Scientific Evidence

Youtube videos, personal anecdotes, gut feelings, parental instincts, some guy you know, websites like Natural News, Info Wars, Natural Health Warriors, Collective Evolution, Green Med Info, Mercola.com, Whale.to, etc.

thelogicofscience.com

Evidence-Based Medicine



How do we actually practice EBM?

5 A's of EBM

Step 1 : **A**sk answerable question

Step 2 : Find an **A**rticle

Step 3 : Critical **A**ppraisal the evidence

Step 4 : **A**pply

Step 5 : **A**ssess

RCTs is the answer for all problems?

	Improved	Not
DRUG	70	30
Placebo/ Standard Rx	60	40

$$RR. = \frac{70 \times 40}{60 \times 30} = 1.55$$


ONE SIZE
DOESN'T FIT ALL


One
Size
Does
Not
Fit
ALL
Especially with Disaster Recovery

1. A brief review on resistance to $P2Y_{12}$ receptor antagonism in coronary artery disease.
Warlo EMK, Arnesen H, Seljeflot I.
Thromb J. 2019 May 20;17:11. doi: 10.1186/s12959-019-0197-5. eCollection 2019. Review.
PMID: 31198410 **Free Article**
Similar articles

2. Antibiotic therapy for chronic infection with Burkholderia cepacia complex in people with cystic fibrosis.
Frost F, Shaw M, Nazareth D.
Cochrane Database Syst Rev. 2019 Jun 13;6:CD013079. doi: 10.1002/14651858.CD013079.pub2. [Epub ahead of print] Review.
PMID: 31194880
Similar articles

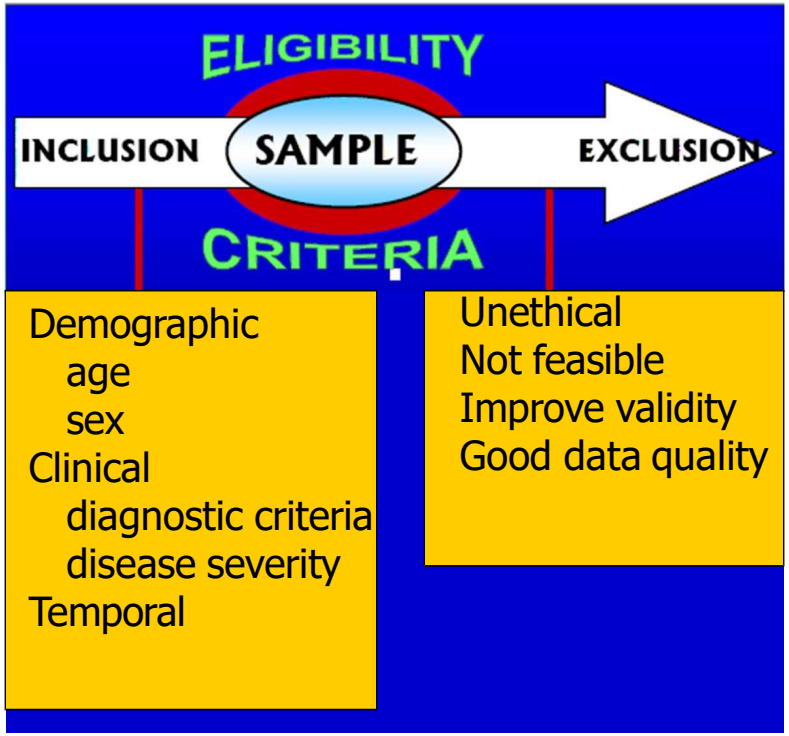
3. CoQ_{10} and Cognition a Review and Study Protocol for a 90-Day Randomized Controlled Trial Investigating the Cognitive Effects of Ubiquinol in the Healthy Elderly.
Stough C, Nankivell M, Camfield DA, Perry NL, Pipingas A, Macpherson H, Wesnes K, Ou R, Hare D, de Haan J, Head G, Lansjoen P, Langsjoen A, Tan B, Pase MP, King R, Rowsell R, Zwalf O, Rathner Y, Cooke M, Rosenfeldt F.
Front Aging Neurosci. 2019 May 29;11:103. doi: 10.3389/fnagi.2019.00103. eCollection 2019.
PMID: 31191293 **Free PMC Article**
Similar articles

4. Modes of e-Health delivery in secondary prevention programmes for patients with coronary artery disease: a systematic review.
Brørs G, Pettersen TR, Hansen TB, Fridlund B, Hølvold LB, Lund H, Norekvål TM.
BMC Health Serv Res. 2019 Jun 10;19(1):364. doi: 10.1186/s12913-019-4106-1.
PMID: 31182100 **Free PMC Article**
Similar articles

A Good Health

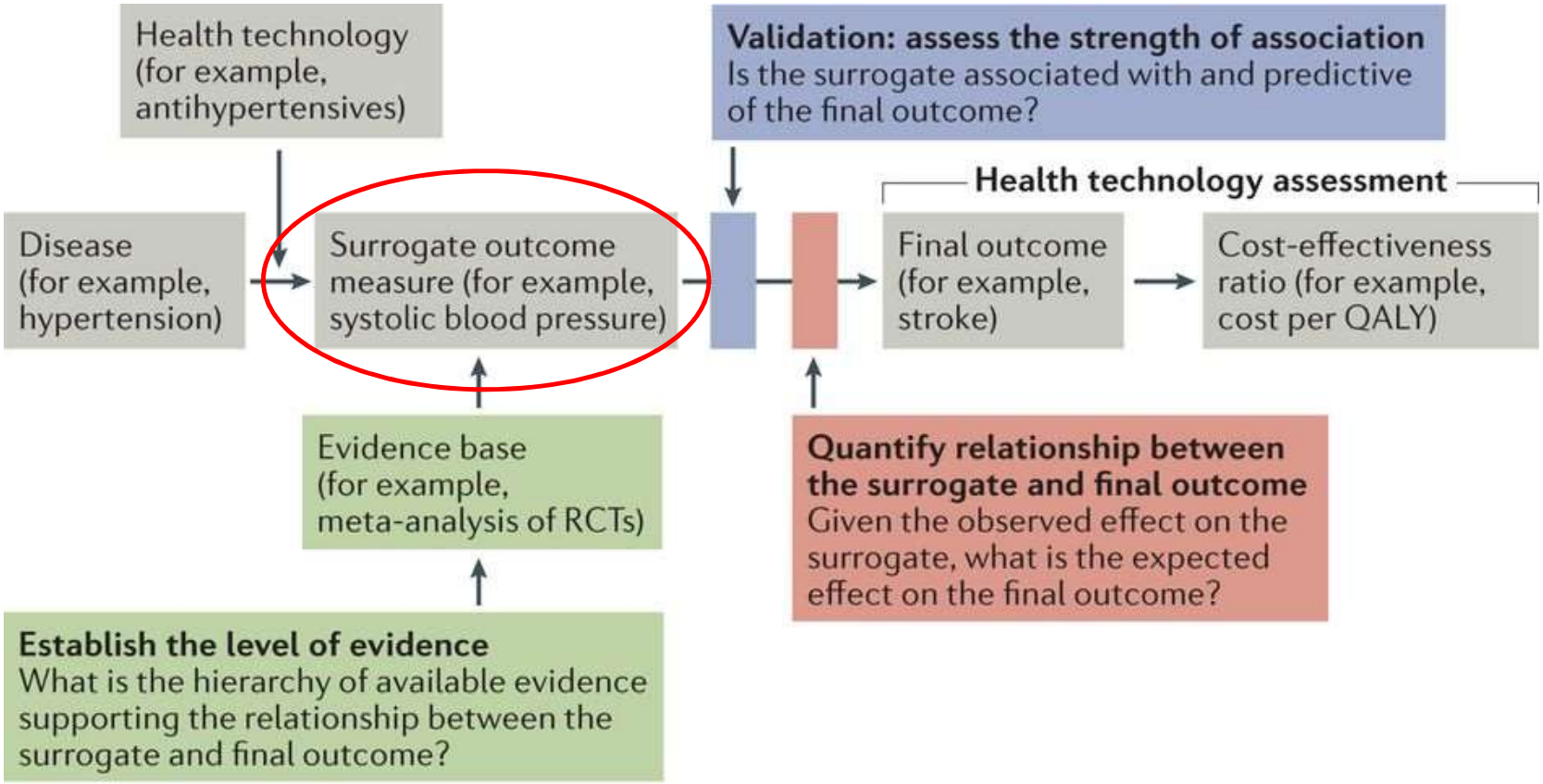
doesn’t come from only one drug or dietary supplement

Selection criteria



Inclusion Criteria

- Not pregnant
- Not children
- Not too old
- No Heart problems
- No Liver problems
- No Kidney problems
- No Drug allergy
- No Drugs…….



Nature Reviews | Drug Discovery

Open Access Research

BMJ Open

Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review

Uffe Ravnskov,[1] David M Diamond,[2] Rokura Hama,[3] Tomohito Hamazaki,[4] Björn Hammarskjöld,[5] Niamh Hynes,[6] Malcolm Kendrick,[7] Peter H Langsjoen,[8] Aseem Malhotra,[9] Luca Mascitelli,[10] Kilmer S McCully,[11] Yoichi Ogushi,[12] Harumi Okuyama,[13] Paul J Rosch,[14] Tore Schersten,[15] Sherif Sultan,[6] Ralf Sundberg[16]

Conclusions High LDL-C is inversely associated with mortality in most people over 60 years.
This finding is inconsistent with the cholesterol hypothesis (ie, that cholesterol, particularly LDL-C, is inherently atherogenic).
Since elderly people with high LDL-C live as long or longer than those with low LDL-C, our analysis provides reason to question the validity of the cholesterol hypothesis.
Moreover, our study provides the rationale for a re-evaluation of guidelines recommending pharmacological reduction of LDL-C in the elderly as a component of cardiovascular disease prevention strategies.

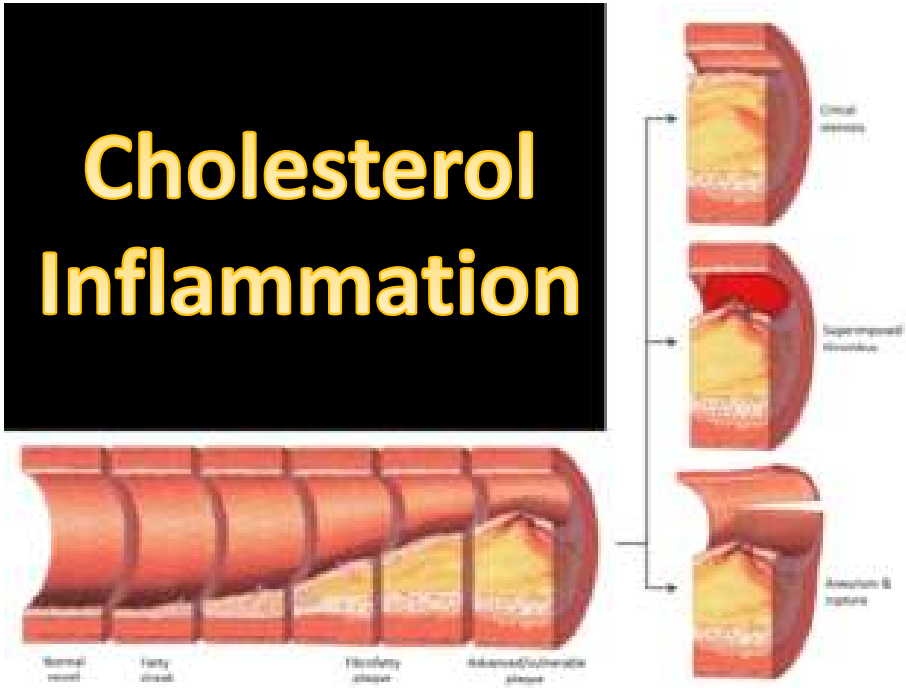
Statins & CVD risk: Primary Prevention

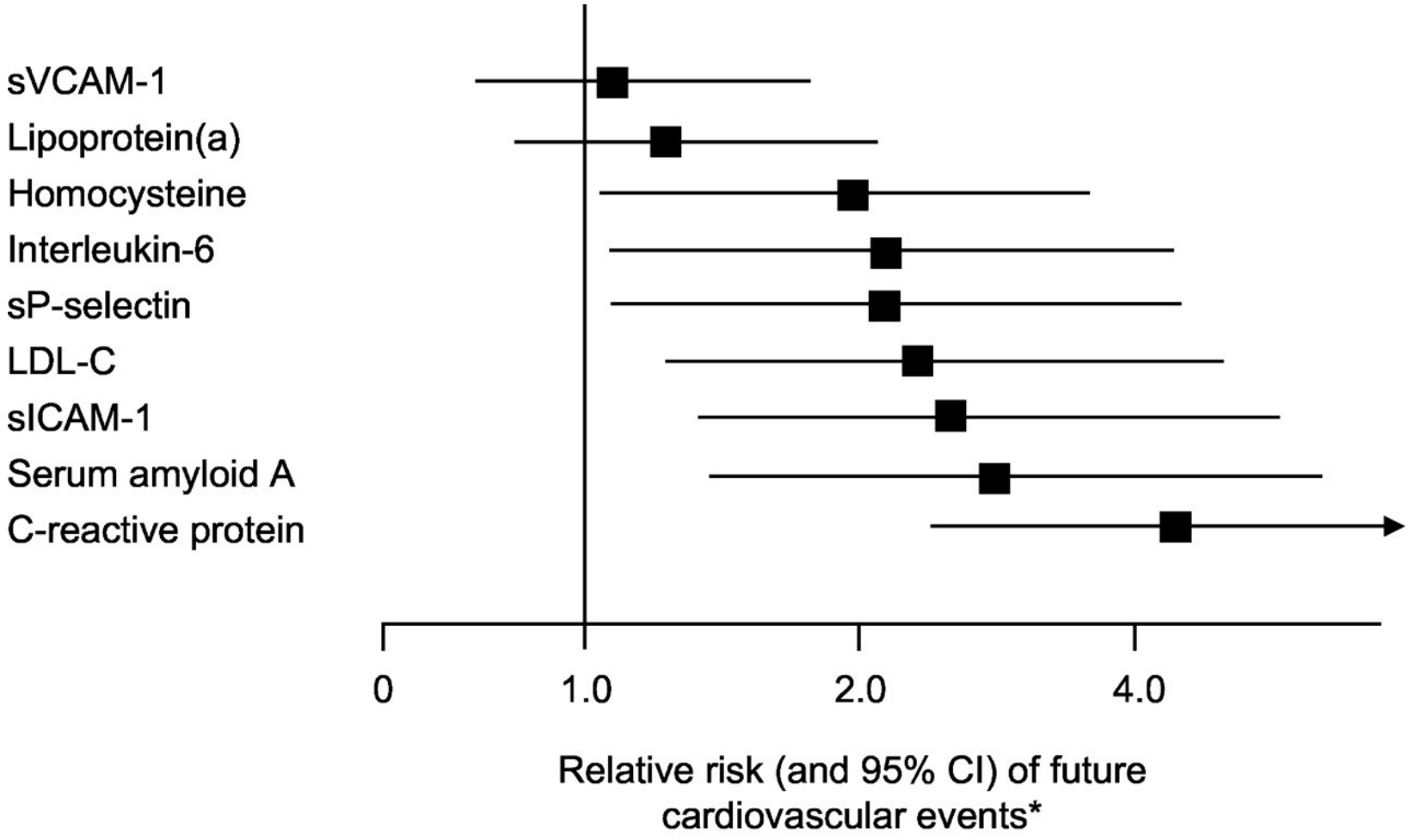
When the American College of Cardiology (ACC) and the American Heart Association (AHA) updated their guidelines for treatment of cholesterol levels in 2013, one recommendation was particularly controversial: use of statins for primary prevention of cardiovascular disease (CVD) among adults with 10-year risk of 7.5% or higher. The recommendation raised important questions about the "right" risk threshold at which to start statin therapy for primary prevention, particularly because many older adults exceed this threshold on the basis of age alone. The guidelines have since made their way into clinical practice, and "7.5%" has become instantly recognizable to primary care physicians and cardiologists. In 2018, an update to the guidelines largely affirmed this approach, although there was also an emphasis on the importance of patient preference and a suggestion that coronary artery calcium scores and clinical risk factors could help guide statin initiation decisions for primary prevention.

Richman, I.B., Ross, J.S. (2018). Weighing the harms and benefits of using statins for primary prevention: raising the risk threshold. Ann Intern Med. Dec 4.

Atherosclerosis

Cholesterol
Inflammation





James T. Willerson and Paul M. Ridker. Inflammation as a Cardiovascular Risk Factor. Circulation. 2004;109:II-2–II-10

Inflammation & CVD Risk

- Inflammation occurs in the vasculature as a response to injury, lipid peroxidation, and perhaps infection.
- Various risk factors, including hypertension, diabetes, and smoking, are amplified by the harmful effects of oxidized low-density–lipoprotein cholesterol, initiating a chronic inflammatory reaction, the result of which is a vulnerable plaque, prone to rupture and thrombosis.
- HMG-CoA reductase inhibitors, in the form of statins, have been shown to provide effective therapy for lowering CRP, in conjunction with their lipid-lowering effects.

James T. Willerson and Paul M. Ridker. Inflammation as a Cardiovascular Risk Factor. Circulation. 2004;109:II-2–II-10

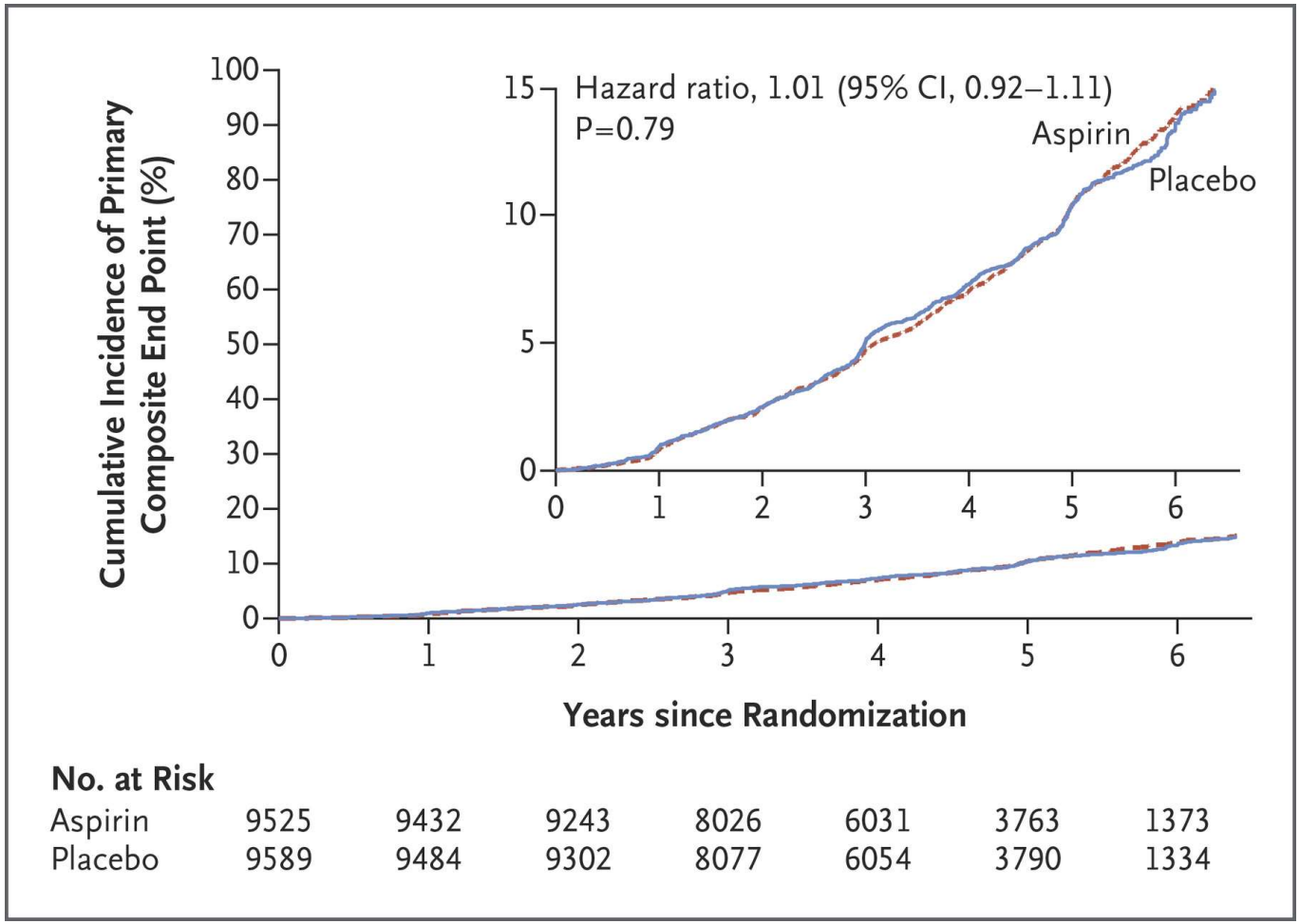
Effect of Aspirin on Disability-free Survival in the Healthy Elderly.

- Information on the use of aspirin to increase healthy independent life span in older persons is limited. Whether 5 years of daily low-dose aspirin therapy would extend disability-free life in healthy seniors is unclear.

CONCLUSIONS

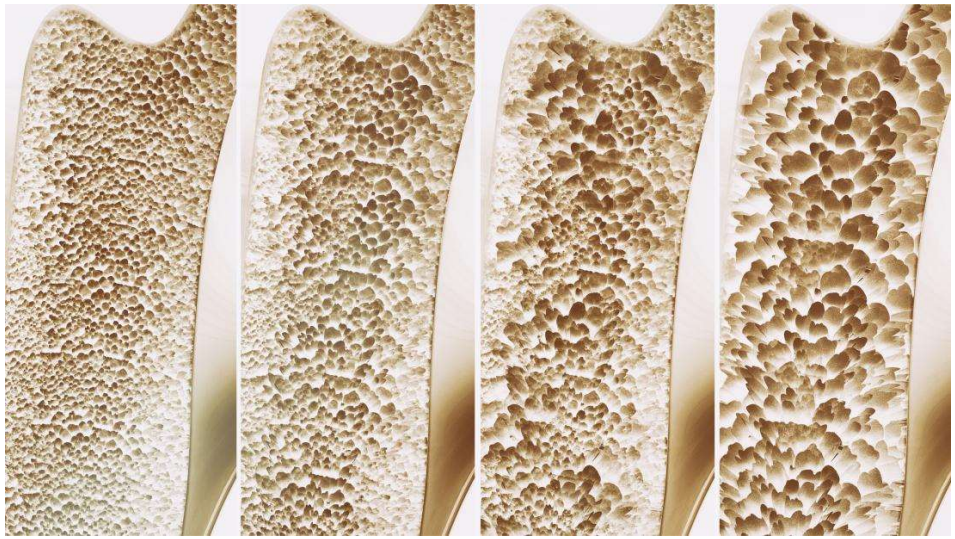
- Aspirin use in healthy elderly persons did not prolong disability-free survival over a period of 5 years but led to a higher rate of major hemorrhage than placebo.

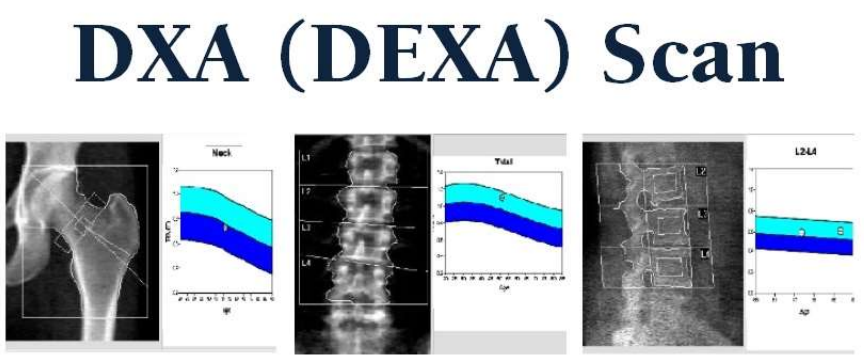
McNeil, J., J., Woods, R., L., Nelson, M., R., Reid, C., M. (2018). Effect of Aspirin on Disability-free Survival in the Healthy Elderly. N Engl J Med, 379:1499-1508.

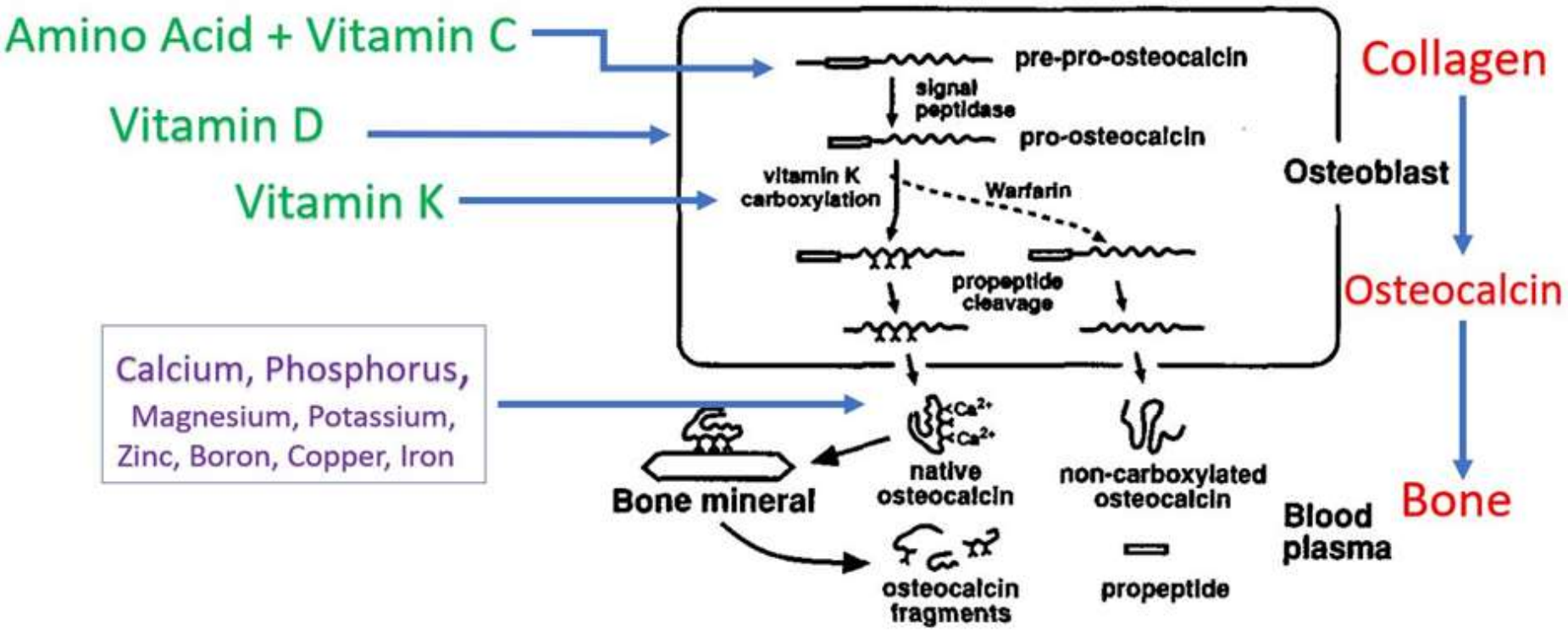


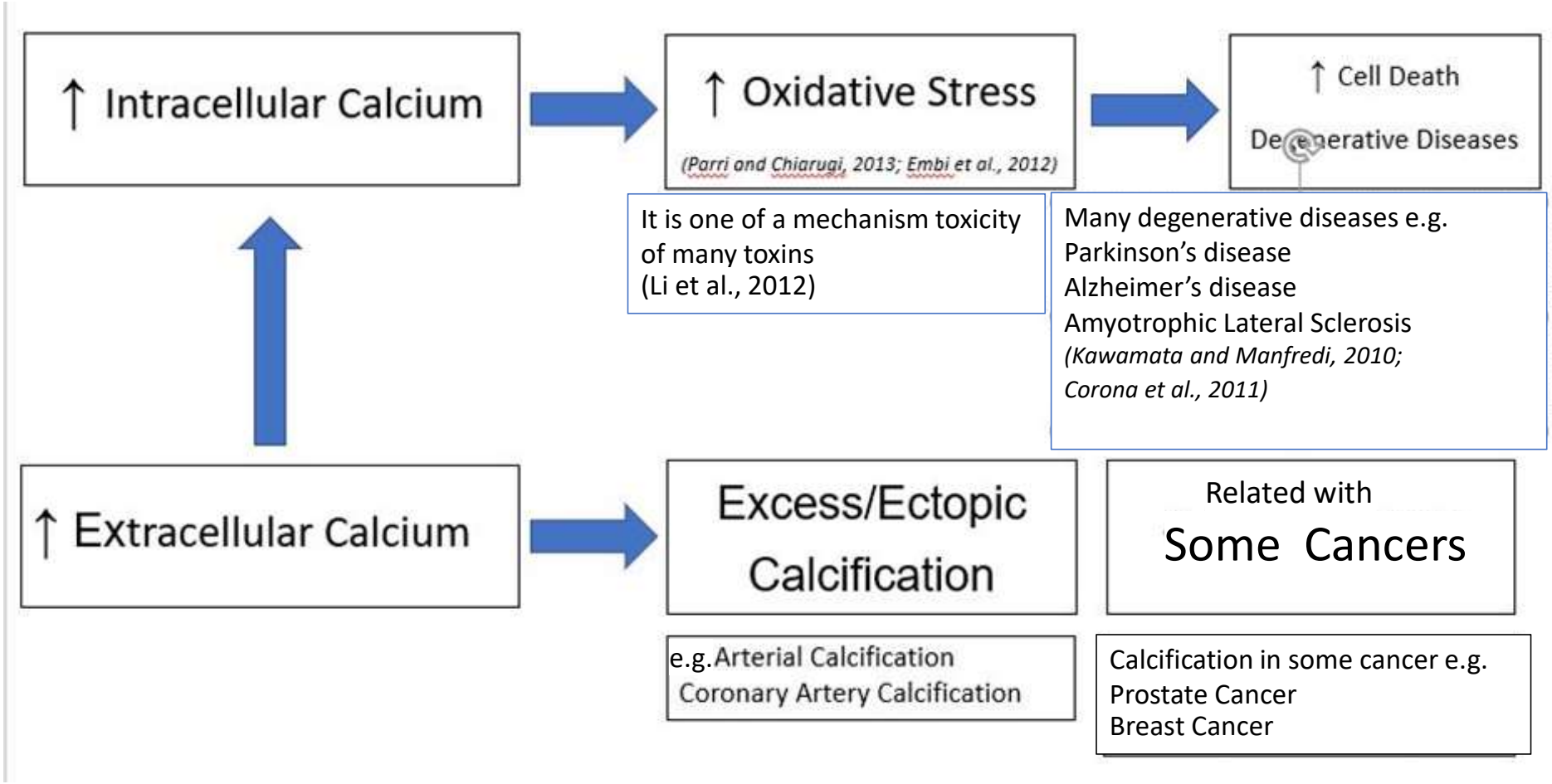
McNeil, J., J., Woods, R., L., Nelson, M., R., Reid, C., M. (2018). Effect of Aspirin on Disability-free Survival in the Healthy Elderly. N Engl J Med, 379:1499-1508.

Osteoporosis V.S. Dexa Scan






Amino Acid + Vitamin C
Vitamin D
Vitamin K
Calcium, Phosphorus,
Magnesium, Potassium,
Zinc, Boron, Copper, Iron
pre-pro-osteocalcin
signal peptidase
pro-osteocalcin
vitamin K carboxylation
Warfarin
propeptide cleavage
Osteoblast
Collagen
Osteocalcin
Bone
Blood plasma
Bone mineral
native osteocalcin
non-carboxylated osteocalcin
osteocalcin fragments
propeptide


↑ Intracellular Calcium
↑ Oxidative Stress
(Parri and Chiarugi, 2013; Embi et al., 2012)
↑ Cell Death
Degenerative Diseases
It is one of a mechanism toxicity of many toxins (Li et al., 2012)
Many degenerative diseases e.g.
Parkinson's disease
Alzheimer's disease
Amyotrophic Lateral Sclerosis
(Kawamata and Manfredi, 2010; Corona et al., 2011)
↑ Extracellular Calcium
Excess/Ectopic Calcification
Related with
Some Cancers
e.g.Arterial Calcification
Coronary Artery Calcification
Calcification in some cancer e.g.
Prostate Cancer
Breast Cancer

JAMA Network | Open.

Original Investigation | Nutrition, Obesity, and Exercise

Association of High Intakes of Vitamins B_6 and B_{12} From Food and Supplements With Risk of Hip Fracture Among Postmenopausal Women in the Nurses' Health Study

Haakon E. Meyer, MD, PhD; Walter C. Willett, MD, DrPH; Teresa T. Fung, ScD, RD; Kristin Holvik, PhD; Diane Feskanich, ScD

VitaminB6, B12 & Hip Fracture

- Meyer, H.,E., Willett., W.,C., Fung., T.,T., Holvik., K. Feskanich., D. (2019). Association of High Intakes of Vitamins B6 and B12 From Food and Supplements With Risk of Hip Fracture Among Postmenopausal Women in the Nurses' Health Study. *JAMA Netw Open,* May 3;2(5).

- **Importance** Vitamin supplementation far exceeding recommended doses is popular in segments of the population. However, adverse effects can occur. In a previous secondary analysis of combined data from 2 double-blind randomized clinical trials (RCTs), an unexpected increased risk of hip fracture was found among those treated with high doses of vitamin B_6 in combination with vitamin B_{12}.

Table 1. Age and Age-Adjusted Characteristics of 61 445 Women in the Nurses' Health Study Across Categories of Total Vitamin B_6 Intake (Diet and Supplements) in 2002, Cumulative Mean[a]

	Vitamin B_6 Intake, mg/d				
Variable	<2	2-4.9	5-14.9	15-34.9	≥35
No. (%) of population[b]	8416 (13.7)	33 660 (54.8)	8022 (13.1)	5965 (9.7)	5382 (8.8)
Age, mean, y	67.2	68.1	68.8	68.3	66.5
Height at baseline, mean, cm	164	164	164	164	164
Current BMI, mean	26.8	26.7	26.6	26.5	26.3
Physical activity, MET, mean, h/wk[c]	13.8	17.4	18.7	18.8	19.3
Current smoker, %	13.9	7.0	6.3	6.5	5.8
Dietary intake, mean					
Vitamin B_6, mg/d[d]	1.7	3.1	8.4	23.3	69.1
Vitamin B_{12}, µg/d[d]	7.4	12.7	22.4	31.6	48.2
Calcium, mg/d[d]	885	1167	1321	1345	1469
Vitamin D, µg/d[d]	5.0	9.9	12.5	12.2	13.7
Retinol, µg/d[d]	557	1104	1520	1596	2068
Protein, g/d[d]	67.7	73.0	73.9	73.0	73.3
Caffeine, mg/d	266	231	215	217	200
Alcohol, g/d	6.2	5.4	5.5	5.4	5.4
Multivitamin supplements, %	17.0	72.7	83.6	77.0	74.5
Vitamin B_6 supplements, %	2.1	0.9	11.9	25.4	45.7
Vitamin B complex, %	0	0	11.9	27.8	36.9
Vitamin B_{12} supplements, %	2.3	3.2	9.0	14.6	24.7
Difficulty climbing stairs or walking 1 block, %	6.2	5.7	6.2	6.5	6.6
≥2 Falls last year	7.1	8.1	8.4	9.1	9.2
Self-rated general health status not excellent, %	10.1	10.7	10.8	11.2	11.1
Cancer, %	15.7	17.2	17.8	18.2	17.6
Diabetes, %	9.4	9.7	9.5	10.2	9.5
Cardiovascular disease, %	12.2	12.3	12.9	12.9	12.3
Osteoporosis, %	21.5	24.3	25.4	25.9	27.2
Medication use, %					
Current postmenopausal hormone therapy	29.0	35.6	39.5	37.3	37.6
Thiazide-like diuretic	13.2	15.2	15.4	15.4	14.0
Furosemide diuretic	3.2	3.9	3.9	3.9	4.8
Oral corticosteroids	2.3	2.5	2.6	2.6	2.8

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent.

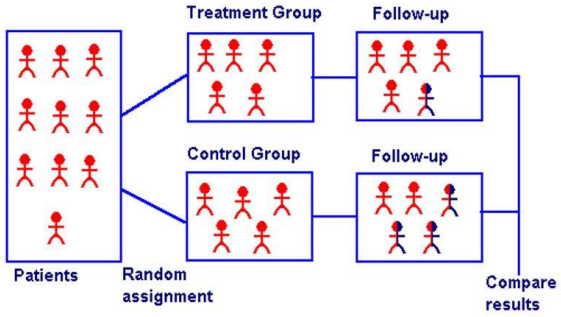
[a] Values are means and percentages and were standardized to the age distribution in 2002.

[b] Number of women participating in the 2002 questionnaire cycle.

[c] Metabolic equivalent hours per week from discretionary physical activity (eg, 12 MET hours per week is equivalent to 4 hours per week of walking or 1 hour per week of running).

[d] Cumulative mean daily intake from foods and supplements adjusted for total energy intake.

Randomized Controlled Trials



Examples include: (aspirin & streptokinase), (simvastatin & vitamins)

Confounding Adjustment Propensity Score

Table 2. Age and Age-Adjusted Characteristics of 61 445 Women in the Nurses' Health Study Across Categories of Total Vitamin B_{12} Intake (Diet and Supplements) in 2002, Cumulative Mean[a]

	Vitamin B_{12} Intake, µg/d				
Variable	<5	5-9.9	10-19.9	20-29.9	≥30
No. (%) of population[b]	4820 (7.8)	19 888 (32.4)	21 940 (35.7)	6144 (10.0)	8653 (14.1)
Age, mean, y	66.5	68.3	68.6	67.7	66.9
Height at baseline, mean, cm	164	164	164	164	164
Current BMI, mean	26.3	26.7	26.7	26.7	26.4
Physical activity, MET, h/wk[c]	16.1	16.4	17.6	18.0	19.1
Current smoker, %	9.8	8.3	7.8	6.9	5.8
Dietary intake, mean					
Vitamin B_6, mg/d[d]	3.8	4.6	7.6	16.4	36.7
Vitamin B_{12}, µg/d[d]	4.0	7.5	13.8	24.1	57.1
Calcium, mg/d[d]	886	1061	1244	1344	1423
Vitamin D, µg/d[d]	4.6	7.7	11.5	12.8	13.4
Retinol, µg/d[d]	393	816	1378	1631	1882
Protein, g/d[d]	66.2	71.5	73.8	74.0	73.2
Caffeine, mg/d	245	243	228	221	203
Alcohol, g/d	6.3	5.6	5.5	5.5	4.2
Multivitamin supplements, %	16.8	51.4	82.8	85.1	77.9
Vitamin B_6 supplements, %	3.0	2.9	5.1	10.5	32.7
Vitamin B complex, %	0.1	0.2	3.7	17.5	31.2
Vitamin B_{12} supplements, %	0.1	0.1	0.2	3.1	47.4
Difficulty climbing stairs or walking 1 block, %	5.3	5.5	6.2	6.2	6.8
≥2 Falls last year	6.5	7.9	8.4	8.8	8.9
Self-rated general health status not excellent, %	9.2	10.6	10.9	11.2	11.3
Cancer, %	15.1	16.6	17.6	18.0	18.1
Diabetes, %	7.8	9.6	9.9	9.7	9.8
Cardiovascular disease, %	12.0	12.6	12.0	12.4	13.9
Osteoporosis, %	21.6	23.3	25.7	24.1	26.0
Medication use, %					
Current postmenopausal hormone therapy	30.9	33.6	36.9	35.6	38.6
Thiazide-like diuretic	12.9	14.4	15.6	15.3	14.7
Furosemide diuretic	3.3	3.6	4.1	3.9	4.5
Oral corticosteroids	2.5	2.2	2.6	2.8	2.7

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[c] Metabolic equivalent hours per week from discretionary physical activity (eg, 12 MET hours per week is equivalent to 4 hours per week of walking or 1 hour per week of running).

[d] Cumulative mean daily intake from foods and supplements adjusted for total energy intake.

Case-Control Study

	Coffee	No Coffee
Pancreatic cancer	**260**	**80**
No Pancreatic cancer	**190**	**150**

Odds ratio = (260 x 150) / (80 x 190) = 2.6

Measure of association

Crude Odds ratio= 2.6

Adjusted Odds ratio = 1.0

Smoking			
	Coffee	No Coffee	Total
Cancer	250	50	300
No cancer	149	30	179
Sum	399	80	479

Odds ratio= 1.0

Non smoking			
	Coffee	No Coffee	Total
Cancer	10	30	40
No cancer	41	120	161
Sum	51	150	201

Odds ratio= 0.98

Positive Confounding

Table 4. Relative Risk of Hip Fracture According to Combined Cumulative Mean Total Intakes of Vitamins B_6 and B_{12} Among Women With 2304 Hip Fractures, the Nurses' Health Study, 1984-2014

Variable[a]	Cases	Crude Incidence per 10 000 Person-Years	Age and Questionnaire Cycle–Adjusted RR (95% CI)	Fully Adjusted RR (95% CI)[b]
Low B_6 and low B_{12}	263	9.5	1 [Reference]	1 [Reference]
Medium B_6 and low B_{12}	564	12.8	1.02 (0.88-1.19)	1.11 (0.94-1.31)
High B_6 and low B_{12}	22	11.2	1.19 (0.77-1.85)	1.27 (0.82-1.98)
Low B_6 and medium B_{12}	42	10.7	1.24 (0.89-1.74)	1.12 (0.79-1.59)
Medium B_6 and medium B_{12}	812	16.5	1.14 (0.99-1.32)	1.18 (0.98-1.42)
High B_6 and medium B_{12}	34	12.4	1.10 (0.77-1.58)	1.17 (0.80-1.72)
Low B_6 and high B_{12}	10	15.6	1.30 (0.69-2.45)	1.17 (0.62-2.22)
Medium B_6 and high B_{12}	419	19.8	1.25 (1.06-1.47)	1.31 (1.07-1.60)
High B_6 and high B_{12}	138	18.9	1.33 (1.08-1.65)	1.47 (1.15-1.89)

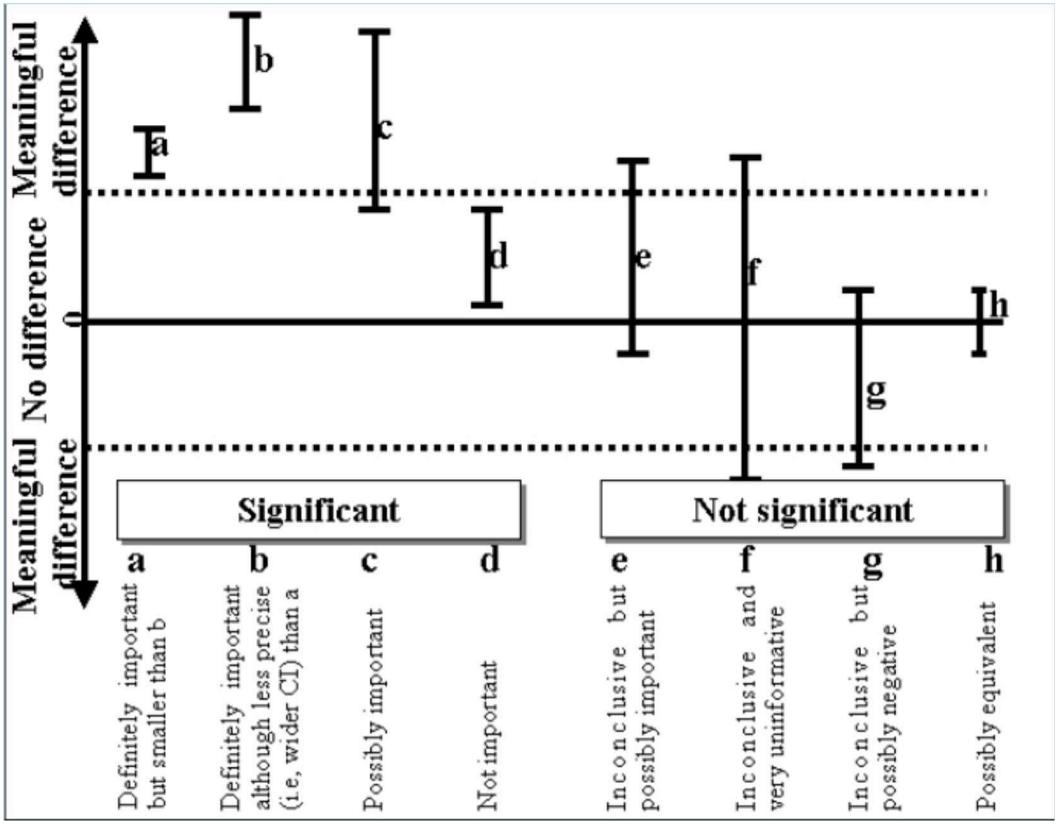
Abbreviation: RR, relative risk.

[a] Cutoffs for vitamin B_6 are 2 and 35 mg/d; cutoffs for vitamin B_{12} are 10 and 20 µg/d.

[b] Adjusted for age; questionnaire cycle; height; body mass index; physical activity; smoking status; dietary intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol; cancer; diabetes; cardiovascular disease; osteoporosis; postmenopausal hormone therapy; and use of thiazide diuretics, furosemide diuretics, and oral corticosteroids.

95% confidence interval & P-value (significant level =0.05)

Type one error =0.05



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High B_6 and low B_{12}	22	11.2	1.19 (0.77-1.85)	1.27 (0.82-1.98)
Low B_6 and medium B_{12}	42	10.7	1.24 (0.89-1.74)	1.12 (0.79-1.59)
Medium B_6 and medium B_{12}	812	16.5	1.14 (0.99-1.32)	1.18 (0.98-1.42)
High B_6 and medium B_{12}	34	12.4	1.10 (0.77-1.58)	1.17 (0.80-1.72)
Low B_6 and high B_{12}	10	15.6	1.30 (0.69-2.45)	1.17 (0.62-2.22)
Medium B_6 and high B_{12}	419	19.8	1.25 (1.06-1.47)	1.31 (1.07-1.60)
High B_6 and high B_{12}	138	18.9	1.33 (1.08-1.65)	1.47 (1.15-1.89)

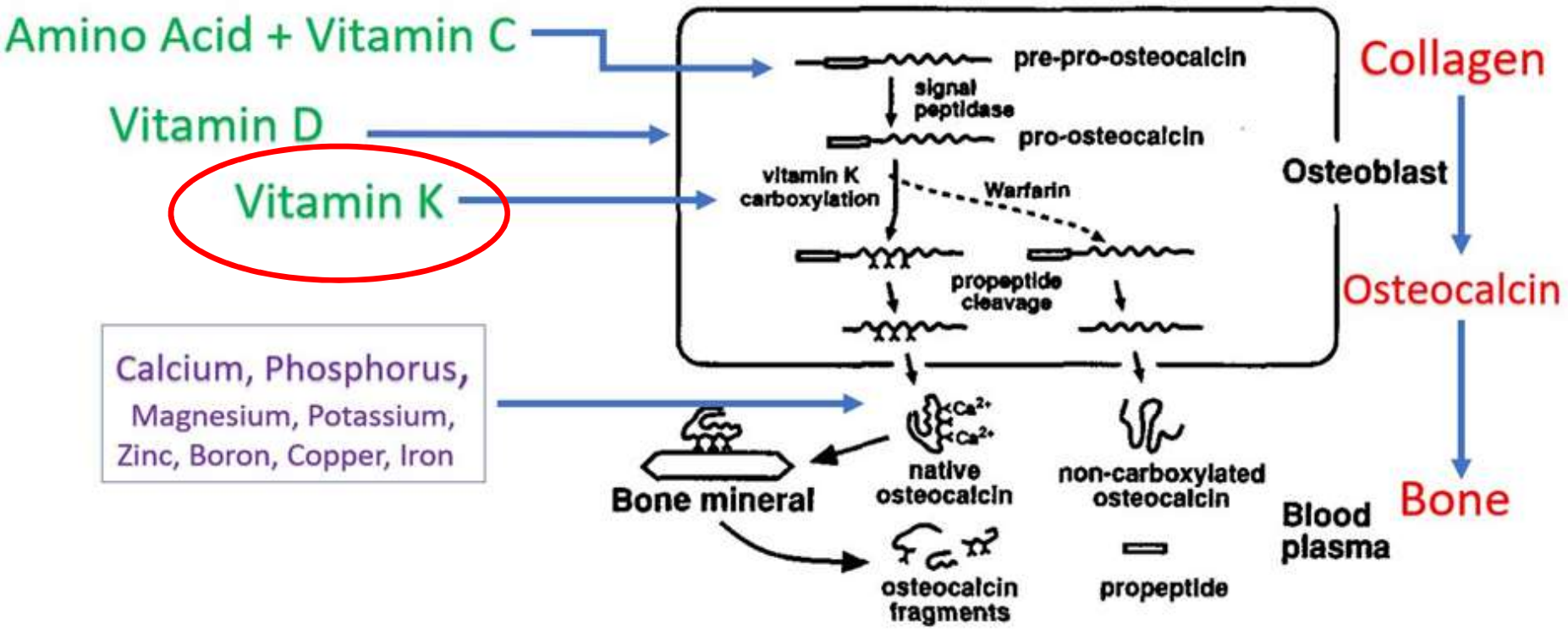
Abbreviation: RR, relative risk.

[a] Cutoffs for vitamin B_6 are 2 and 35 mg/d; cutoffs for vitamin B_{12} are 10 and 20 µg/d.

[b] Adjusted for age; questionnaire cycle; height; body mass index; physical activity; smoking status; dietary intakes of calcium, vitamin D, retinol, protein, caffeine, and alcohol; cancer; diabetes; cardiovascular disease; osteoporosis; postmenopausal hormone therapy; and use of thiazide diuretics, furosemide diuretics, and oral corticosteroids.

Multivariable RRs were computed from models that adjusted for potential dietary and nondietary confounding factors. For categorical covariates, missing data were assigned as a separate category. Less than 2% of the observations had missing data for BMI, physical activity, and smoking, and 5% of the observations had missing data for postmenopausal hormone therapy.

the other vitamins, vitamin D, and Retinol.


Amino Acid + Vitamin C
Vitamin D
Vitamin K
Calcium, Phosphorus,
Magnesium, Potassium,
Zinc, Boron, Copper, Iron
pre-pro-osteocalcin
signal peptidase
pro-osteocalcin
vitamin K carboxylation
Warfarin
propeptide cleavage
Osteoblast
Collagen
Osteocalcin
Bone
Bone mineral
native osteocalcin
non-carboxylated osteocalcin
osteocalcin fragments
propeptide
Blood plasma

Implications

The RDAs are established to meet the nutritional requirements of almost the entire population. Despite that, use of high-dose vitamin supplementation far exceeding the RDAs is common, often without any definite indication and in the absence of clear evidence of benefit.

Our results are in line with several reports suggesting that unexpected adverse effects can occur with high-dose vitamin supplementation. For example, high-dose beta-carotene supplementation increased the risk of lung cancer in smokers, and high-dose vitamin E supplementation may increase all-cause mortality. Higher risk of fracture was reported in 2 RCTs after treatment with annual megadoses of vitamin D, and possible adverse effects of homocysteine-lowering treatment with B vitamins have been observed, including a potentially increased risk of cancer. Although we acknowledge the limitations of our cohort design, the findings herein add to the body of literature that suggests caution should be used in vitamin supplementation when there is no apparent deficiency.

Biological plausibility

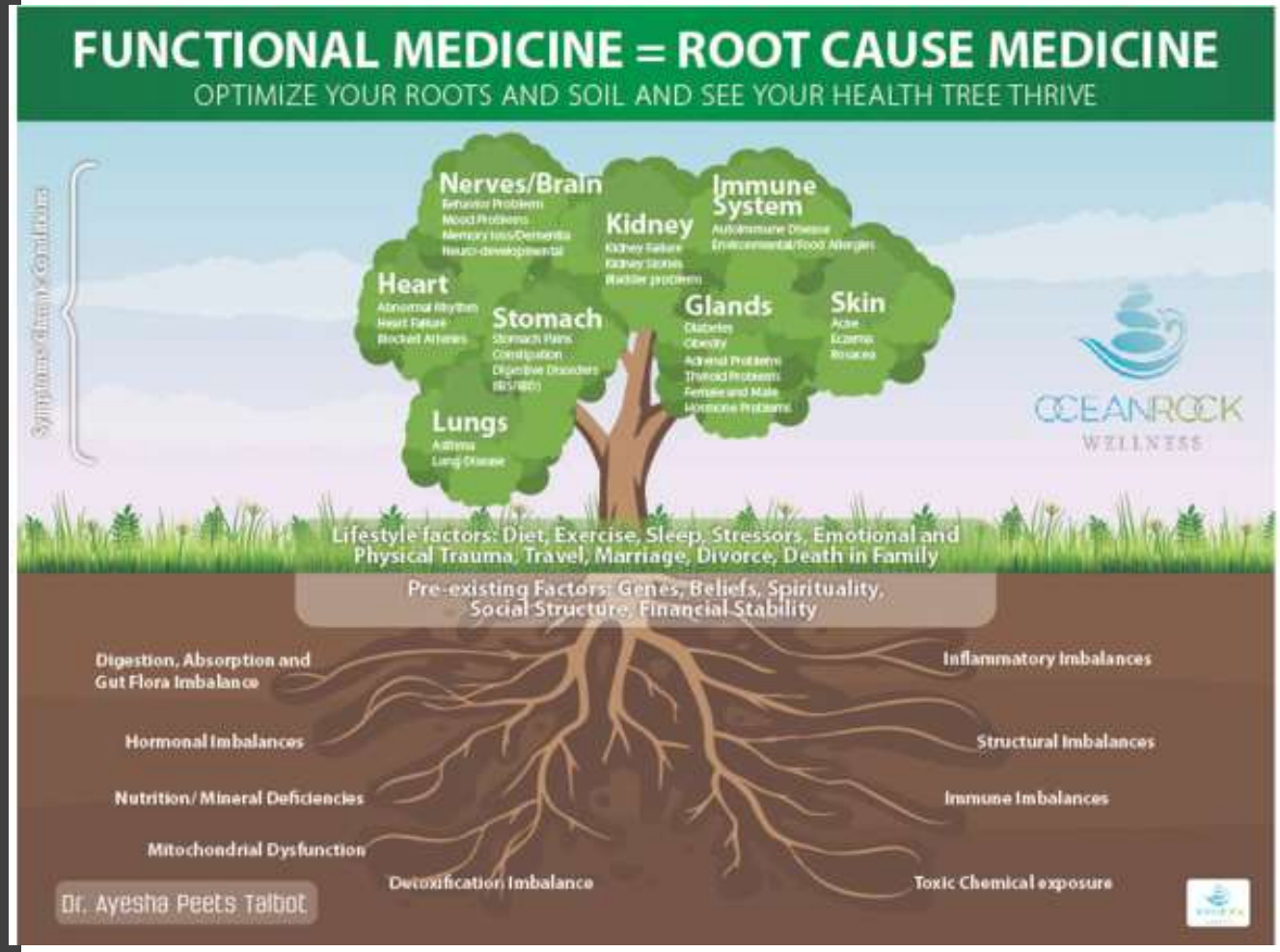
- Vitamin B6 Vitamin B12
- Combination
- High doses

Hip fracture

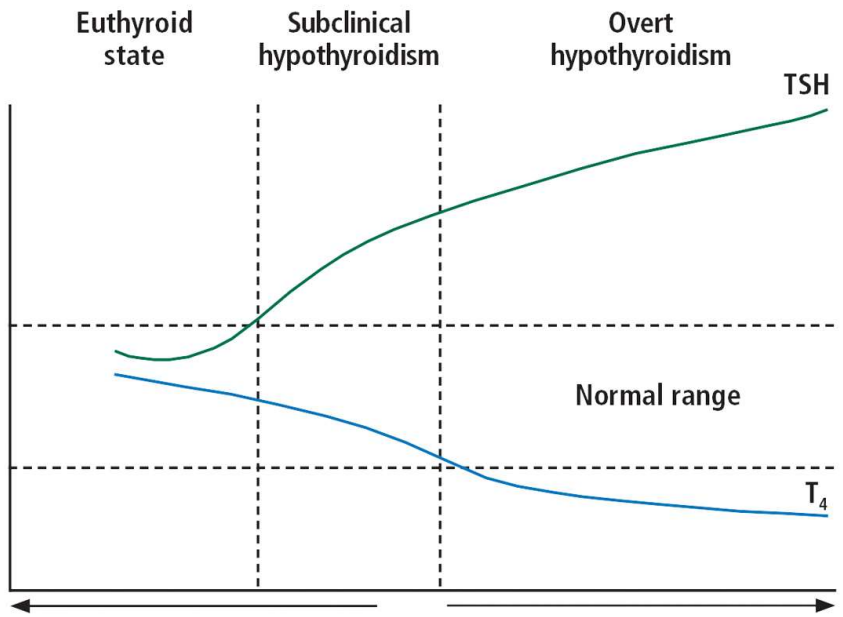
- High doses Vitamin B12 → Neurological symptoms → Risk of falls
- High doses Vitamin B6 → Estrogen & Steroids Receptors → Bone loss
- Genetic trigger???

Functional Medicine

- Musculoskeletal Structural Imbalance
- Environmental Inputs: diet, nutrition, exercise, trauma
- Oxidative stress and Energy Production
- Intoxication and Detoxification
- Gastrointestinal Status Imbalance
- Immune & Inflammatory Imbalance
- Hormonal and Neurotransmitter Imbalance
- Mind, Spirit, Emotion and Community



"It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has."



JAMA | Original Investigation

Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism
A Systematic Review and Meta-analysis

Martin Feller, MD, MSc; Marieke Snel, MD, PhD; Eltsavet Moutzouri, MD, PhD; Douglas C. Bauer, MD; Maria de Montmollin, MD; Drahomir Aujesky, MD, MSc; Ian Ford, PhD; Jacobijn Gussekloo, MD, PhD; Patricia M. Kearney, MD, PhD, MPH; Simon Mooijaart, MD, PhD; Terry Quinn, MD; David Stott, MD; Rudi Westendorp, MD, PhD; Nicolas Rodondi, MD, MAS; Olaf M. Dekkers, MD, MA, MSc, PhD

Feller, M., Snel, M., Moutzouri, E. (2018) Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism **A Systematic Review and Meta-analysis.** *JAMA.* 320(13):1349-1359.

Figure 1. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Quality-of-Life and Mood-Related Outcomes

Source	Quality of Life/Mood Scale	No. of Participants		Standardized Mean Difference (95% CI)	Weight, %
		Levothyroxine	Placebo		
General quality of life					
Kong et al,[27] 2002	General Health Questionnaire at 6 mo	20	14	-1.00 (-1.73 to -0.27)	3.70
Jorde et al,[26] 2006	General Health Questionnaire at 12 mo	35	32	-0.25 (-0.74 to 0.23)	8.42
Reuters et al,[31] 2012	Short Form 36 at 6 mo	32	25	0.35 (-0.18 to 0.87)	7.02
Stott et al,[12] 2017	EQ-5D at 12 mo	318	320	-0.10 (-0.25 to 0.06)	80.86
Subtotal				-0.11 (-0.25 to 0.03)	100.00
Overall effect: I^2 = 66.7%, P = .03					
Thyroid-related symptoms					
Meier et al,[22] 2001	Billewicz score at 12 mo	31	32	0.10 (-0.39 to 0.59)	7.34
Razvi et al,[32] 2007	ThyD QoL at 3 mo	100	100	0.11 (-0.29 to 0.50)	11.66
Reuters et al,[31] 2012	Zulewski score at 6 mo	32	25	-0.22 (-0.74 to 0.31)	6.52
Stott et al,[12] 2017	ThyPRO hyperthyroid score at 12 mo	318	320	0.01 (-0.15 to 0.16)	74.48
Subtotal				0.01 (-0.12 to 0.14)	100.00
Overall effect: I^2 = 0.0%; P = .79					
Fatigue and tiredness					
Stott et al,[12] 2017	ThyPRO tiredness score at 12 mo	318	320	-0.01 (-0.16 to 0.15)	100.00
Depressive symptoms					
Jorde et al,[26] 2006	Beck Depression Inventory at 12 mo	35	32	-0.26 (-0.74 to 0.22)	24.09
Parle et al,[16] 2010	HADS at 12 mo	52	42	-0.11 (-0.52 to 0.29)	33.72
Reuters et al,[31] 2012	Beck Depression Inventory at 6 mo	32	25	0.06 (-0.47 to 0.58)	20.39
Najafi et al,[24] 2015	Beck Depression Inventory at 3 mo	30	30	-0.05 (-0.56 to 0.46)	21.80
Subtotal				-0.10 (-0.34 to 0.13)	100.00
Overall effect: I^2 = 0.0%; P = .84					

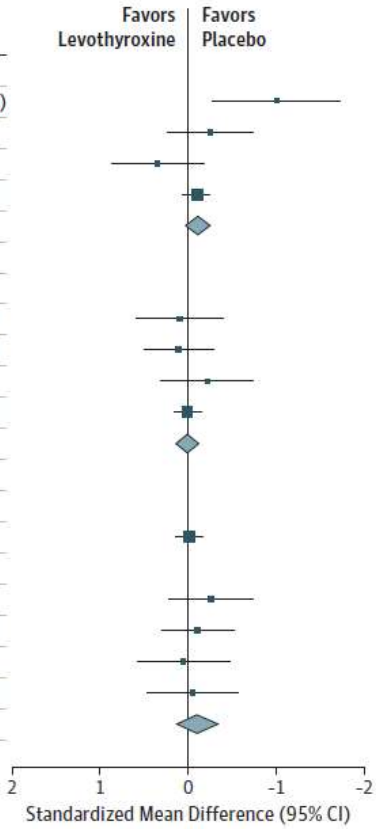


Figure 2. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Cognitive Function

Source	Cognition Function Scale	No. of Participants		Standardized Mean Difference (95% CI)	Weight, %
		Levothyroxine	Placebo		
Jorde et al,[26] 2006	Composite cognitive score at 12 mo	35	32	0.32 (-0.17 to 0.80)	7.72
Parle et al,[16] 2010	MMSE score at 12 mo	52	42	0.01 (-0.39 to 0.42)	10.87
Aghili et al,[25] 2012	Wechsler memory score at 3 mo	30	30	0.47 (-0.04 to 0.98)	6.82
Stott et al,[12] 2017	Letter-Digit Coding Test score at 18 mo	318	320	0.04 (-0.12 to 0.19)	74.59
Overall effect: $I^2 = 14.7\%$; $P = .32$				0.09 (-0.05 to 0.22)	100.00

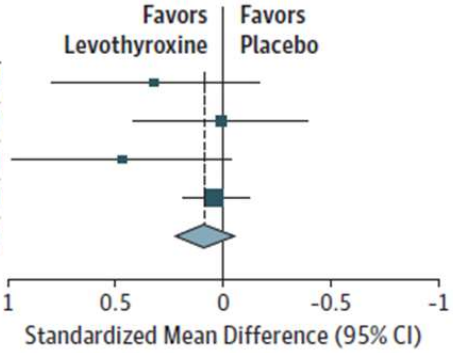
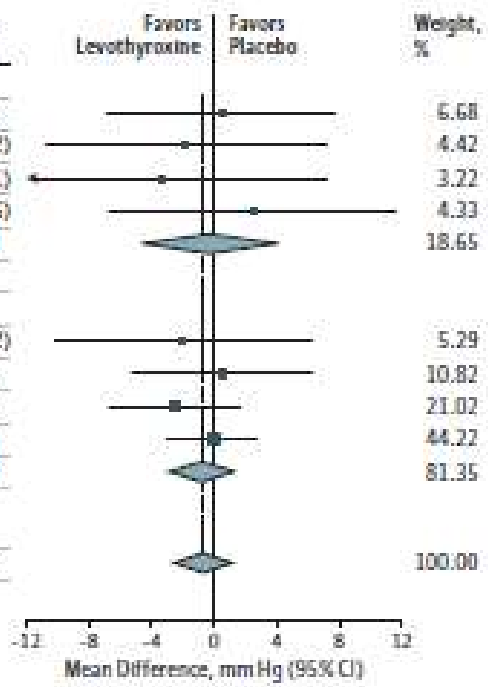


Figure 3. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Systolic Blood Pressure

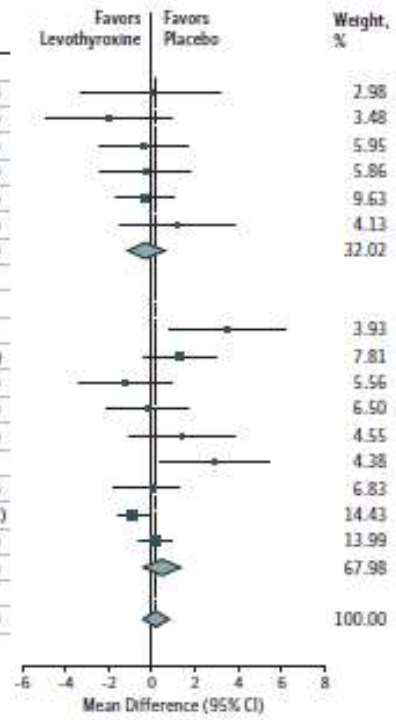
Source	No. of Participants		Systolic Blood Pressure, mm Hg (95% CI)		Mean Difference, mm Hg (95% CI)	Weight, %
	Levothyroxine	Placebo	Levothyroxine	Placebo		
After 3-6 mo of treatment						
Monzani et al,[33] 2001	10	10	117.3 (104.0-130.6)	116.8 (98.0-135.6)	0.5 (-6.8 to 7.8)	6.68
Razvi et al,[32] 2007	100	100	132.8 (88.1-177.5)	134.6 (89.7-179.5)	-1.8 (-10.8 to 7.2)	4.42
Nagasaki et al,[26] 2009	48	47	128.8 (77.6-180.0)	132.2 (81.0-183.4)	-3.4 (-13.9 to 7.1)	3.22
Ersoy et al,[29] 2012	30	30	131.7 (96.6-166.8)	129.2 (94.1-164.3)	2.5 (-6.6 to 11.6)	4.33
Subtotal					-0.3 (-4.6 to 4.1)	18.65
Overall effect: I^2 = 0.0%; P = .84						
After 12 mo of treatment						
Monzani et al,[34] 2004	23	22	112.0 (82.6-141.4)	114.0 (88.5-139.5)	-2.0 (-10.2 to 6.2)	5.29
Yazici et al,[35] 2004	23	22	123.6 (104.4-142.8)	123.1 (103.9-142.3)	0.5 (-5.2 to 6.2)	10.82
Zhao et al,[11] 2016	210	199	136.0 (96.6-175.5)	138.6 (99.7-177.4)	-2.5 (-6.6 to 1.6)	21.02
Stott et al,[12] 2017	318	320	138.3 (101.6-175.0)	138.4 (103.5-173.3)	-0.1 (-2.9 to 2.7)	44.22
Subtotal					-0.8 (-2.9 to 1.3)	81.35
Overall effect: I^2 = 0.0%; P = .75 Heterogeneity between groups: P = .83						
Overall					-0.7 (-2.6 to 1.2)	100.00
Overall effect: I^2 = 0.0%; P = .95						



Weights are derived from a fixed-effects meta-analysis of differences in blood pressure. Sizes of data markers indicate weight of studies. Dashed vertical line represents overall mean effect. Numbers differ between participants randomized and participants with available outcome data in the study by Stott et al[12] (see Table and eTable 2 in Supplement 1). The study by Razvi et al[32] is a crossover study that included 100 participants.

Figure 4. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Body Mass Index

Source	No. of Participants		Body Mass Index (95% CI)		Mean Difference (95% CI)	Weight, %
	Levothyroxine	Placebo	Levothyroxine	Placebo		
After 3-6 mo of treatment						
Monzani et al,[33] 2001	10	10	23.1 (13.9-32.3)	23.1 (18.8-27.4)	0.0 (-3.2 to 3.2)	2.98
Kong et al,[27] 2002	20	14	25.4 (19.1-31.7)	27.4 (17.8-37.0)	-2.0 (-4.9 to 0.9)	3.48
Caraccio et al,[38] 2005	12	11	22.3 (16.4-28.2)	22.7 (19.0-26.4)	-0.4 (-2.4 to 1.6)	5.95
Razvi et al,[32] 2007	100	100	28.1 (17.9-38.3)	28.4 (18.0-38.8)	-0.3 (-2.4 to 1.8)	5.86
Nagasaki et al,[36] 2009	48	47	21.8 (15.5-28.1)	22.1 (15.4-28.8)	-0.3 (-1.6 to 1.0)	9.63
Ersoy et al,[29] 2012	30	30	30.1 (18.3-41.9)	28.9 (20.7-37.1)	1.2 (-1.4 to 3.8)	4.13
Subtotal					-0.3 (-1.1 to 0.6)	32.02
Overall effect: I^2 = 0.0%; P = .76						
After 12 mo of treatment						
Cooper et al,[23] 1984	17	16	28.1 (22.9-33.3)	24.6 (15.0 -34.2)	3.5 (0.8 to 6.2)	3.93
Caraccio et al,[39] 2002	24	25	24.1 (18.0-30.2)	22.8 (17.5-28.1)	1.3 (-0.3 to 2.9)	7.81
Monzani et al,[34] 2004	23	22	23.7 (16.8-30.6)	24.9 (17.5-32.3)	-1.2 (-3.3 to 0.9)	5.56
Yazici et al,[35] 2004	23	22	22.8 (16.1-29.5)	23.0 (16.9-29.1)	-0.2 (-2.1 to 1.7)	6.50
Iqbal et al,[37] 2006	32	32	28.4 (17.0-39.8)	27.0 (19.0-35.0)	1.4 (-1.1 to 3.9)	4.55
Teixeira et al,[30] 2008	11	15	27.4 (21.1-33.7)	24.5 (18.0-31.0)	2.9 (0.4 to 5.4)	4.38
Cabral et al,[28] 2011	14	18	25.8 (21.3-30.2)	25.7 (19.8-31.6)	0.1 (-1.7 to 1.9)	6.83
Zhao et al,[11] 2016	210	159	25.8 (19.6-32.0)	26.7 (19.7-33.6)	-0.9 (-1.6 to -0.2)	14.43
Stott et al,[12] 2017	318	320	27.9 (17.9-37.9)	27.7 (18.7-36.7)	0.2 (-0.6 to 1.0)	13.99
Subtotal					0.5 (-0.4 to 1.3)	67.98
Overall effect: I^2 = 64.9%; P = .004						
Overall					0.2 (-0.4 to 0.8)	100.00
Overall effect: I^2 = 45.5%; P = .03						



Weights are derived from a random-effects meta-analysis of differences in body mass index (calculated as weight in kilograms divided by height in meters squared). Sizes of data markers indicate weight of studies. Dashed vertical line represents overall mean effect. Numbers differ between participants randomized and participants with available outcome data in the studies by Kong et al,[27] Teixeira et al,[30] and Stott et al[12] (see Table and eTable 2 in Supplement 1). The study by Razvi et al[32] is a crossover study that included 100 participants.

Table. Characteristics of 21 Included Randomized Clinical Trials on Thyroid Hormone Therapy for Subclinical Hypothyroidism in Adults

Source	Country	Funding Source	Definition of Subclinical Hypothyroidism	No. of Participants	Age, Mean (SD), y	Women, No. (%)	Intervention	Control	Planned Follow-up Duration, mo	Outcomes[a]	Hypothyroid Symptoms at Baseline, Intervention vs Control
Stott et al,[32] 2017	The Netherlands, Switzerland, United Kingdom, Ireland	Nonindustry	Thyrotropin 4.6-19.99 mIU/L on 2 occasions and normal free thyroxine	737	74 (6.3)	396 (54)	Levothyroxine	Placebo	≥12[b]	ThyPRO,[40] EQ-5D,[41] Letter-Digit Coding Test,[42] hand-grip strength, blood pressure, BMI, cardiovascular events, mortality, adverse effects[40]	ThyPRO hypothyroid symptom score: 17.5 (SD, 18.8) vs 16.9 (SD, 17.9)
Zhao et al,[11] 2016	China	Nonindustry	Thyrotropin 4.2-10.0 mIU/L and normal free thyroxine on 2 occasions	369	55 (7.6)	270 (73)	Levothyroxine	No intervention	15	Blood pressure, BMI	NR
Najafi et al,[24] 2015	Iran	Nonindustry	Thyrotropin >4.5 mIU/L, normal free thyroxine, and positive TPO-Ab	60	34 (10.0)	51 (85)	Levothyroxine	Placebo	3	BDI[43]	Mean number of hypothyroid symptoms per participant (range, 0-12): 4.8 vs 5.1
Ersoy et al,[29] 2012	Turkey	Not declared	Thyrotropin 5.0-10.0 mIU/L and normal free thyroxine	60	46 (13.1)	58 (97)	Levothyroxine	No intervention	6	Blood pressure, BMI	NR
Aghili et al,[25] 2012	Iran	Nonindustry	Thyrotropin >4.5 mIU/L, normal free thyroxine, and positive TPO-Ab	60	34 (10.8)	51 (85)	Levothyroxine	Placebo	3	Cognitive function (Wechsler memory scale[44])	Mean number of hypothyroid symptoms per participant (range, 0-7): 3.2 vs 3.7
Reuters et al,[31] 2012	Brazil	Not declared	Thyrotropin >4.0 mIU/L and normal free thyroxine on 2 occasions	71	50 (10.9)	62 (87)	Levothyroxine	Placebo	6	Zulewski score,[45] Short Form 36,[46] BDI,[43] quadriceps strength	Zulewski score (only change from baseline reported)
Cabral et al,[28] 2011	Brazil	Not declared	Thyrotropin >4 mIU/L and normal free thyroxine on 2 occasions	32	46 (9.0)	32 (100)	Levothyroxine	No intervention	12	BMI[c]	NR
Parle et al,[16] 2010	United Kingdom	Nonindustry	Thyrotropin >5.5 mIU/L and normal free thyroxine	94	74 (5.8)	57 (61)	Thyroxine	Placebo	12	HADS,[47] cognitive function (MMSE,[48] MEAMS,[49] SCOLP,[50] and Trail Making Test[51])	NR
Nagasaki et al,[36] 2009	Japan	Nonindustry	Increased thyrotropin and normal free triiodothyronine/free thyroxine	95	65 (19.3)	95 (100)	Levothyroxine	Placebo	5	Blood pressure, BMI	NR
Teixeira et al,[30] 2008	Brazil	Industry supported	Thyrotropin >4 mIU/L and normal free thyroxine on ≥2 occasions	60	48 (10.5)	57 (95)	Levothyroxine	Placebo	12	BMI	NR
Razvi et al,[32] 2007	United Kingdom	Nonindustry	Thyrotropin >4 mIU/L and normal free thyroxine on ≥2 occasions	100	54 (12.6)	82 (82)	Levothyroxine	Placebo	3	ThyDQoL,[52] blood pressure, BMI[c]	ThyDQoL (only change from baseline reported)
Jorde et al,[26] 2006	Norway	Nonindustry	Thyrotropin 3.5-10 mIU/L	69	62 (11.9)	32 (46)	Thyroxine	Placebo	12	GHQ-30,[53] BDI,[43] composite cognitive score[26]	Mean number of hypothyroid symptoms per participant (range, 0-19): 4.0 vs 4.0

(continued)

Table. Characteristics of 21 Included Randomized Clinical Trials on Thyroid Hormone Therapy for Subclinical Hypothyroidism in Adults (continued)

Source	Country	Funding Source	Definition of Subclinical Hypothyroidism	No. of Participants	Age, Mean (SD), y	Women, No. (%)	Intervention	Control	Planned Follow-up Duration, mo	Outcomes[a]	Hypothyroid Symptoms at Baseline, Intervention vs Control
Iqbal et al,[37] 2006	Norway	Nonindustry	Thyrotropin 3.5-10 mIU/L on 2 occasions and normal free triiodothyronine/free thyroxine	64	64 (12.2)	31 (48)	Thyroxine	Placebo	12	BMI	NR
Caraccio et al,[38] 2005	Italy	Nonindustry	Thyrotropin >3.6 mIU/L and normal free triiodothyronine	23	32 (9.6)	21 (91)	Levothyroxine	Placebo	6	BMI	NR
Yazici et al,[35] 2004	Turkey	Not declared	Increased thyrotropin and normal free triiodothyronine/free thyroxine	45	40 (7.9)	38 (84)	Levothyroxine	Placebo	12	Blood pressure, BMI	NR
Monzani et al,[34] 2004	Italy	Not declared	Thyrotropin >3.6 mIU/L	45	37 (11.0)	37 (82)	Levothyroxine	Placebo	6	Blood pressure, BMI	NR
Kong et al,[27] 2002	United Kingdom	Not declared	Thyrotropin 5-10 mIU/L and normal free thyroxine	40	50 (15.2)	40 (100)	Thyroxine	Placebo	6	GHQ-30,[53] HADS,[47] BMI	Overall, 33/40 (83%) reported fatigue and 32/40 (80%) reported weight gain
Caraccio et al,[39] 2002	Italy	Nonindustry	Thyrotropin >3.6 mIU/L on 2 occasions and positive TPO-Ab	49	35 (9.1)	42 (86)	Levothyroxine	Placebo	6	BMI	NR
Monzani et al,[33] 2001	Italy	Not declared	Thyrotropin >3.6 mIU/L for >1 y and normal free thyroxine	20	32 (12.1)	18 (90)	Levothyroxine	Placebo	6	Blood pressure, BMI	NR
Meier et al,[22] 2001	Switzerland	Nonindustry and industry supported[d]	Thyrotropin >5 mIU/L on 2 consecutive blood tests and normal free thyroxine	66	57 (10.6)	66 (100)	Levothyroxine	Placebo	12	Billewicz score[54,e]	Billewicz score: −25.7 (SD, 5.2) vs −28.3 (SD, 14.1)
Cooper et al,[23] 1984	United States	Nonindustry	Increased thyrotropin and normal free triiodothyronine/free thyroxine	33	54 (10.1)	32 (97)	Levothyroxine	Placebo	12	BMI	Mean number of hypothyroid symptoms per participant (range, 0-6): 2.1 vs 2.4

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; EQ-5D, Euro Quality of Life 5 Dimensions Questionnaire; GHQ-30, General Health Questionnaire (30 items); HADS, Hospital Anxiety and Depression Scale; MEAMS, Middlesex Elderly Assessment of Mental State; MMSE, Mini Mental State Examination; NR, not reported; SCOLP, Speed and Capacity of Language Processing Test; ThyDQoL, 18-Item Underactive Thyroid-Dependent Quality of Life; ThyPRO, Thyroid-Related Quality-of-Life Patient-Reported Outcome Measure (hypothyroid score: 4 items; range, 0-100; higher scores indicate more hypothyroid symptoms; tiredness score: 7 items); TPO-Ab, thyroid peroxidase antibody.

[a] Only outcomes relevant to this systematic review are listed; ie, outcomes that were included in the study protocol and published in the PROSPERO database.

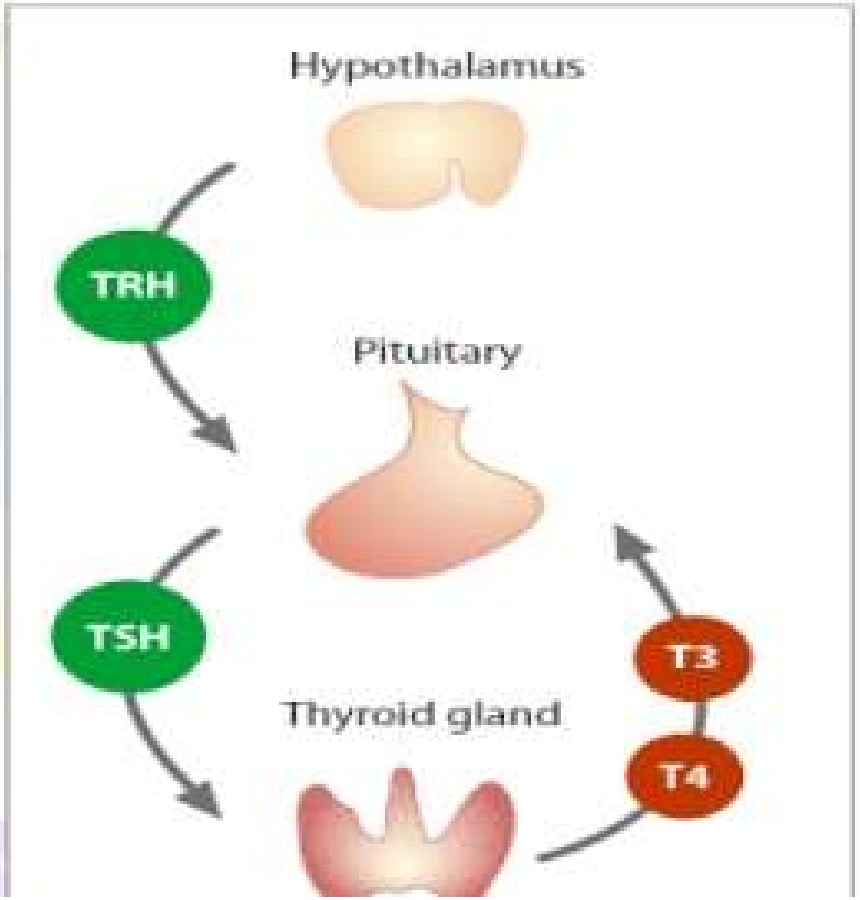
[b] The Letter-Digit Coding Test outcome was available after 18 months of levothyroxine or placebo intervention; the other outcomes after 12 months.

[c] Data obtained through direct communication with author.

[d] This work was supported by the Swiss Research Foundation and by unconditional research grants from Henning Berlin, Sandoz Research, and Roche Research Foundations.

[e] Billewicz score ranges from −47 to 67; higher scores indicate worse hypothyroid symptoms.

Thyroid physiology



- > 99% of T4 and T3 is bound to TBG, TBPA and albumin
- 80% of T3 comes from T4
- 0.3% of T3 and 0.02% of T4 are free
- fT3 : metabolically active hormone

Clinical Outcomes

SUBJECTIVE OUTCOMES

OBJECTIVE OUTCOMES

WHO Burnout

- **Burn-out an "occupational phenomenon": International Classification of Diseases**
- Burn-out is included in the 11th Revision of the International Classification of Diseases (ICD-11) as an occupational phenomenon. It is **not**classified as a medical condition.
- It is described in the chapter: ‘Factors influencing health status or contact with health services’ – which includes reasons for which people contact health services but that are not classed as illnesses or health conditions

Burn-out is defined in ICD-11 as follows:

“Burn-out is a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed. It is characterized by three dimensions:

- feelings of energy depletion or exhaustion;
- increased mental distance from one’s job, or feelings of negativism or cynicism related to one's job; and
- reduced professional efficacy.

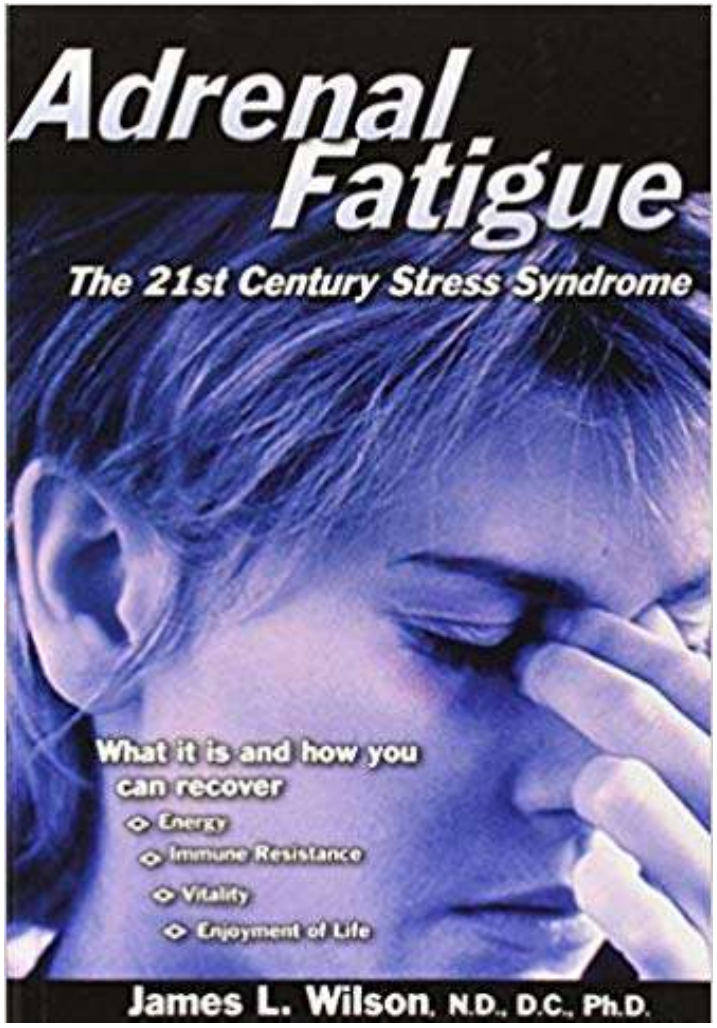
Burn-out refers specifically to phenomena in the occupational context and should not be applied to describe experiences in other areas of life.”

Burn-out was also included in ICD-10, in the same category as in ICD-11, but the definition is now more detailed.

The World Health Organization is about to embark on the development of evidence-based guidelines on mental well-being in the workplace.

Adrenal Fatigue

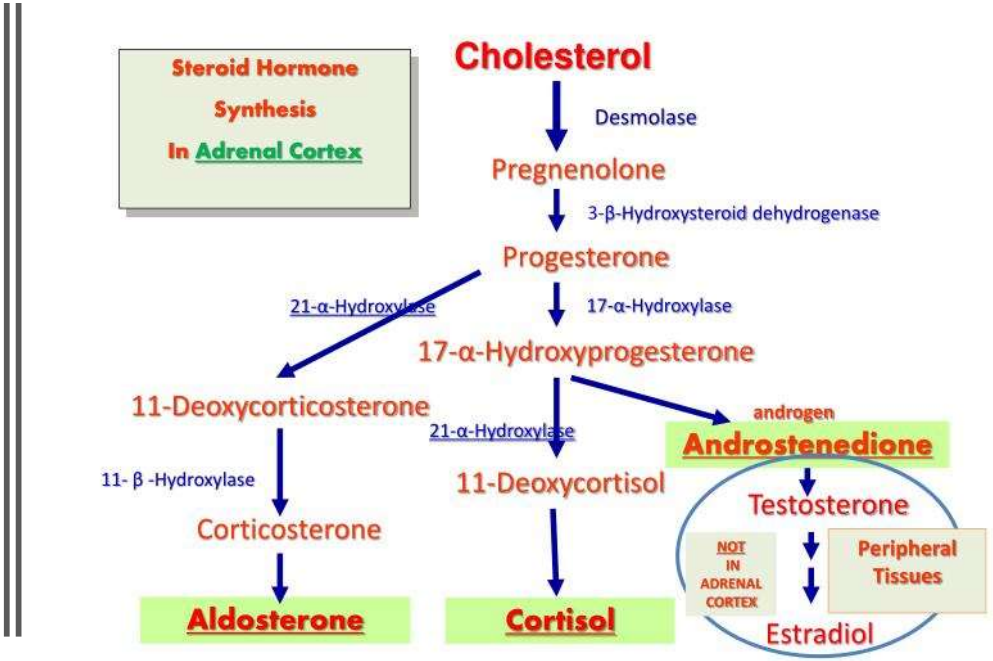
The 21st Century Stress Sydrome



Adrenal Dysfunction

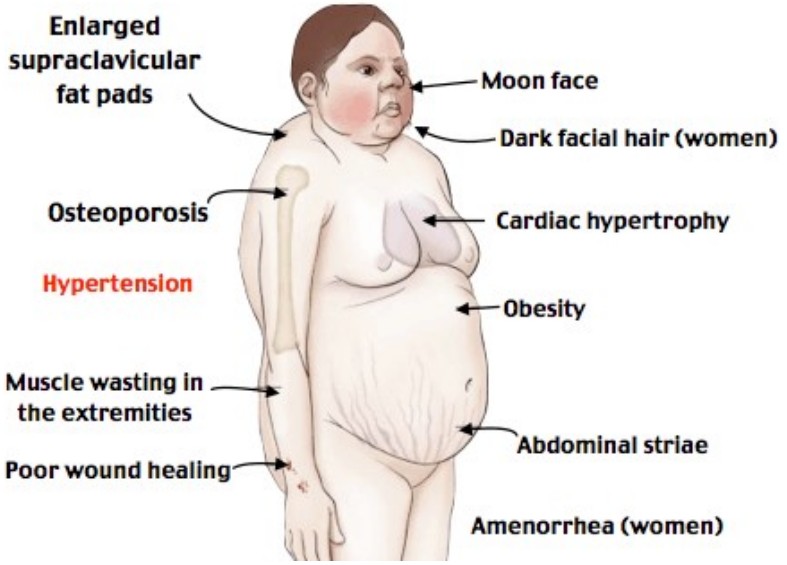
Adrenal Fatigue Symptoms

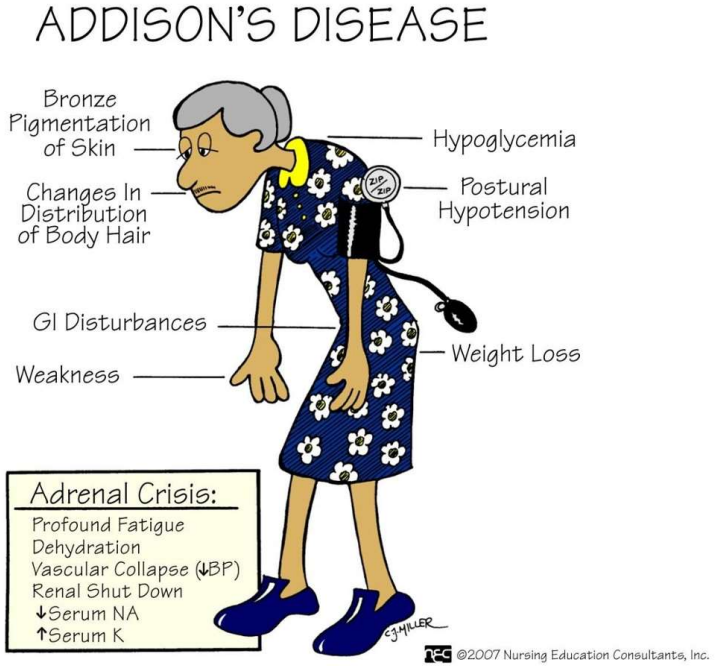
Excessive fatigue and exhaustion, chronic fatigue
Non-refreshing sleep
Sleep disturbance, insomnia
Feeling overwhelmed or unable to cope
craving salty and/or sweet foods
Sensitivity to light
Low stamina and slow to recover from exercise
Slow to recover from injury or illness
Difficulty concentrating, brain fog
Poor digestion
Irritable bowel syndrome,
IBS Low immune function
premenstrual syndrome
Menopause symptoms
Low blood pressure
Sensitivity to cold



Hydrocortisone therapy

↳ Due to **excess cortisol-like medication** (prednisone) or **tumor** that produces or results in production of **excessive cortisol**
[Cases due to a pituitary adenoma = Cushing's disease]





Non-specific/Vague Symptoms

- Fatigue
- Obesity
- Aging face
- Insomnia
- Stress intolerance
- Poor performance
- Depression
- Anxiety
- Multiple Allergy
- Allergic skin conditions
- Auto-immune disorders
- NCDs
- Metabolic X Syndrome
- Cancers
- Etc.

Basic knowledge of Health Intervention

- Nutrition
- Dietary Supplements
- Sleep
- Stress
- Exercise
- Mind-Body-Spirit
- Pollutions: Water, Air, Home, etc.
- Toxins
- Detoxification
- Immune Function
- Inflammation
- Hormone
- Neurotransmitters
- Stem cells

Evidence-Based Medicine

Clinical Pathophysiology

- Anatomy & Histology
- Physiology & Biochemistry
- Pathology

- Diseases (Diagnosis, Therapy, Protocol, Pharmacology) ??

Clinical Epidemiology

- Research Methodology
- Clinical Statistics

“A good physician treats the disease; the great physician treats the patient who has the disease.”

Conclusions

- Treatment & Prevention may have the same purpose, but each one do not have the same concept.
- RCTs may be not all the answer for customized the intervention for each patient.
- Many papers nowadays is increasing with complicated data.
- Is this the time to learn and understanding the advanced knowledge of Research Methodology and Clinical Statistics.

Prof. Jayanton Patumanond, MD., Ph.D.

Clinical Research Methodology & Analysis

CRMA

Certificate in Clinical Research Methodology & Analysis

DPU
DHURAKIJ PUNDIT UNIVERSITY
มหาวิทยาลัยธุรกิจบัณฑิตย์

RCR NetS

Date	Topics	Date	Topics
25 Jan 2020 26 Jan 2020	Essential clinical epidemiology and concept of clinical research design Clinical measurements and clinical statistics From basic to advanced analysis (Stata®)	22 Aug 2020 23 Aug 2020	Prognostic prediction models Time-to-event prediction: Beyond Cox's model: Flexible parametric prediction (stpm2)
22 Feb 2020 23 Feb 2020	Diagnostic research: types and variants Diagnostic indices Analysis of diagnostic research	26 Sep 2020 27 Sep 2020	Therapeutic research design and analysis Randomized controlled trial Other clinical trial variants
28 Mar 2020 29 Mar 2020	Diagnostic prediction research Development and analysis of diagnostic risk scoring	24 Oct 2020 25 Oct 2020	Non-randomized therapeutic research design and analysis Propensity score methods for clinicians
23 May 2020 24 May 2020	Causal inference and covariate adjustment Classical and novel etiognostic research Analysis of etiognostic research	7 Nov 2020 8 Nov 2020	Advanced statistical analysis I Analysis of repeated measurements and correlated data
27 Jun 2020 28 Jun 2020	Prognostic research: PROGRESS group Basic survival analysis Analysis of prognostic research	26 Dec 2020 27 Dec 2020	Advanced statistical analysis II Complex survival analysis for correlated data and competing time-to-event

Place: มหาวิทยาลัยธุรกิจบัณฑิตย์
Available: ลงทะเบียน: 30 ที่นั่ง
Applicants:มีค่าลงทะเบียน: หลักสูตรละ 5,000 บาท (ข้าราชการ/รัฐวิสาหกิจ เบิกได้ตามสิทธิ์)
Program: โปรแกรมสถิติ: Stata®15.1 (มีลิขสิทธิ์ถูกต้องตามกฎหมาย)
Computer: โปรดนำคอมพิวเตอร์ส่วนตัว (notebook) มาด้วย

Early bird: 4,000 บาท

เข้าครบ 9 ครั้ง ฟรี 1 ครั้ง

2.5 Eggs/day →Prostate cancer risks 81%

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232297/

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PMID: 21930800

Egg, red meat, and poultry intake and risk of lethal prostate cancer in the prostate specific antigen-era: incidence and survival

Erin L. Richman,[1,2,3] Stacey A. Kenfield,[1,4] Meir J. Stampfer,[1,2,4] Edward L. Giovannucci,[1,2,4] and June M. Chan[3,5]

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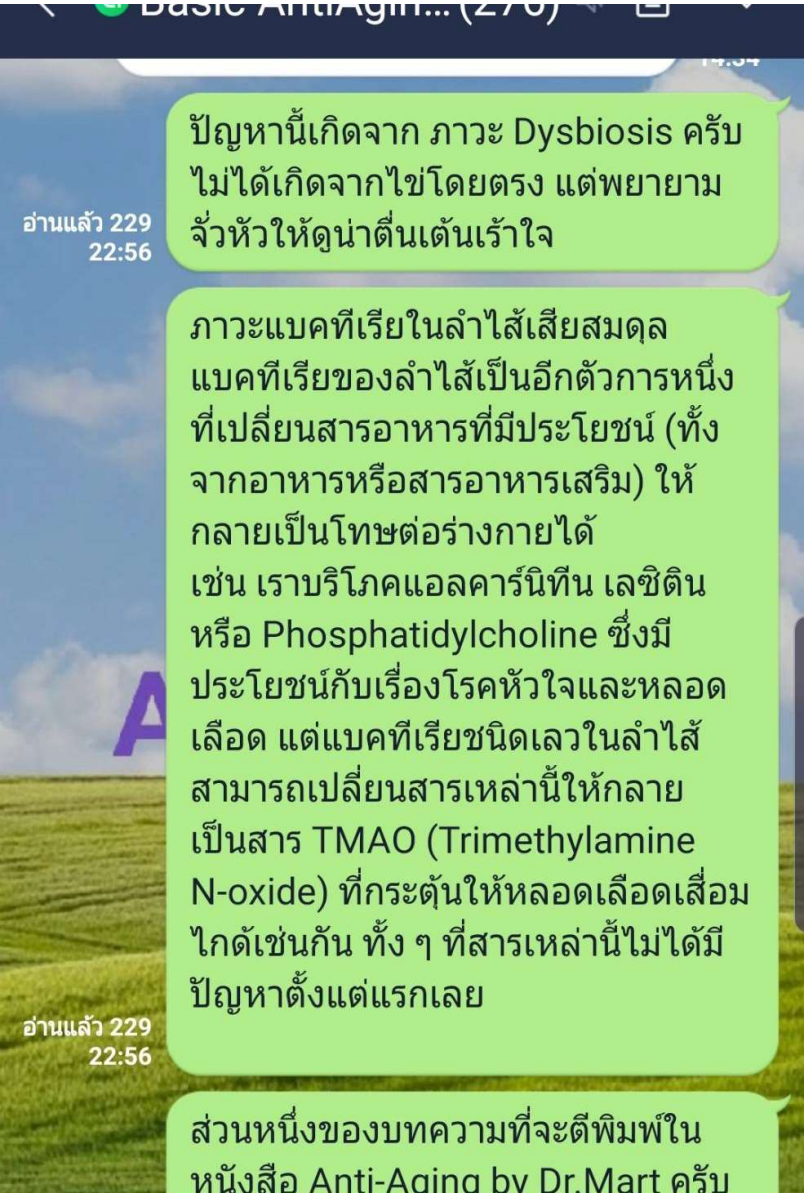
Abstract Go to:

Red and processed meat may increase risk of advanced prostate cancer. Data on post-diagnostic diet and prostate cancer are sparse, but post-diagnostic intake of poultry with skin and eggs may increase risk of disease progression. Therefore, we prospectively examined total, unprocessed, and processed red meat, poultry, and eggs in relation to risk of lethal prostate cancer (e.g. men without cancer at baseline who developed distant organ metastases or died from prostate cancer during follow-up) among 27, 607 men followed from 1994–2008. We also performed a case-only survival analysis to examine post-diagnostic consumption of these foods and risk of lethal prostate cancer among the 3,127 men initially diagnosed with non-metastatic prostate cancer during follow-up. In the incidence analysis, we observed 199 events during 306,715 person-years. Men who consumed 2.5 or more eggs per week had an 81% increased risk of lethal prostate cancer compared to men who consumed less than 0.5 eggs per week (HR: 1.81; 95% confidence interval (CI): 1.13, 2.89; *p*-trend: 0.01). In the case-only survival analysis, we observed 123 events during 19,354 person-years. There were suggestive, but not statistically significant, positive associations between post-diagnostic poultry (HR ≥3.5 vs. <1.5 servings per week: 1.69; 95%CI: 0.96, 2.99; *p*-trend: 0.07) and post-diagnostic processed red meat (HR ≥3 vs. <0.5 servings per week: 1.45; 95%CI: 0.73, 2.87; *p*-trend: 0.08) and risk of progression of localized prostate cancer to lethal disease. In conclusion, consumption of eggs may increase risk of developing a lethal-form of prostate cancer among healthy men.

Keywords: Eggs, red meat, poultry, prostate cancer, survival



- Eggs → Lecithin (Phosphatidyl choline) → TMAO
- Dysbiosis

10 foods is harmful for kidney!!