Is It Medical, Psychiatric or a Little of Both?

Sarah K Rivelli, MD, FACP
Assistant Professor of Psychiatry and Behavioral Sciences
Assistant Professor of Medicine
Duke University Medical Center

“I feel so weak and tired”

- 62 yo AA female presents for refractory depression x 4years
- Complains of fatigue, weakness, depressed mood, poor concentration, insomnia
  - “I feel tired all the time and I can’t do anything!”
- Unemployed
- Husband ill w/prostate cancer

History

- Medical Hx
  - HTN
  - DM2, insulin dependent (HbA1C 8.2%)
  - Obesity (BMI 32)
  - Asthma
  - Breast cancer 2006
  - Chronic back pain
  - Right Knee OA
  - Peripheral neuropathy
  - Fibromyalgia

- Psych Hx
  - MDD recurrent
  - No hospitalizations
  - Outpatient therapy and meds x 2 years
  - No substance misuse

Current Medications

- Effexor 225 mg po qd
- Trazodone 50mg po qhs
- Gabapentin 600 mg q8h
- Insulin
- Metformin
- Lisinopril
- HCTZ
- Simvastatin
- Pantoprazole
- Fluticasone inh
- Albuterol inh prn
- Naprosyn
- Acetaminophen +diphenhydramine prn

What laboratory test might be the most high yield in this clinical situation?

Cyanocobalamin level (vit B12)

Thyroid stimulating hormone (TSH) level

Hemoglobin

Hemoglobin A1C

Vitamin D level

Which of her medical conditions might be related to vitamin d deficiency?

Hypertension

Obesity

Breast cancer

Knee arthritis

Pain

Depression

Clinical Importance of Vitamin D

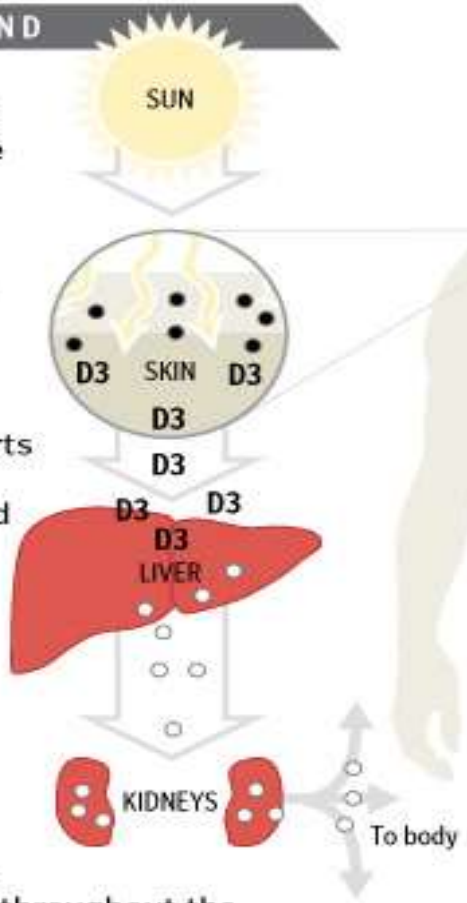
- Bone homeostasis
- Muscle function
- Cancer risk
- Autoimmune disorders
- Cardiovascular risk
- Metabolic syndrome
- Neuropsychiatric

THE SUN AND VITAMIN D

1 **Ultraviolet-B rays** convert a derivative of cholesterol — already present in the **skin** — into Vitamin D3, which then travels to the liver.

2 The **liver** converts Vitamin D3 to another form called 25-hydroxy-Vitamin D, which is what doctors measure in the blood.

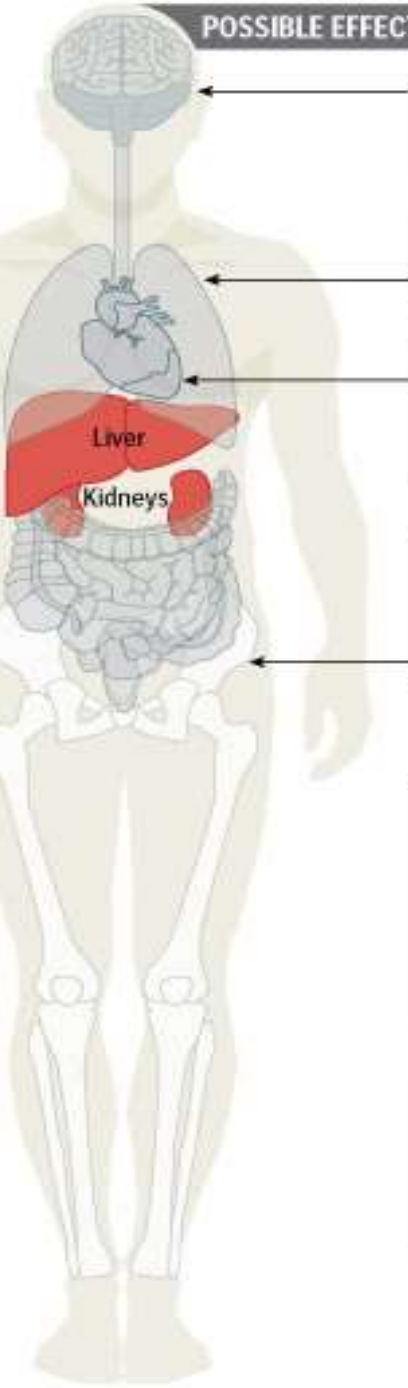
3 The **kidneys** convert this form to the final active hormone that may have many effects throughout the body, including enabling calcium absorption in the intestines.



OTHER SOURCES OF VITAMIN D

Vitamin D3 can be found in fortified milk, some foods and supplements. Ingested this way, the Vitamin D3 makes its way to the liver and is converted, just like skin-produced Vitamin D3. But some scientists say current recommendations for daily Vitamin D intake are inadequate.

POSSIBLE EFFECTS OF VITAMIN D DEFICIENCY



Brain
- Schizophrenia
- Depression

Lungs
- Asthma
- Wheezing

Circulatory
- High blood pressure
- Coronary heart disease
- Stroke

Muscles/bones
- Muscle weakness, aches
- Rickets
- Osteoporosis
- Osteomalacia (soft bones)

Immune System
- Type 1 diabetes
- Multiple sclerosis
- Rheumatoid arthritis
- Weakened response to fight turberculosis, influenza and other infectious diseases

Cancer
Possibly associated with a variety of cancers, including colon, breast, prostate and ovarian

Groups at high risk for deficiency

- Elderly
- Institutionalized
- Dark skinned
- Limited effective sun exposure
- Obese
- Hospitalized
- Pregnant women
- Malabsorption
- Taking medications that accelerate the metabolism of vitamin D (phenytoin)
- Alcoholics




Prevalence

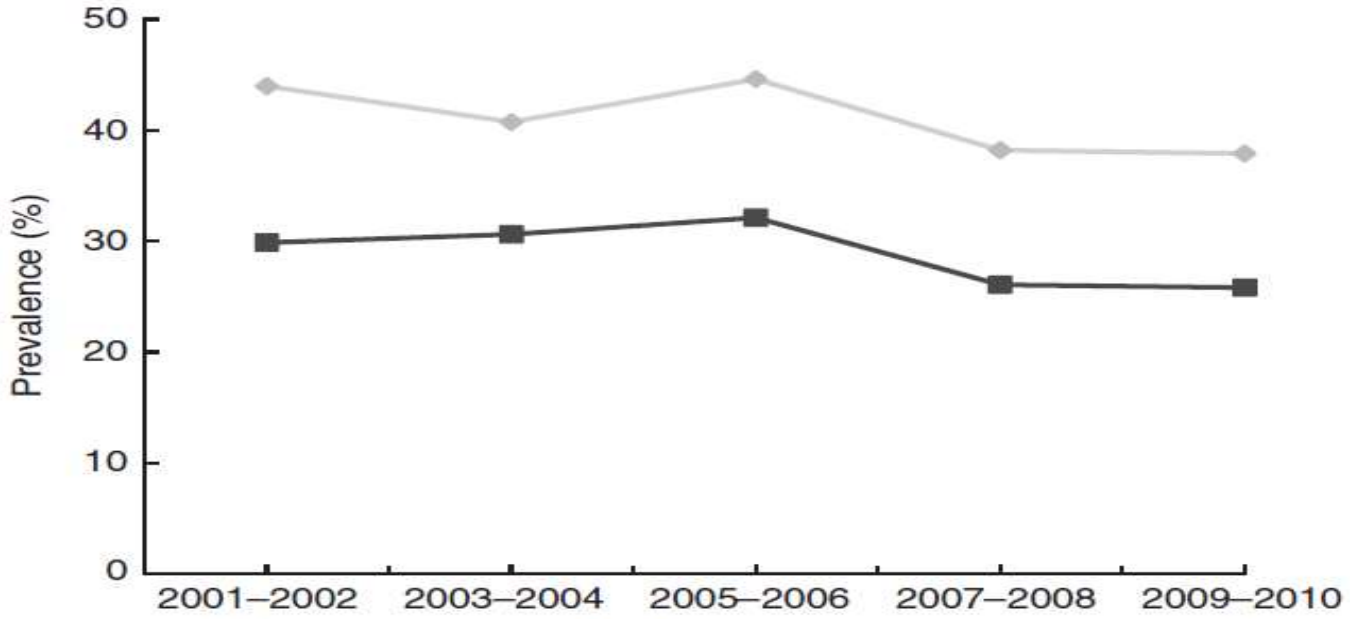


Fig. 1. Trends in the prevalence of vitamin D deficiency (—■—) and insufficiency (—◆—) among adults ≥18 years in the National Health and Nutrition Examination Survey 2001–2010 (vitamin D deficiency was defined as 25-hydroxyvitamin D (25(OH)D) < 50 nmol/l and vitamin D insufficiency was defined as 50 ≤ 25(OH)D < 75 nmol/l).

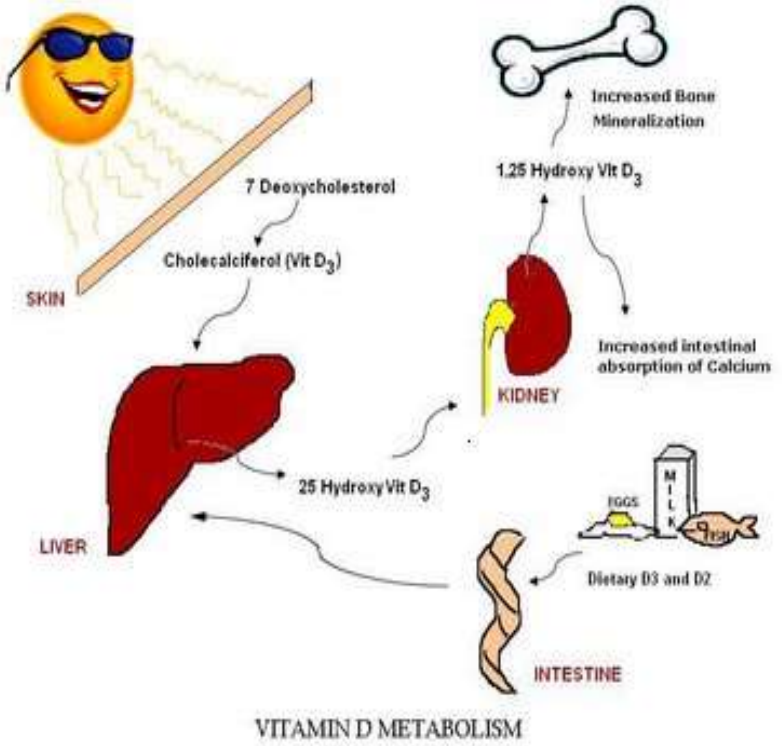
Deficiency higher among elderly, obese, dark-skinned, poor, less education, physically inactive, smokers, chronic diseases

British Journal of Nutrition (2018), 119, 928–936

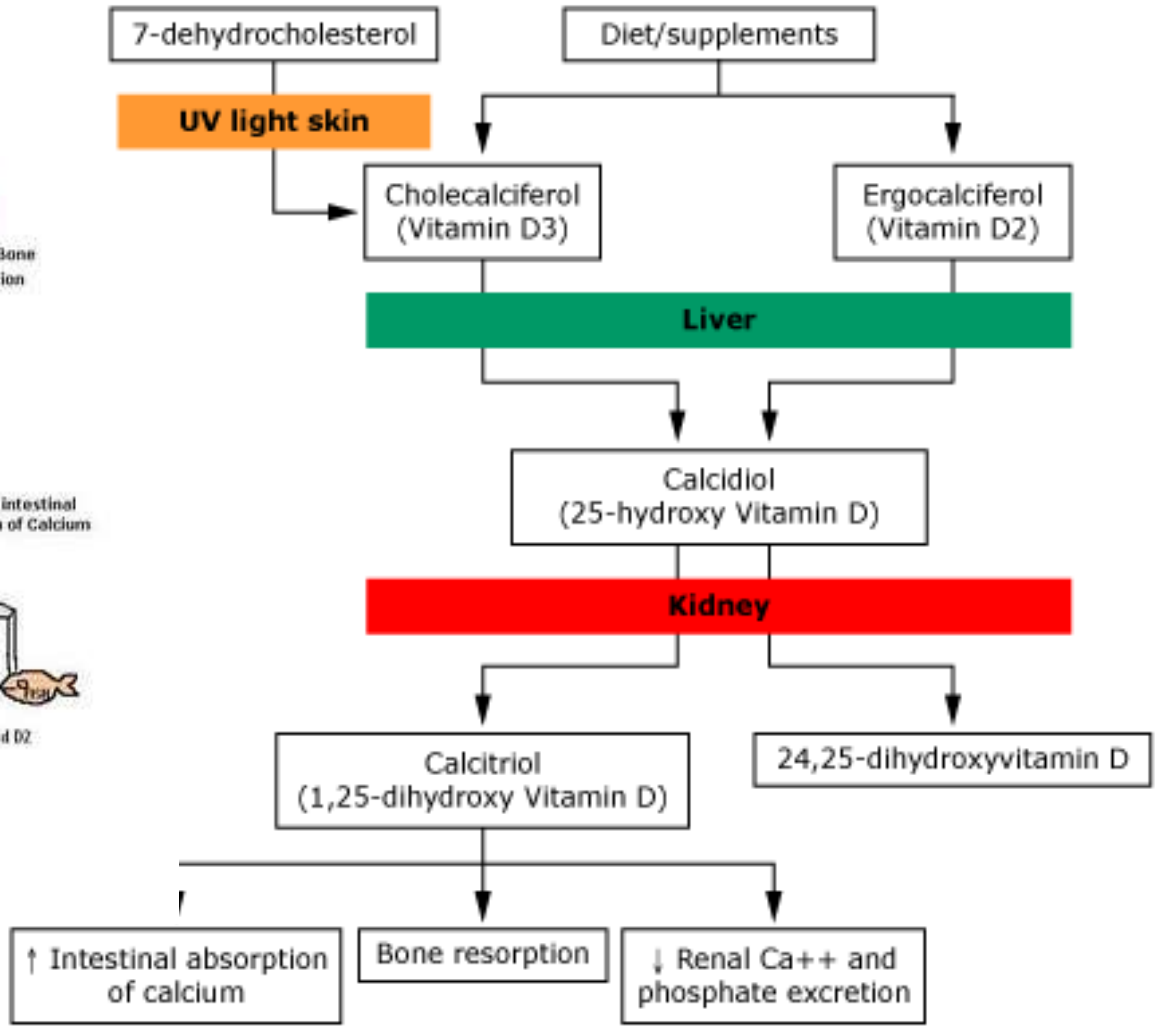
Prevalence varies by race

	Insufficiency (50 ≤ 25(OH)D < 75 nmol/l)			Deficiency (25(OH)D < 50 nmol/l)		
Characteristics	Prevalence	95 % CI	Count (*n*)	Prevalence	95 % CI	Count (*n*)
Race/ethnicity						
Non-Hispanic white	43·6	42·3, 44·9	5485	18·6	17·0, 20·3	2494
Non-Hispanic black	22·6	20·2, 25·0	1179	71·9	68·9, 74·9	3680
Hispanic	43·7	41·5, 45·9	2951	42·8	39·4, 46·1	3081
Other race	38·8	35·1, 42·4	432	46·1	41·8, 50·5	509

Pathways of vitamin D synthesis



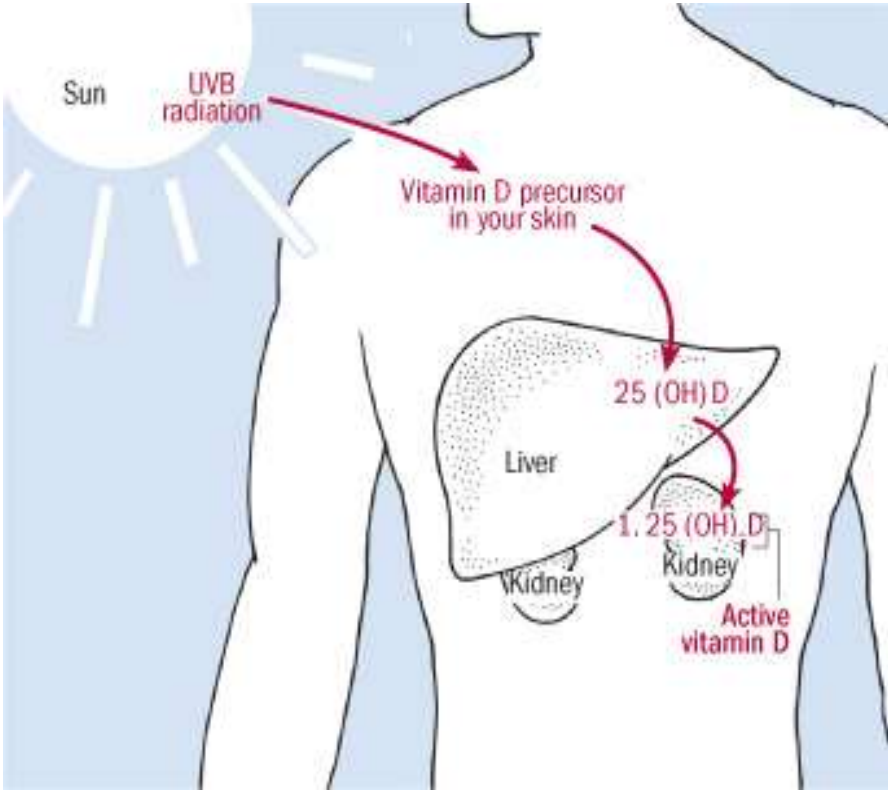
VITAMIN D METABOLISM



Metabolic activation of vitamin D to calcitriol and its effects on calcium and phosphate homeostasis. The result is an increase in the serum calcium and phosphate concentrations.

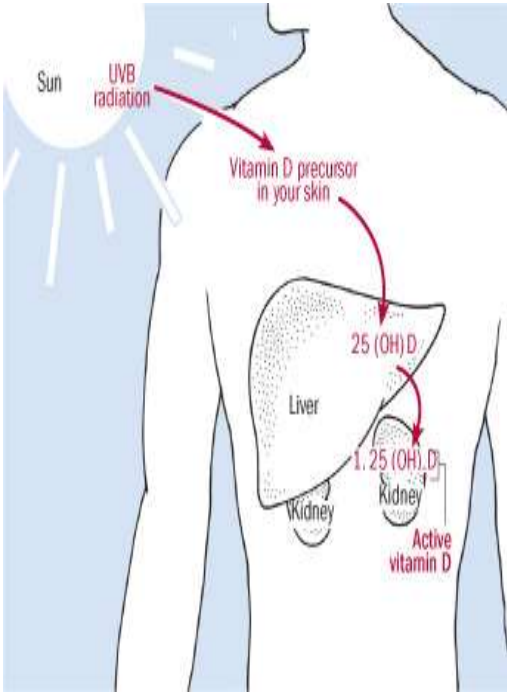
Causes of vitamin D deficiency or resistance

- Deficient Intake or absorption
  - Inadequate sunlight exposure
  - Inadequate intake
  - Malabsorption
  - Gastrectomy
  - Small bowel disease
  - Pancreatic insufficiency



Causes of vitamin D deficiency or resistance

- Defective 25-hydroxylation
  - Biliary cirrhosis
  - Alcoholic cirrhosis
  - Anticonvulsants
- Loss of Vit D binding protein
  - Nephrotic syndrome
- Defective 1-alpha 25-hydroxylation
  - Hypoparathyroidism
  - Renal failure



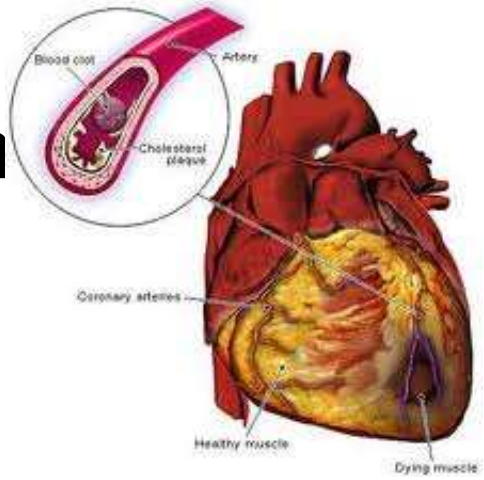
Hypertension

- Blood Pressure tends to be higher in winter
- Blood Pressure is higher with increasing latitude
- Blood Pressure is higher among people with darker skin pigmentation
- BP is reduced significantly by ultraviolet radiation comparable to about oral intake of 3,000 IU of vitamin D a day
- Low 25(OH)D associated with incident hypertension

Kraus R, 1998;352:709-710
Pfeifer 2001;86(4):258

Heart Disease

- Low 25OHVitD predicts incident CAD over 5.4 yrs
  - < 10 ng/ml: 80% increased risk of cardiovascular incident
  - 10-15 ng/m: 53% increased risk
- Risk of MI risk double in pts with 25OHVitD levels < 34ng/ml
- CHF pts have lower 25OHVitD levels than controls
- Deaths from CAD more common in winter



Wang TJ *Circulation* 2008;117:503-511.
Scragg *Int J Epidemiol.* 1990;19(3):559
Zitterman *J Am Coll Cardiol.* 2003;41:105

Obesity

Low 25OH predicts obesity

Mai, *Epidemiology* 2012

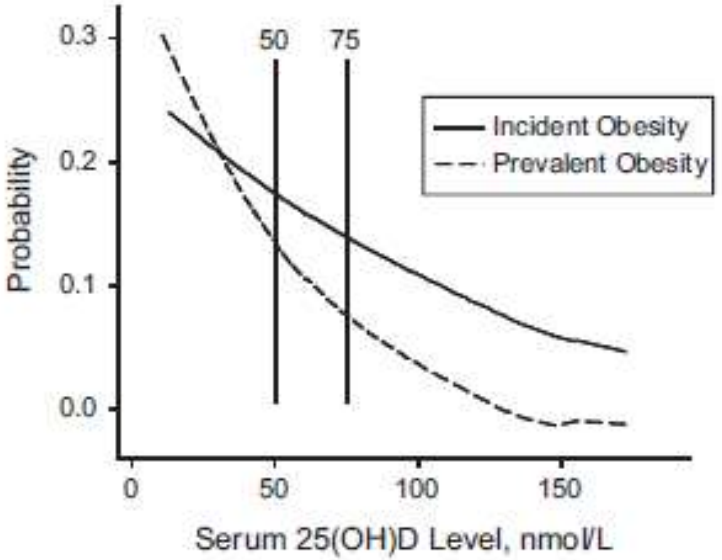


Table 3. Association of Baseline Serum 25-Hydroxyvitamin D Level With Prevalent Obesity at Baseline and Incident Obesity During Follow-up, With Obesity Defined by Body Mass Index,[a] Nord-Trøndelag Health Study, 1995–1997 to 2006–2008

25-Hydroxyvitamin D Level, nmol/L	No. of Participants	No. of Cases	%	Crude OR	95% CI	Adjusted[b] OR	95% CI
Prevalent Obesity at Baseline (n = 2,460)							
≥75.0	565	27	4.8	1.00	Referent	1.00	Referent
50.0–74.9	922	97	10.5	2.34	1.51, 3.64	2.19	1.40, 3.41
<50.0	973	171	17.6	4.25	2.79, 6.47	3.96	2.58, 6.08
Incident Obesity During Follow-up (n = 2,165)							
≥75.0	538	58	10.8	1.00	Referent	1.00	Referent
50.0–74.9	825	122	14.8	1.44	1.03, 2.00	1.38	0.99, 1.94
<50.0	802	147	18.3	1.86	1.34, 2.57	1.73	1.24, 2.41

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Obesity was defined as body mass index (weight (kg)/height $(m)^2$) ≥30.

[b] Multivariable logistic regression model including sex, age, smoking, education, physical activity, social benefits, and economic difficulties at baseline.

Muscle weakness

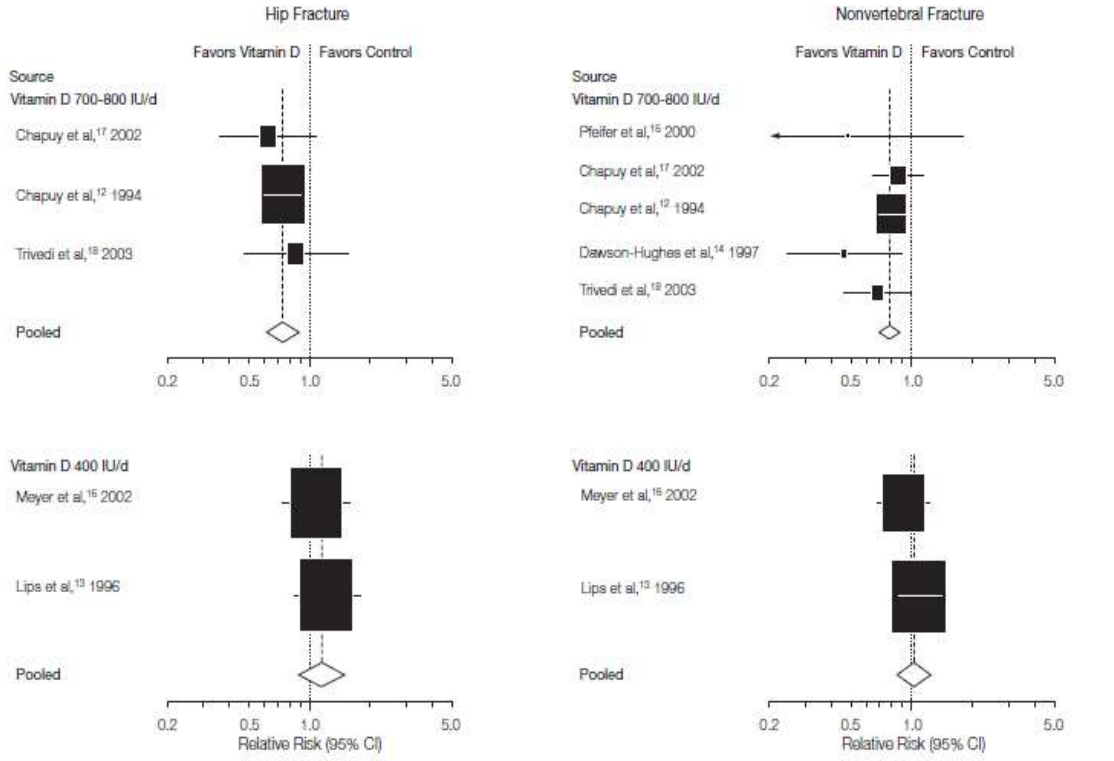
- VDRs in skeletal muscle
- Vitamin D deficiency impacts weight-bearing muscles of the lower limb, which are necessary for postural balance and walking
- Significant inverse correlation between serum 25(OH)D3 concentration and falls in elderly
- Vitamin D supp in deficient pts improves weakness
- Vitamin D supplementation reduces falls by up to 20%

Glerup H et al. Calcif Tissue Int 2000;66:419.
Stein MS et al. J Am Geriatr Soc 1999;47:1195
Dawson-Hughes et al. N Engl J Med 1997;337:670

Fracture Prevention

Need at least 700-800IU daily
26% reduction in hip fx; 23% reduction in nonvertebral fx
400 IU did not significantly prevent fracture

Figure 2. Forest Plots Comparing the Risk of Hip and Nonvertebral Fractures Between Vitamin D (700-800 IU/d and 400 IU/d) and Control Groups



Squares represent relative risks (RRs) and size of squares is proportional to the size of the trials. Error bars represent 95% confidence intervals (CIs). Trials are sorted by trial duration ranging from 24 to 60 months for hip fracture and 12 to 60 months for nonvertebral fracture. For 3 trials with hip fractures,[12,17,18] which included 5572 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.74 (95% CI, 0.61-0.88; Q test $P=.74$). For 5 trials with nonvertebral fractures,[12,14,15,17,18] which included 6098 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.77 (95% CI, 0.68-0.87; Q test $P=.41$). For the 2 trials,[13,16] with a vitamin D dose of 400 IU/d, trial duration ranged from 24 months to 36 to 41 months.

Pain

- Diabetic neuropathy improves with vitamin D supplementation
  - Deficiency lowers pain threshold, worsens nerve damage
- Persistent, nonspecific musculoskeletal pain
  - 93% with Vitamin D deficiency
- Low Back Pain
  - 83% with Vitamin D deficiency
    - Supplementation 5000-10,000iu/d decreases need for pain medication after 3 months
- Statin induced myalgias

Plotnikoff. Mayo Clin Proc. 2003;78(12):1463
Al Faraj. Spine 2003;28(2):177

Deficiency likely with severe pain

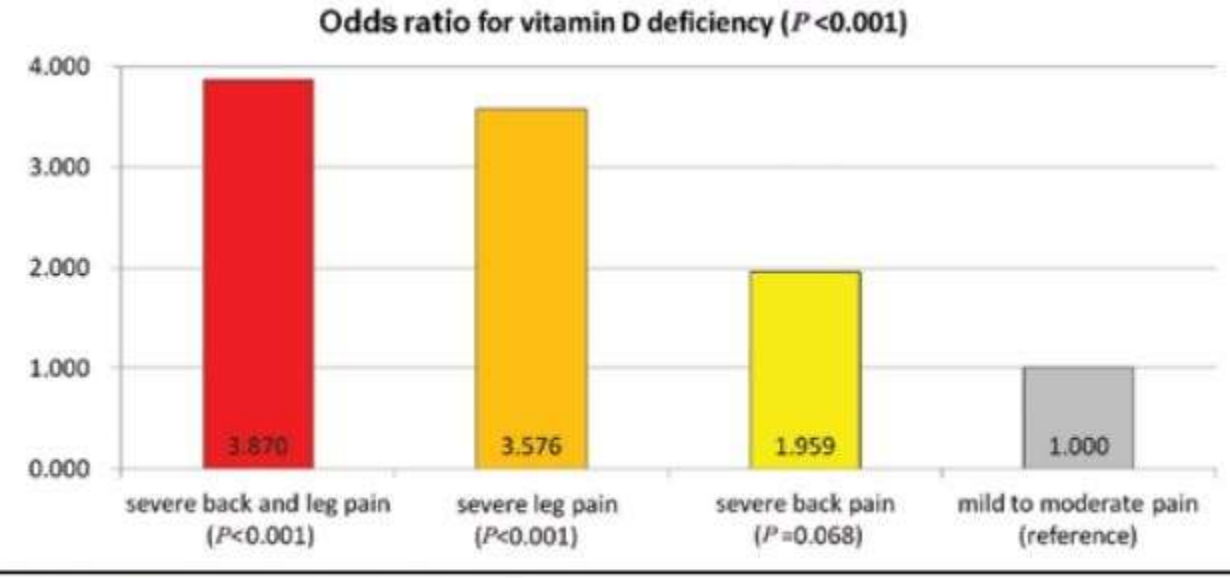


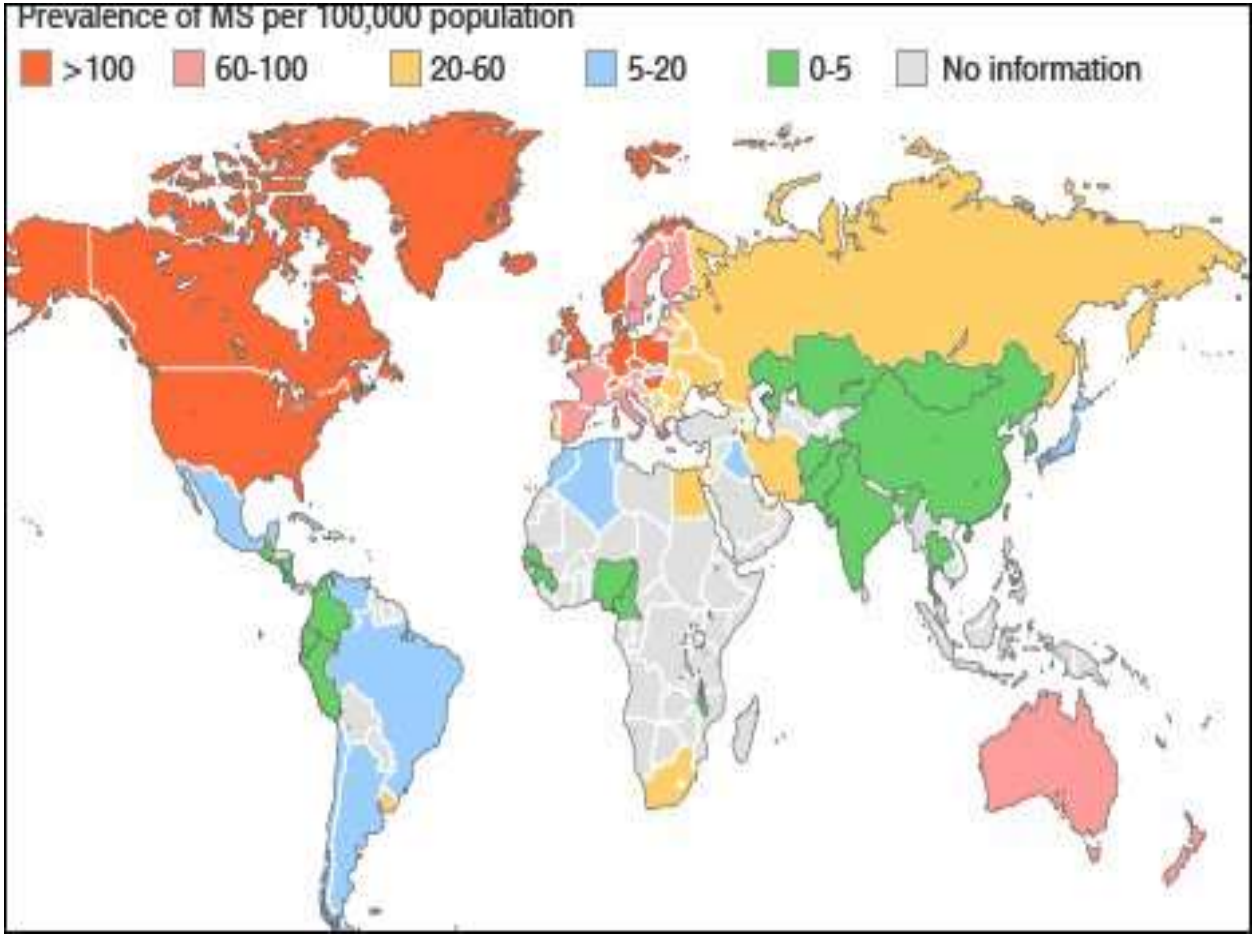
Fig. 2. *Prevalence of vitamin D deficiency according to pain category.*

Autoimmune Disease

- Vitamin D deficiency associated with
  - Diabetes Type 1
    - >10,000 children 2000 IU x1year reduced RR of T1DM by 78% at 30yrs
  - Multiple Sclerosis
    - More prevalent among winter births and northern latitudes
  - Rheumatoid Arthritis
  - Crohn's
  - Psoriasis
  - Atopic dermatitis

Hypponen et al. Lancet. 2001;358(9292):1500

Multiple Sclerosis



- Immigrants: after age 15, MS risk closer to home country
- Vit D interacts with genes associated with MS

Vitamin D predicts depressive symptoms

Serum 25-Hydroxyvitamin D and Depressive Symptoms in Older Women and Men

Yuri Milaneschi, Michelle Shardell, Anna Maria Corsi, Rosamaria Vazzana, Stefania Bandinelli, Jack M. Guralnik, and Luigi Ferrucci

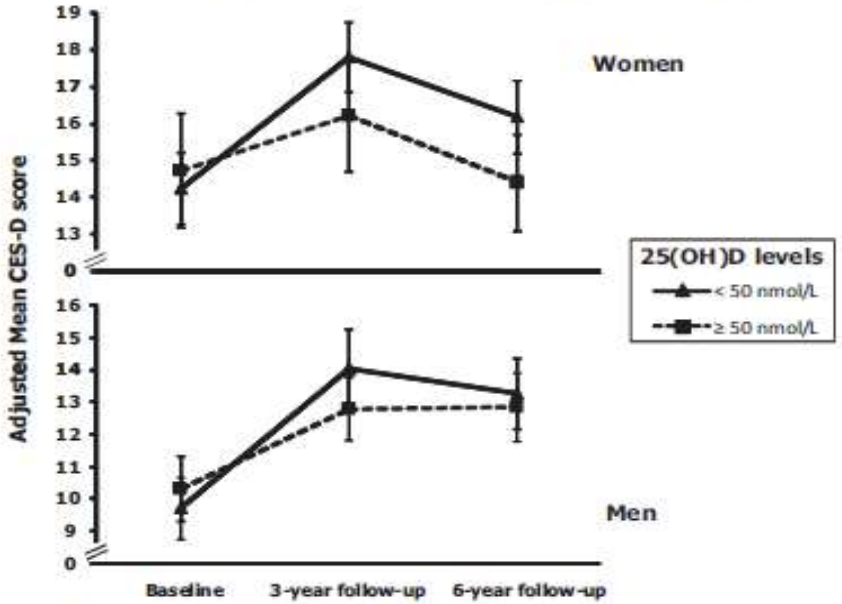


FIG. 3. CES-D scores during 6 yr of follow-up according to baseline 25(OH)D levels in women and men. Estimated means and 95% CI are adjusted for age, education, MMSE score, physical activity, BMI, ADL and IADL disabilities, use of antidepressants, number of chronic diseases, SPPB score, energy intake, high PTH, and season collection.

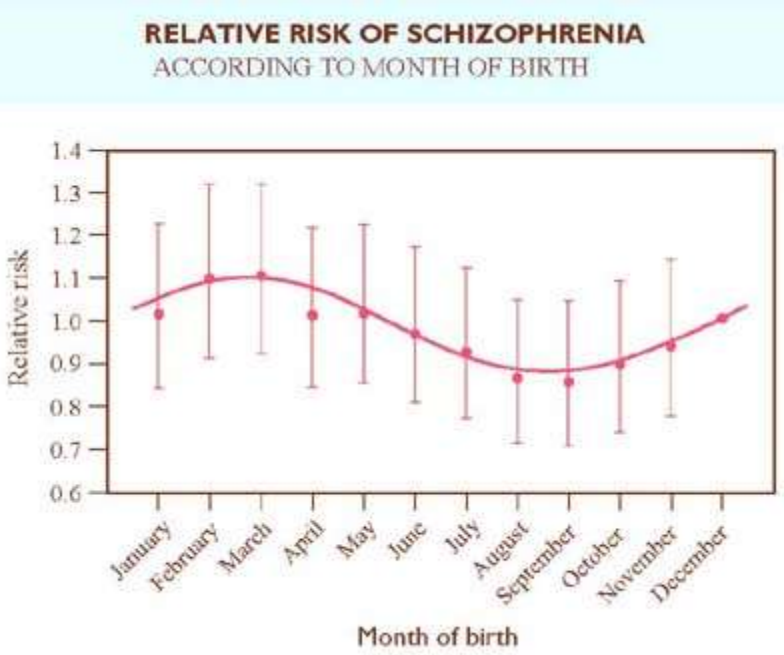
J Clin Endocrinol Metab, July 2010, 95(7):3225–3233

Vitamin D supplementation???

Clinical Trials

Sample	Duration	Vit D dose	Outcome Measure	Results	Reference
High BMI adults (n 441)	12 months	40,000 or 20,000 IU /week	BDI	Sig decrease in BDI vs pbo	Jorde, 2008
Adults 30-75yo w 25OHVIt<55nmol/L	6 months	40,000 IU /week	BDI, HADS, MADRS	No difference	Kjaergaard, 2012
Women >70yo (n 2258)	3-5 years	Annual 500,000 IU	SF12, Gen Health Q, Well Being Index	No Difference	Sanders, 2011

Schizophrenia



- More likely among
  - Individuals born in winter
  - Darker skin migrants to northern latitudes
  - Children of mothers w/ low levels of vitamin D
- 25OH lower in winter birth and AA mothers
- 25OH deficiency common in schizophrenia
- VDR is rich in the substantia nigra

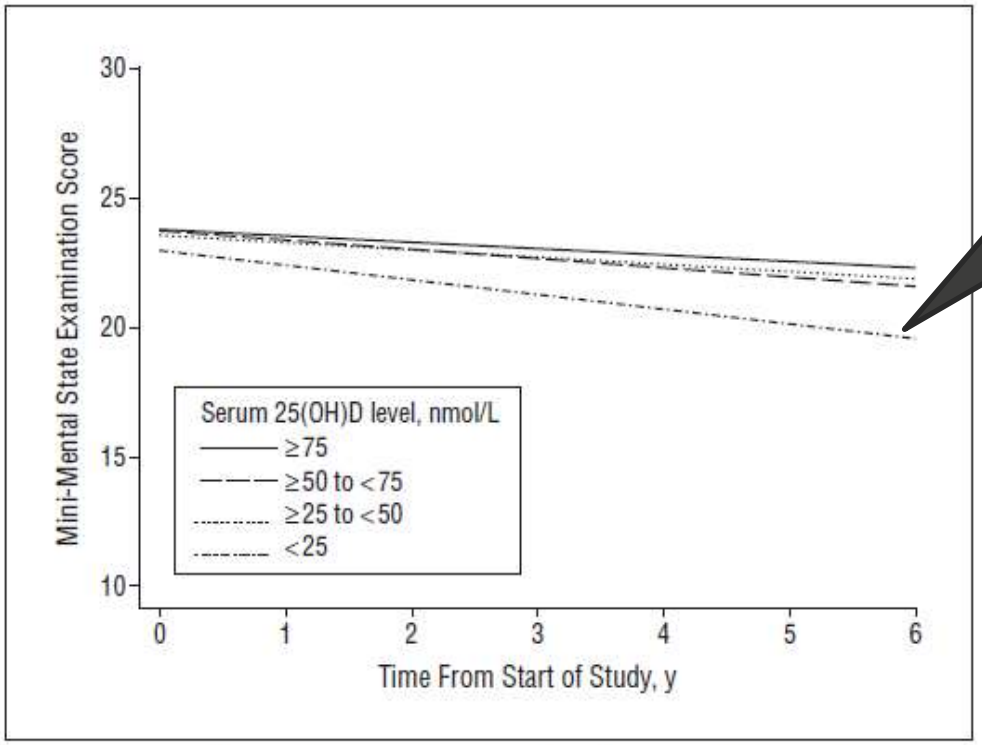
Itzhaky D 2012 Feb;14(2):88-92.

Alzheimer disease

- Vitamin D levels significantly lower among those with AD
- Among patients with vitamin D deficiency, 2.5 times more AD
- Vit D deficiency predicts MMSE decline
  - 0.3 MMSE points per year (Llewellyn 2010)
- MMSE scores lower among those with lower 25(OH)D levels (Balion 2012)

Vitamin D and Risk of Cognitive Decline in Elderly Persons

David J. Llewellyn, PhD; Iain A. Lang, PhD; Kenneth M. Langa, MD, PhD; Graciela Muniz-Terrera, PhD; Caroline L. Phillips, MS; Antonio Cherubini, MD; Luigi Ferrucci, MD, PhD; David Melzer, PhD



3 MMSE pts lost in 6 years

Figure. Change in cognitive function for 858 older persons by serum 25-hydroxyvitamin D (25[OH]D) concentration. Results are based on a random-effects model with multivariate adjustment for age, sex, education, baseline cognitive score, season tested, body mass index, impaired mobility, diabetes, and stroke.

Arch Intern Med. 2010;170(13):1135-1141

Role of Vit D in Alzheimer Disease

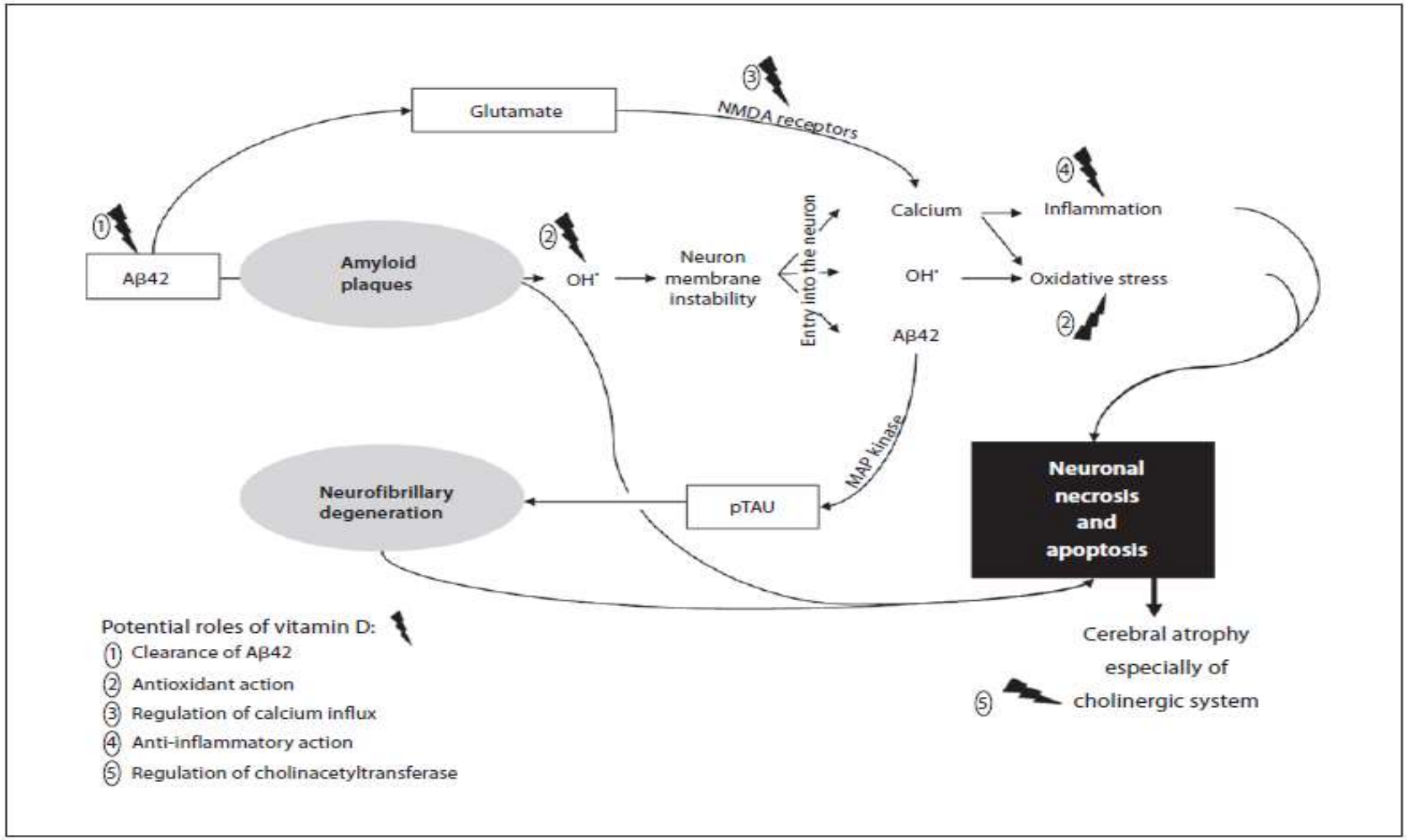


Fig. 1. Potential targets and neuroprotective mechanisms of vitamin D in AD. OH^- = Superoxide anion; NMDA = N-methyl D-aspartate; pTAU = phospho-tubule associated unit.

Treatment for Alzheimer disease?

- Vitamin D3 supplementation in pts in memory clinic over 16 months (Annweiler 2012)
  - 25(OH)D levels increased, control group decreased
  - Significantly increased MMSE, FAB, CAB

- Memantine, vitamin D and combination (Annweiler 2012)
  - 44 outpatients with new dx of AD
  - Significant increase in MMSE over 6 months for those patients taking combination of memantine + vitamin D
  - No change among memantine or vitamin D alone

Vit D measurement

Status	25(OH) Vitamin D ng/dL
Normal	>30
Insufficient	20-29
Deficiency	10-19
Severe Deficiency	<10

OPTIMAL ? 40-65 ng/dl

PTH levels suppressed at 40 ng/dl or higher

Supplementation in Deficiency

- Vitamin D3 (cholecalciferol)
  - 1000-4000 IU daily
  - Vit D3 is preferred source
    - Raises 25(OH) levels more, higher affinity for VDR
- Vitamin D2 (ergocalciferol)
  - Available as 50,000IU given every 1-2 weeks
  - Less effective for conversion to calcitriol
- Age-appropriate supplementation
  - 800-1000 IU Vit D3 *in all elderly*

Supplementation in Obesity

- Double the Vitamin D dosage in the patient with obesity
- Excessive adipose tissue absorbs Vitamin D and decreases bioavailability by 57%
  - 62% morbidly obese patients are deficient

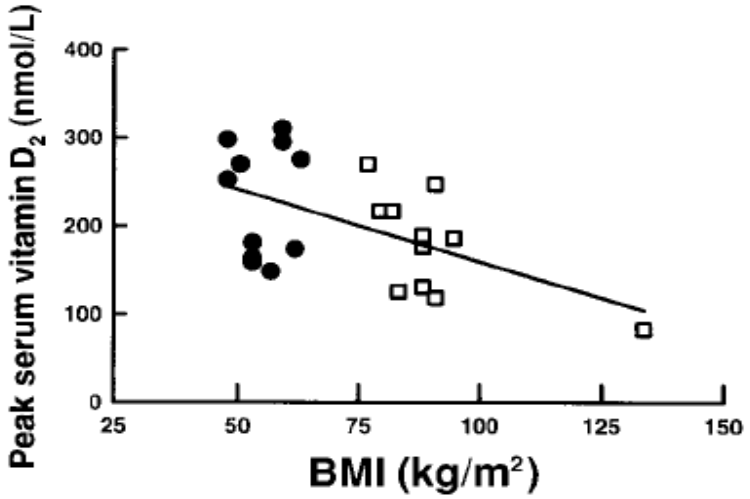


FIGURE 4. Correlation between BMI and peak serum vitamin D_2 (ergocalciferol) concentrations in the control (●) and obese (□) groups after oral intake of vitamin D_2 (50 000 IU, 1.25 mg). The correlation coefficient ($r = -0.56$) was highly significant ($P = 0.007$).

Questions?

- 36 yo f complaining of lack of appetite, tired, taste feels “off”
- Medical Hx
  - HTN, high cholesterol
  - Sinus surgery
  - Roux en Y 3 yrs ago
  - Depression->Bipolar disorder

Psychosomatics. 2018 Mar - Apr;59(2):206. doi: 10.1016/j.psym.2017.10.003. Epub 2017 Oct 14.

Progression of symptoms

- Lethargy
- Ataxia
- Tremor
- Nausea
- Poor appetite
- Blurry vision

Vitamins?

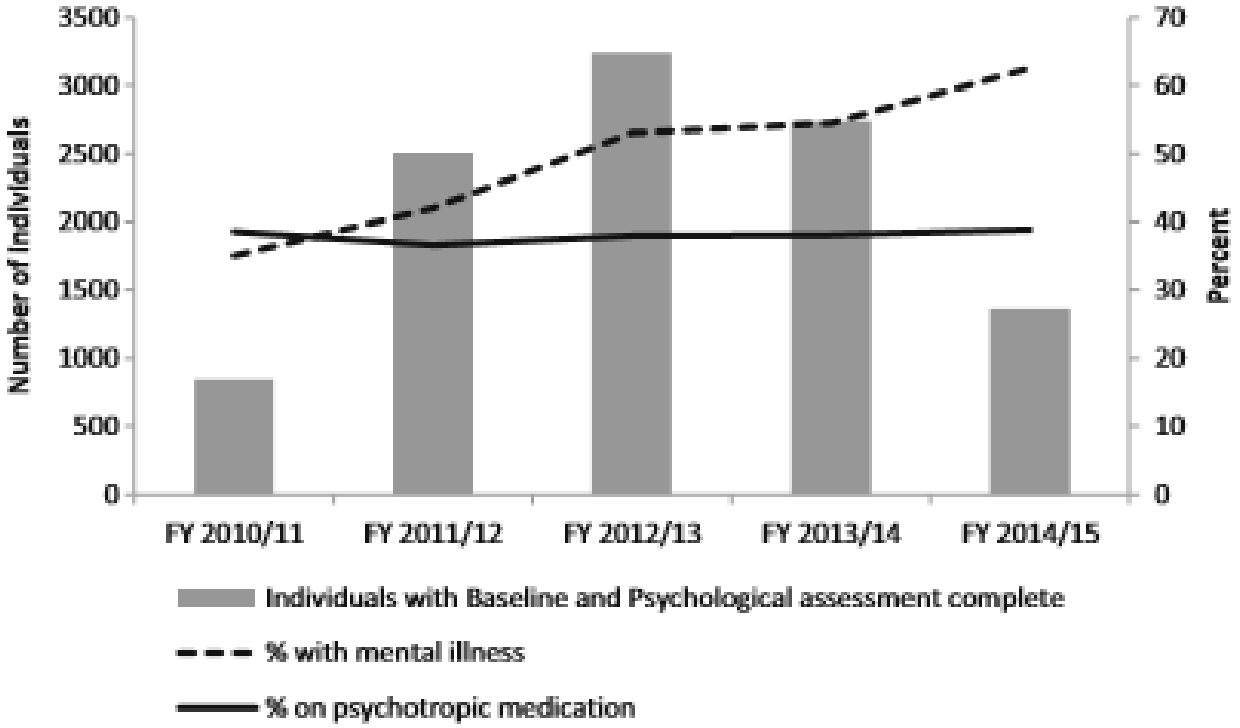
Deficiency-associated Symptoms	Potential Deficiency
Visual Impairment	Vitamin A, copper, vitamin E, thiamine
Gait disturbance	Vitamin E, B1, B12, copper, niacin
Neuropathy	Copper, vitamin E, thiamine, B6
Skin disorder/dermatitis	Niacin, vitamin A, zinc, B2, B6
Glossitis/cheilitis/stomatitis	Vitamin C, zinc, B2, B6

Progression of symptoms

- Lethargy
- Ataxia
- Tremor
- Nausea
- Poor appetite
- Blurry vision
- Medications
  - Lithium 900mg qhs

Lithium level 2.48

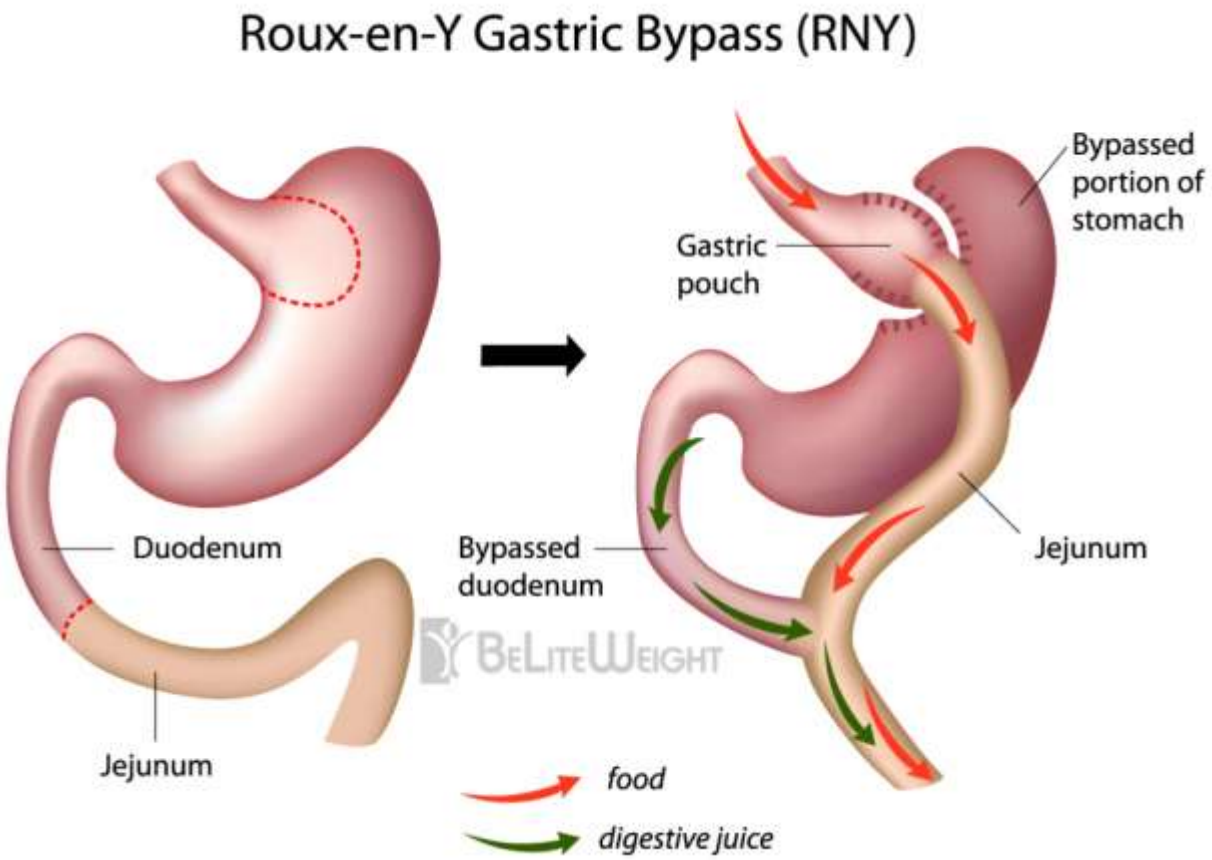
Creatinine 0.9



FY: fiscal year
Note: Fiscal year 2014/15 only contains data up to February 9, 2015

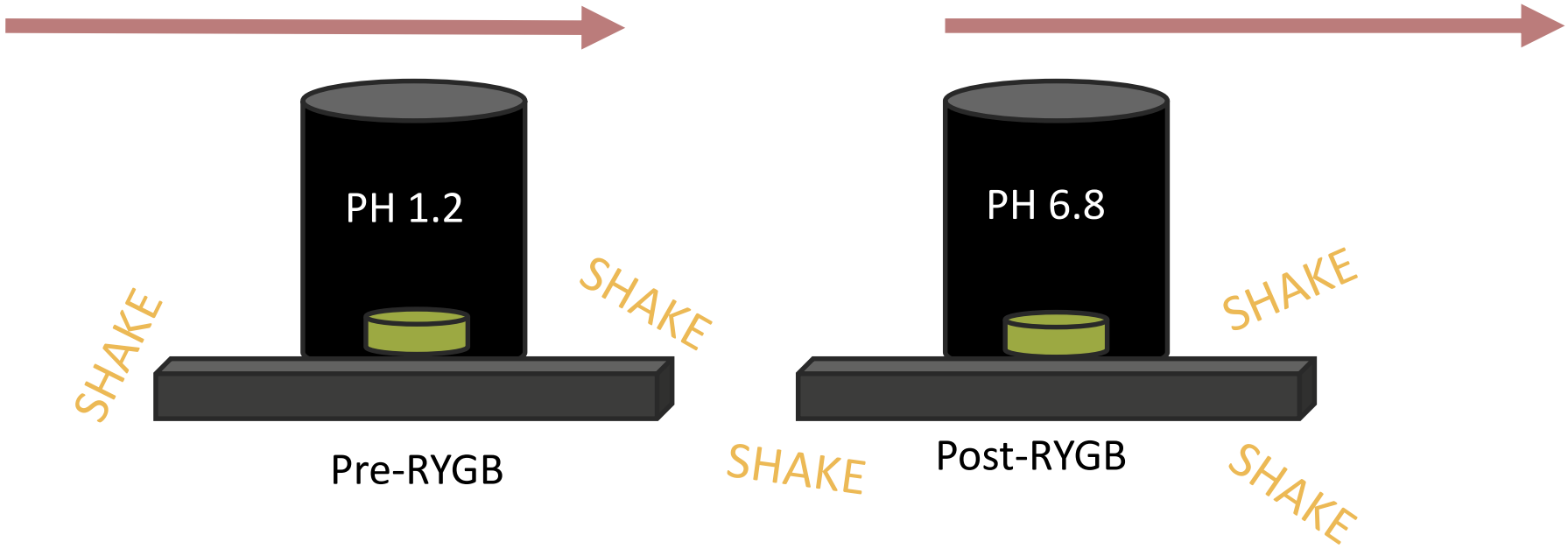
Gastric bypass and Psychiatric Diagnosis

What is Roux En Y?



https://www.beliteweight.com/wp-content/uploads/2014/01/Gastric-Bypass-Roux-en-Y-1024x751.png

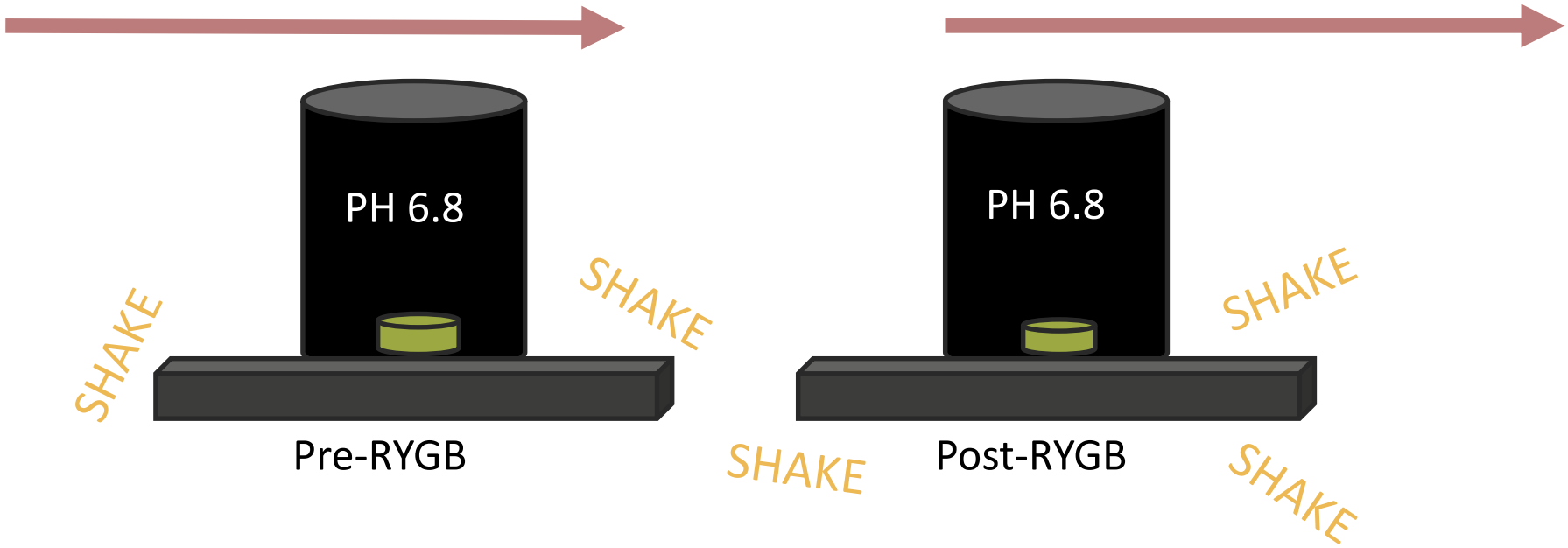
Gastric bypass and Lithium Dissolution Experiment



Gastric bypass and Lithium Dissolution Experiment

Gastric bypass and Lithium Dissolution Experiment

Gastric bypass and Lithium Dissolution Experiment

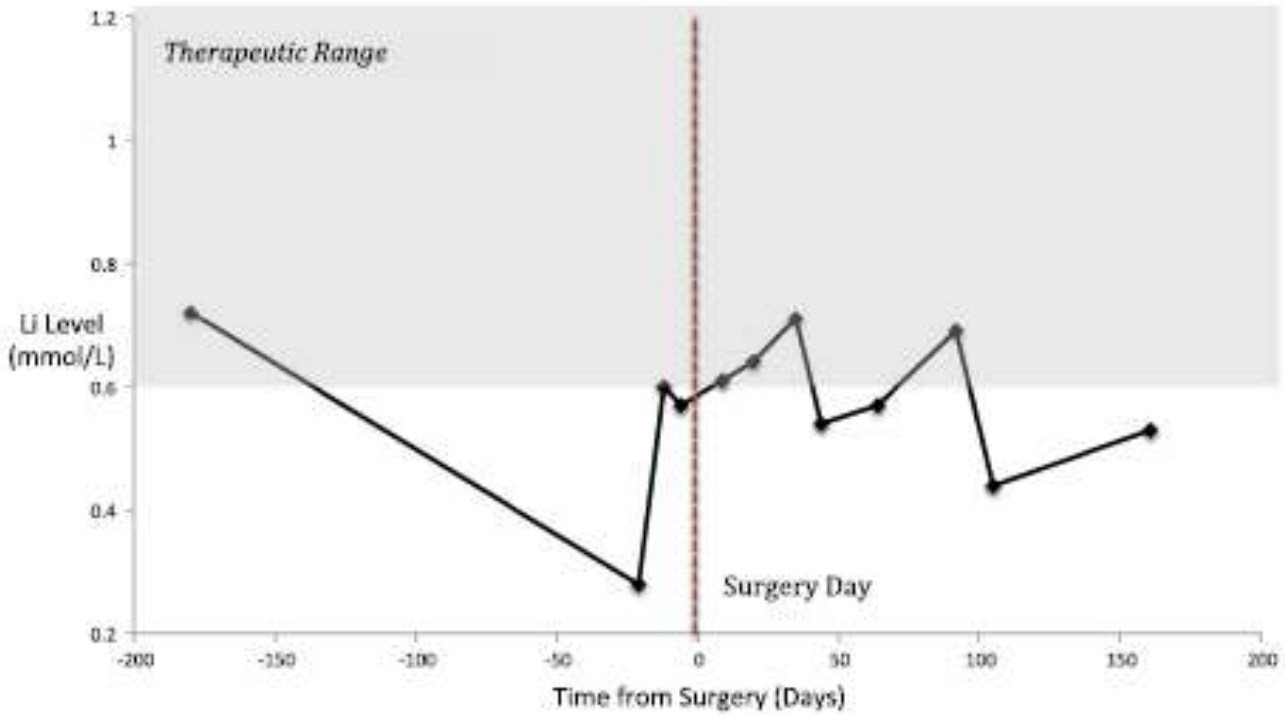


Gastric bypass and Lithium Dissolution Experiment

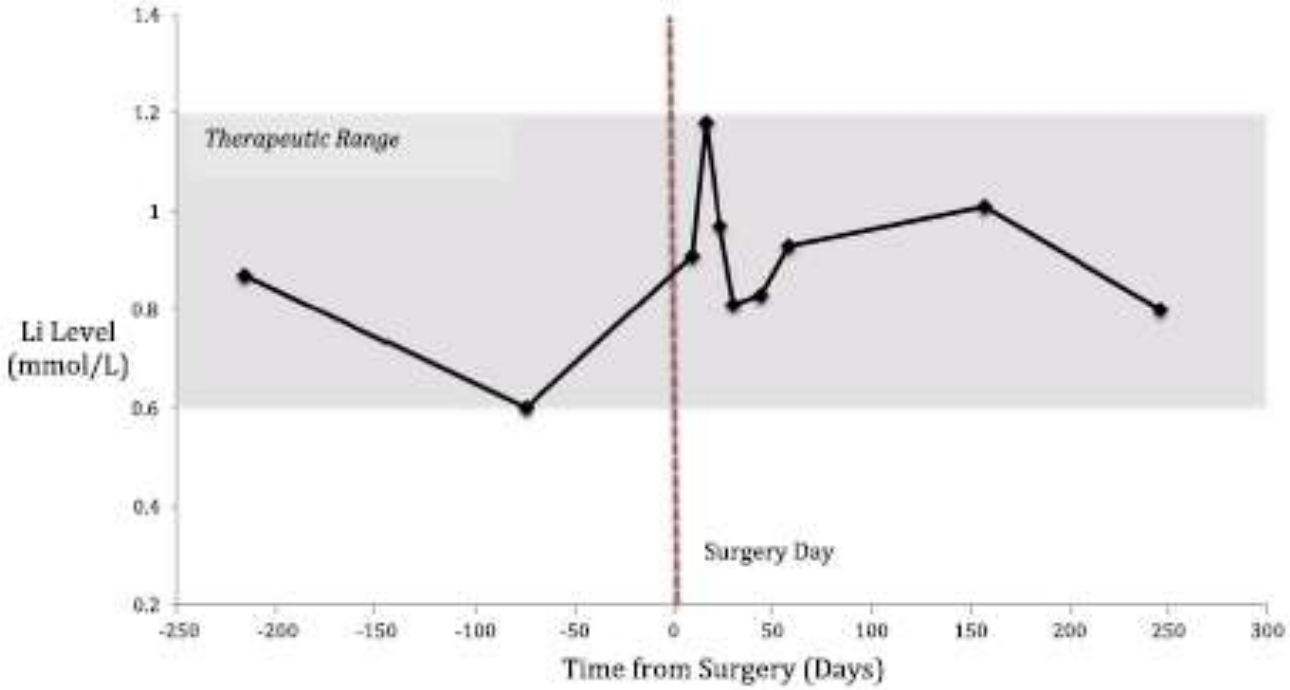
Gastric bypass and Lithium Dissolution Experiment

Gastric bypass and Lithium Dissolution Experiment

FIGURE 1. Ms. A's Perioperative Lithium Levels



GURE 2. Ms. B's Perioperative Lithium Levels

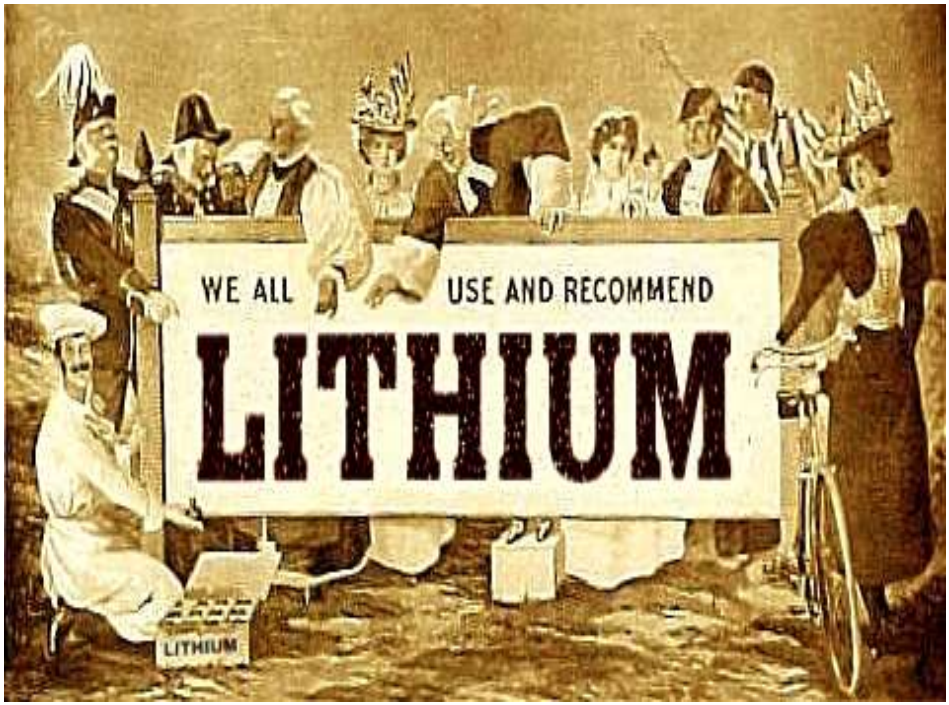


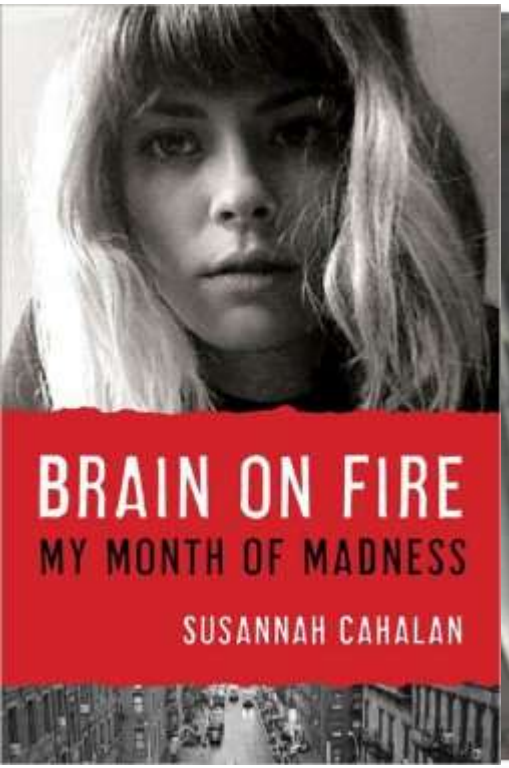
Pearls

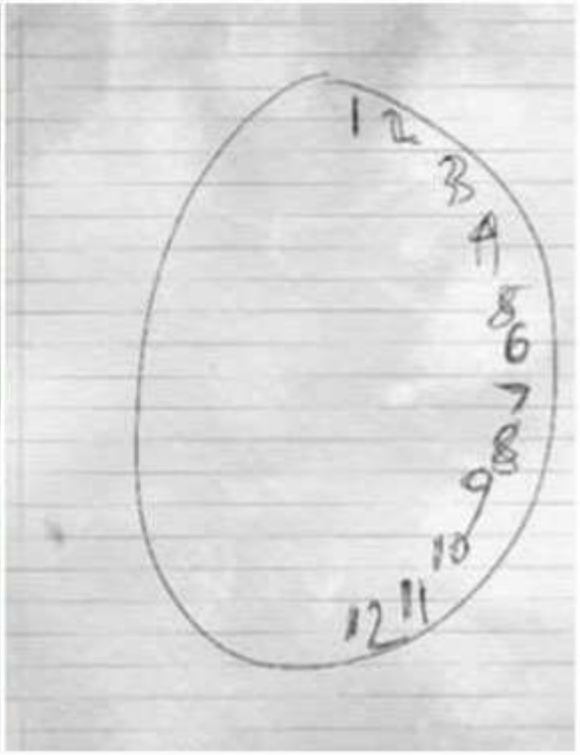
- Lithium levels can vary unpredictably in post- RYGB patients
- Can experience toxicity in absence of acute kidney injury
- Need close monitoring of lithium levels
- Can see toxicity even at some delay from RYGB

Follow-up from Case

- Lithium level at time of discharge was 0.77.
- Restarted on conservative dose of lithium 300 mg QHS.
- Lithium level 7 days post-discharge was 0.21
- Increased lithium to 450 mg QHS 1 month post discharge
- Lithium level 2 months later was 0.65




BRAIN ON FIRE
MY MONTH OF MADNESS
SUSANNAH CAHALAN



Psychiatric Presentations

TABLE 2 | Presenting clinical symptoms in all 100 patients.

Initial signs and symptoms	All patients (100)	NMDAR (53)	Non-NMDAR (24)	Intracellular antigens (23)
Psychiatric				
Acute behavioral changes	56 (56%)	46 (87%)	7 (29%)	3 (13%)
Hallucinations (visual, auditory)	25 (25%)	23 (43%)	1 (4%)	
Memory deficits (retro- and anterograde amnesia)	22 (22%)	11 (21%)	8 (33%)	4 (17%)
Confusion/aggression	18 (18%)	11 (21%)	6 (25%)	1 (4%)
Paranoid delusions	17 (17%)	13 (26%)	2 (8%)	1 (4%)
Depressed mood	13 (13%)	10 (19%)	4 (16%)	1 (4%)
Catatonia	10 (10%)	10 (19%)		
Mutism	8 (8%)	8 (15%)		
Anorexia	1 (1%)	1 (2%)		
Any of the above symptoms	65 (65%)	53 (100%)	14 (58%)	7 (30%)
Neurological				
Sensorimotor deficits	30 (30%)	8 (15%)	7 (29%)	13 (57%)
Seizures		10 (19%)	2 (8%)	5
Generalized tonic-clonic	13 (13%)	9 (17%)	1 (4%)	3 (13%)
Focal	4 (4%)	1 (2%)	1 (4%)	2 (9%)
Faciobrachial dystonic seizures	7 (7%)		7 (29%)	
Speech dysfunction (pressured speech, verbal reduction)	15 (15%)	10 (19%)	4 (16%)	
Movement disorders	11 (11%)	7 (13%)	1 (4%)	3 (13%)
Headache	12 (12%)	9 (17%)	1 (4%)	2 (9%)
Reduced levels of consciousness	7 (7%)	5 (9%)	2 (8%)	
Paralysis	7 (7%)	4 (8%)	1 (4%)	2 (9%)
Cerebellar ataxia	10 (10%)	1 (2%)	3 (12%)	7 (30%)
Diplopia	7 (7%)	3 (6%)		4 (17%)
Any of the above symptoms	67 (67%)	39 (74%)	20 (83%)	20 (87%)

Panel 4: Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation
2 At least one of the following laboratory study results:
   - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands
3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

What symptoms are missing?

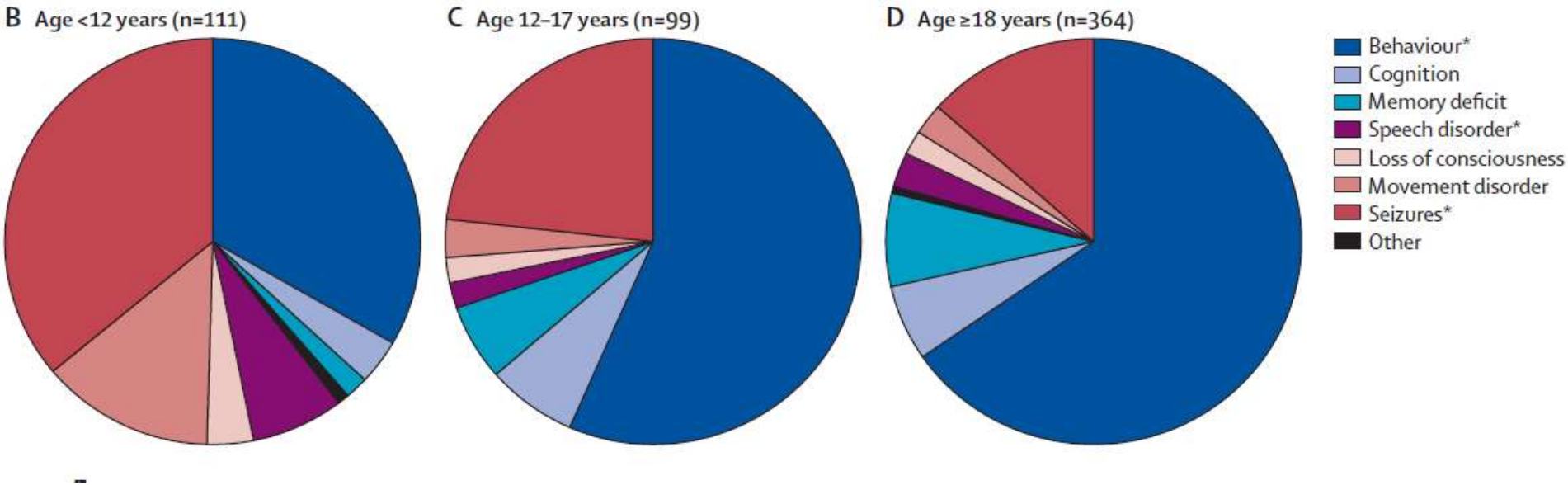
Catatonia

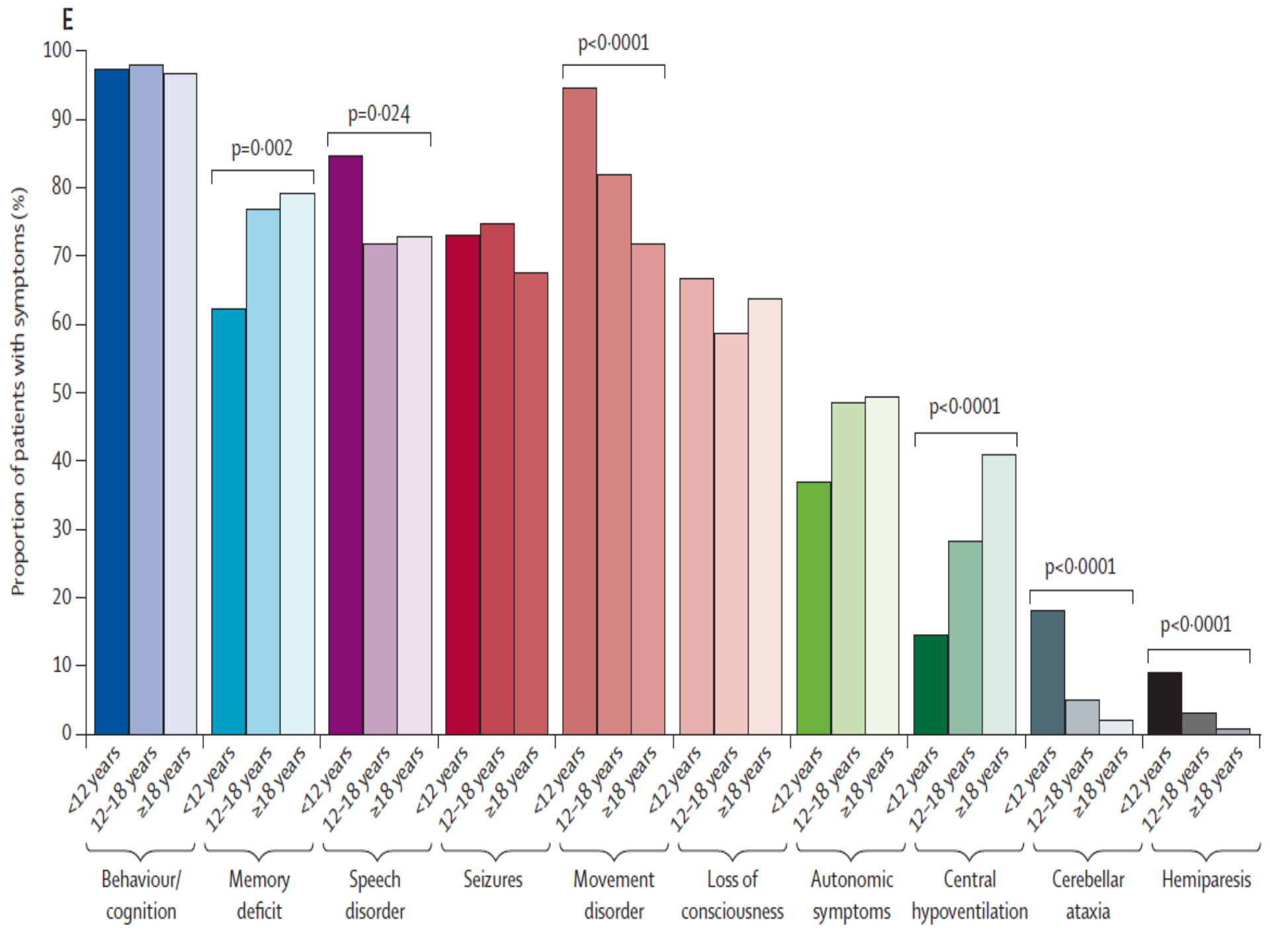
- More often agitated than stuporous
- Possibly different from classic catatonia with less affective components
- Requiring impressive doses of lorazepam
- Responding to ECT but rellapsingmitting in between treatments

Sleep disturbance

- Severe
- Mostly insomnia
- Some alteration of wake-sleep cycle
- Requiring impressive doses of hypnotic/ sedating agents
- Often last symptoms to remit

First symptom at disease onset according to patients' age




E
Proportion of patients with symptoms (%)
100
90
80
70
60
50
40
30
20
10
0
p=0·002
p=0·024
p<0·0001
p<0·0001
p<0·0001
p<0·0001
<12 years
12–18 years
≥18 years
Behaviour/ cognition
Memory deficit
Speech disorder
Seizures
Movement disorder
Loss of consciousness
Autonomic symptoms
Central hypoventilation
Cerebellar ataxia
Hemiparesis

Warning Signs

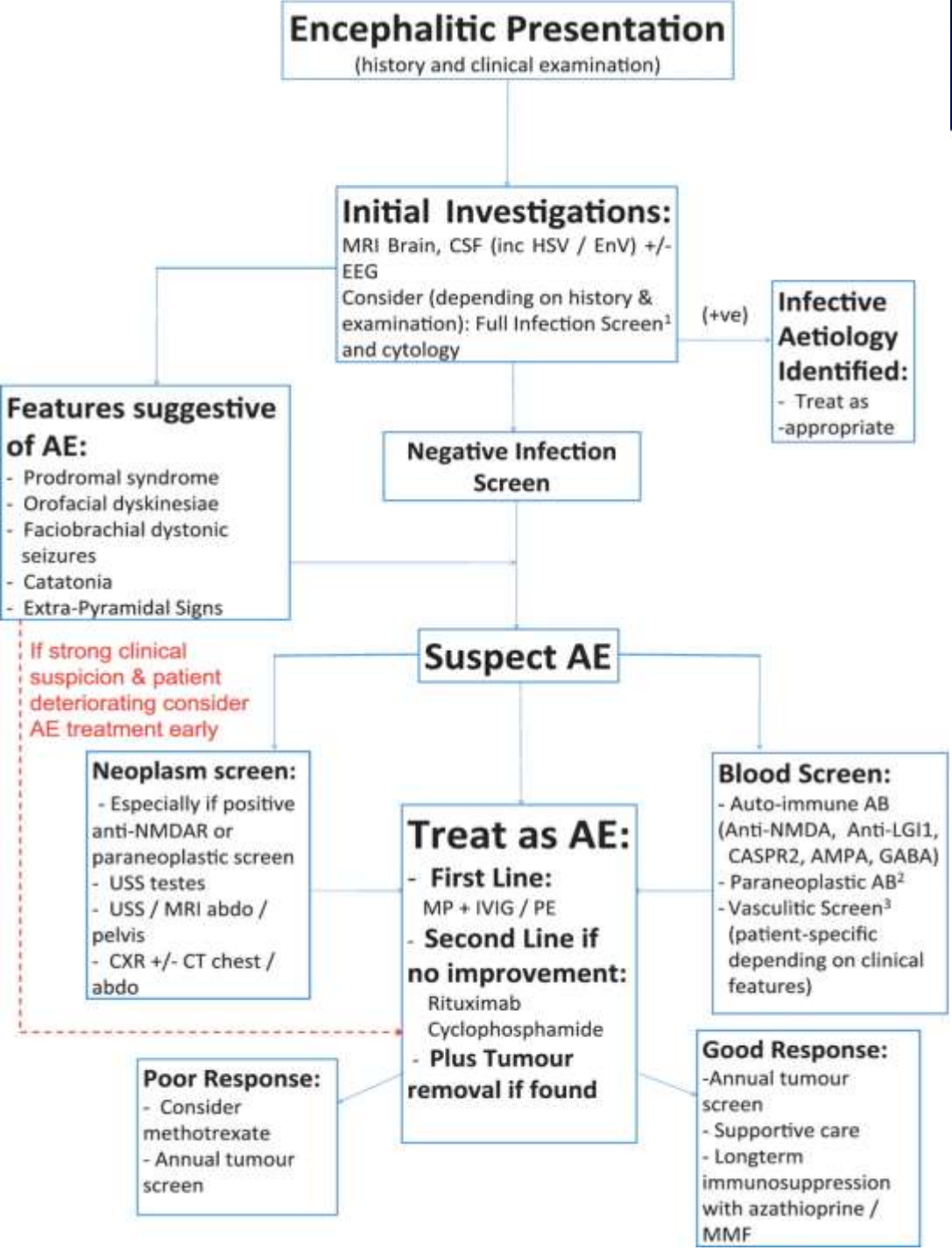
TABLE 4 | Warning signs pointing to an autoimmune etiology in new-onset psychosis.

Yellow flags 	• Decreased levels of consciousness • Abnormal postures or movements (orofacial, limb dyskinesia) • Autonomic instability • Focal neurological deficits • Aphasia or dysarthria • Rapid progression of psychosis (despite therapy) • Hyponatremia • Catatonia • Headache • Other autoimmune diseases (e.g., thyroiditis)
Red flags 	• Cerebrospinal fluid (CSF) lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence for infection • Epileptic seizures • Faciobrachial dystonic seizures • Suspected malignant neuroleptic syndrome • MRI abnormalities (mesiotemporal hyperintensities, atrophy pattern) • EEG abnormalities (slowing, epileptic activity or extreme delta brush)

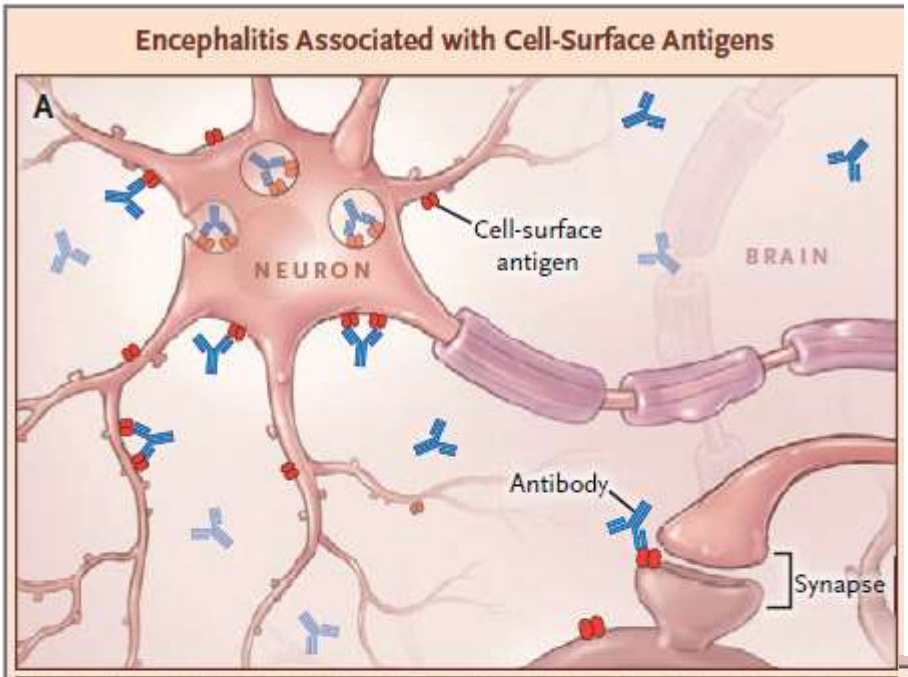
"Red flag" criteria should always prompt determination of anti-neuronal autoantibodies in psychiatric patients. "Yellow flag" criteria should raise suspicion of an autoimmune etiology and include autoimmune encephalitis in the differential diagnoses, in either case if several findings are present.

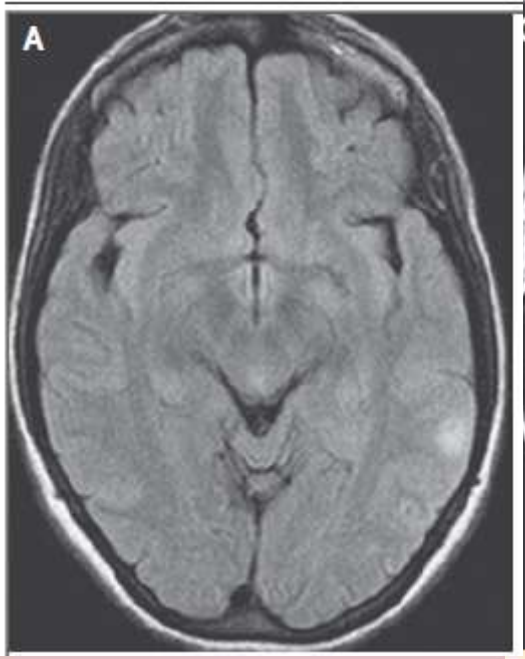
Q J Med 2011; 104:921–931

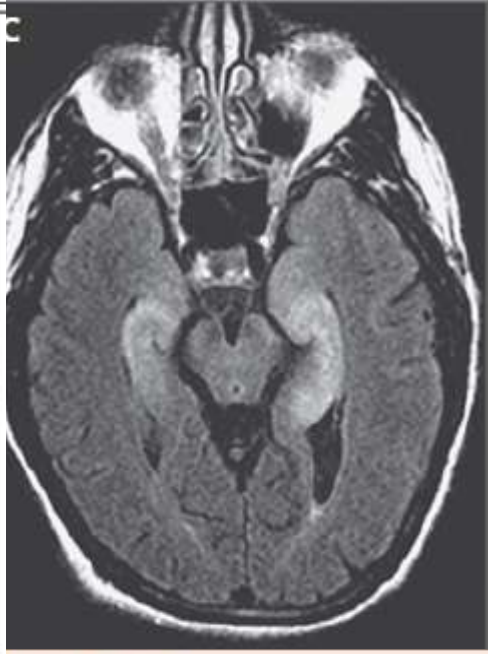
Clinical Algorithm for the diagnosis of AE



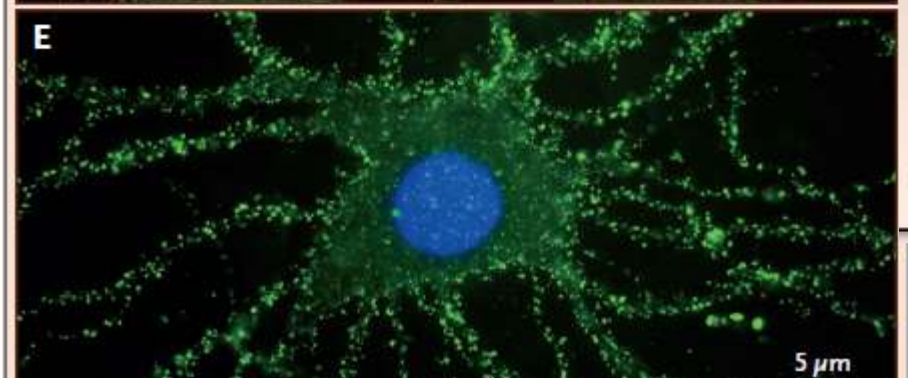
nesses, these cases also highlight the need for aggressive, early and appropriate treatment of patients with AE to achieve good outcomes. It is a disease process that if considered early, diagnosed promptly and treated appropriately (including aggressive treatment with therapies such as high-dose steroids, IVIG, plasma exchange, rituximab and cyclophosphamide) can be reversed and the patient restored to their premorbid state.

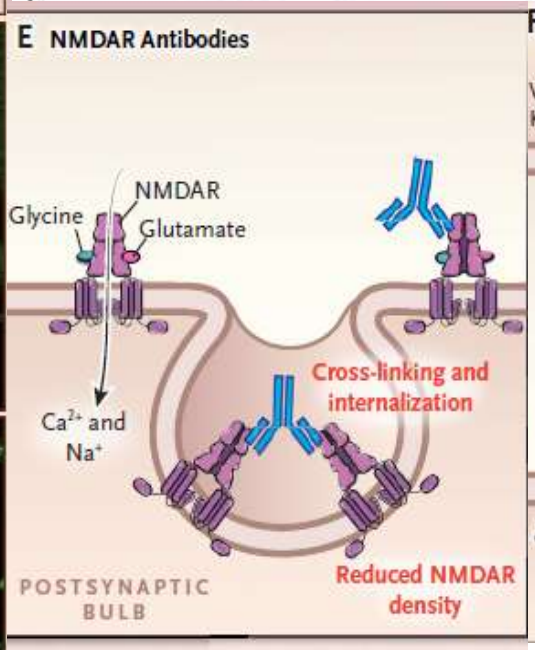

Encephalitis Associated with Cell-Surface Antigens
A
NEURON
Cell-surface antigen
BRAIN
Antibody
Synapse


A


C


C
1 mm


E
5 μm


E NMDAR Antibodies
Glycine
NMDAR
Glutamate
Ca2+ and Na+
Cross-linking and internalization
Reduced NMDAR density
POSTSYNAPTIC BULB

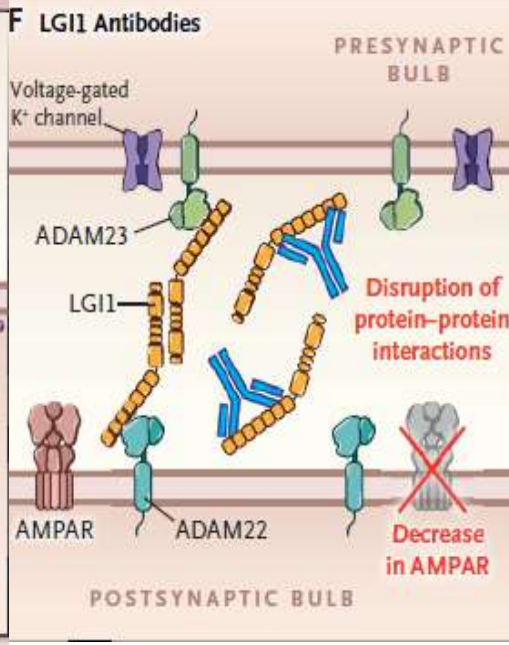
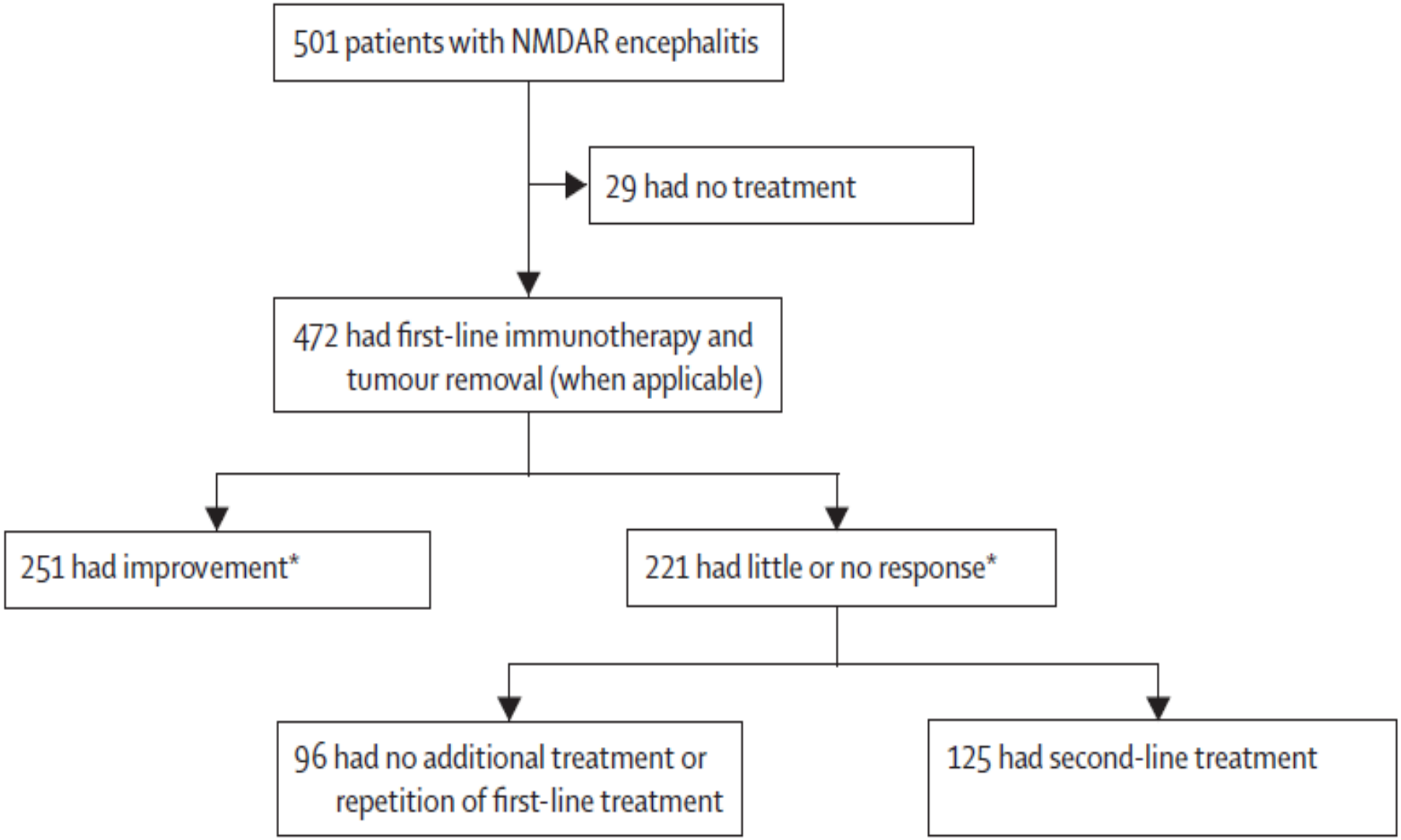

F LGI1 Antibodies
PRESYNAPTIC BULB
Voltage-gated K+ channel
ADAM23
LGI1
Disruption of protein–protein interactions
AMPAR
ADAM22
Decrease in AMPAR
POSTSYNAPTIC BULB

Table 2. Autoimmune encephalitis associated with antibodies against neuronal cell-surface or synaptic proteins

Antigen Target	Syndrome	Cancer Association if Present	Observations
NMDA receptor	Characteristic neuropsychiatric syndrome with movement disorders, seizures, autonomc dysfunction	Age-related association with ovarian teratoma	Predominantly affects young adults, adolescents, and children
AMPA receptor	Limbic encephalitis, psychosis	Lung, breast, thymus in ~70% of cases	Frequent coexisting autoimmunities
$GABA_B$ receptor	Limbic encephalitis with early, prominent, and severe seizures	SCLC or other neuroendocrine tumor of lung in ~50% of cases	Frequent coexisting autoimmunities
LGI1	Limbic encephalitis, seizures, hyponatremia, myoclonus	Thymoma in <10% of cases	Frequent tonic seizures that may be misdiagnosed as myoclonus or startle
Caspr2	Encephalitis and/or peripheral nerve hyperexcitability	Rarely thymoma	Symptoms of overlapping immune disorders such as myasthenia have led to misdiagnosis of motor neuron disease
$GABA_A$ receptor	Status epilepticus or refractory seizures and encephalitis	None	Frequent coexisting autoimmunities; extensive and often multifocal MRI abnormalities
DPPX	Encephalopathy, agitation, tremor, startle with muscle rigidity, seizures, and gastrointestinal dysfunction	None	Severe gastrointestinal symptoms can mislead diagnoses
Glycine receptor	Stiff-person, hyperekplexia, PERM, and encephalitis	Rare associations with cancer but usually not paraneoplastic	
mGluR1	Cerebellar ataxia	Hodgkin lymphoma	
mGluR5	Limbic encephalitis	Hodgkin lymphoma	Known as Ophelia syndrome
Dopamine-2 receptor	Basal ganglia encephalitis, Sydenham chorea	None	
Amphiphysin	Stiff-man syndrome	Breast, SCLC	
GAD	Stiff-man syndrome at times with cerebellar ataxia, refractory seizures	Rarely thymoma or other tumors	Have been reported in other syndromes, such as limbic encephalitis and epilepsy; frequent coexisting autoimmunities

Abbreviation: PERM, progressive encephalomyelitis with rigidity and myoclonus.



Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

Maarten J Titulaer, Lindsey McCracken, Iñigo Gabilondo, Thaís Armangué, Carol Glaser, Takahiro Iizuka, Lawrence S Honig, Susanne M Benseler, Izumi Kawachi, Eugenia Martinez-Hernandez, Esther Aguilar, Núria Gresa-Arribas, Nicole Ryan-Florance, Abiguei Torrents, Albert Saiz, Myrna R Rosenfeld, Rita Balice-Gordon, Francesc Graus, Josep Dalmau

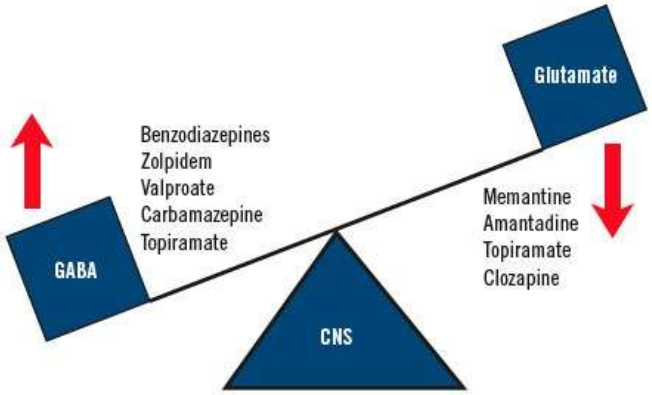
	Non-tumour (n=304)	Tumour (n=197)	All (N=501)	p value*
Median time from symptom onset until treatment in days (IQR)	21 (14–49)	21 (14–42)	21 (14–46)	0·090
First-line immunotherapy	283 (93%)	179 (91%)	462 (92%)	0·40
Steroids	265 (87%)	156 (79%)	421 (84%)	0·024
Intravenous immunoglobulins	221 (73%)	125 (63%)	346 (69%)	0·030
Plasmapheresis	80 (26%)	83 (42%)	163 (33%)	0·0003
Second-line immunotherapy†	93 (31%)	41 (21%)	134 (27%)	0·017
Rituximab	71 (23%)	30 (15%)	101 (20%)	0·030
Cyclophosphamide	50 (16%)	31 (16%)	81 (16%)	0·90
Other immunotherapy‡	23 (8%)	8 (4%)	31 (6%)	0·13
Median time from symptom onset until tumour removal in months (IQR, range)	..	1·4 (0·7–2·6, −13 to 177)	..	
Surgery§	14 (5%)	189 (96%)	..	<0·0001
During initial episode	14 (5%)	169 (86%)	..	
At relapse	0	7 (4%)	..	
After recovery	0	13 (7%)	..	
Failure of first-line immunotherapy¶				
Yes	145 (48%)	76 (39%)	221 (44%)	0·069
No	138 (45%)	103 (52%)	241 (48%)	
Surgery with no immunotherapy	1 (<0·5%)	9 (5%)	10 (2%)	
No treatment	20 (7%)	9 (5%)	29 (6%)	

Psychiatric treatment

- Lorazepam
- ECT
- Zolpidem
- Memantine, amantadine
- Low dose antipsychotics
- Supportive care for catatonia
    - Fluids, VTE prophylaxis, nutrition

FIGURE 3

GABA GLUTAMATE HYPOTHESIS THREE



According to this hypothesis, pharmacologic treatment tend to restore GABA-glutamate imbalance, decreasing glutamate transmission or increasing GABA transmission. Decrease of dopaminergic transmission may act indirectly, increasing GABA-glutamate imbalance.

GABA=γ-aminobutyric acid; CNS=central nervous system.

Carroll BT, Lee JWY, Appiani F, Thomas C. *Primary Psychiatry*. Vol 17, No 4. 2010.