3D Dilemma of This Century

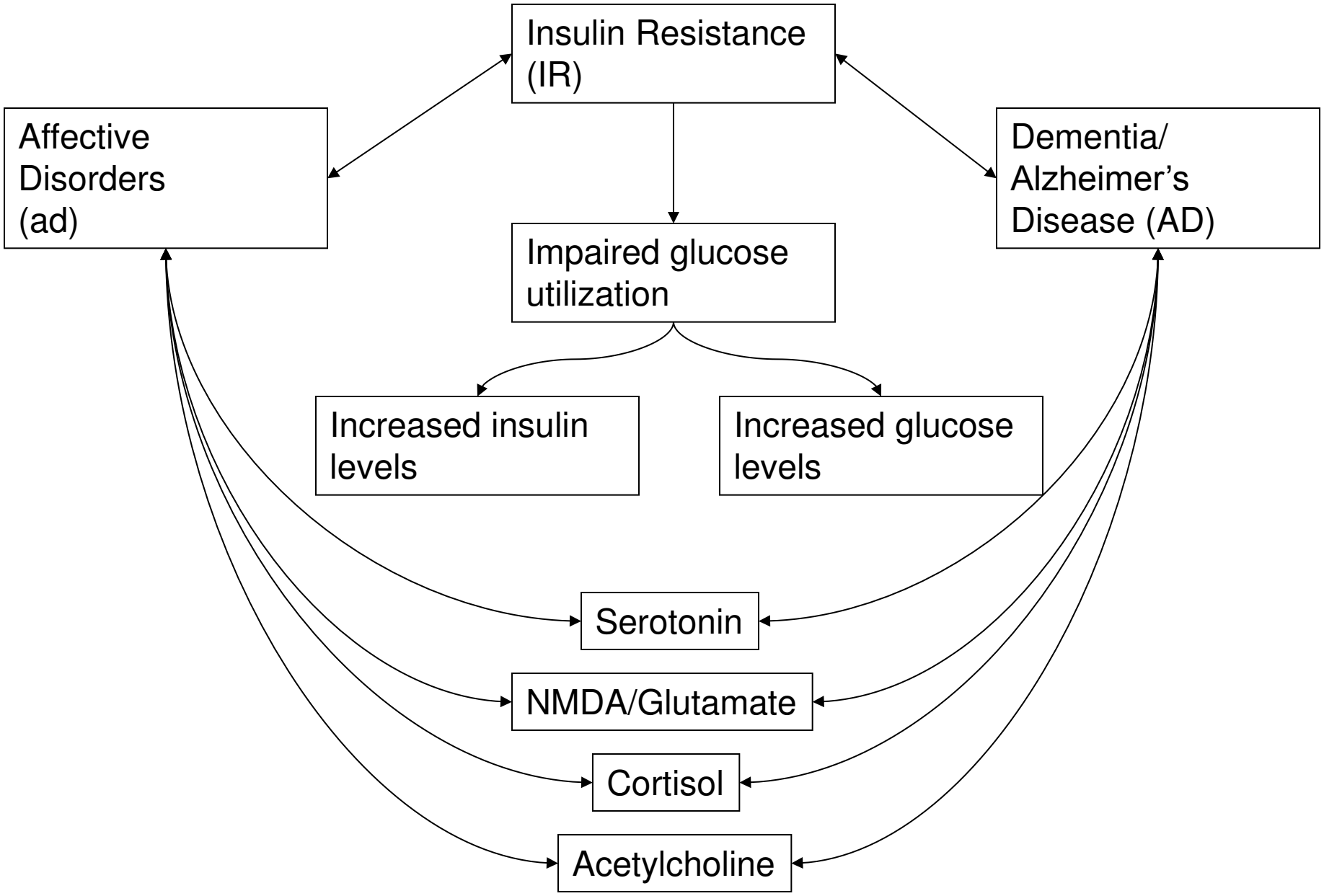
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Overview

	Diabetes[1,2]	Dementia[3]	Depression[4,5]
Global prevalence	4.6 billion	47.5 million	350 million
Disability	19th disease to cause maximum disability (YLL)	12th most burdensome disease in the US	2.53% of all global DALYs
Cost	$612.2 billion	$604 billion year	$2.5 trillion

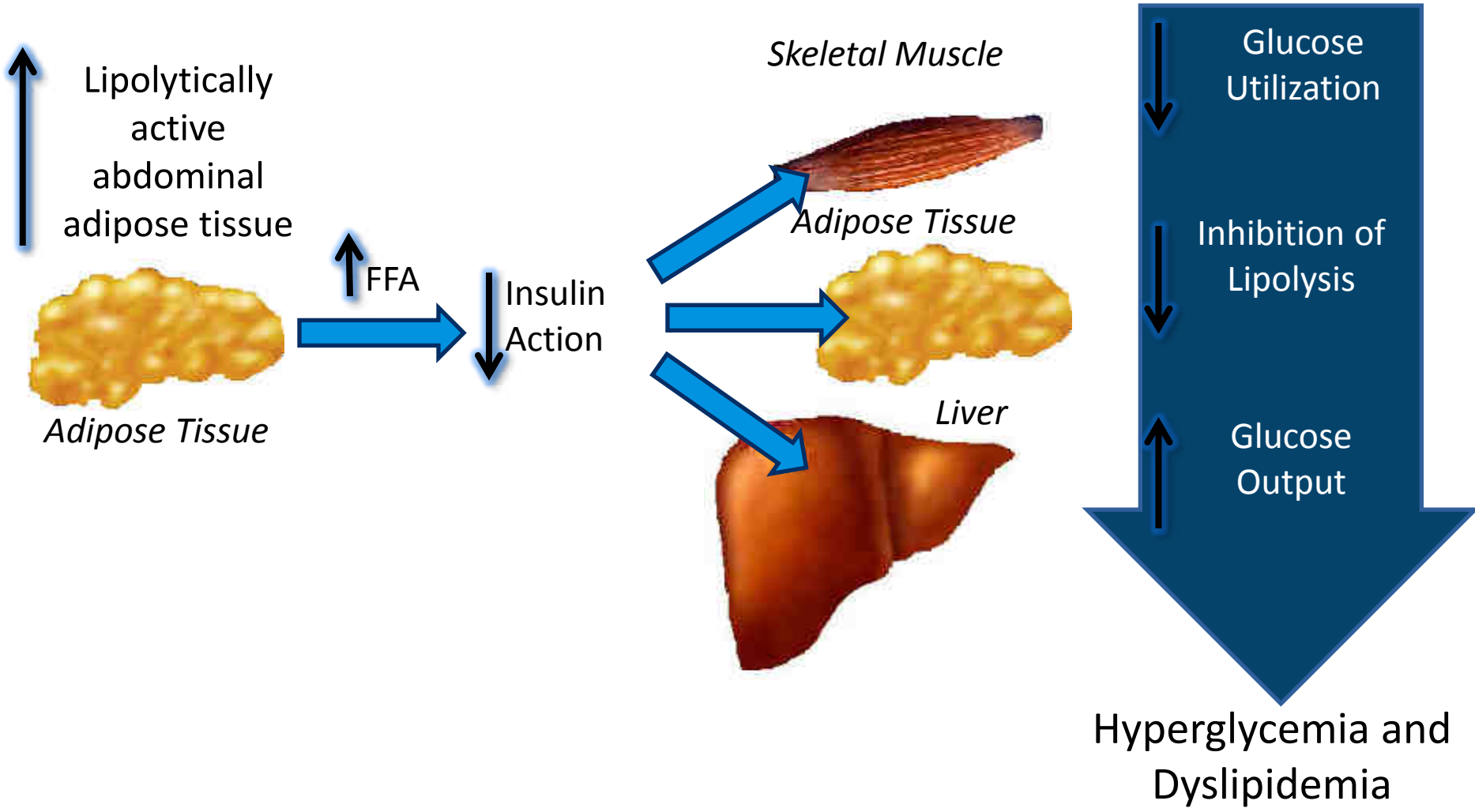

Insulin Resistance (IR)
Affective Disorders (ad)
Dementia/ Alzheimer's Disease (AD)
Impaired glucose utilization
Increased insulin levels
Increased glucose levels
Serotonin
NMDA/Glutamate
Cortisol
Acetylcholine

Insulin Resistance (IR)

- A condition in which tissue responsiveness to the normal action of insulin is impaired
- It is a major risk factor for DM, CVD, and mood disorders
- May or may *not* be a consequence of weight gain

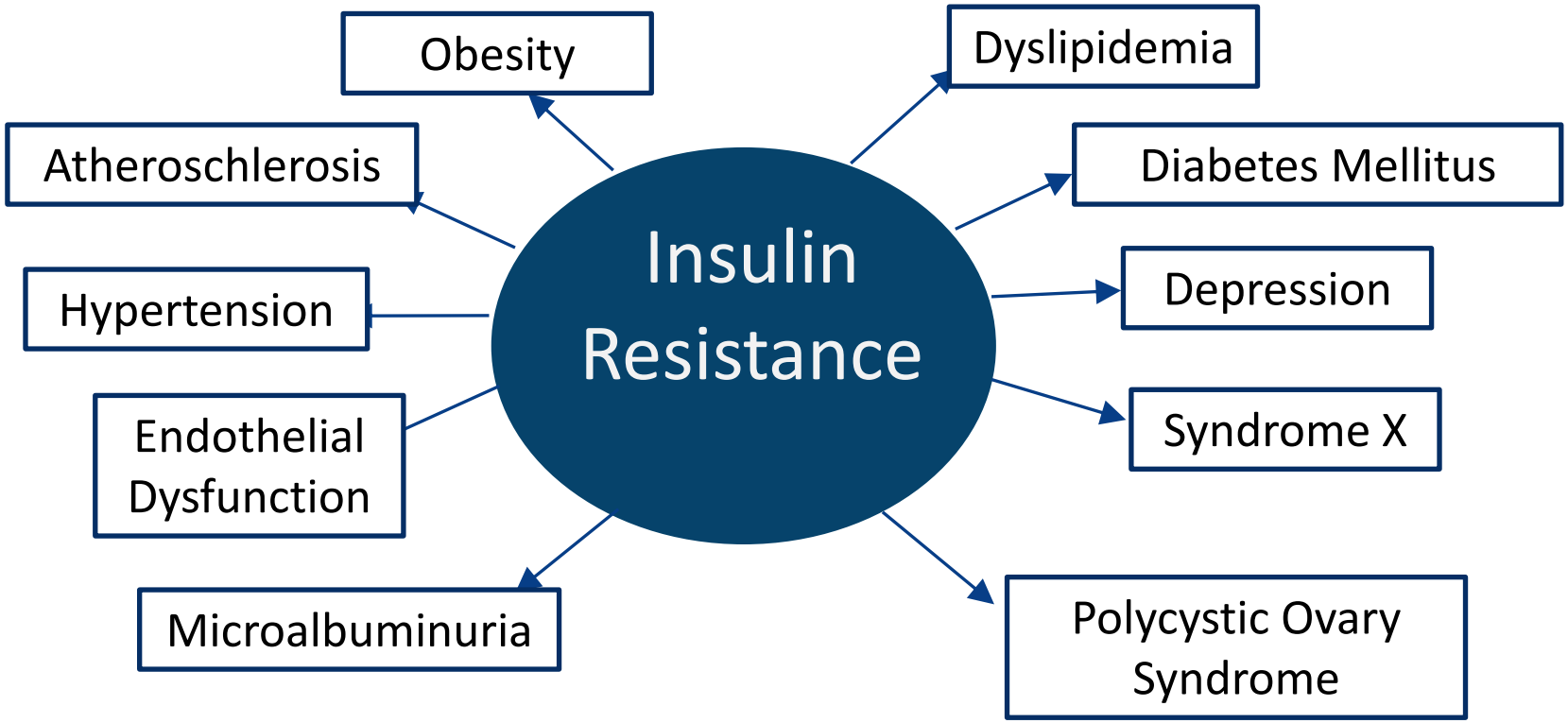
NCEP ATP III. Circulation 2002; 106: 3143; Rasgon & Jarvik. J Gerontol A Biol Sci Med Sci 2004; 59: 178-183; Rasgon et al. 2002

Underlying Mechanisms: Obesity and Insulin Resistance



Steinberg HO, Baron AD. *Diabetologia*. 2002;45:623-634; Caballero AE. *Obesity Res*. 2003;11:1278-1289; Reaven GM. *Diabetes*. 1988;37:1595-1607

Clinical Conditions Associated with Insulin Resistance



NCEP ATP III. Circulation 2002; 106: 3143; Rasgon & Jarvik. J Gerontol A Biol Sci Med Sci 2004; 59: 178-183; Rasgon et al. 2002

Insulin Resistance in CNS

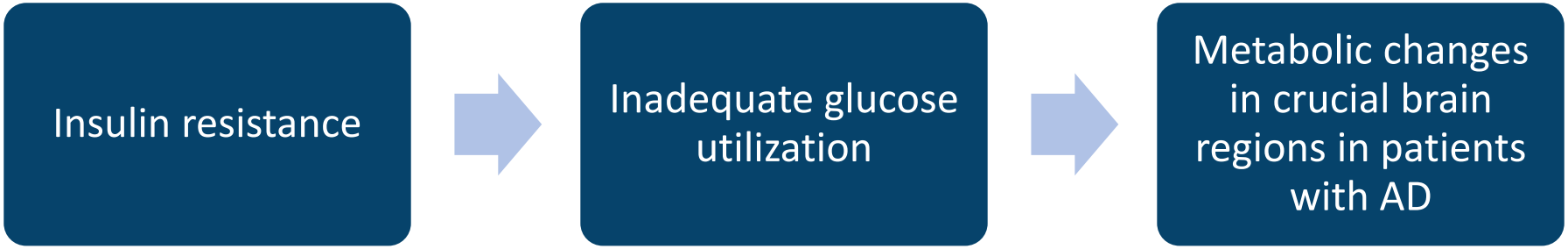
- High prevalence of depression in patients with primary IR
- Non-diabetic patients with major depression often have IR, even after remission of depressive symptomatology
- IR results in
  - Reduced insulin transport into the brain
  - CNS glucose deprivation leads to impairment in brain function
    - Depression
    - Cognitive decline
    - Detrimental affects on behavior that influence quality of glycemic control

Insulin Resistance and Cognition

- Majority of previous studies relating IR and cognition conducted with elderly individuals
  - Increasing age is a major confounder in this association
  - IR generally worsens with increasing age in the elderly
  - Age-related cognitive changes heterogeneous across older adults
    - May be harder to detect specific effects due to IR
    - Global, rather than specific, deficits in relation to metabolic dysfunction
- IR may exist in younger adults even with normal BMI
  - BMI may not be a sensitive measure for younger adults with depression
- High BMI over time
  - Independent predictor of cognitive decline with advancing age



Cognition in Depression, IR, and AD



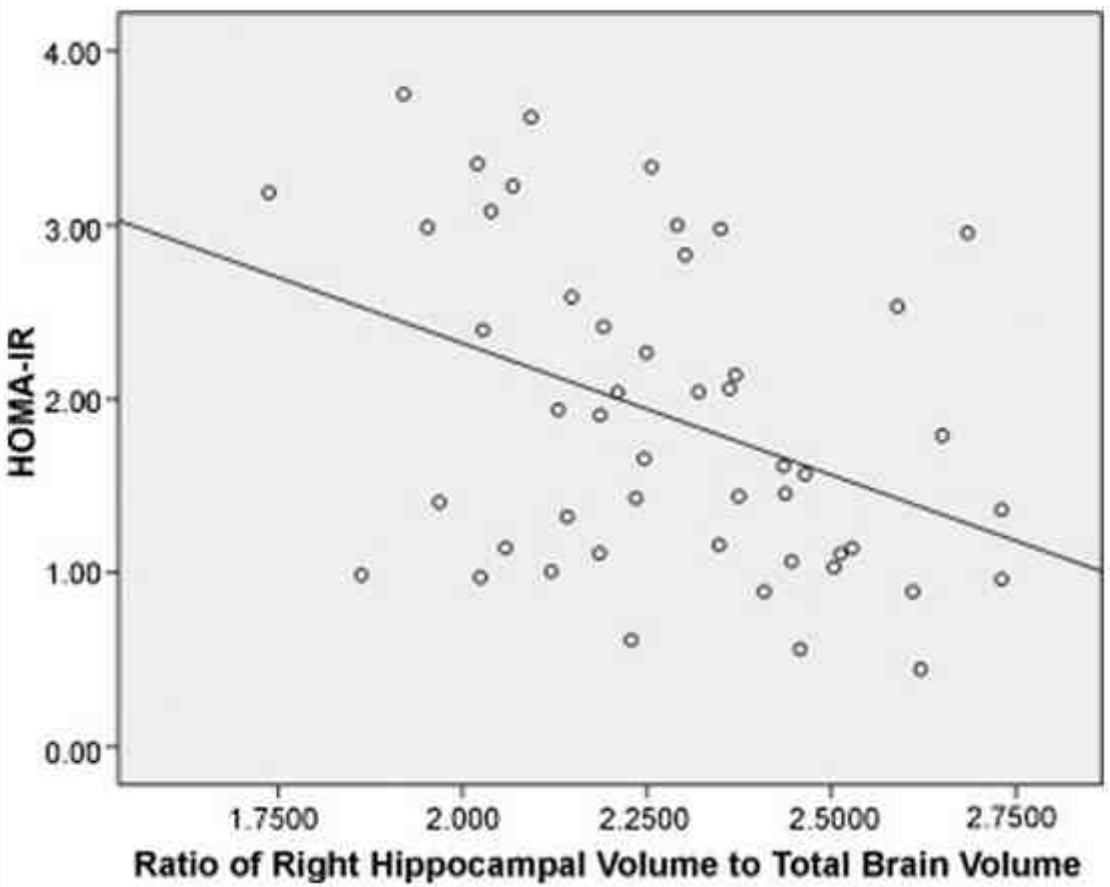
- ***Clinical evidence:*** Affective disorders more common in persons with diabetes than in nondiabetic persons
- ***Neurochemical evidence:*** Reduced serotonergic activity and hyperactivity of the HPA axis
- ***Neuroimaging evidence:*** Reduced cerebral glucose utilization in the limbic area

Rasgon, N., & Jarvik, L. (2004). Insulin resistance, affective disorders, and Alzheimer's disease: review and hypothesis. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59(2), M178-M183. Chicago

Insulin Resistance and Decreased Hippocampal Volume

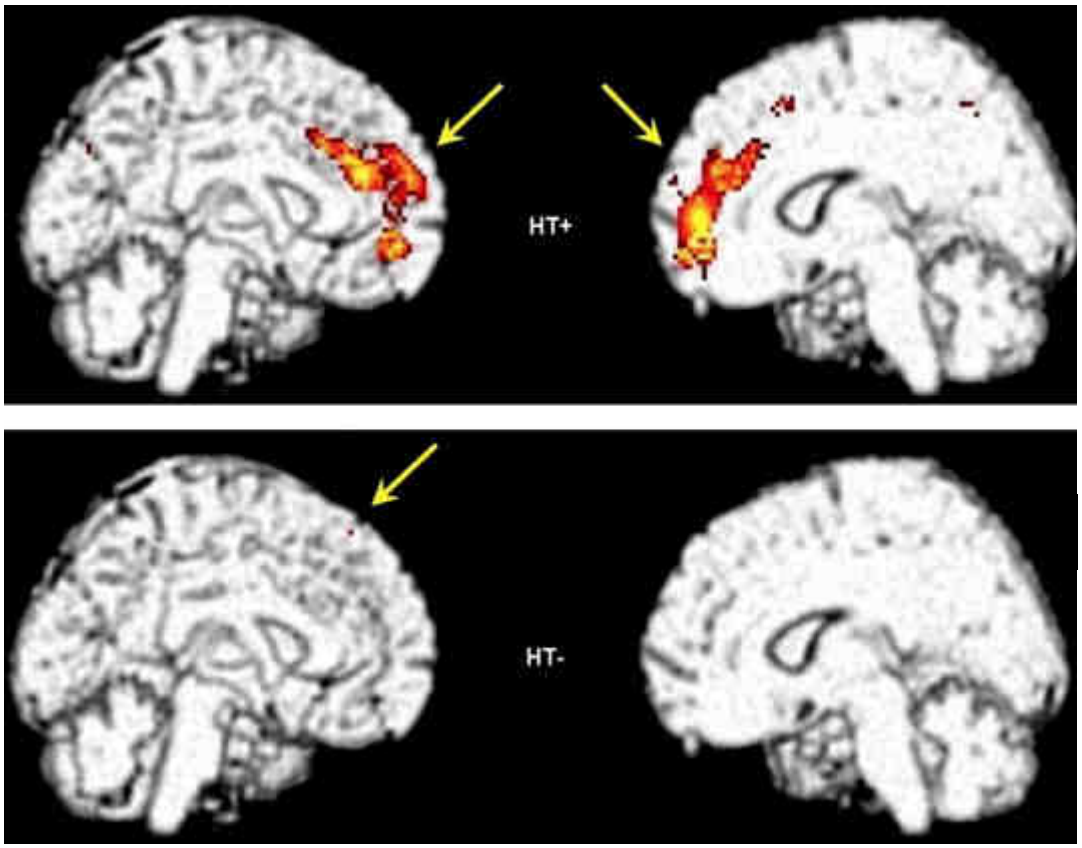
<u>Women at risk for AD:</u>
Multiple regression analysis using raw right hippocampal volume as the dependent variable and total brain volume as an independent variable in addition to HOMA-IR.

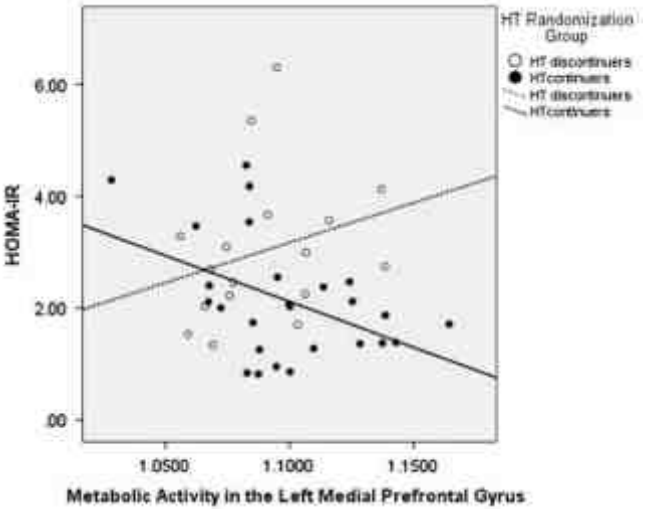
Significant main effect of HOMA-IR on right hippocampal volume (t = −2.768, p = .008).

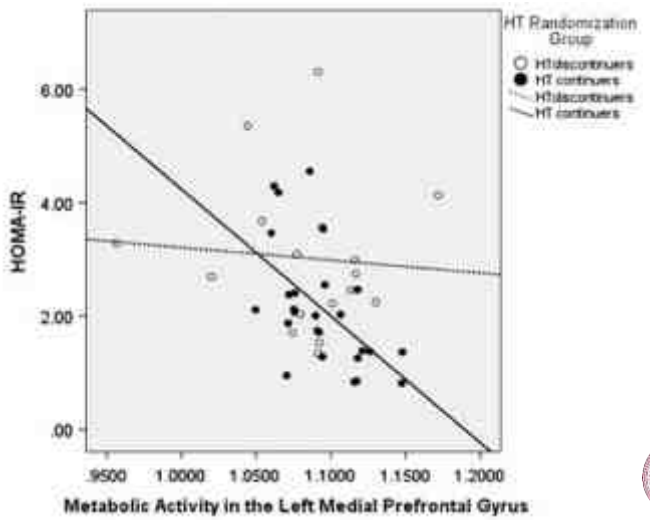


Rasgon, N. L., Kenna, H. A., Wroolie, T. E., Kelley, R., Silverman, D., Brooks, J., ... & Reiss, A. (2011). Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiology of aging, 32(11), 1942-1948. Chicago.

Insulin Resistance and Prefrontal Gyrus Metabolism







HOMA-IR and metabolic activity in the medial prefrontal gyrus within HT continuers (HT+) and discontinuers (HT−).

Rasgon, N. L., Kenna, H. A., Wroolie, T. E., Williams, K. E., DeMuth, B. N., & Silverman, D. H. (2014). Insulin resistance and medial prefrontal gyrus metabolism in women receiving hormone therapy. Psychiatry Research: Neuroimaging, 223(1), 28-36.

Association between insulin resistance and cognition in patients with depressive disorders

Demographics

	Total Sample (N=39)		< 45 years (N=14)		≥ 45 years (N=25)			
	Mean	SD	Mean	SD	Mean	SD	t	p
Age (range)	48.41 (19-71)	13.38	33.79 (19-44)	8.22	56.60 (45-71)	7.23	-9.00	<.001
Education (range)	16.56 (12-23)	2.35	16.00 (12-20)	2.29	16.88 (12-23)	2.37	-1.13	.27 (ns)
HDRS-21 (range)	9.36 (1-20)	4.63	12.07 (5-20)	4.18	7.84 (1-16)	4.21	3.02	.01
Age of MDD onset	26.71 (10-68)	14.55	19.69 (10-32)	6.66	30.86 (12-68)	16.40	-2.83	.01
SSPG (range)	140.64 (52-323)	69.67	161.46 (65-304)	68.12	128.87 (52-323)	69.21	1.37	.18 (ns)
BMI (range)	27.68 (19.6-49.2)	5.50	30.32 (19.6-39.3)	7.09	26.20 (20.4-38.6)	3.79	2.02	.06 (ns)
FSIQ (range)	122.55 (98-142)	10.22	117.36 (98-138)	11.33	125.14 (109-142)	8.77	-2.18	.04

Methods

- Subjects
  - Non-diabetic adults (N=39)
  - Men and women aged 19-71
  - BMI < 40 kg/m2
  - History of MDD currently not in a mood episode
  - Cognitively intact (MMSE score>28)
- Procedures
  - Insulin suppression test for steady state plasma glucose
  - Cognitive testing

Wroolie, T. E., Kenna, H. A., Singh, M. K., & Rasgon, N. L. *J Psychiatr Res.* 2014; 60, 65-72.

Analyses

- Multiple linear regressions
  - Model 1: Age, education, SSPG, and any significantly associated predictors
  - Model 2: Age, education, BMI, and any significantly associated predictors
  - Post hoc analyses within dichotomized age groups (<45 and ≥45 years)

Wroolie, T. E., Kenna, H. A., Singh, M. K., & Rasgon, N. L. *J Psychiatr Res.* 2014; 60, 65-

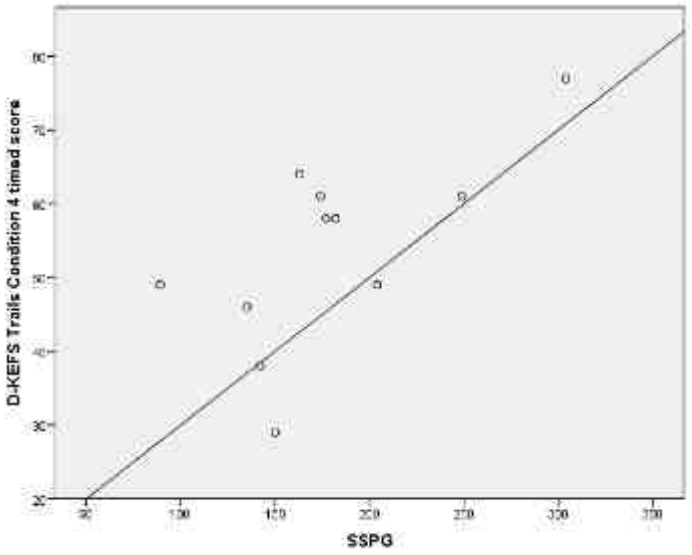
IR vs. BMI Effects on Cognition: Whole Group

- Model 1: not significant
  - SSPG level was not significantly associated with performance on any cognitive variables
- Model 2: ($F(3,30)=4.562$, $p<.05$)
  - Higher BMI was associated with worse dominant hand fine motor ability($t=-2.21$, $p=.04$)
  - Higher age ($t=-3.23$, $p<.01$) and lower level of educational attainment ($t=-2.21$, $p=.04$) also associated with worse dominant hand fine motor ability

Wroolie, T. E., Kenna, H. A., Singh, M. K., & Rasgon, N. L. *J Psychiatr Res.* 2014; 60, 65-

IR vs. BMI Effects on Cognition: Age-related

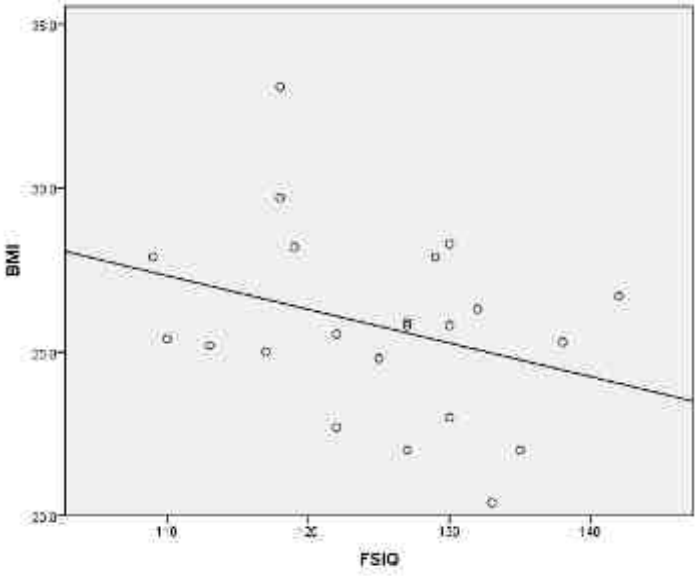
Cognition in subjects < 45 years



- Model 1: (F(3,7)=8.26, p<.05)
  - Higher SSPG associated with worse (cognitive flexibility; (t=4.24, p=.004)*
- Model 2: not significant
  - BMI ***not*** significantly associated with any cognitive variables

*significant with Bonferroni correction

Cognition in subjects ≥ 45 years



- Model 1: not significant
  - SSPG was ***not*** significantly associated with any cognitive variables
- Model 2: (F(3,18)=7.60, p<.01)
  - Higher BMI was significantly associated with lower FSIQ

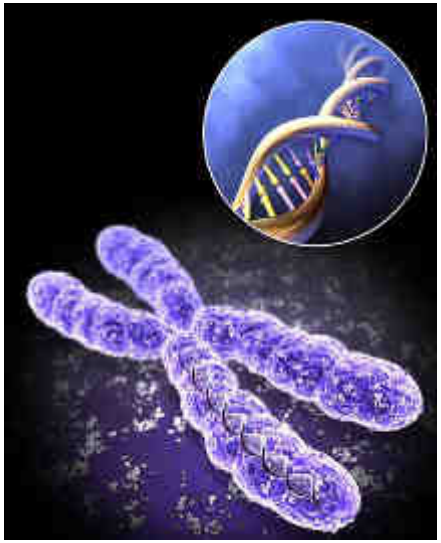
Wroolie, T. E., Kenna, H. A., Singh, M. K., & Rasgon, N. L. *J Psychiatr Res.* 2014; 60, 65-

Conclusion

- Differential cognitive effects of IR and BMI are age-specific
- Higher IR associated with executive function deficits in younger adults
  - Similar to what is seen in adolescents with Metabolic Syndrome
- Higher BMI associated with global decline in older adults
  - Similar to what is seen in older adults with DM2

Wroolie, T. E., Kenna, H. A., Singh, M. K., & Rasgon, N. L. *J Psychiatr Res.* 2014; 60, 65-

Telomeres and Biological Aging





- Telomeres shorten over time
- Accelerated shortening due to inflammation & oxidative stress
- Emerging index of biological age
- Short TL predicts subsequent morbidity and mortality
- Social and psychological factors (chronic perceived stress, pessimism, social disadvantage) are associated with short TL

Blackburn, *Nature* 1981; Epel, *PNAS* 2004; O'Donovan, *BBI* 2009; Steptoe, *BBI* 2011

Genetic Risk Factor & Cell Aging

APOE-e4 is a major genetic risk factor for Alzheimer's disease and early mortality

Table 2. *Odds ratios and 95% CI for predictors of telomere shortening*

	Odds Ratio (CI)	
Hormone group		
OFF†		
ON	3.97	(0.59, 26.6)
APOE carrier		
NO†		
YES	**6.26***	(1.02, 38.39)

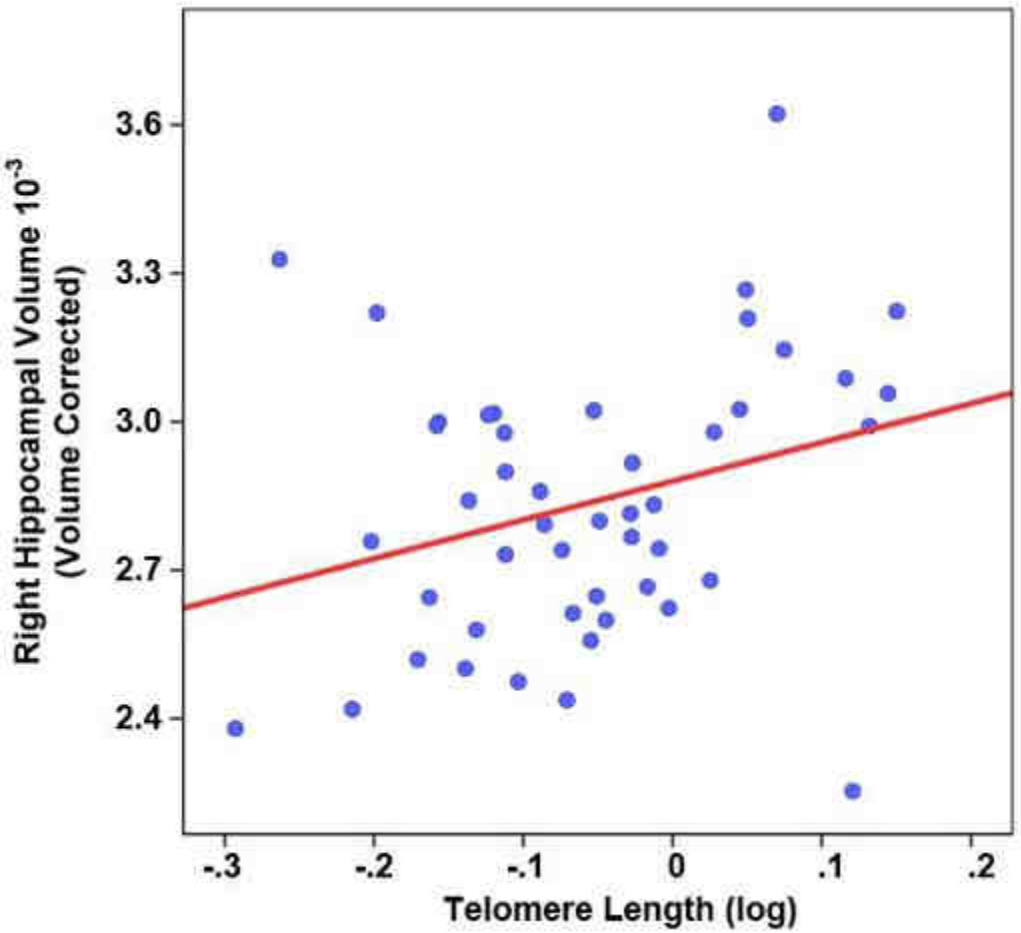
* $p < 0.05$
† Reference group
Adjusted for age, education and baseline TL.
Note: R^2= .30 (Cox & Snell). Model $\chi^2(1) = 14.81$, $p = .011$
Non-carrier, Carrier (n = 24, 18) On, Off HT (n = 26, 16)



Prospective study, APOE-e4 carriers had 6x greater odds of TL shortening
High-functioning, healthy mid-life women with the e4 allele bear markers of cellular aging

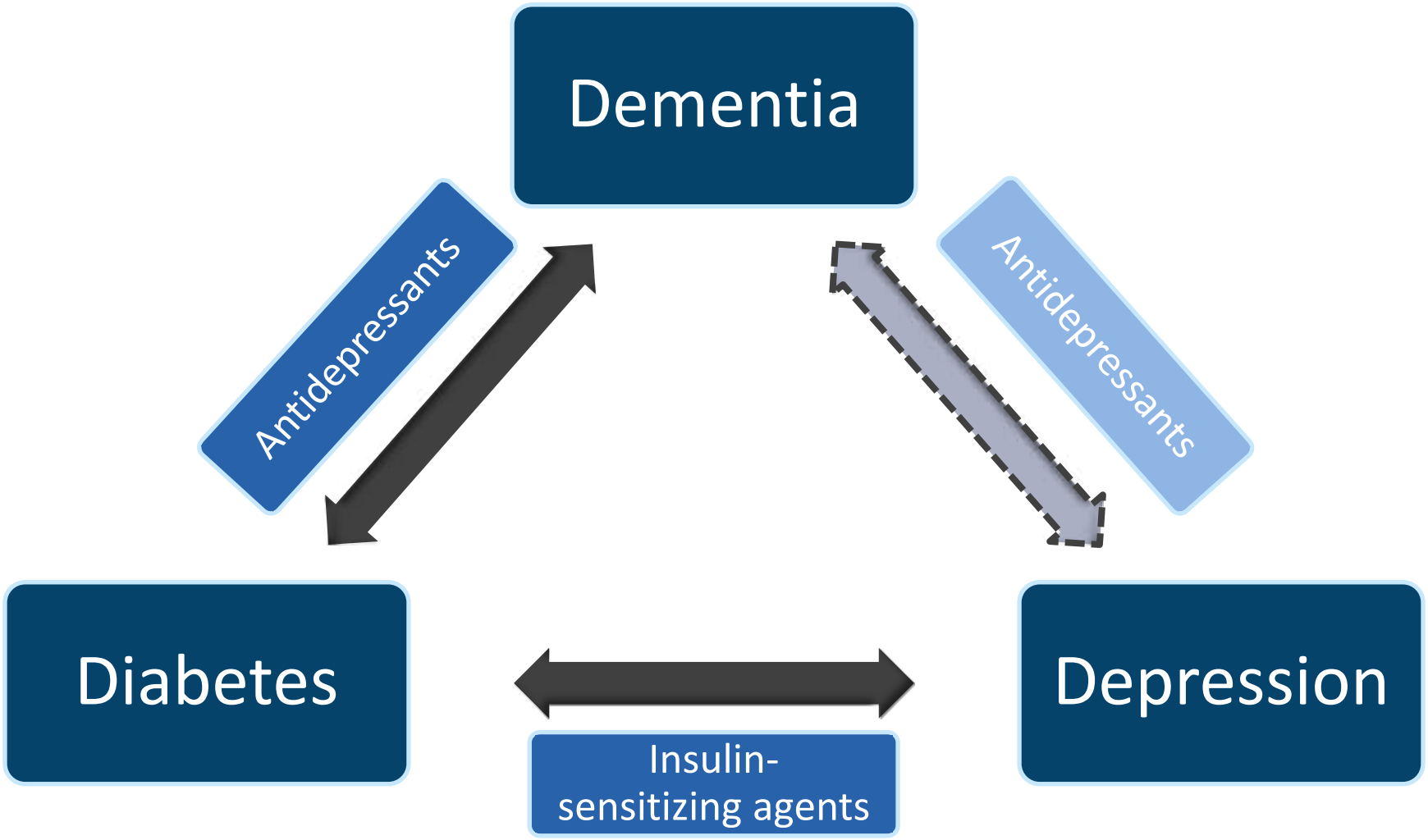
Jacobs, Epel, Blackburn et al. *Under review, PNAS*

TL Correlated with Hippocampal Volume



N = 47, p = 0.029

Breaking Through the Vicious Cycle: Pharmacological Disruption



Identifying Patients Who Are at Risk for Insulin Resistance



- Abdominal obesity
  - WC: men, >40 inches; women, >35 inches
- Elevated triglycerides
  - >149 mg/dL
- Decreased HDL
  - Men: <40 mg/dL;
    women: <50 mg/dL
- Elevated blood pressure
  - >129/>84 mm Hg
- Increased fasting glucose
  - >99

Breaking Through the Vicious Cycle: Pharmacological Disruption

Improve diet

Exercise

Decrease obesity

Future Directions: Primary Prevention

Pharmacological

- Optimal treatment of depression
- Early diagnosis and management of metabolic dysfunction
- Aggressive treatment of diabetes

Non-pharmacological

- Stress reduction and management
- Exercise
- Ketogenic diet

Key Points

- Alzheimer's disease (AD) frequently occurs with diabetes, CAD, and depression, which may contribute to the development of AD and other dementias
- Insulin resistance may be a link between mood disorders, vascular disease, and dementia
- Patients with diabetes, CAD, or depression are at risk for dementia and their cognitive performance should be monitored; these conditions should be treated to improve patient health and reduce the risk of dementia
- After dementia has been identified, it should be managed with the appropriate lifestyle modifications and treatments

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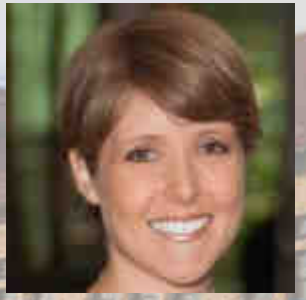
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