营养对糖尿病并发认知功能障碍作用的研究

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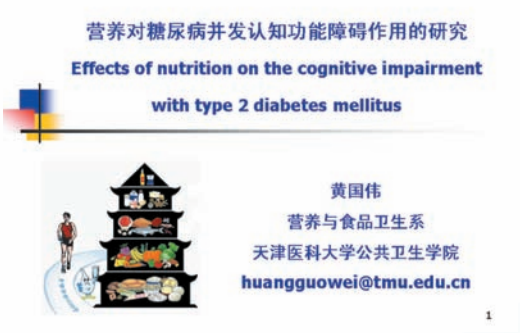
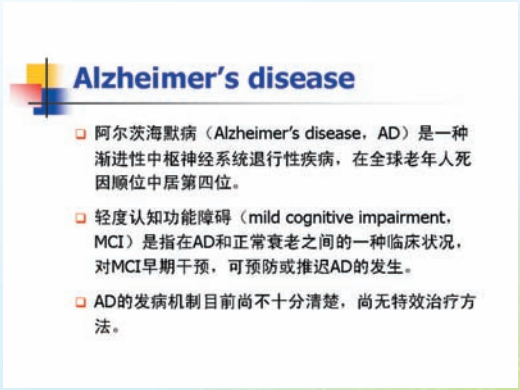
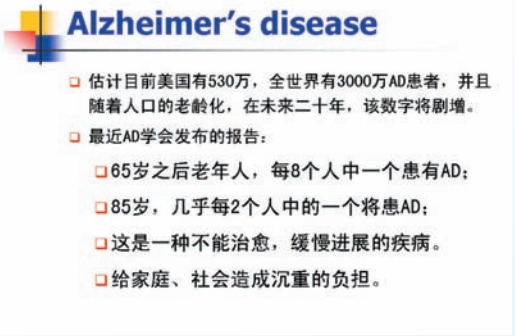
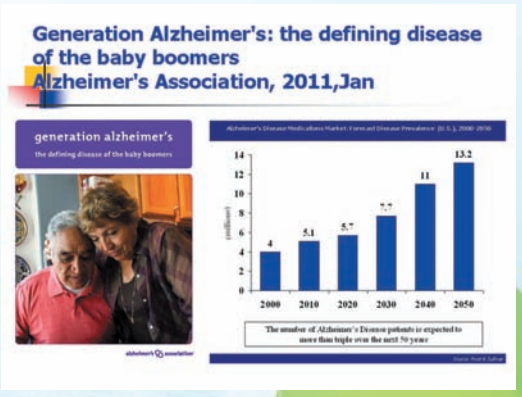
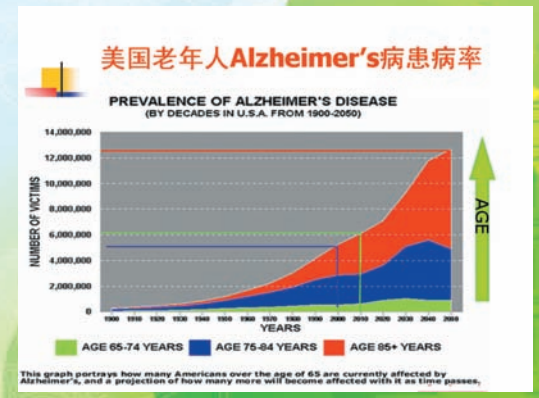


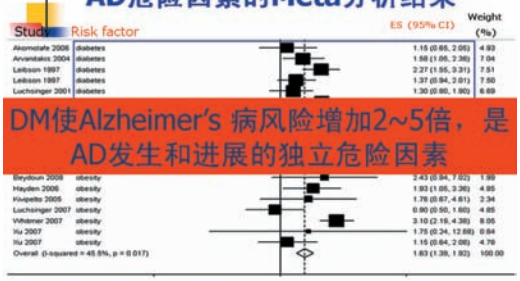






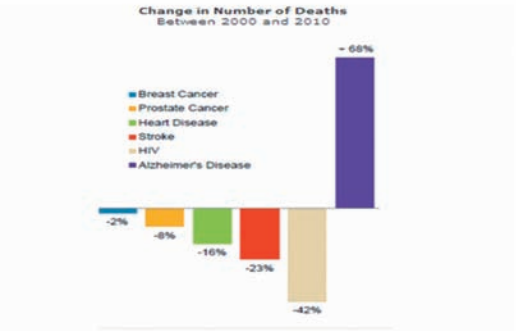


AD危险因素的Meta分析结果



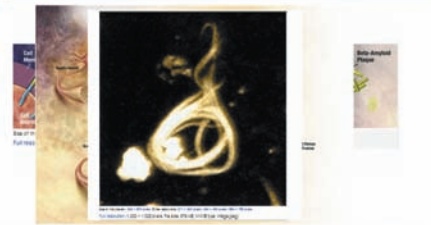
DM使Alzheimer's 病风险增加2~5倍，是AD发生和进展的独立危险因素

Profenno LA, et al. Biol Psychiatry, 2010 Mar IF=8.674



阿尔茨海默病（AD）病理学特征

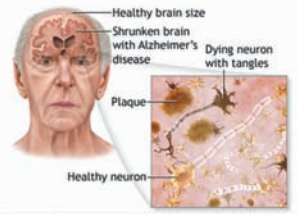
①细胞外Aβ的蓄积形成的神经斑块
②神经元内磷酸化tau蛋白蓄积形成的神经纤维缠结



Kronenberg G, Colla M, Endres M. Folic Acid, Neurodegenerative and Neuropsychiatric Disease. Current Molecular Medicine 2009; 9:315-323

阿尔茨海默病（AD）病理学特征

触发神经元变性：引起程序性细胞死亡（凋亡）；抑制酶功能以及神经元对糖的利用。



Alzheimer's disease

- AD临床表现为记忆力进行性减退，并伴有不同程度的认知、语言和人格方面的异常症状。
- 病理表现为脑萎缩，中枢神经区域神经元和神经突触明显减少或消失，并伴有大量神经纤维缠结（NFTs）和老年斑等特征性病理变化。
- 神经细胞内tau蛋白形成NFTs，β-淀粉样蛋白（Aβ）大量沉积在海马和皮质神经细胞内，形成以Aβ为核心的老年斑，并诱导神经元的凋亡。

T2DM与AD有共同的病理生理基础

- AD：β-淀粉样蛋白（Aβ）堆聚是AD特征性病理变化。
- T2DM：β细胞丢失和淀粉样蛋白沉积是T2DM胰岛最具特征性的两种病理变化。
- tau蛋白过磷酸化形成神经原纤维缠结(NFTs)是AD的主要病理特征之一，脑内胰岛素抵抗可引起tau蛋白过度磷酸化。
- 糖基化产物-高级糖化物终末产物(AGEs)的堆聚：不仅是AD和T2DM共同的病理学变化，也促发代谢综合征。

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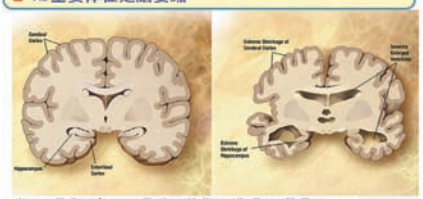
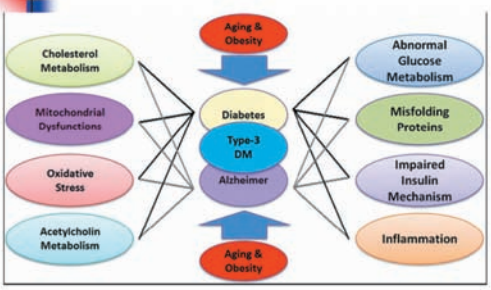
阿尔茨海默病（AD）病理学特征

- AD临床特征主要是记忆损失和认知障碍。
- AD主要体征是脑萎缩



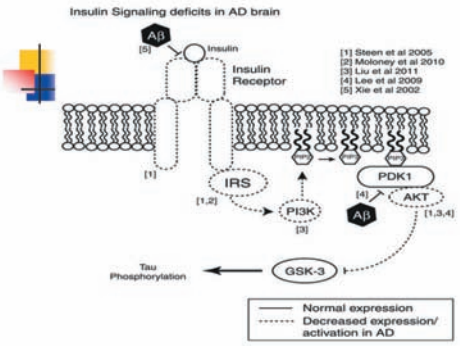
Liu L, Green T, Kadish I, et al. DNA methylation impacts on learning and memory in aging. Neurobiology of Aging 2009;30:549-560.

The common links between diabetes and AD

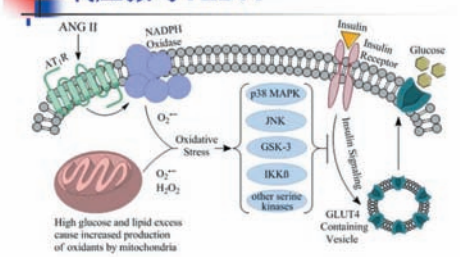


3型糖尿病

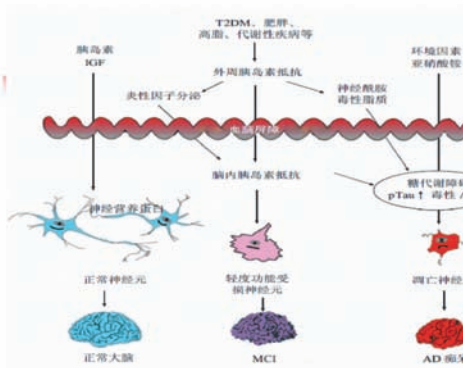
- T2DM两大主要病理生理基础：胰岛β细胞功能衰退导致胰岛素分泌缺乏和胰岛素抵抗(IR)。
- AD两大主要病理生理基础：患者脑内亦存在胰岛素减少和胰岛素抵抗情况，具备与T2DM相似的改变，只是病变部位不同。
- 因此有学者提出AD可能是另一种类型的糖尿病，即"3型糖尿病"。



氧应激与T2DM



Free Radic Biol Med. 2011 September 1; 51(5): 993–999



T2DM与AD

Xu W, Caracciolo B, Wang HX, et al. Risk Factors and Preventive Accelerated progression from mild cognitive impairment(MCI) to dementia in people with diabetes. Diabetes, 2010 Nov;59 IF=8.889

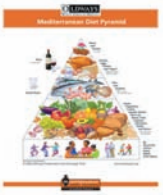
- Objective: Whether diabetes and pre-diabetes accelerate the progression from to dementia?
- Methods: 963 cognitively intact participants and 302 with MCI, followed 9 y.
- Result: In a Kaplan-Meier survival analysis, diabetes and pre-diabetes accelerated the progression from MCI to dementia by 3.18 years.

T2DM与AD有共同的病理生理基础

- T2DM和AD的共同病理生理基础，决定对二者的防治具有一定的共性和密切相关。
- 对T2DM的防治和膳食干预措施同样可以预防许多AD相关的神经退行性病变。

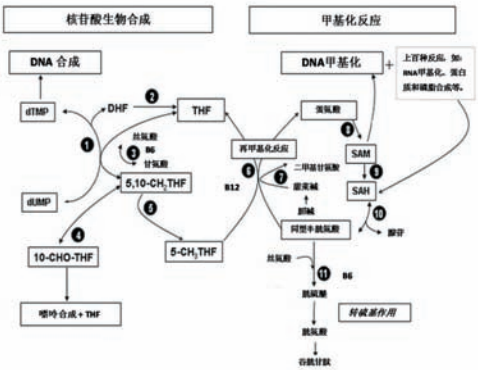
改善T2DM与AD相关的膳食因素

- 甲基化循环相关的营养素：叶酸、维生素B12、维生素B6、S-腺苷甲硫氨酸（SAM）。
- n-3脂肪酸。
- 抗氧化物。
- Mediterranean-type diet。

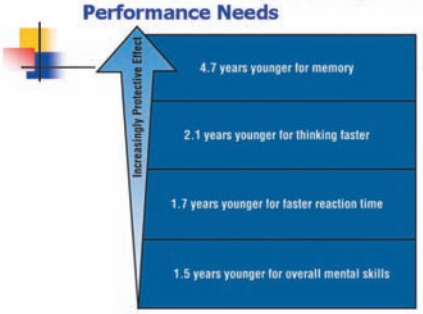


叶酸对T2DM和AD的作用

- 甲基化循环相关的营养素：叶酸、维生素B12、维生素B6、S-腺苷甲硫氨酸（SAM）。
- T2DM和AD患者都可表现为高Hcy血症，体内叶酸水平的降低；
- 研究显示补充叶酸可减低T2DM和AD患者血Hcy水平，减轻炎症反应，增加抗氧化能力，并能改善血糖控制和胰岛素抵抗以及认知功能。



Folate Benefits Supports Cognitive Performance Needs



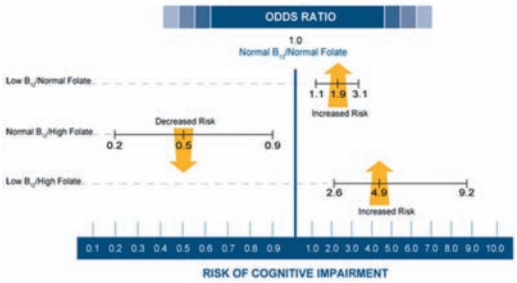
— Durga J et al. The Lancet 2007;369:208-16.

叶酸与AD

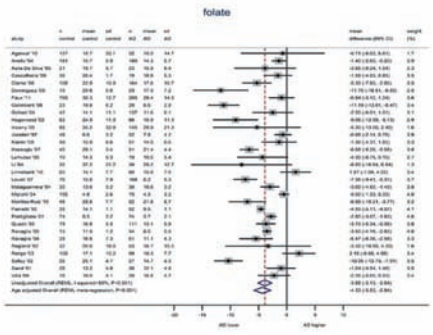
Daviglus ML, Plassman BL, Pirzada A, et al. Risk Factors and Preventive Interventions for Alzheimer Disease: State of the Science. Arch Neuro, 2011 May 9. IF=7.108

- **DATA SOURCES: MEDLINE and the Cochrane Database of Systematic Reviews from 1984 through October 27, 2009.**
- **Study Selection: 300 for cohort studies and 50 for randomized controlled trials.**
- **DATA SYNTHESIS: Mediterranean-type diet, folic acid intake, low or moderate alcohol intake, cognitive activities, and physical activity were associated with decreased risk. The quality of evidence was low for all of these associations.**

HIGH FOLATE AND NORMAL B_{12} ARE PROTECTIVE AGAINST COGNITIVE IMPAIRMENT



— Morris et al. Am J Clin Nutr 2007;85:193-200



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叶酸对糖尿病认知功能的影响

- DM患者存在高Hcy血症，并且与认知功能障碍相关，DM患者高Hcy血症与认知功能障碍的相关性要强于非糖尿病患者。
- DM患者体内叶酸水平的研究很少，报道补充叶酸能降低DM患者血Hcy水平，减轻炎症反应，增加抗氧化应激能力，并能改善血糖控制和胰岛素抵抗。

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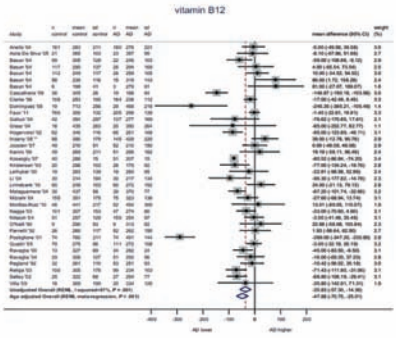

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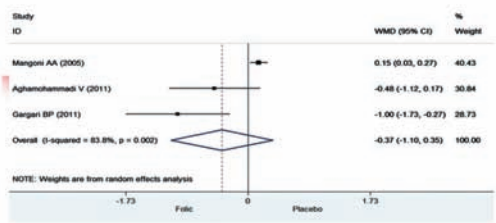

Fig. 3 Effect of folic acid supplementation versus placebo on HbA1c levels

Patcharaporn Sudchada , Surasak Saokaew , Sorattaya Sridetch , Siriwan Incampa , Sopida Jaiyen , Warangkana Khaith...

Effect of folic acid supplementation on plasma total homocysteine levels and glycemic control in patients with type 2 diabetes: A systematic review and meta-analysis

Diabetes Research and Clinical Practice Volume 98, Issue 1 2012 151 - 158

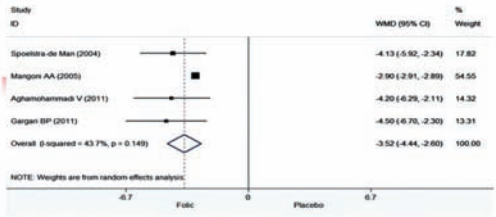

Fig. 2 Effect of folic acid supplementation versus placebo on serum homocysteine.

Patcharaporn Sudchada , Surasak Saokaew , Sorattaya Sridetch , Siriwan Incampa , Sopida Jaiyen , Warangkana Khaith...

Effect of folic acid supplementation on plasma total homocysteine levels and glycemic control in patients with type 2 diabetes: A systematic review and meta-analysis

Diabetes Research and Clinical Practice Volume 98, Issue 1 2012 151 - 158

叶酸与T2DM

- Folic acid supplementation in patient with T2DM
  - may reduce tHcy levels
  - have a trend to associate with better glycemic control compared with placebo.
  - improved the total plasma antioxidant capacity in hemodialysis patients.

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Odds ratios of mild cognitive impairment for folate, methyl donor and Hcy in T2DM

Variables	Unadjusted		Adjusted	
	OR(95%CI)	P value	OR(95%CI)	P value
SAM (per nmol/L increase)	0.97(0.95-0.99)	0.005	0.96（0.93-0.99）	0.011
SAH (per nmol/L increase)	1.20(1.02-1.42)	0.030	1.22（0.98-1.53）	0.081
SAM/SAH ratio	0.71(0.56-0.89)	0.004	0.68（0.50-0.91）	0.011
Folate (per μg/L increase)	0.87(0.78-0.98)	0.020	0.72(0.56-0.93)	0.013
Hcy (per μg/L increase)	1.28(1.02-1.59)	0.034	1.34（0.97-1.85	0.076

Fatty acids and AD

- Elevated saturated fatty acids could have negative effects on age-related cognitive decline and mild cognitive impairment (MCI).
- Epidemiological evidence suggests a possible association between fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; in particular, n-3 PUFA) and a reduced risk of cognitive decline and dementia.

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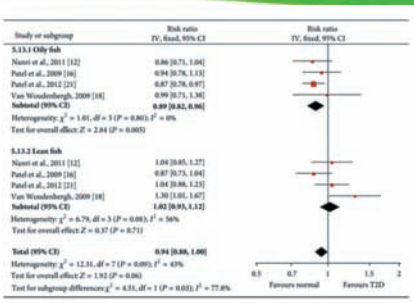

Figure 3: Forest plot of the meta-analysis for oily fish and lean fish intake and incidence of type 2 diabetes.

Ming Zhang, et al. International Journal of Endocrinology, 2013, 1-11

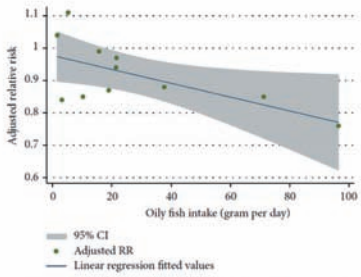

FIGURE 4: Linear regression of adjusted RR of T2D versus oily fish intake. The upper and lower bands denote the 95% confidence interval on mean of the predicted value, $R^2 = 0.40$.

Ming Zhang, et al. International Journal of Endocrinology, 2013, 1-11

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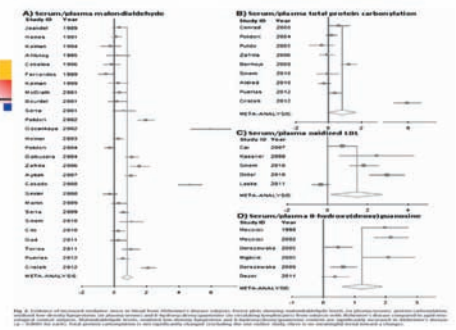
抗氧化物与AD

- **Alzheimer's disease and mild cognitive impairment:**
  - Lipid peroxidation are elevated in blood.
  - copper metabolism is dysregulated.
  - total antioxidant capacity is decreased.
  - none of the major antioxidative enzymes are significantly decreased.
  - non-enzymatic antioxidants in blood (particularly uric acid, vitamins A, E and C, α - and β -carotene) are significantly decreased.

Neurobiol Dis. 2013 Nov;59:100-10. Oxidative stress in blood in Alzheimer's disease and mild cognitive impairment: a meta-analysis.



M. Schrag, et al. Neurobiology of Disease 59 (2013) 100–110.

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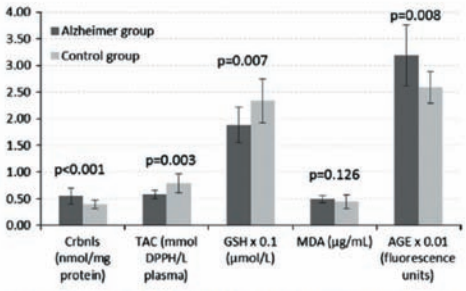

Fig. 2. Markers of oxidative stress for the AD patients compared to controls.

Miriana Gubandru, et al. Food and Chemical Toxicology xxx (2013) xxx–xxx.

Table 2
Results of meta-analyses

Nutrient	Number of publications	Meta-analysis In all cases levels were lower in AD patients than in controls	Subtotals on AD and control populations reported not to differ in protein and energy nourishment	
			Number of publications	Meta-analysis In all cases levels were lower in AD vs controls
Vitamin A	9 studies [44,65,72,74,75,78,100–102]	$P < .001$	6 studies [44,65,74,75,78,100]	$P = .052$
Folate	31 studies [36,37,46,84,85,103–128]	$P < .001$	14 studies [46,84,105,107,109–112,114, 116,120,122,123,125]	$P \leq .001$
Vitamin B12	33 studies [35–37,44,46,49,84,85,103,105, 107–112,114–123,125–131]	$P < .001$	16 studies [44,46,49,84,105,107,109–112, 114,116,120,122,123,125]	$P \leq .001$
Vitamin C	8 studies [44,74,75,77,79,132–134]	$P < .001$	5 studies [44,74,75,79,133]	$P \leq .001$
Vitamin D	5 studies [47,98,99,135,136]	$P = .075$	NA	NA
Vitamin E	20 studies [44,65,69,71–78,100,101,132, 133,137–141]	$P < .001$	11 studies [44,65,69,74,75,78,100,133,137, 139,141]	$P \leq .001$
Copper	5 studies [70,80,51,53,142]	NS	NA	NA
Iron	5 studies [70,51,53,129,142]	NS	NA	NA
Zinc	5 studies [70,51,53,142,143]	$P = .05$	NA	NA

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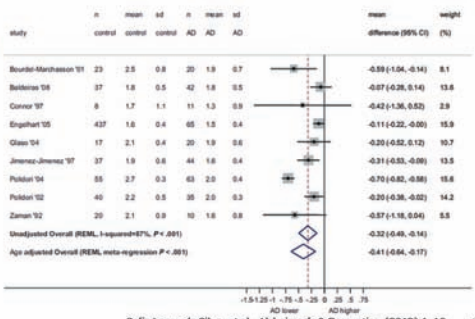
vitamin A



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Dietary Antioxidant Intake and Risk of T2DM

- Vitamin E intake was significantly associated with a reduced risk of type 2 diabetes. The relative risk (RR) of type 2 diabetes between the extreme quartiles of the intake was 0.69 (95% CI 0.51– 0.94, *P* for trend 0.003).
- Among single carotenoids, β -cryptoxanthin intake was significantly associated with a reduced risk of type 2 diabetes (RR 0.58, 95% CI 0.44–0.78, *P* 0.001).

DIABETES CARE, 2004,27(2):362-366.

vitamin C

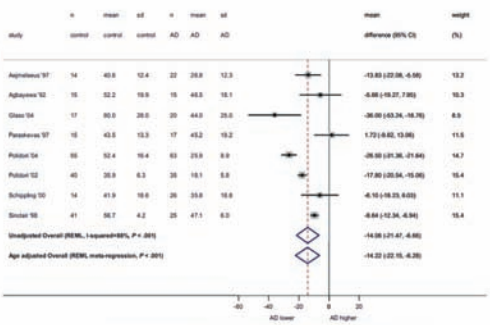

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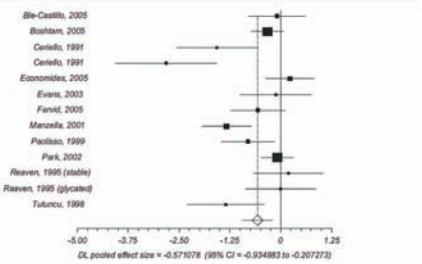
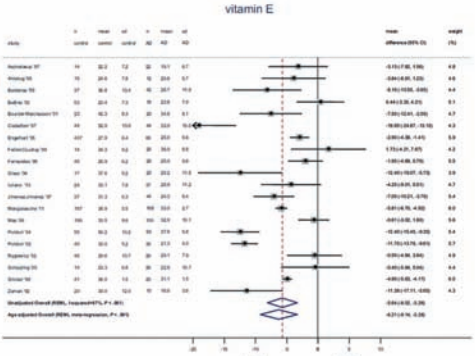
Figure 2. Meta-analysis of 13 randomised clinical trials that describe the effects of antioxidant vitamins C or E consumption on glycated haemoglobin (HbA_{1c}) in type 2 diabetes



Key: Random-effects model of meta-analysis of weighted mean difference of HbA_{1c} levels compared to control group, showing the mean difference for each study and 95% confidence intervals, with the pooled meta-statistic shown as a diamond.

2011 11: 62 *British Journal of Diabetes & Vascular Disease*

vitamin E



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Dietary Antioxidant Intake and Risk of T2DM

- Oxidative stress is strongly linked to the development of diabetes and its complications.
- While laboratory and animal studies show benefits from antioxidant treatments, human clinical trials of the major dietary antioxidants—vitamin E, vitamin C, and carotenoids—have been largely negative.
- The year 2000 report of the National Academy of Sciences panel on Dietary Antioxidants and Related Compounds, which states that the evidence does not warrant increased intakes of the antioxidants to protect against chronic degenerative diseases, including diabetes.

Mediterranean Diet Pyramid

Mediterranean vs industrialized diet

- Olive oil
- Greens
- Fresh fruits
- No corn
- Raw, lightly cooked
- Unprocessed
- Natural flavors
- Fish
- Some dairy products/Goat milk
- Other oils/ Trans fats
- Fries, Potatoes, Fries...
- Canned fruits
- Corn, Corn, Corn....
- Charred, Deep fried
- Highly processed
- Artificial flavors, colors, sweeteners
- Redmeat
- High dairy/ Cow milk

The Mediterranean Diet

- From countries near the Mediterranean Sea
- Characterized by:
  - **Lots of fruit, vegetables, bread, grains, beans, nuts, and seeds**
  - **Olive oil as the main source of fat**
  - **Dairy products, fish, and poultry**
  - **Little red meat**
  - **Wine in moderation**

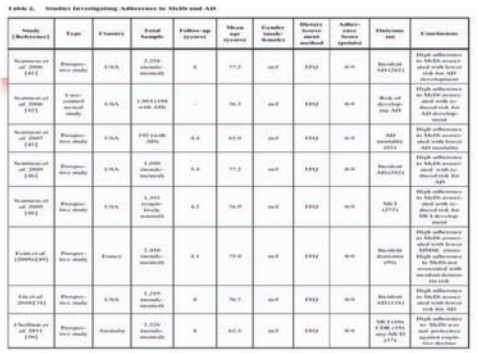
Health Benefits

- It has been proven that the Mediterranean Diet helps reduce the risk of:
  - Metabolic Syndrome
  - Coronary heart disease: decreases LDL and increases HDL
  - Hypertension
  - Cancers
  - Stroke
  - **Diabetes**
  - **Alzheimer's disease**

To Your Good Health!

There are many reasons to follow the Med Diet! Scientific evidence shows that it can help you:

- Achieve Weight Loss and Weight Management Goals
- Lower Your Risk of Heart Disease and High Blood Pressure
- Fight Certain Cancers and Chronic Diseases
- Reduce Asthma
- Avoid Diabetes
- Resist Depression
- Nurture Healthier Babies
- Ward off Parkinson's Disease



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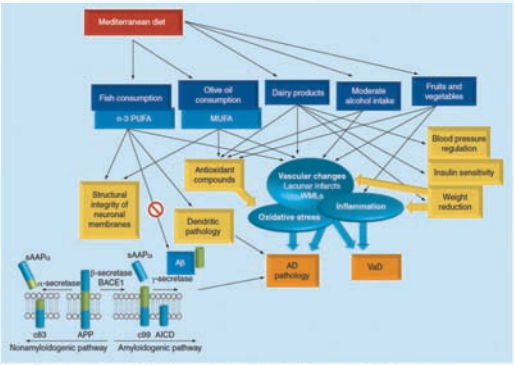
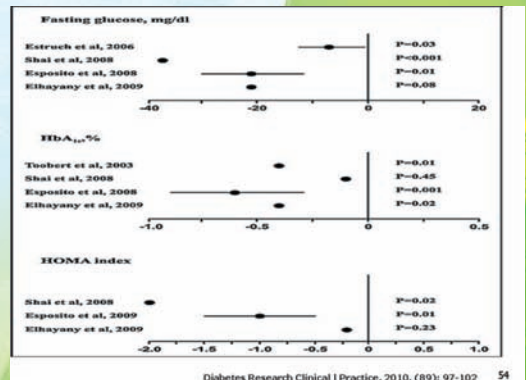


Figure 1. Overview of the principal underlying mechanisms linking the Mediterranean diet and its principal components to Alzheimer's disease and vascular dementia.



Diabetes Research Clinical I Practice, 2010, (89): 97-102 54

Summary

- T2DM使AD风险增加2-5倍，是AD发生和进展的独立危险因素。
- T2DM与AD有共同的病理生理基础。
- 有学者提出AD可能是另一种类型的糖尿病，即“3型糖尿病”。
- T2DM和AD的共同病理生理基础，决定对二者的防治具有一定的共性和密切相关。
- 改善T2DM与AD相关的膳食因素：叶酸、维生素B12、B6、SAM；n-3脂肪酸；抗氧化物；地中海模式的膳食。

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Thank You !