

失智症之早期診斷

Early Diagnosis of Dementia

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Why early diagnosis?

- Early diagnosis and early treatment?
 - Treatable or reversible dementia.
 - Current treatment of degenerative dementia.
 - Coming treatment of Alzheimer's disease.
 - Factors affecting progression of dementia.
- How to do early diagnosis?
 - Symptoms and signs
 - Screening test or formal test battery
 - Laboratory diagnosis
 - Neuroimaging study

Early diagnosis and early treatment

- Treatable or reversible dementia
 - Vitamin B12 and folic acid deficiency
 - Hypothyroidism
 - CNS infection/ TB/ Syphilis / Cryptococcus
 - Subdural hematoma/ Hydrocephalus / Meningioma
 - Vascular dementia or cognitive impairment

Early diagnosis and early treatment

Current treatment for dementia

- Cholinesterase inhibitor*
 - donepezil (Aricept), rivastigmine (Exelon), galanthamine (Reminyl)
- NMDA receptor antagonist (uncompetitive)
 - memantine (Ebixa, Witgen)#
- Combo therapy (CHEI + NMDA)
- * Approved for mild to moderate AD;
- # Approved for moderate to severe AD

用在輕至中度的阿茲海默症患者的 乙醯膽鹼水解酶抑制劑

- 認知功能改善平均 **-2.7 分** (95%CI -3.0至 -2.3, $p < 0.00001$) ADAS-Cog 70 分量表的中間值範圍。
- 臨床醫師的臨床整體印象 (CIGIC或CIBIC+) 在治療組通常可得到正面改變評價。
- 治療效果也包括在日常生活功能 (ADL) 及精神行為症狀 (BPSD) 的改善。
- 各方面的治療效果皆不大。 (Cochrane 2006)

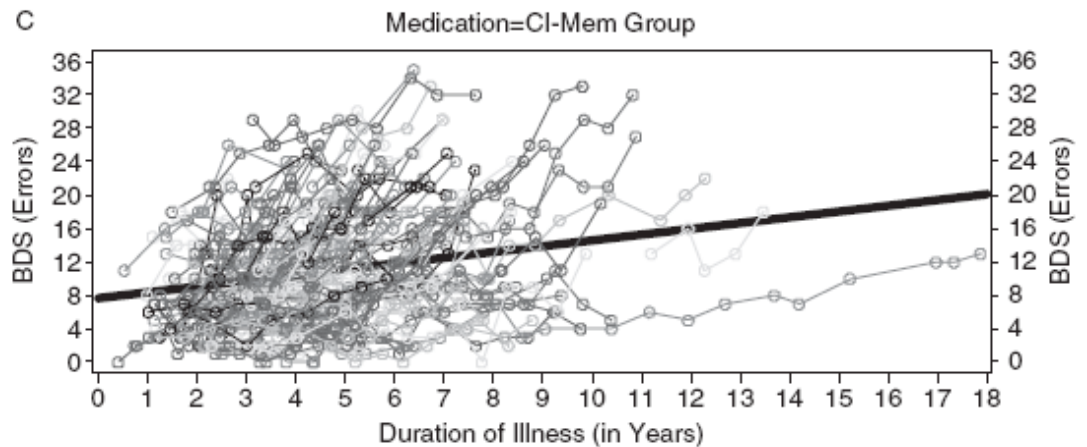
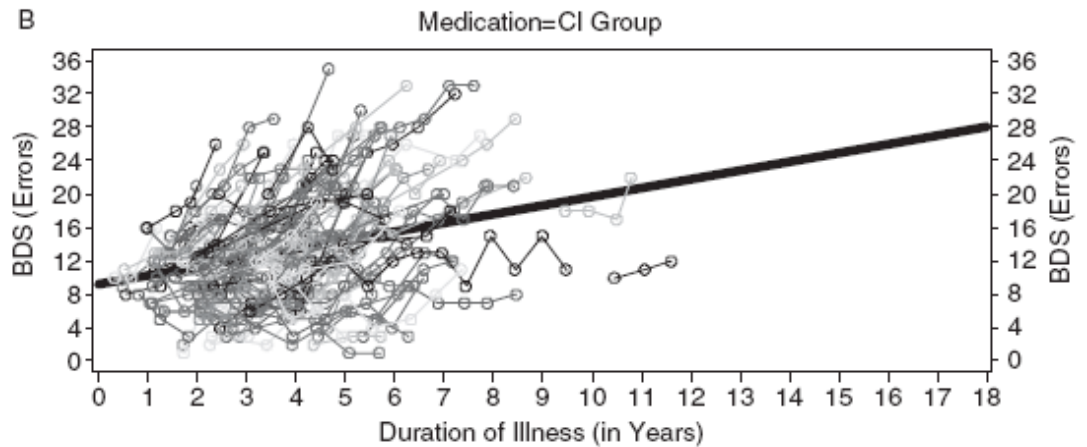
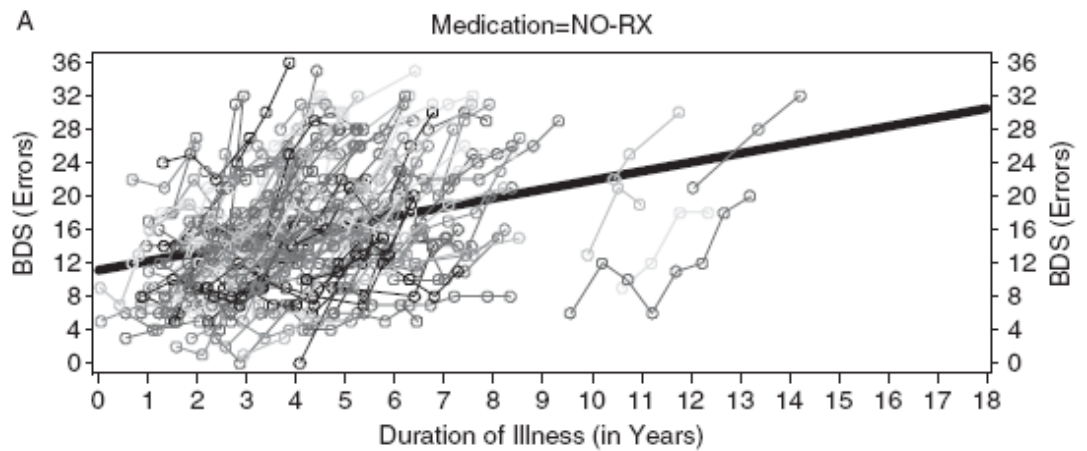
用在中至重度患者的美金剛胺

- 使用六個月後認知功能的改善為SIB 的2.97分 (95% CI 1.68 to 4.26, $P < 0.00001$) SIB滿分為100 分。
- 日常生活功能的改善程度為ADCS-ADL的1.27分 (95% CI 0.44 to 2.09, $P = 0.003$) ADCS-ADL總分54分。行為的改善程度為NPI2.76 分 (95% CI 0.88 to 4.63, $P=0.004$)NPI滿分144。
- 臨床整體印象 (CIGIC或CIBIC) 在治療組通常可得到正面改變評價。在7分法的CIBIC+得到平均約0.28 points (95% CI 0.15 to 0.41, $P < 0.0001$)的改善。
(*Cochrane 2006*)

合併治療

Atri et al, (Alzheimer Dis Assoc Disord 2008)

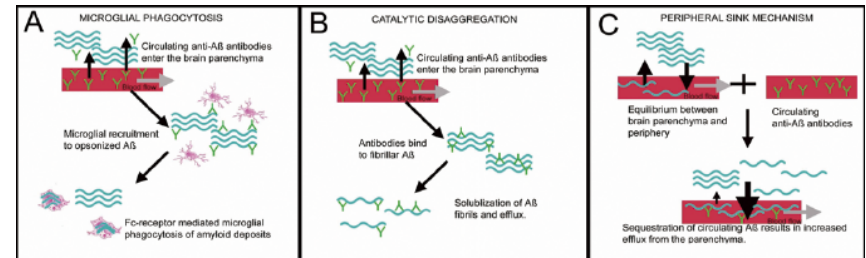
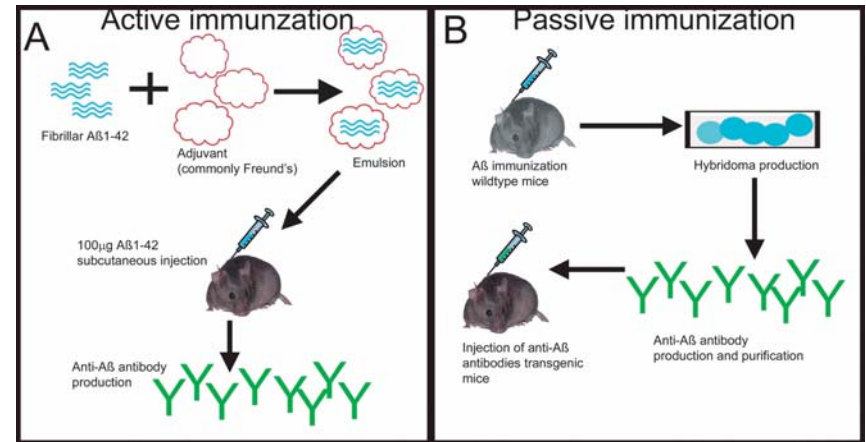
MGH & MADRC $n=382$



Early diagnosis and early treatment

Coming treatment for dementia

- Active vaccine for β amyloid protein
- Passive vaccine for β amyloid protein
- Vaccine for tau amyloid protein



Early diagnosis and early treatment

Factors affecting progression of dementia

- Vascular risk factors
- Nutritional factors
- Physical activity and life style factors
- Other diseases e.g., Obstructive Sleep Apnea (OSA)

Table 2. Separate GEE Models Measuring Decline in Cognitive Function Associated With Vascular Risk Factors^a

Predictor	Outcome: Composite Cognitive z Score			
	Age-Adjusted		Multivariable-Adjusted	
	β	P Value	β	P Value
Total cholesterol	.000	.95	-.001	.31
Time \times total cholesterol, y	-.001	.04	-.001	.03
HDL-C, log-transformed	.35	.02	.22	.15
Time \times HDL-C, y	-.02	.61	-.06	.20
LDL-C, log-transformed	.001	.70	-.001	.31
Time \times LDL-C, y	-.001	.04	-.001	.045
Triglyceride concentration, log-transformed	-.17	.15	-.15	.22
Time \times triglyceride concentration, y	-.01	.66	-.006	.85
Diabetes	-.11	.37	-.08	.46
Time \times diabetes, y	-.05	.03	-.05	.045
Hypertension	-.21	.16	-.21	.14
Time \times hypertension, y	.01	.77	.000	.99
History of stroke	-.03	.88	-.05	.77
Time \times stroke, y	-.045	.29	-.04	.31
History of heart disease	.049	.69	.02	.91
Time \times heart disease, y	-.07	.07	-.06	.16
Ever smoked, baseline	-.11	.28	-.04	.68
Time \times ever smoked, y	.03	.36	.03	.33

Contribution of Vascular Risk Factors to the Progression in Alzheimer Disease

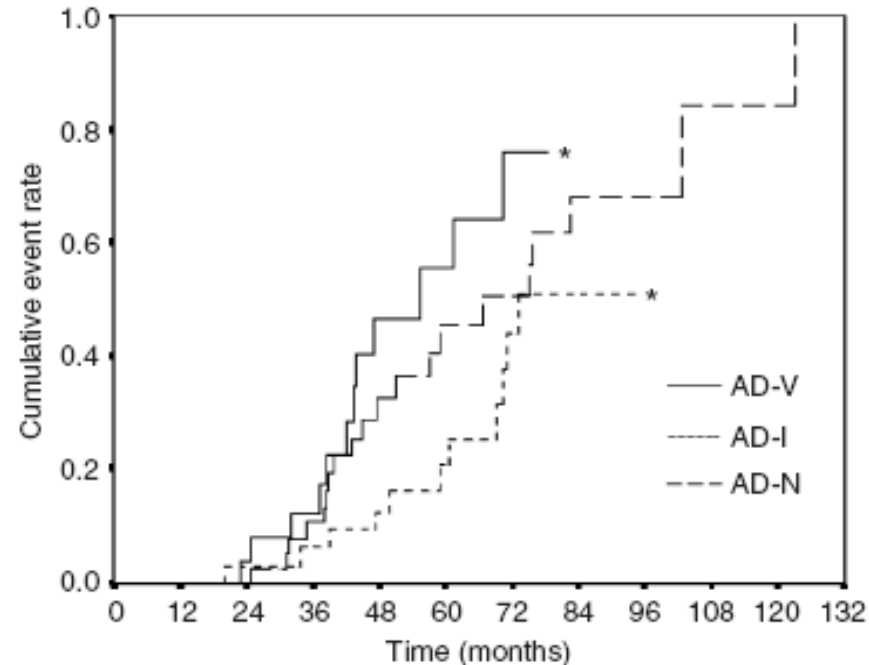
Helzner et al, *Arch Neurol.* 2009; NY

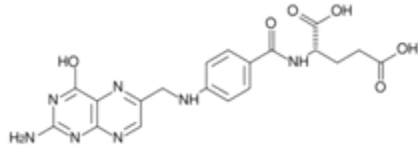
Table 2. Vascular Risk Factor Profile of Different Groups of Patients

Vascular Risk Factor	AD-N	AD-I	AD-V	P-value
	%			
Presence of vascular risk factor	62.3	61.9	82.4	NS
Presence of > 1 vascular risk factor	13.2*	28.6	40*	.02
Hypertension	35.8	52.4	48.6	NS
Diabetes mellitus	15.1	21.4	37.1	.05
Hyperlipidemia	15.1	14.3	11.4	NS
Ischemic heart disease	7.5	4.8	11.4	NS
Atrial fibrillation	3.8	4.8	14.3	NS

腦梗塞導致阿茲海默症快速惡化

(Sheng et al, JAGS 2007; HK)





Vitamin B9

Folate

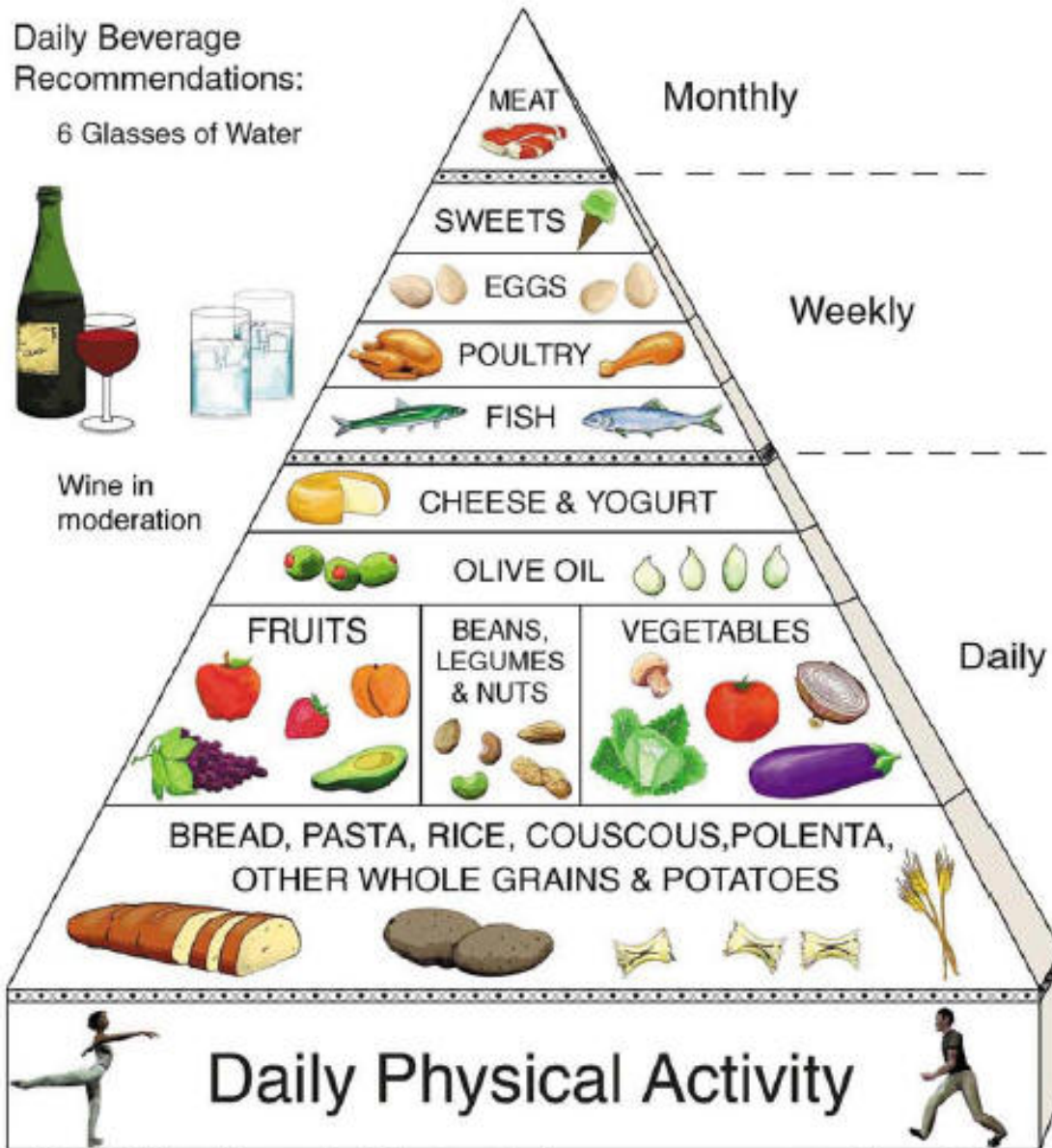
Food sources of folate include beans and legumes, citrus fruits and juices, whole grains, dark green leafy vegetables, poultry, pork, shellfish and liver



ADAM.



地中海食譜 與飲食習慣



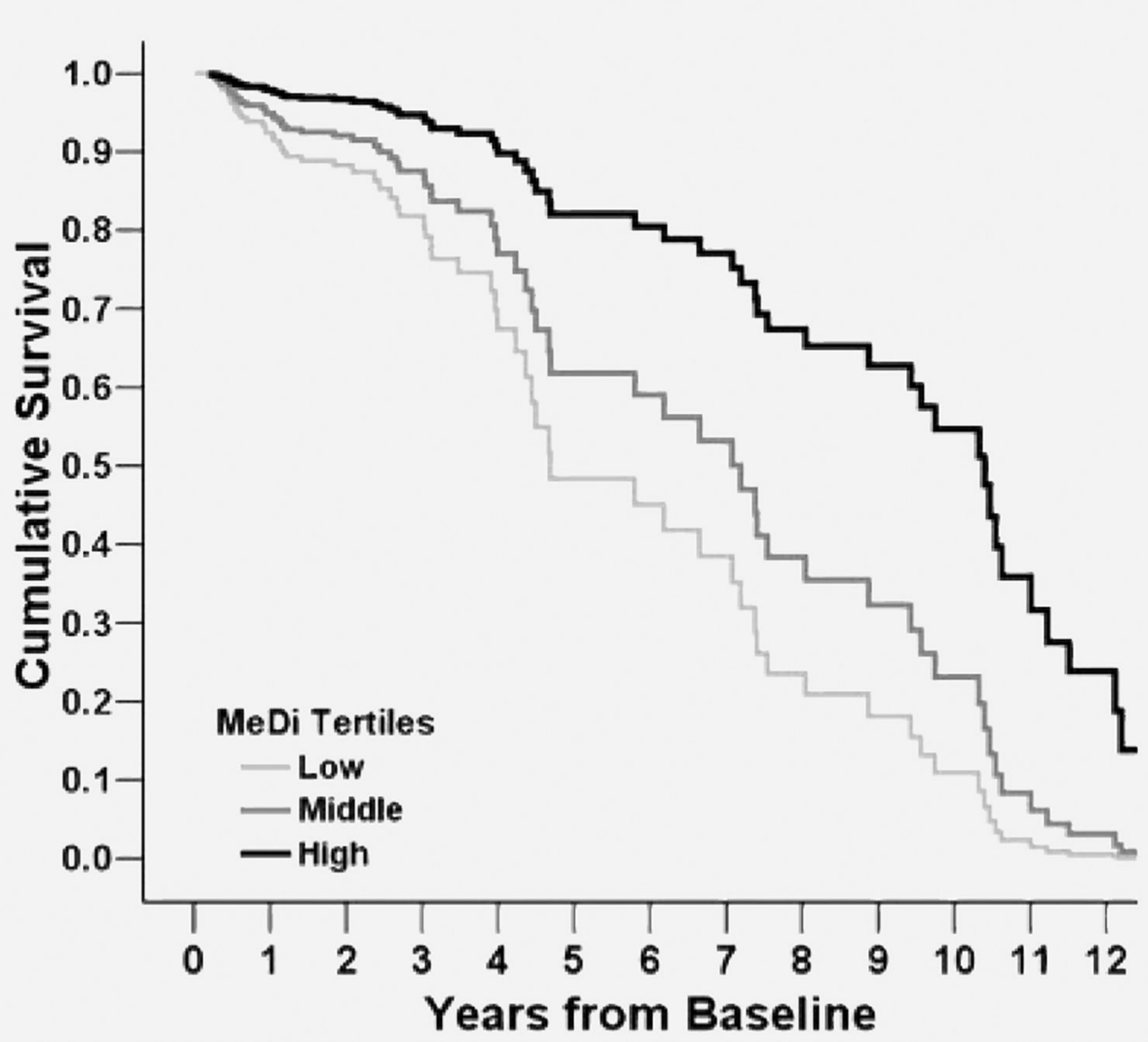


Figure 2. Survival curves based on Cox analyses comparing Alzheimer disease mortality in subjects belonging to each Mediterranean diet (MeDi) tertile (p for trend = 0.004)
Model adjusted for period of recruitment, age, gender, ethnicity, education, *APOE* genotype, caloric intake, smoking, and body mass index. (Scarmeas, 2007 Neurology)

治療睡眠呼吸中止症可改善阿茲海默症的認知功能

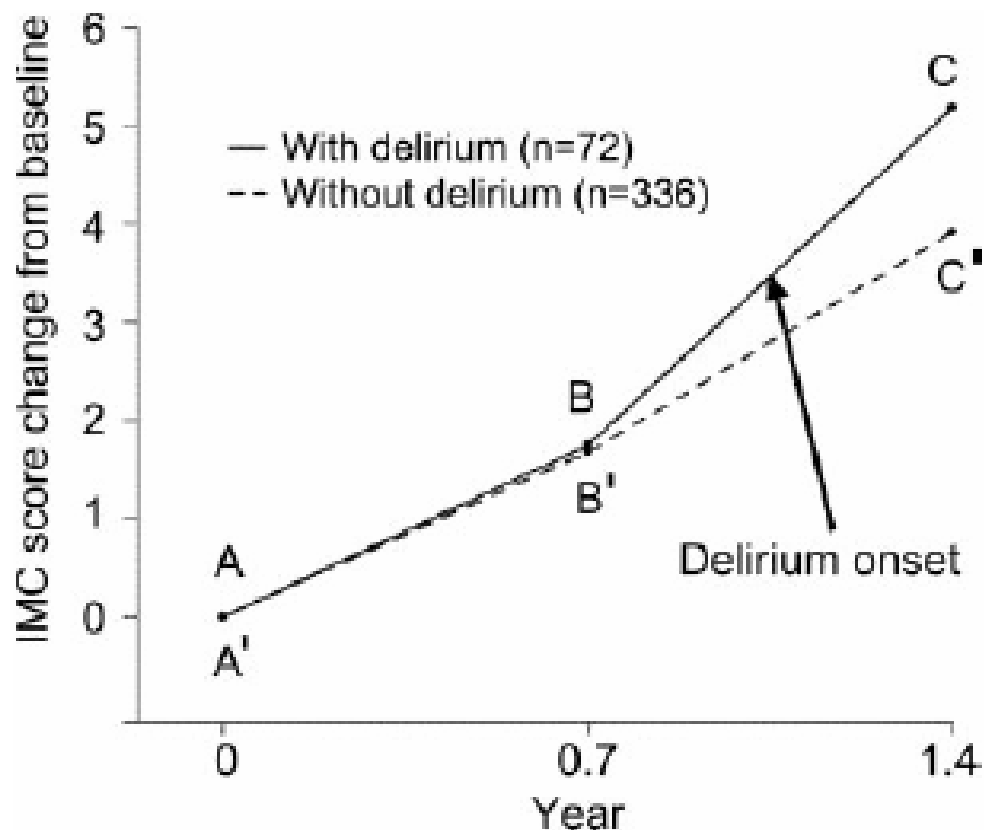
Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer's Disease: A Randomized Controlled Study

Table 1. Participant Baseline Characteristics

Characteristic	Therapeutic CPAP (n = 27)	Placebo CPAP (n = 25)
Female, n (%)	8 (29.6)	5 (20.0)
Ethnicity, n (%)		
Hispanic	3 (11.1)	1 (4.0)
Non-Hispanic	24 (88.9)	24 (96.0)
Race, n (%)		
Caucasian	26 (96.3)	25 (100.0)
African American	0	0
Asian American	0	0
Pacific Islander	1 (3.7)	0
Age, mean ± SD	78.6 ± 6.8	77.7 ± 7.7
Education, years, mean ± SD	14.7 ± 3.1	15.6 ± 2.7
Apnea-hypopnea index, mean ± SD	29.8 ± 16.1	26.9 ± 15.5
Body mass index, mean ± SD	26.1 ± 4.2	25.0 ± 3.6
Mini-Mental State Examination, mean ± SD*	24.3 ± 2.8	24.8 ± 4.2
Patients stable on medications, n (%)		
Acetylcholinesterase inhibitors	25 (92.6)	20 (80.0)
Analgesics	18 (66.7)	17 (68.0)
Anticonvulsants	1 (3.7)	1 (4.0)
Antidepressants	14 (51.9)	5 (20.0)
Antihistamines	3 (11.1)	5 (20.0)
Major tranquilizers	2 (7.4)	1 (4.0)
Minor tranquilizers	3 (11.1)	0
Over the counter (diphenhydramine)	0	1 (4.0)
Comell Depression Score, mean ± SD	5.1 ± 3.9	4.7 ± 3.3
Neuropsychological functioning composite score, mean ± SD	-0.17 ± 0.57	0.13 ± 0.87
Wide Range Achievement Test—Third Edition Reading Recognition Standard Score, mean ± SD†	106.6 ± 9.1	108.5 ± 9.1
Mattis Dementia Rating Scale total, mean ± SD‡	116.0 ± 13.0	120.1 ± 15.4

(Ancoli_Israel et al, JAGS 2008; UCSD)

譫妄加速阿茲海默症的認知功能退化



(Fong et al, *Neurology* 2009; Boston)

This figure depicts the slopes of the cognitive trajectories in patients with Alzheimer disease over time in our cohort. The median time to delirium from point B was 0.3 years (75% interquartile range, 0.13-0.45 years). The slopes are based on the changes in the Blessed Information-Memory-Concentration (IMC) subscore over time, and the scores presented are calculated adjusting for baseline differences.

體能活動改善阿茲海默症高風險老人的認知功能

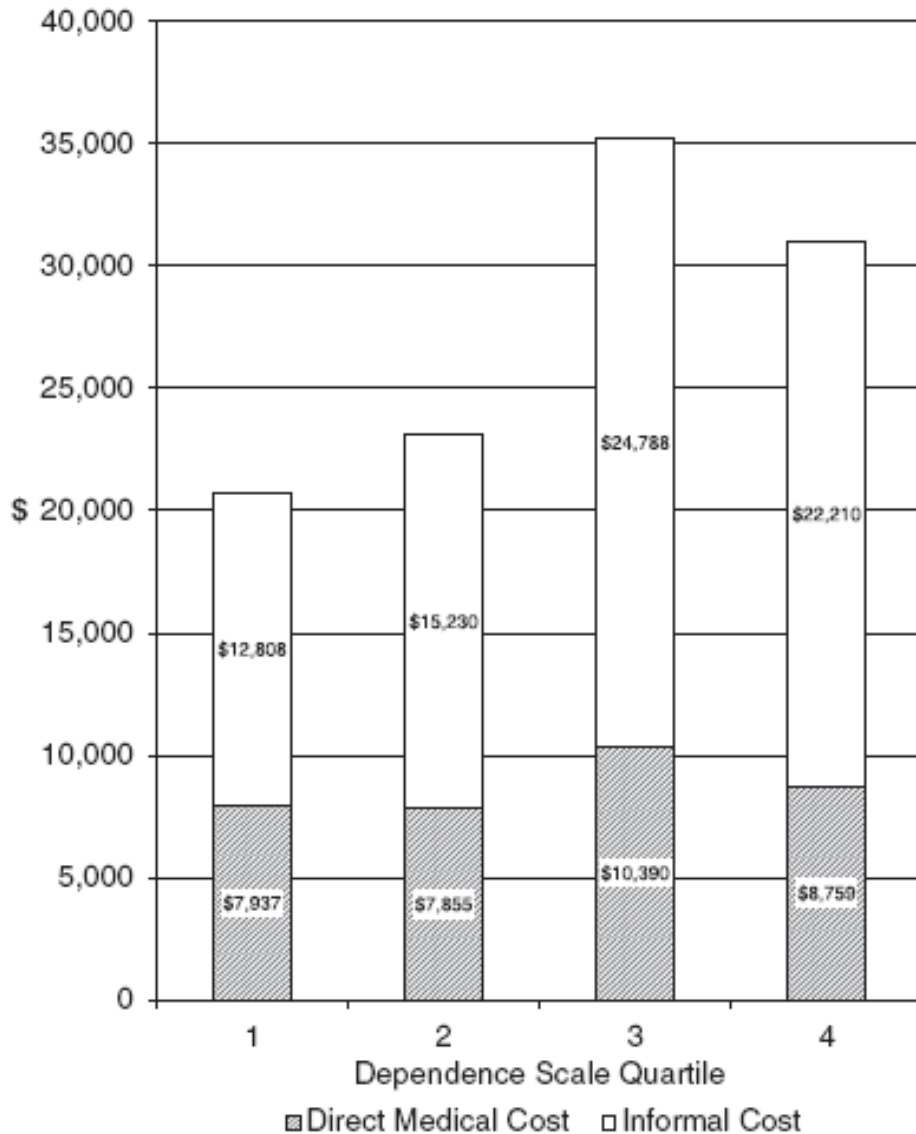
Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease – A Randomized Trial

Table 2. Effects of the Intervention and Time on Cognitive Outcomes, Mood, and Quality of Life of Participants (Intention-to-Treat Method Using Multiply Imputed Data)^a

Measure, mo	Mean Difference From Baseline (95% CI)		P Value ANCOVA for Repeated Measures ^b	
	Exercise Group (n = 85)	Control Group (n = 85)	Between Participants	Within Participants
Total ADAS-Cog score				
6	-0.26 (-0.89 to 0.54)	1.04 (0.32 to 1.82)	.04	.54
12	-0.55 (-1.15 to 0.20)	0.04 (-0.66 to 0.64)		
18	-0.73 (-1.27 to 0.03)	-0.04 (-0.46 to 0.88)		
Word list total immediate recall				
6	1.09 (0.42 to 1.77)	0.91 (0.21 to 1.61)	.48	.18
12	1.20 (0.40 to 2.00)	1.17 (0.49 to 1.84)		
18	1.56 (0.88 to 2.23)	1.19 (0.5 to 1.88)		
Word list delayed recall				
6	0.45 (0.03 to 0.87)	0.38 (-0.01 to 0.77)	.02	.10
12	0.37 (-0.07 to 0.82)	-0.22 (-0.66 to 0.22)		
18	0.76 (0.41 to 1.10)	-0.02 (-0.36 to 0.32)		
Digit symbol coding total				
6	2.62 (1.15 to 4.08)	3.43 (1.96 to 4.91)	.19	.22
12	2.75 (1.31 to 4.18)	3.89 (2.45 to 5.34)		
18	3.72 (2.26 to 5.18)	3.02 (1.47 to 4.56)		
Verbal fluency total score				
6	1.88 (0.20 to 3.72)	0.43 (-1.24 to 1.69)	.13	.78
12	2.77 (1.28 to 4.28)	0.88 (-1.09 to 2.02)		
18	1.90 (0.13 to 3.74)	1.42 (-0.86 to 3.29)		
CDR sum of boxes				
6	-0.16 (-0.32 to 0.01)	0.03 (-0.13 to 0.18)	.05	.05
12	-0.21 (-0.36 to -0.05)	-0.02 (-0.17 to 0.13)		
18	-0.33 (-0.46 to -0.2)	-0.20 (-0.33 to -0.03)		

(Lautenschlager et al, JAMA 2008; Melbourne)

延緩失智惡化的經濟效益



依賴量表 (DS) 增加一分，增加美金1,832元 (台幣6萬元) 的醫療與照顧費用，其中的美金1,690元 (台幣5萬6千元) 是照顧費用。

失智症狀量表 (BDRS) 增加一分美金3,333元 (台幣11萬元) 的醫療與照顧費用，其中美金1,406元 (台幣4萬6千元) 是直接醫療費用。

(Zhu et al, 2008 JAGS)

How to do early diagnosis?

- Symptoms and signs
 - Initial symptoms
 - 10 warning signs of dementia

起始症狀

- ◆ 記憶不好
重複問一樣的問題、說同樣的事情、到處找東西。
- ◆ 迷路
- ◆ 妄想
東西找不到被偷了！
- ◆ 語言困難
命名困難
- ◆ 個性改變
- ◆ 抽象思考 判斷
- ◆ 幻覺

早期有那些徵兆

失智症十大警訊

一、記憶減退影響到工作：一般人偶而忘記開會時間、朋友電話，過一會兒或經提醒會再想起來。但失智症患者忘記的頻率較高，且即使經過提醒也無法想起該事件。

二、無法勝任原本熟悉的事務：如英文老師不知「book」是什麼；自年輕即開車的司機伯伯現在經常走錯路；銀行行員數鈔票有困難；廚師不知如何炒菜等。

三、言語表達出現問題：一般人偶而會想不起某個字眼，失智症患者想不起來的機會更頻繁，甚至以替代方式說明簡單的辭彙，如「送信的人（郵差）」「用來寫字的（筆）」等。

四、喪失對時間、地點的概念：一般人偶而會忘記今天是幾日，在不熟的地方可能會迷路。但失智患者會搞不清年月、白天或晚上，在自家周圍迷路，找不到回家的路。

五、判斷力變差、警覺性降低：開車常撞車或出現驚險畫面；過馬路不看左右紅綠燈；借錢給陌生人；聽信廣告買大量成藥；一次吃下一周的藥量；買不新鮮的食物等。

六、抽象思考出現困難：對言談中抽象意涵無法理解，而有錯誤反應。日常生活操作電器如微波爐、遙控器、提款機的操作，對指示說明的意思無法理解。

七、東西擺放錯亂：一般人偶而會任意放置物品，但失智症患者更頻繁，將物品放在非習慣性或不太恰當的位置，如水果放在衣櫥裡、拖鞋放在被子裡、到處塞衛生紙等。

八、行為與情緒出現改變：一般人都會有情緒的變化，失智患者的情緒轉變較快，一下子哭起來或生氣罵人，情緒的改變不一定有可理解的原因。可能出現異於平常的行為，如隨地吐痰、拿店中物品卻未給錢、衣衫不整等。

九、個性改變：一般人年紀大了，性格也會有少許改變，失智患者可能會更明顯，如疑心病重、口不擇言、過度外向、失去自我克制或沈默寡言。

十、活動及開創力喪失：一般人偶而會不想做家事、不想上班工作，失智患者變得更被動，需要許多催促誘導才會參與事務。原本的興趣嗜好也不想去做。

How to do early diagnosis?

Screening test

- AD-8
- Mini-Cog
 - 3-objects recall
 - Draw a clock test
- Mini Mental State Examination (MMSE)
- Cognitive Abilities Screening Instrument (CASI)

AD8極早期失智症篩檢量表

填表說明：若您以前無下列問題，但在過去幾年中有以下的改變，請勾選「是，有改變」。若無，請勾「不是，沒有改變」；若不確定，請勾「不知道」。	是，有改變	不是，沒有改變	不知道
1. 判斷力上的困難：例如落入圈套或騙局、財務上不好的決定、買了對受禮者不合宜的禮物。			
2. 對活動和嗜好的興趣降低。			
3. 重複相同的問題、故事和陳述。			
4. 在學習如何使用工具、設備和小器具上有困難。例如：電視、音響、冷氣機、洗衣機、熱水爐(器)、微波爐、遙控器。			
5. 忘記正確的月份和年份。			
6. 處理複雜的財務上有困難。例如：個人或家庭的收支平衡、所得稅、繳費單。			
7. 記住約會的時間有困難。			
8. 有持續的思考和記憶方面的問題。			
AD8總得分		←請填入回答「是，有改變」總題數	



衛生署補助



台灣失智症協會

楊淵緯、劉景寬譯，NEUROLOGY，2005；65：559-564

簡短心智量表—— MMSE

I、定向感(共10分)：

1. 時間
2. 地方

II、注意力(共8分)：

1. 訊息登錄
2. 系列減七

III、記憶(共3分)：

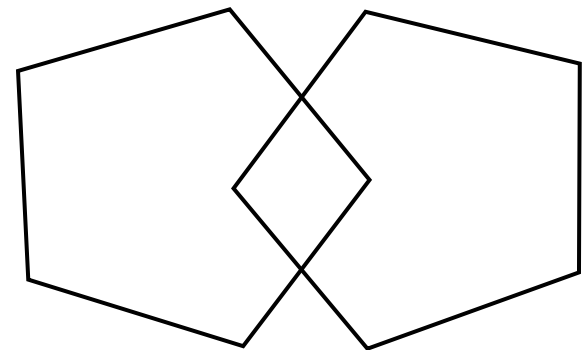
IV、語言(共5分)：

1. 命名
2. 覆誦
3. 閱讀理解
4. 書寫造句

V、口語理解及行用能力(共3分)：

VI、建構力(共1分)：

- 滿分30分
- 教育程度與文化背景相關性高
- 高教育組(高中以上)25分以下為失智。
- 低教育組(小學以下)19分為失智。



I、定向感(共10分)：	得分	
1. 時間(5分)： 年 月 日，星期 ， 季	I-1.	分
2. 地方(5分)： 市 醫院 樓 科(病房) 診(床)	I-2.	分

II、注意力(共8分)：		
1. 訊息登錄(3分)：腳踏車 快樂 紅色	II-1.	分
2. 系列減七(5分)：100-7 93 86 79 72 65	II-2.	分
III、記憶(共3分)：腳踏車 快樂 紅色	III.	分

Give 1 point for each recalled word after the CDT distractor. Score 1-3.

CLOCK DRAW TEST

Patient name _____
 Patient ID # _____
 Date / /

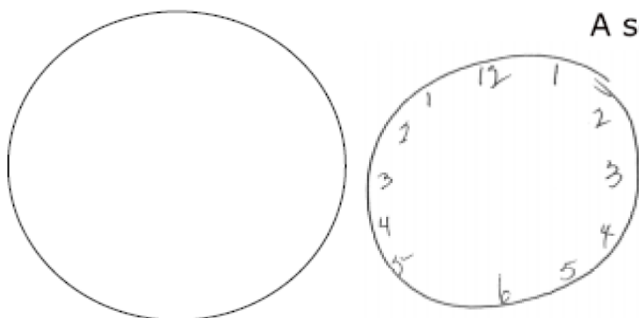
- 1) Inside the circle, please draw the hours of a clock as they normally appear
- 2) Place the hands of the clock to represent the time: "ten minutes after eleven o'clock"

A score of 0 indicates positive screen for dementia.

A score of 1 or 2 with an abnormal CDT indicates positive screen for dementia.

A score of 1 or 2 with a normal CDT indicates negative screen for dementia.

A score of 3 indicates negative screen for dementia.

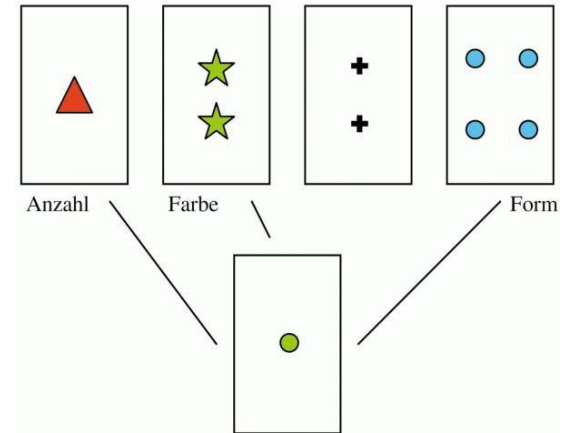


Mini-Cog Scoring

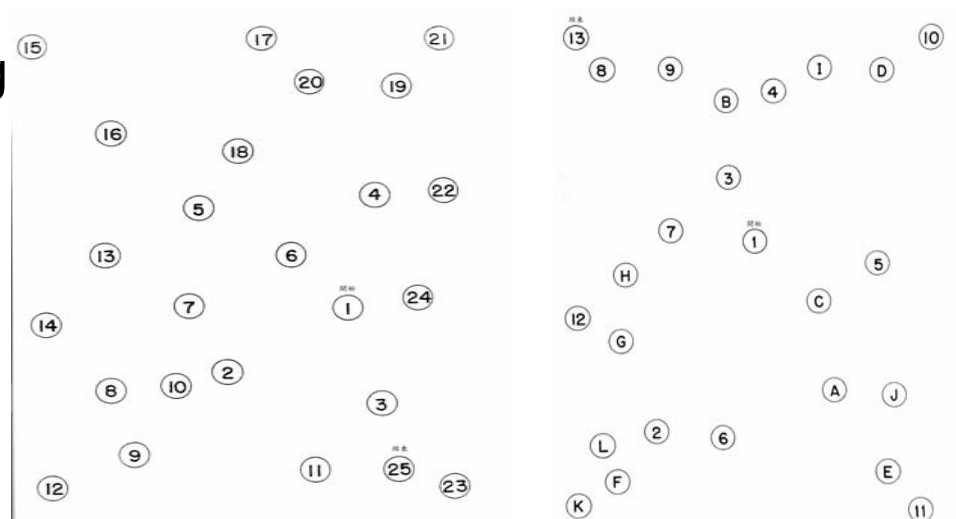
How to do early diagnosis?

Test battery

- Comprehensive Neuropsychological test
 - Wechsler Adult Intelligence Scale-III (WAIS-III)
 - Attention
 - Executive
 - Wisconsin Card Sorting Test (WCST)
 - Trail making A, B
- Clinical Dementia Rating (CDR)



Hilger E, Kasper S Journal für Neurologie, Neurochirurgie und Psychiatrie 2002; 3 (4): 17-22 ©



Clinical Dementia Rating (CDR)

臨床失智症評分量表 (Clinical Dementia Rating ; CDR)

林口長庚醫院神經內二科 神經心理檢查室

病患姓名: _____

性別: 男 女

年齡: _____ y/o

病歷號碼: _____

主治醫師: Dr. _____

評估日期: _____ 年 _____ 月 _____ 日

	Memory	Orientation	Judgment & Problem solving	Community Affairs	Home & Hobbies	Personal Care
None (0)	無記憶喪失: 包含稍微、非經常性遺忘	完全能定向	問題解決能力: *包括日常問題、財務及商業性事物都處理得很好 判斷力: *相較於從前仍良好	社區活動: *包括工作、購物、參加義工及其他社區活動均能獨立處理	家居生活: *沒問題 嗜好及知性興趣: *仍維持良好	自我照料: *完全沒問題
Questionable (0.5)	經常性的輕度遺忘: *事情只能部分想起 *良性遺忘	時間順序性: *稍有困難 *其他定向力均正常	問題解決及分析事物之異同: *稍有困難	社區活動: *對這些活動稍有障礙	家居生活: *稍有障礙 嗜好及知性興趣: *稍有障礙	自我照料: *完全沒問題
Mild (1)	中度記憶喪失: *最近的事不易記得 *會影響日常生活	時間順序性: *中度困難 地點定向力: *檢查時對地點仍有定向力 *某些場合地點定向力可能有障礙	問題解決及分析事物之異同: *中度困難 社交判斷力: *通常還能維持	社區活動: *雖然還能從事某些活動，但無法獨立擔負整體活動 *偶有正常表現	家居生活: *輕度障礙 *較困難之家事已經不做 嗜好及知性興趣: *比較複雜之嗜好及興趣都已放棄	自我照料: *需旁人督促或提醒
Moderate (2)	嚴重記憶喪失: *只有高度學過的事才會記得 *新學的事物很快忘記	時間順序性: *嚴重困難 時、地定向力: *經常有障礙	問題解決及分析事物之異同: *嚴重困難 社交判斷力: *通常已受影響	社區活動: *看似可被帶至社區參與活動 *實際上無法獨立擔負	家居生活: *只能做簡單家事 嗜好及知性興趣: *興趣相當侷限且難以維持	自我照料: *需別人協助穿衣、維持個人衛生及保存個人私有物品
Sever (3)	非常嚴重記憶喪失: *只能記得片段	只能維持對人的定向力	判斷或解決問題: *完全喪失	社區活動: *病情明顯嚴重，無法被帶至屋外參與活動	在家中已無顯著功能	自我照料: *需極大幫助 大小便失禁: *經常發生
小項評分						

How to do early diagnosis?

- Laboratory test
 - CSF and plasma β amyloid
 - Genetic screening

- Low p-tau-181/tau ratio was the strongest predictor with a dose-dependent effect (lowest vs highest quintile: 2.9 vs 1.3 MMSE points annual decline, p for trend 0.001).
- Low A42, high tau, and high tau/A42-ratio were associated with rapid cognitive decline (p 0.05).

Table 2 CSF biomarkers as predictors for cognitive deterioration on MMSE

CSF biomarkers	Estimated effects on baseline MMSE	Estimated effects on annual MMSE change
$A\beta_{42}$	0.28 (0.22)	0.27 (0.12)*
Tau	-0.09 (0.21)	-0.25 (0.12)*
p-tau-181	-0.04 (0.22)	-0.15 (0.12)
Tau/ $A\beta_{42}$ ratio	-0.14 (0.22)	-0.27 (0.12)*
p-tau-181/ $A\beta_{42}$ ratio	-0.11 (0.22)	-0.18 (0.12)
p-tau-181/tau ratio	0.34 (0.22)	0.42 (0.12)*

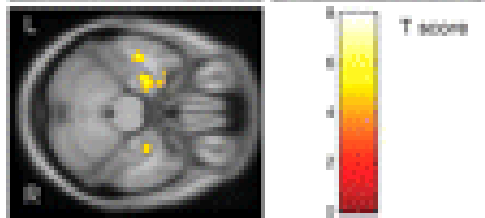
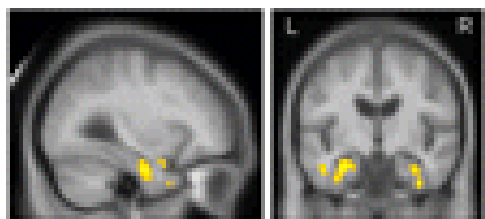
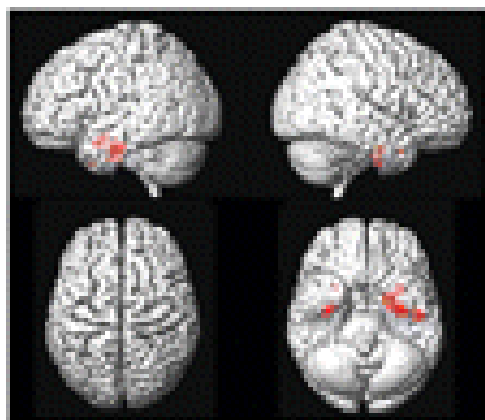
Kester, et al. Neurology 2009;73:1353-8

How to do early diagnosis?

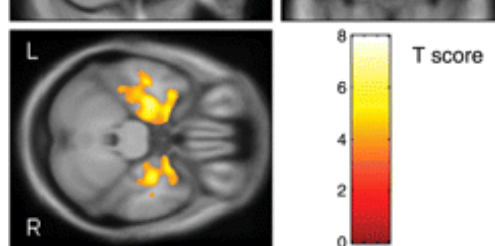
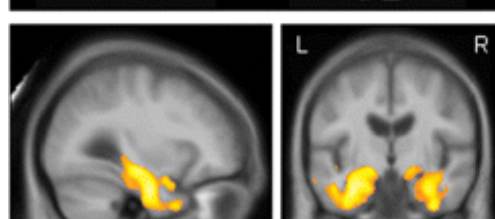
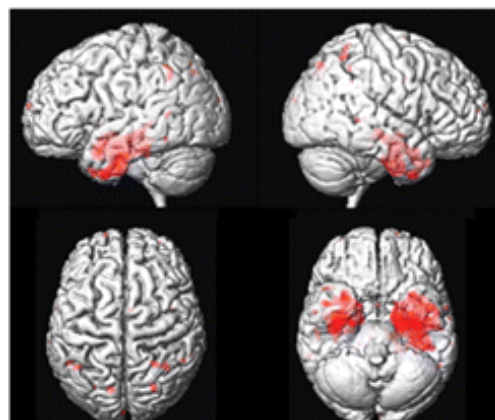
- MRI
 - Voxel Based Morphometry (VBM)
 - Tensor Based Morphometry (TBM)
- PET
 - FDG-PET: GMR
 - PIB-PET: Amyloid protein

VBM from MCI to AD

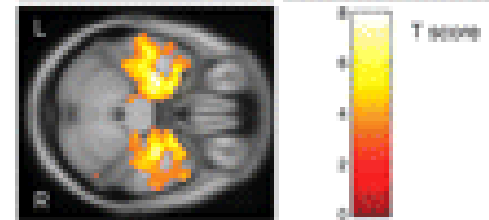
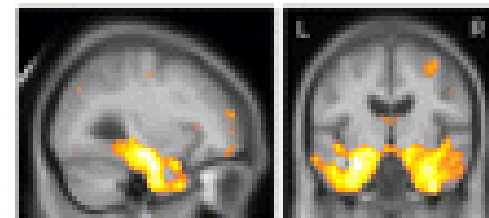
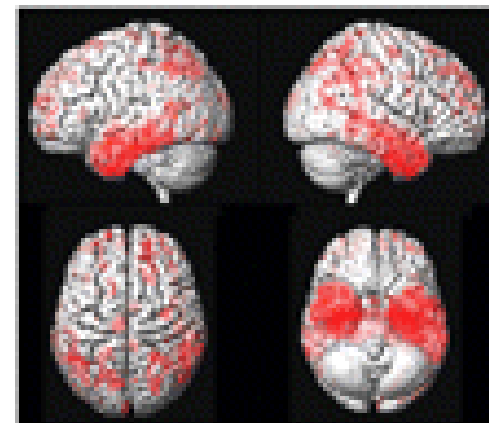
Jennifer, et al. Brain 2007;130:1777-1786.



3 years before AD
(18-54 months)



1 years before AD
(9-18 months)



At the time of AD
diagnosis

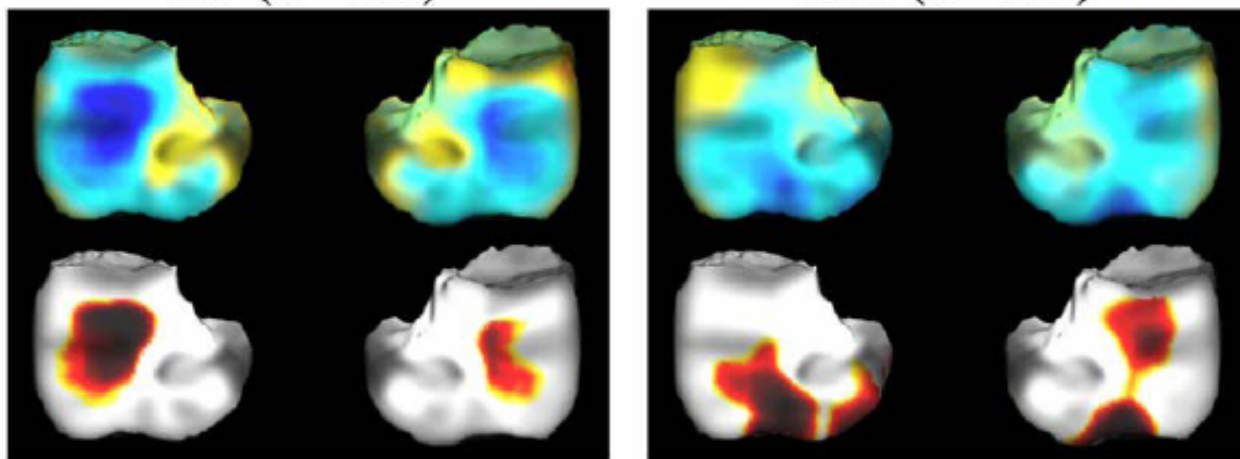
TBM: neuroimaging biomarker for AD

Hua et al. / NeuroImage 43 (2008) 458–469

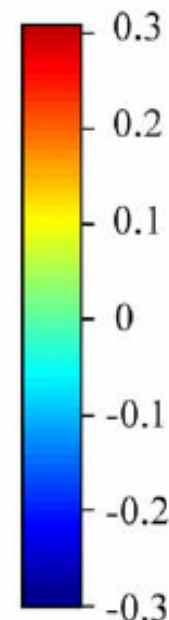
a. Regression with Sum-of-Boxes CDR

AD (n = 156)

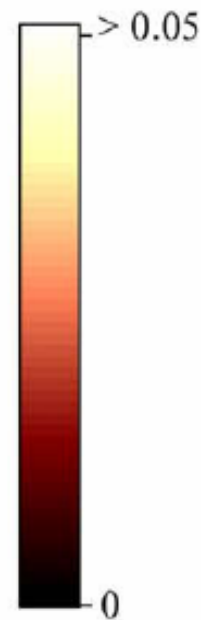
MCI (n = 323)



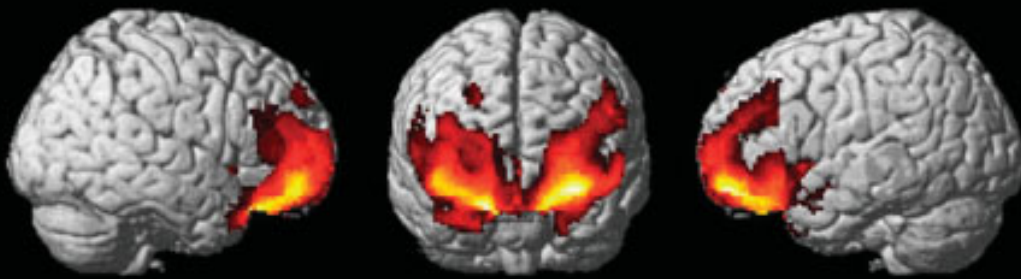
trR



P map

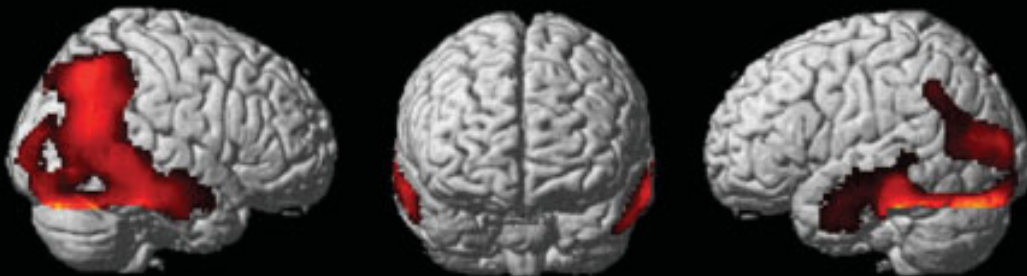


	AD	MCI	NORMAL
Sum-of-Boxes CDR	4.41 ± 1.62 (range [1, 9])	1.59 ± 0.86 (range [0.5, 5])	0.03 ± 0.11 (range [0, 0.5])
Corrected P value	0.01	0.004	0.6



PIB

Amyloid



GMR

FDG

(Kemppainen et al, Ann Neurol 2008)

