רשת ערים בריאות בישראל

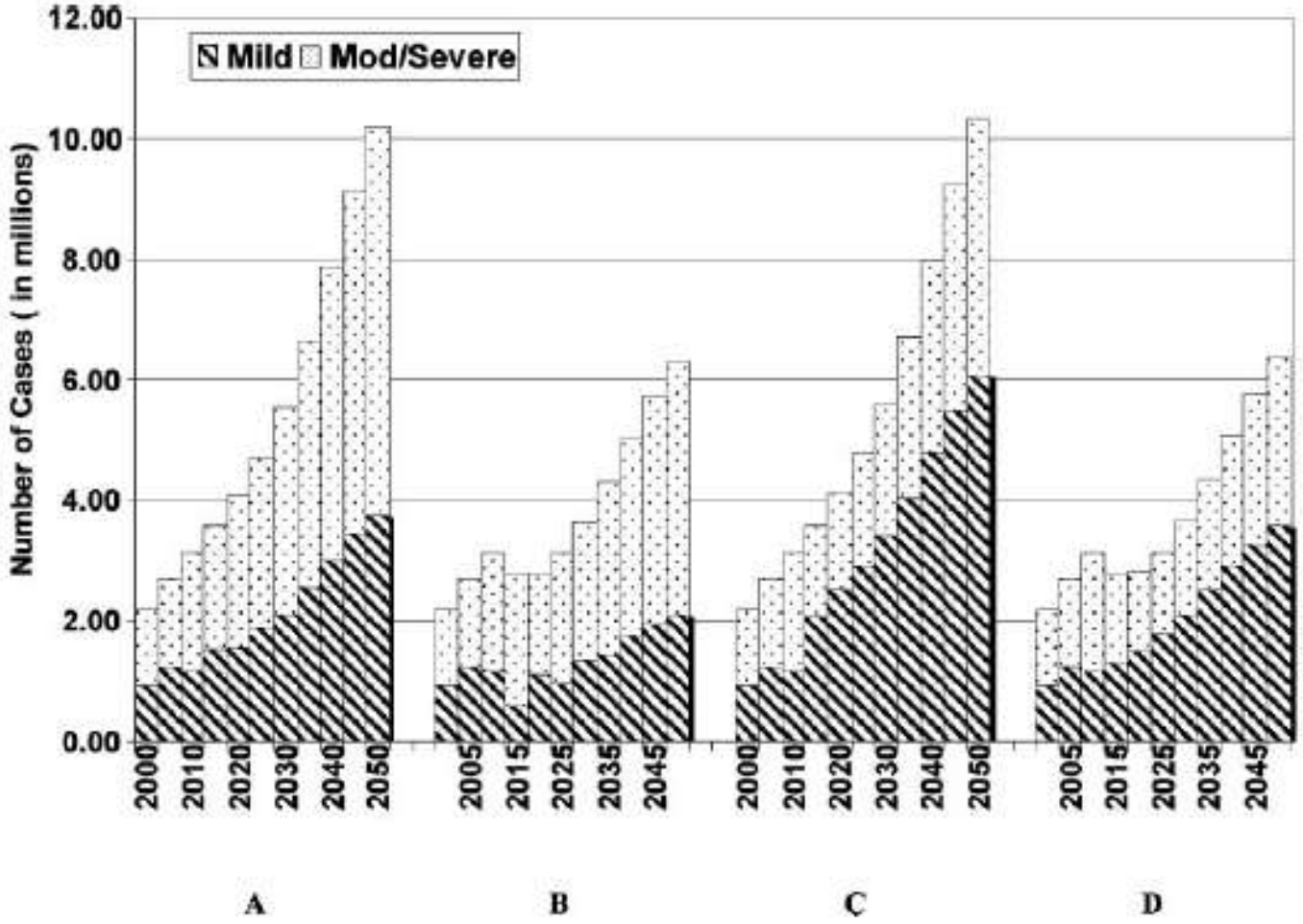
מפגש למידה של חברי רשת ערים בריאות
בנושא קידום הגיל השלישי / זקנה פעילה /עיר ידידותית גיל

דמנציה- הדרכים להתמודדות

בקונטקסט ערים בריאות

מניעת ירידה קוגניטיבית
ודמנציה בגיל השלישי

Prevalence of AD in the US-2000-2050

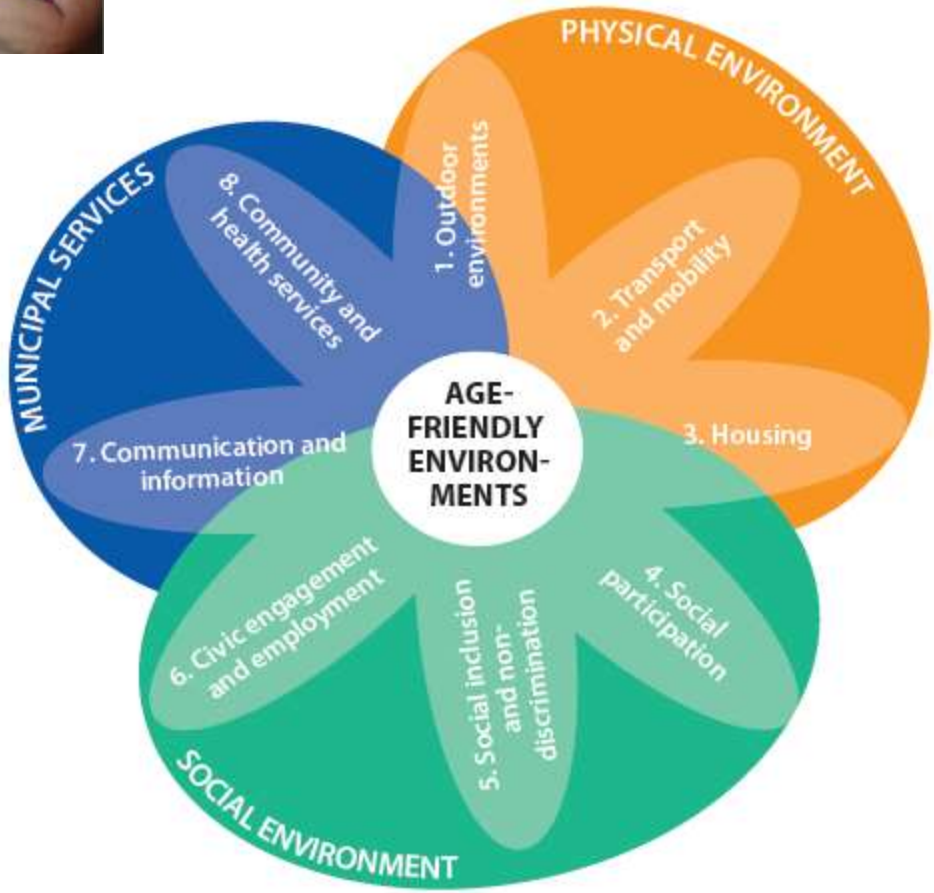


A	B	C	D
no therapeutic advances	delayed disease onset	delayed disease progression	both B+C

(Sloane et al.,2002)

Guiding Model for Healthy Aging

SOURCE: Modified from: Rowe JW, Kahn RL. Successful Aging. New York: Pantheon, 1998; and Marshall VW, Altpeter M. Health & Social Work 2005; 30(2):135-144.


PHYSICAL ENVIRONMENT
1. Outdoor environments
2. Transport and mobility
3. Housing
SOCIAL ENVIRONMENT
4. Social participation
5. Social inclusion and non-discrimination
6. Civic engagement and employment
MUNICIPAL SERVICES
7. Communication and information
8. Community and health services
AGE-FRIENDLY ENVIRON-MENTS

סיכום עד כה

-סיכום עד כה

-המודל המניעתי

האם ממצה יעד "עיר ידידותית גיל?"

גורמי אי-הנחת...

-כשלון תרופות CH

-כשלון הנחת העמילואיד

Ageing Research Reviews 25 (2016) 70–84

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Review

Why therapies for Alzheimer's disease do not work: Do we have consensus over the path to follow?

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Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan

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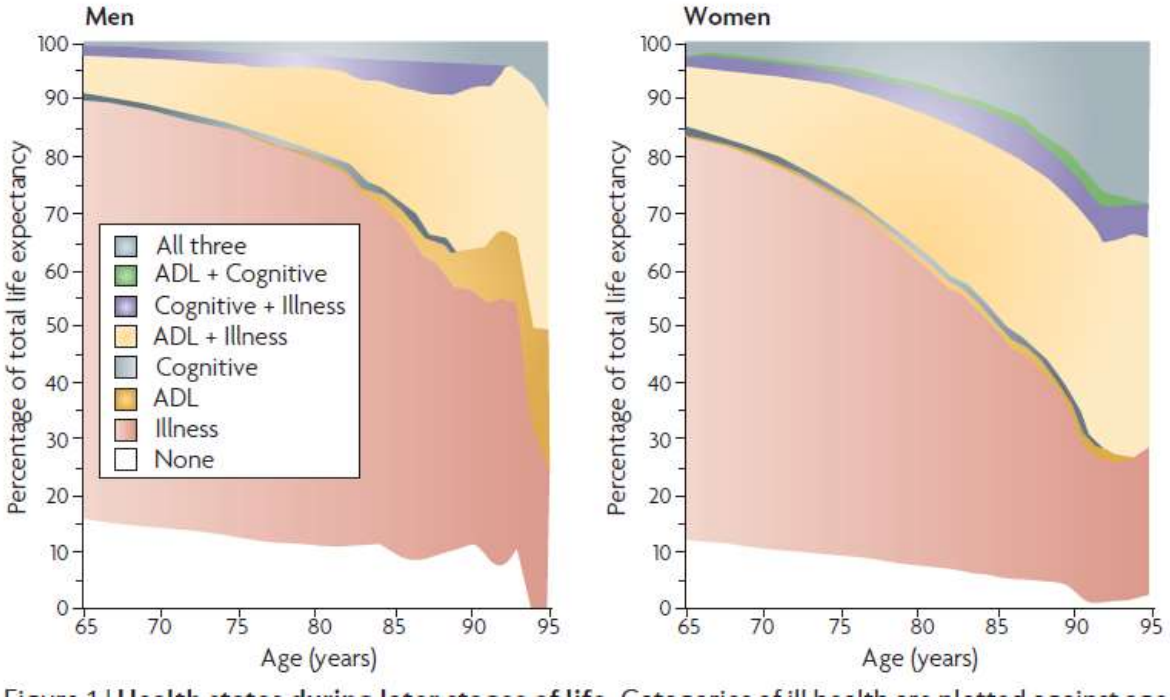
ABSTRACT

Alzheimer's disease (AD) represents a personal tragedy of enormous magnitude, which imposes a daunting worldwide challenge for health-care providers and society as well. In last five decades, global research in clinics and laboratories has illuminated many features of this sinister and eventually fatal disease. Notwithstanding this development, the Alzheimer's research apparently has come across a phase of disappointment and a little reservation about the direction to follow. Persistently distressing controversies and a significant number of missing facts shed further uncertainty about the path forward. A detailed description of some of the main controversies in AD research may assist the field towards finding a resolution. Here I reviewed some alarming concerns or controversies related to these primary issues and emphasized on a possible mechanism to settle them.

SCIENCE AND SOCIETY

The elephant in the room — healthy brains in later life, epidemiology and public health

Carol Brayne



(2007)

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אינדיבידואלי –לעומת סטטיסטי

מטרה -

-חייבת להיות משולבת-

-פסיכוסוציאלית

-סביבתית-פסיכולוגית

-רפואית

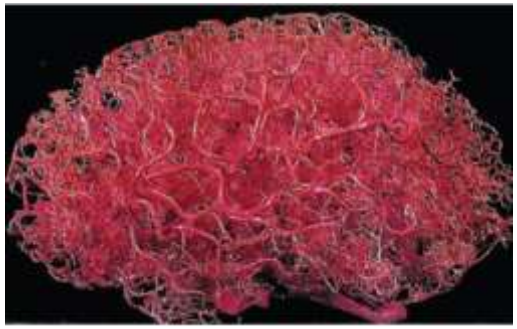
-כללית

-קוגניטיבית- התנהגותית- תפקודית

A.הפתולוגיה העיקרית

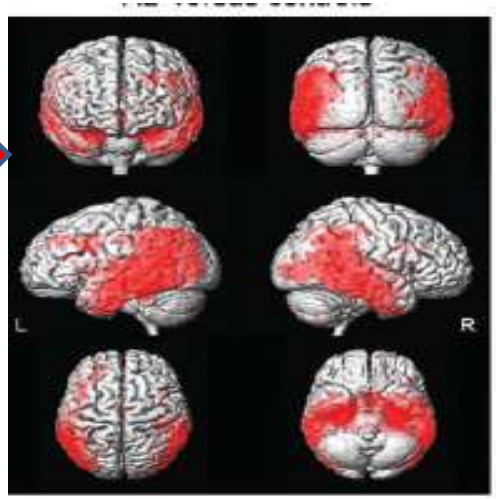
לשינויים קוגניטיביים בגיל השלישי

COMORBIDITY

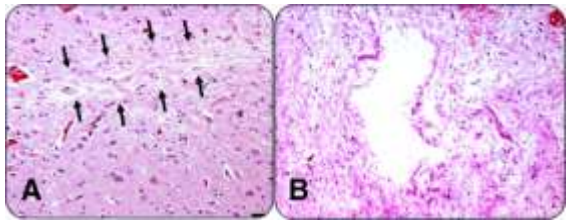


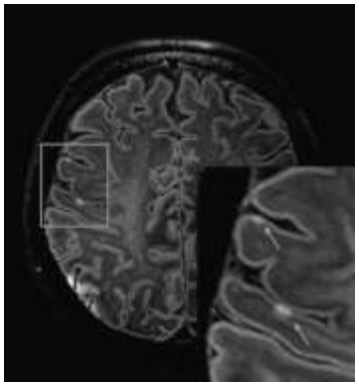
פתולוגיה וסקולרית

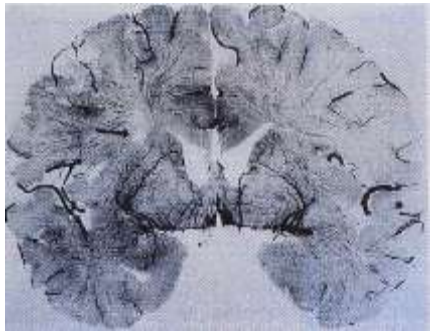
פתולוגית Alzheimer's Disease (AD)



הפתולוגיה הוסקולרית בגיל השלישי-







microinfarcts

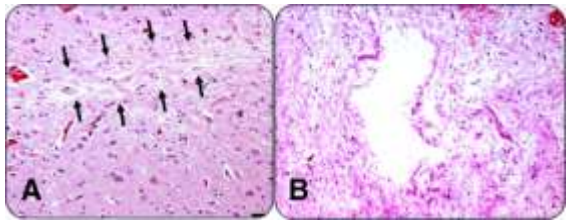
small vessel disease

-גורמי Framingham הבסיסיים–

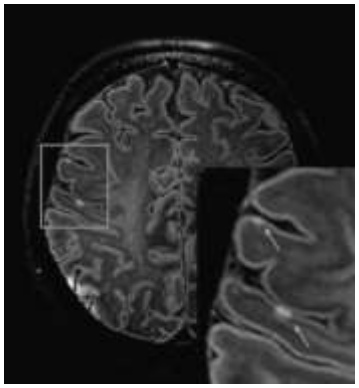
-midlife לעומת מטופלים חדשים (PreDIVA)

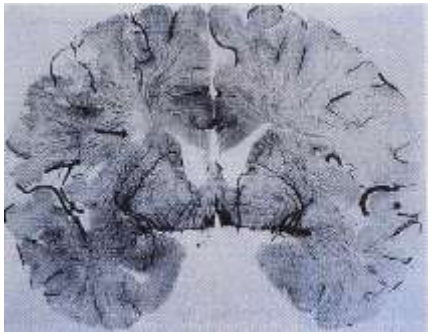
-נורמות שונות –אפשרי

הפתולוגיה הווסקולרית בגיל השלישי



microinfarcts





small vessel disease

-גורמי הגיל השלישי

-נורמות גורמי Framingham (ליפידים, לחץ דם וכו')

- גורמי Framingham מסדר שני

-סיבוכים-טיפול יתר בלחץ דם, אי-ספיקת לב

-פרמטרים יחודיים להשגחה –pulse pressure, תנודות לחץ הדם,

-אפקט comorbidity (אנמיה, תסמונת דם נשימה,תרופות וכו')

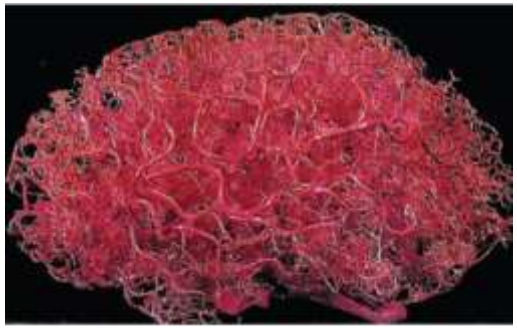
-האצת נזק מצטבר -משמעות למעקב

-בסיס lifestyle לא שמור

גורמים סיבתיים בעלי פוטנציאל לשיפור

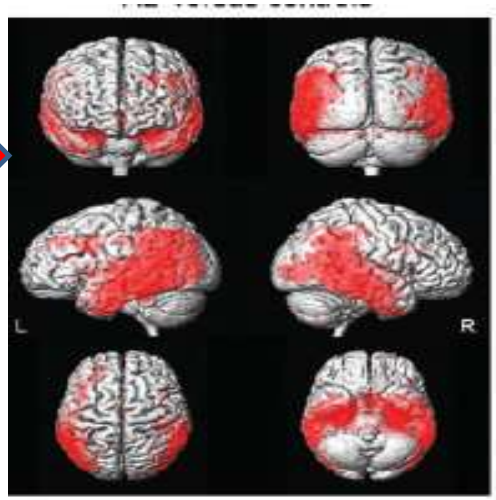
הפתולוגיה העיקרית
לשינויים קוגניטיביים בגיל השלישי

COMORBIDITY

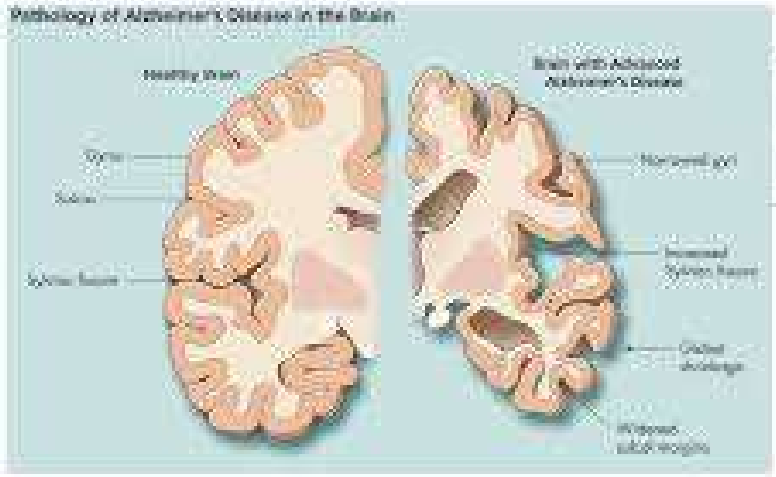


פתולוגיה וסקולרית

פתולוגית Alzheimer's Disease (AD)

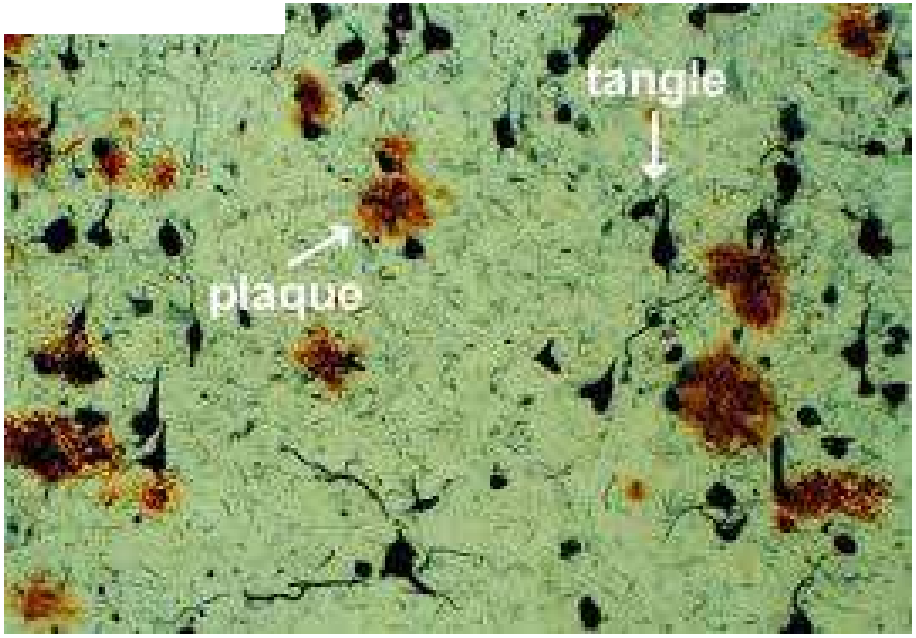


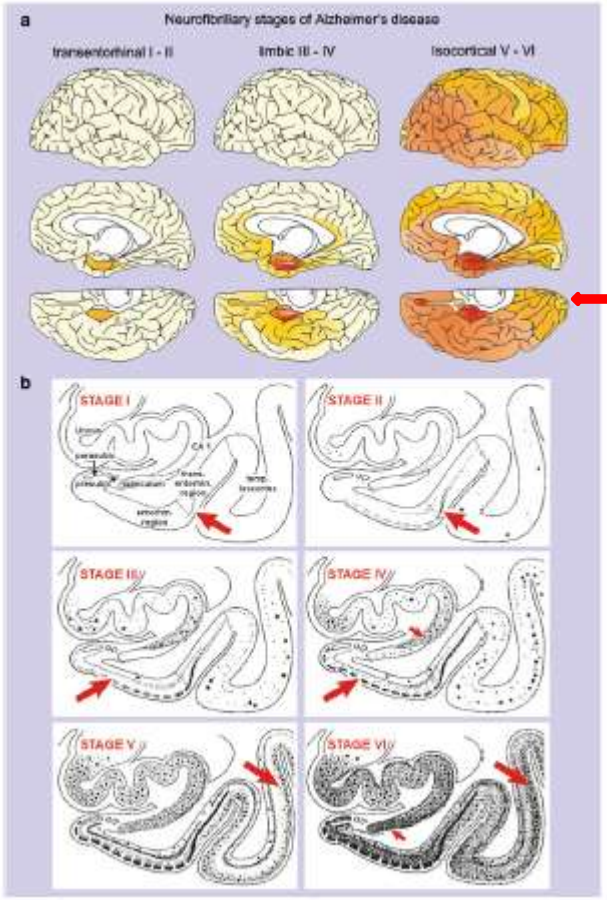
Alzheimer's Disease פתולוגית

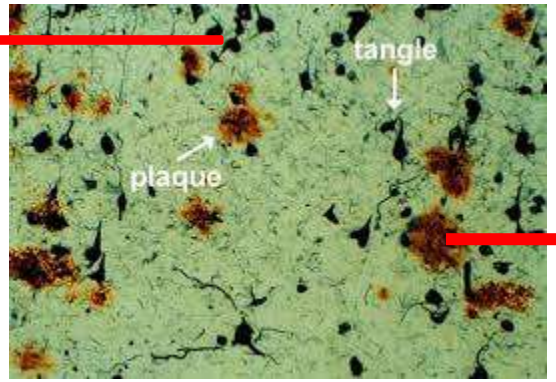


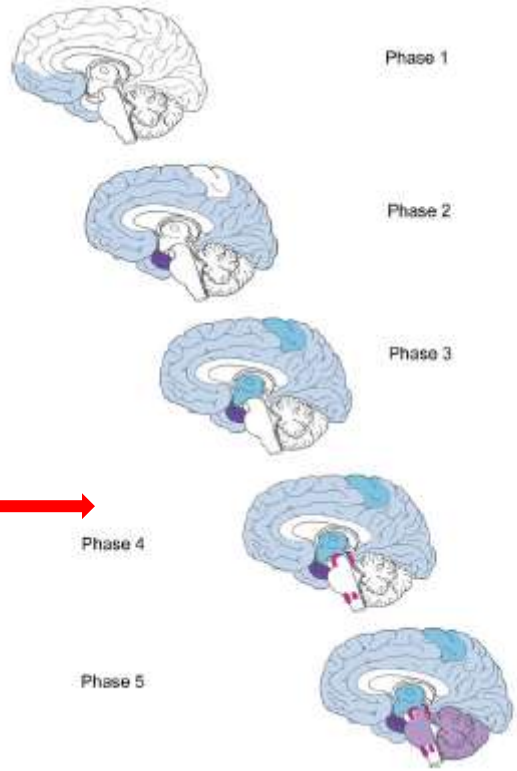
Alzheimer's Disease Pathology

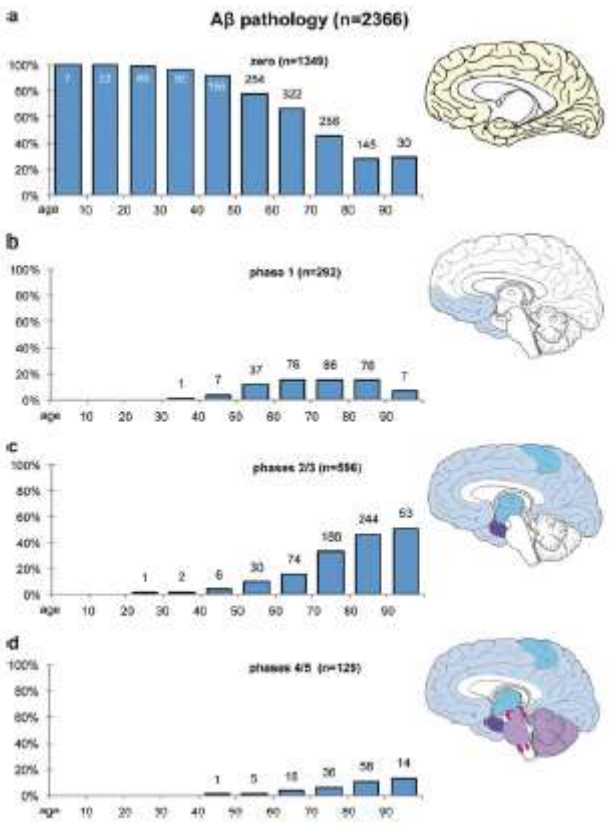
Significant loss of brain mass

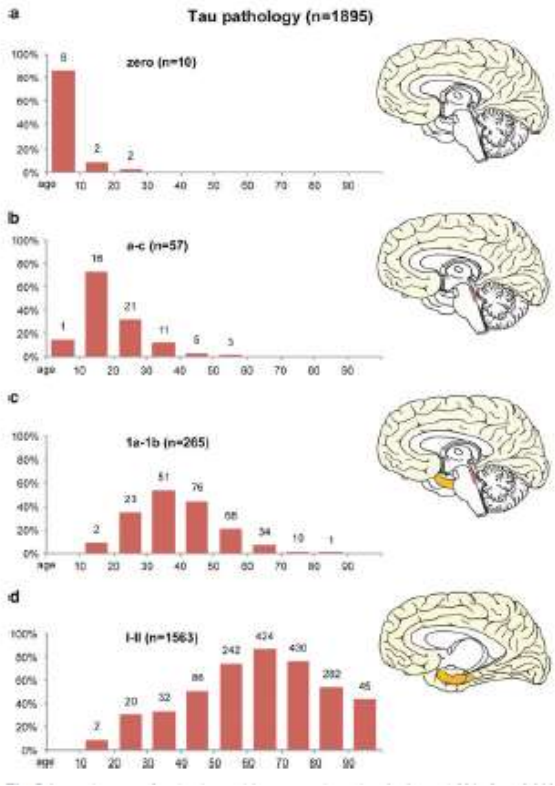


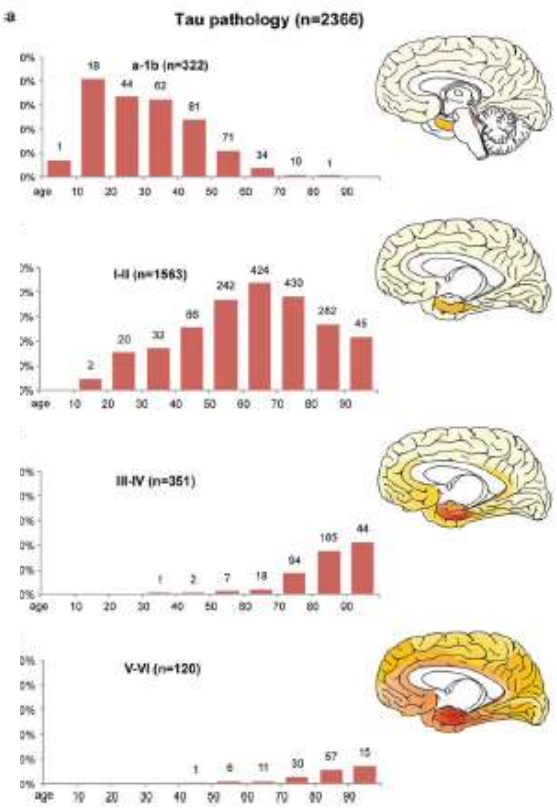

a
Neurofibrillary stages of Alzheimer's disease
transentorhinal I - II
limbic III - IV
isocortical V - VI
b
STAGE I
STAGE II
STAGE III
STAGE IV
STAGE V
STAGE VI

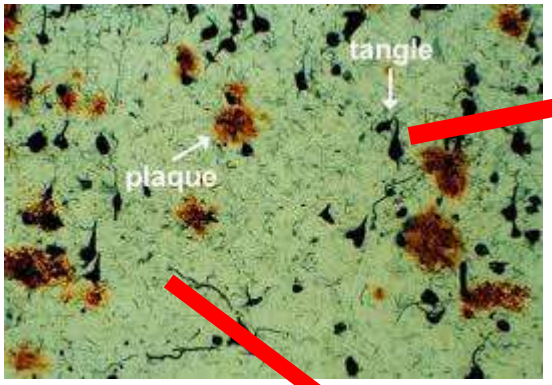

tangle
plaque


Phase 1
Phase 2
Phase 3
Phase 4
Phase 5

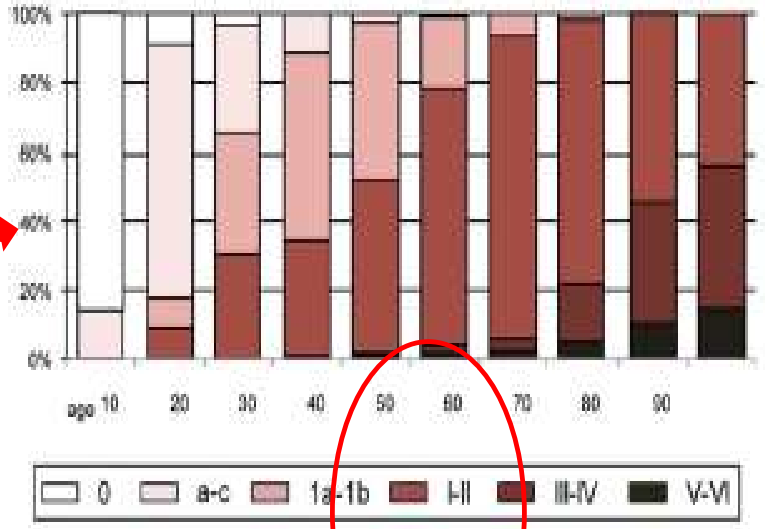

a
Aβ pathology (n=2366)
zero (n=1349)
b
phase 1 (n=292)
c
phases 2/3 (n=596)
d
phases 4/5 (n=125)
age


a
Tau pathology (n=1895)
zero (n=10)
b
a-c (n=57)
c
1a-1b (n=265)
d
I-II (n=1563)
age

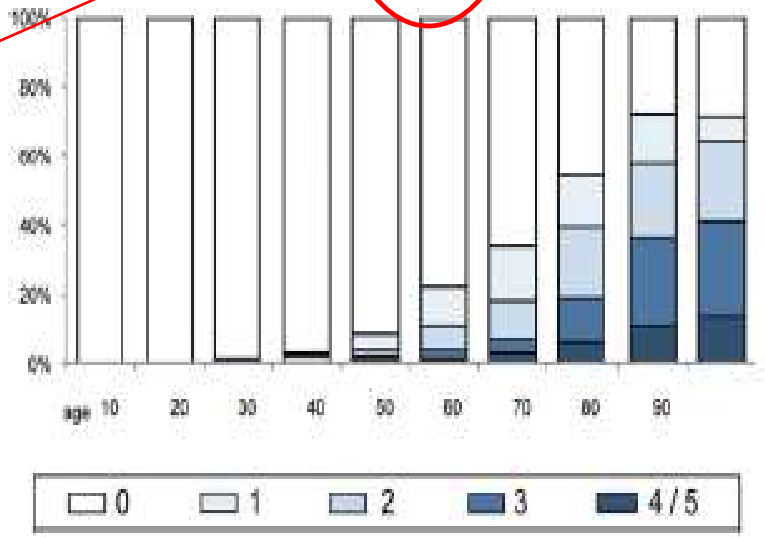

a
Tau pathology (n=2366)
a-1b (n=322)
I-II (n=1563)
III-IV (n=351)
V-VI (n=120)
age

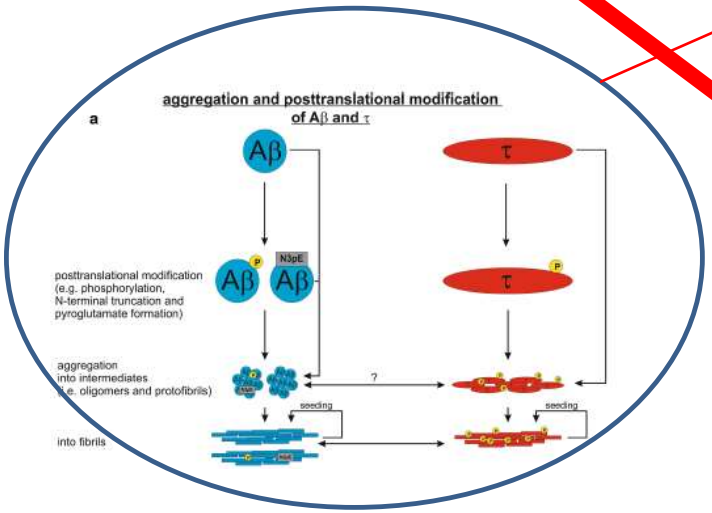


a Development of tau pathology by decade (n=2366)

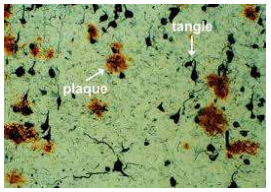


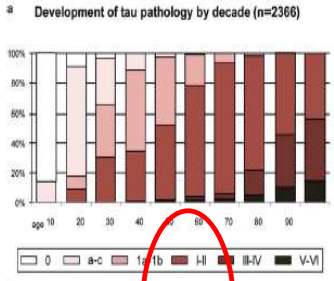
b Development of Aβ pathology by decade (n=2366)

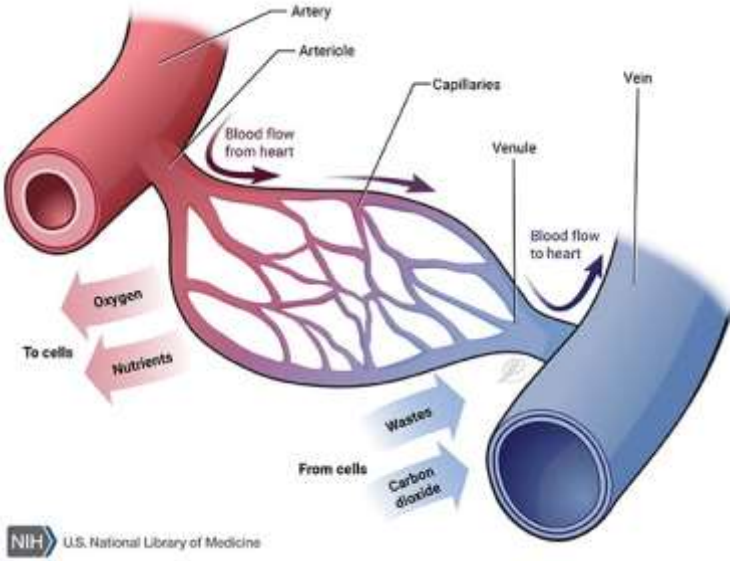


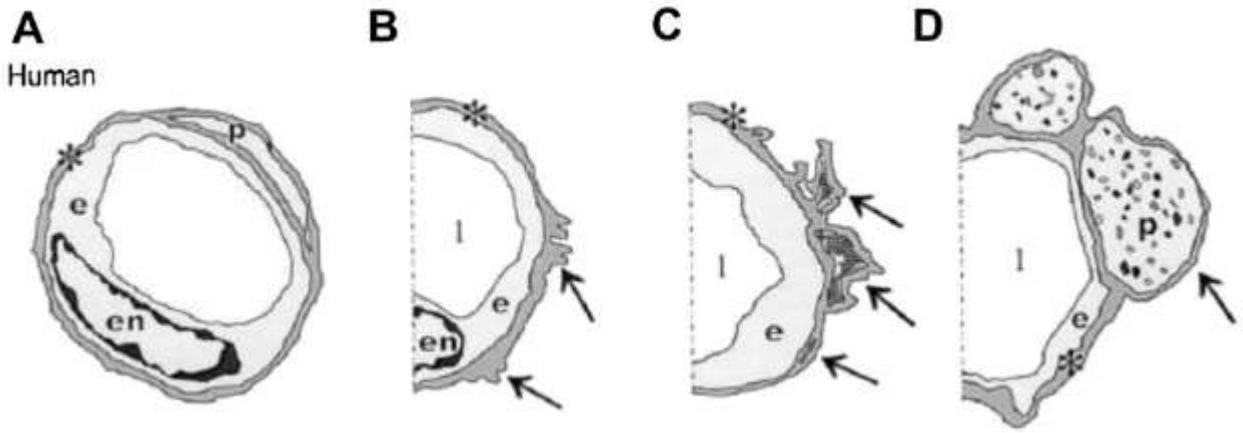


פתולוגיה מיקרו-וסקולרית מגבירת עמילואיד



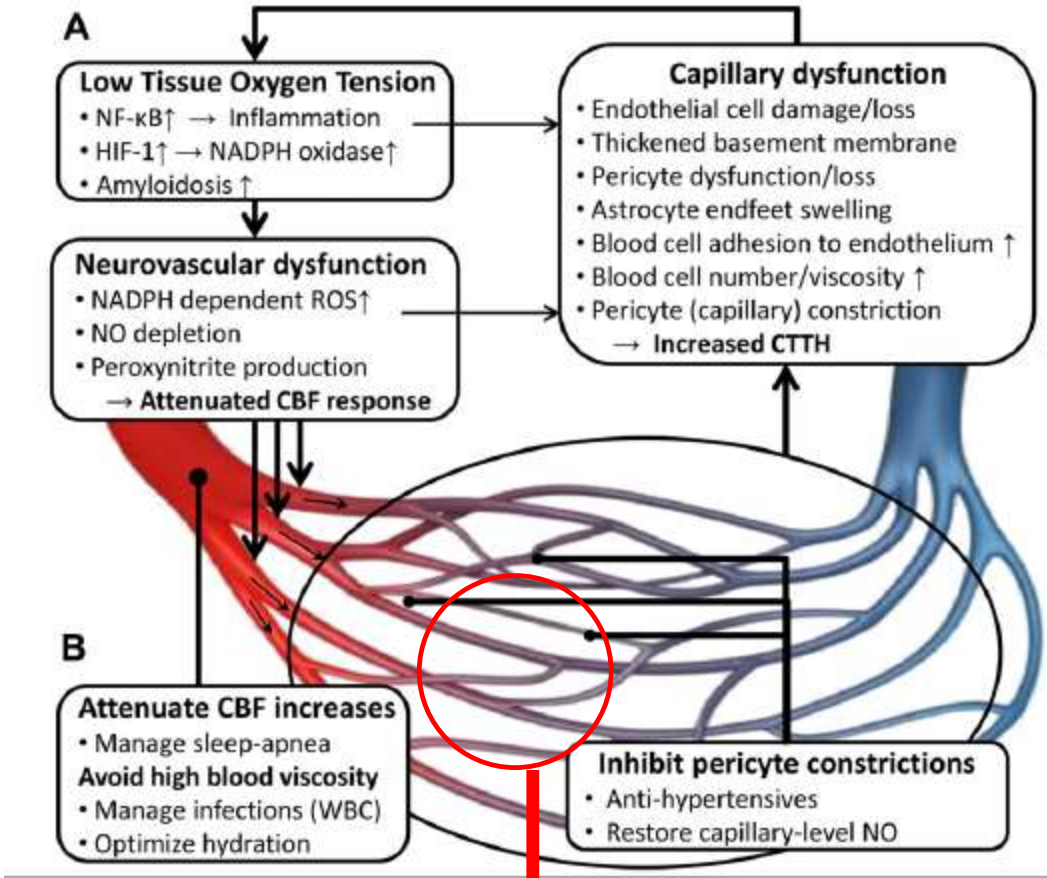


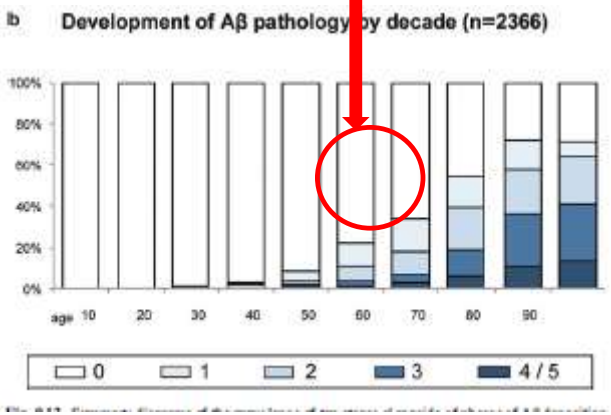


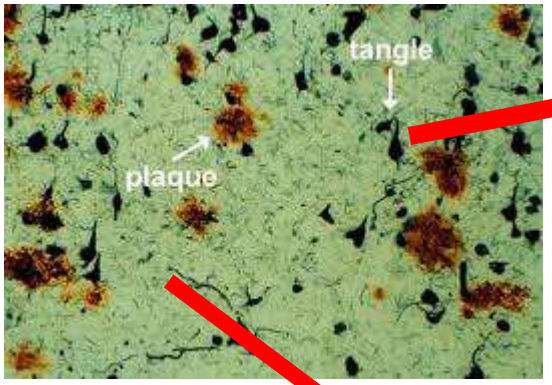


Changes in capillary wall morphology in common AD risk factors

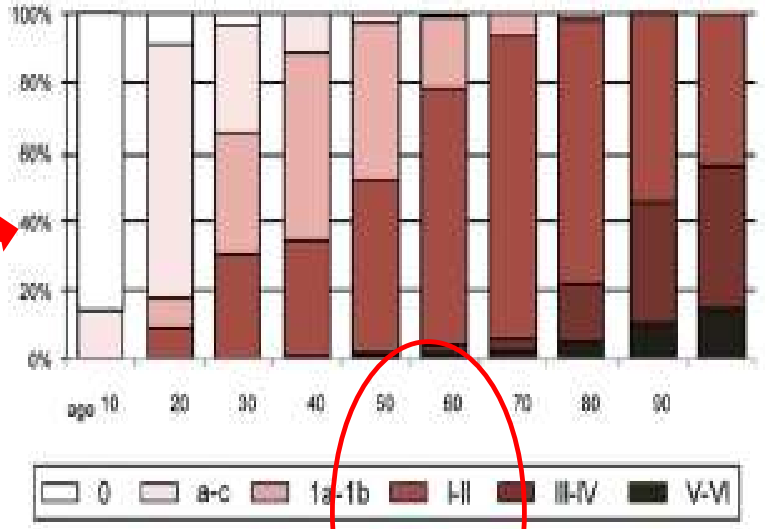
Risk factor	Changes in capillary morphology	Reference
Aging (human)	Increased tortuosity, twisting, and looping of capillaries. Thickening basement membranes with inclusions. Pericapillary fibrosis. Pericyte loss.	Kalaria (1996)
Hypertension	Pericyte degeneration, swelling of endothelium and surrounding astrocyte end-feet (spontaneously hypertensive rats).	Tagami et al. (1990)
Ischemic stroke	Pericyte constrictions (animal models)	Dalkara et al. (2011); Yemisci et al. (2009)
APOE ε4 genotype	Microvascular degeneration, reduction in capillary length, reduced pericyte coverage (mice).	Bell et al. (2012)
Diabetes	Loss of pericytes and thickening of capillary basement membrane of the cerebral capillaries (animal models).	Junker et al. (1985); McCuskey and McCuskey (1984)
	Thickening of basement membrane (humans).	Johnson et al. (1982)
Brain trauma	Dislocation of pericytes, away from capillaries (animal models).	Dore-Duffy et al. (2000)
Smoking	Endothelial cell damage, subendothelial edema (peripheral arterial and arteriolar endothelium).	Mayhan and Sharpe (1998)



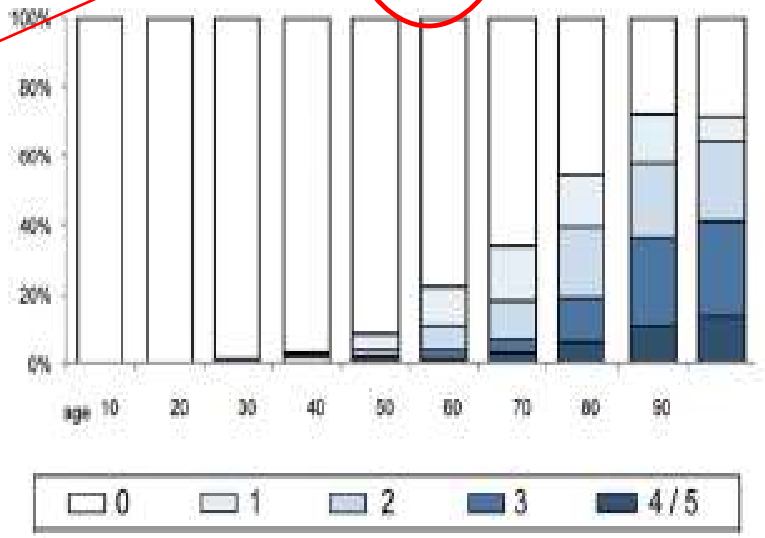


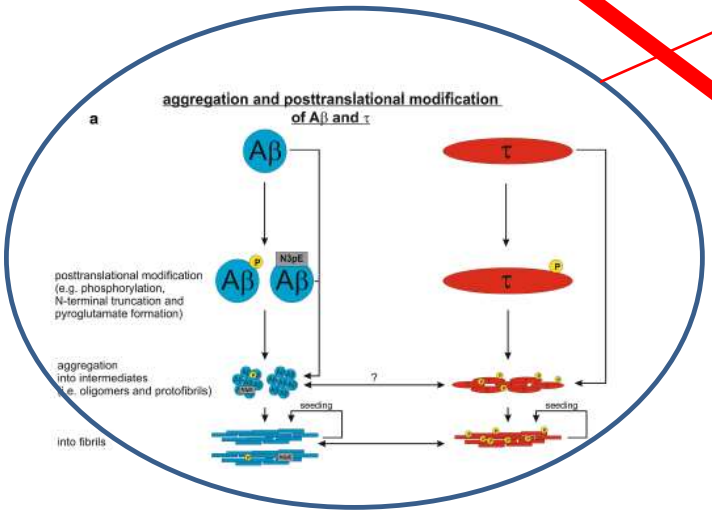


a Development of tau pathology by decade (n=2366)



b Development of Aβ pathology by decade (n=2366)





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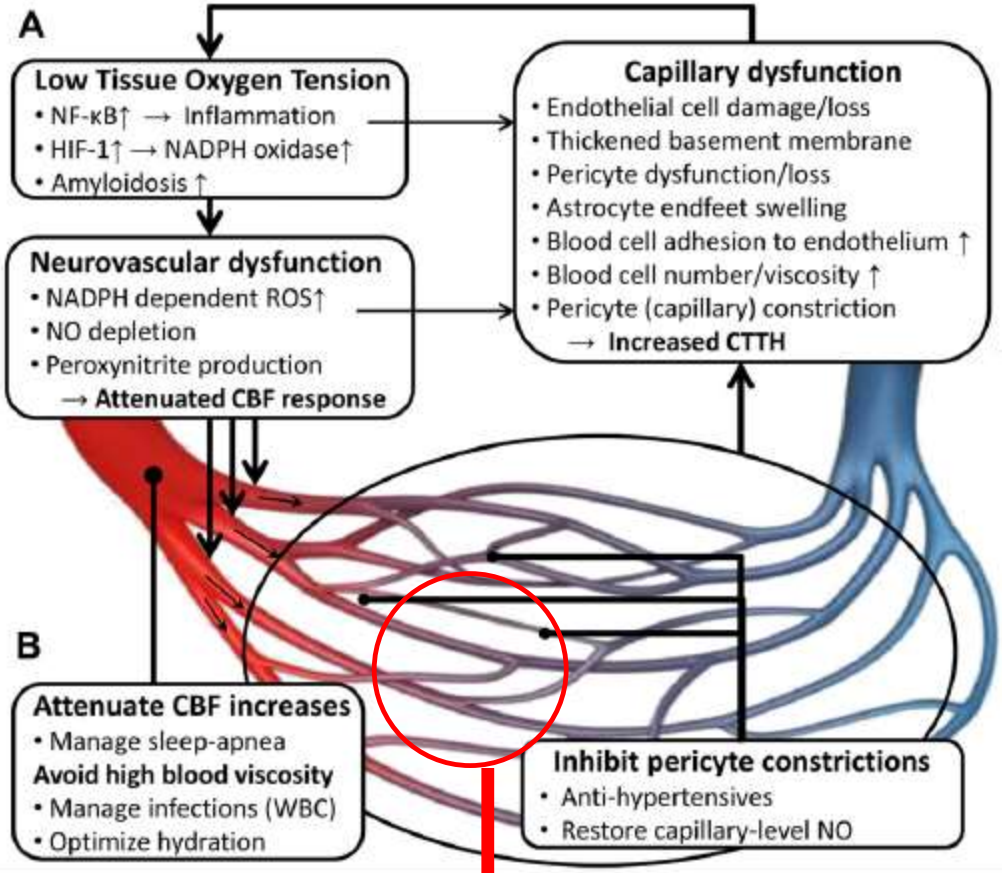
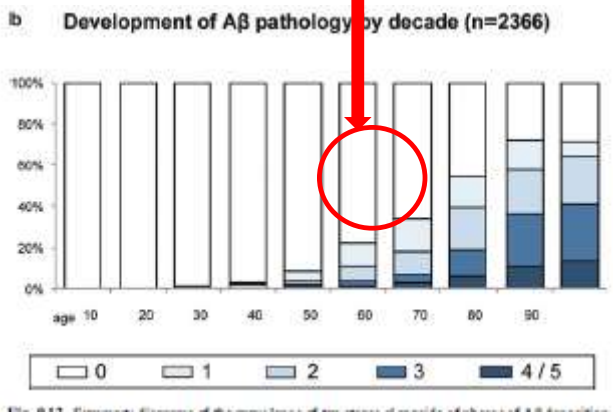




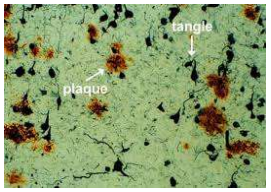
תוצאה-אינדיבידואליות

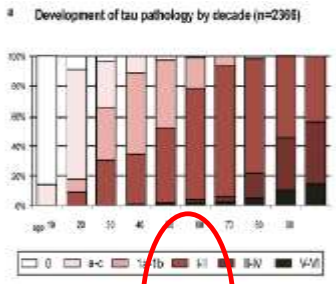
שילובי גורמים פעילים

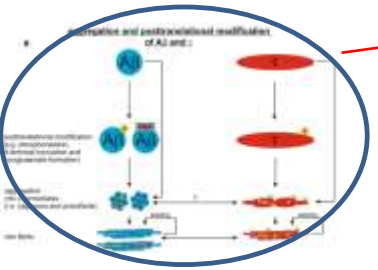
-כללי

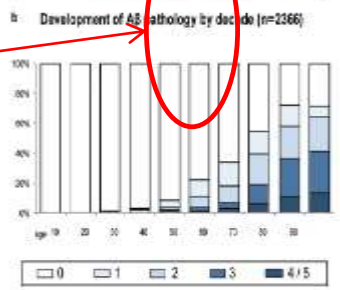
-תרופתי- CCBs ליתר לחץ דם

פתולוגיה סיסטמית מגבירת עמילואיד









-תסמונת דם נשימה

-אי ספיקת כליות

-מחלה ריאתית כרונית

-מגורים בסביבה רועשת ומזוהמת...

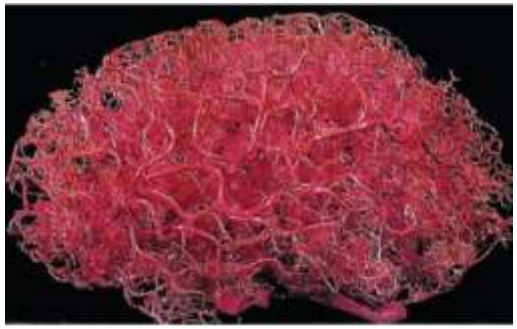
-עישון

-ועוד

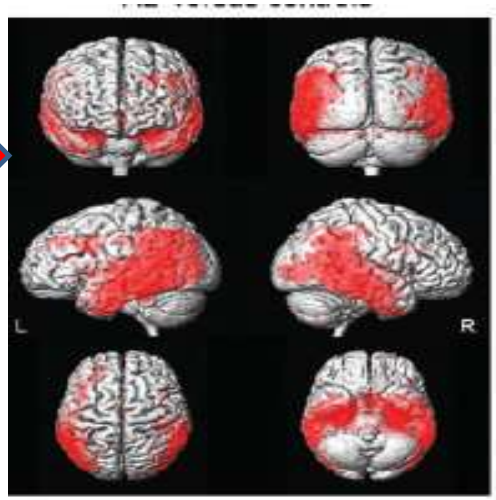
הפתולוגיה העיקרית
לשינויים קוגניטיביים בגיל השלישי

COMORBIDITY

פתולוגיה וסקולרית

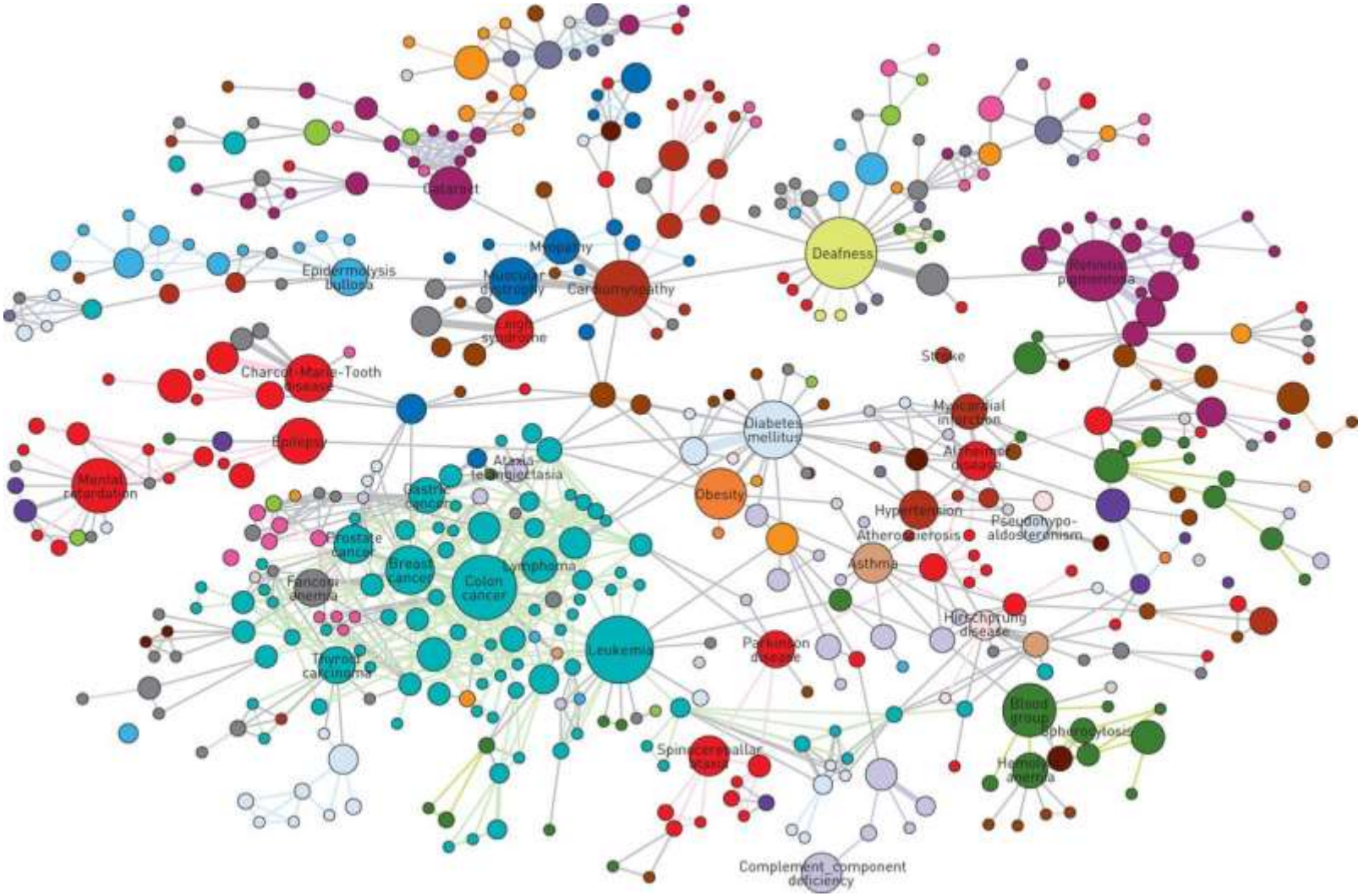


פתולוגית Alzheimer's Disease (AD)

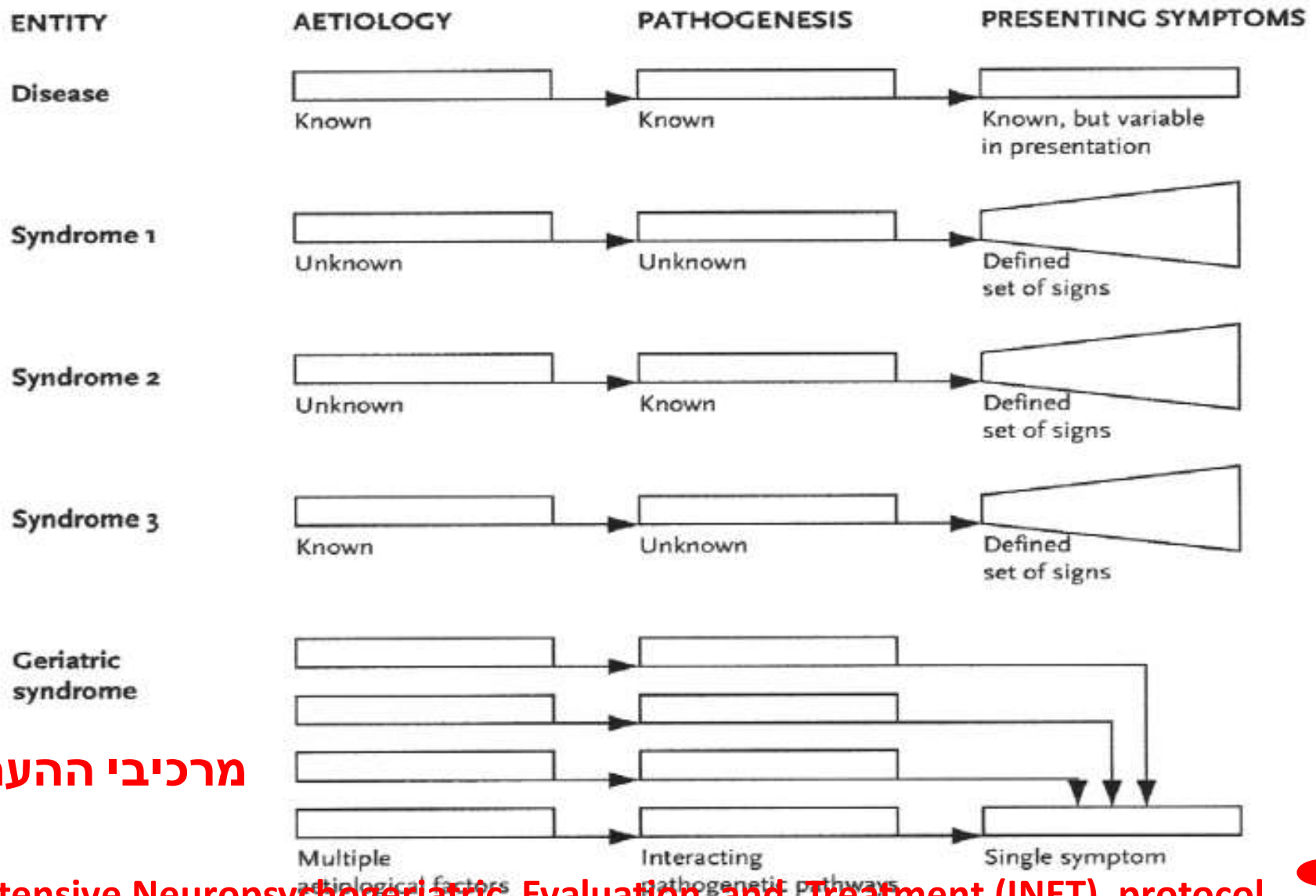


יש ריבוי מצבים טיפוליים !!!
יש לאן ללכת ממוקד!!!

Phenomenological Disease Network



התסמונת הגריאטרית-Geriatric syndrome



מרכיבי ההערכה

Intensive Neuropsychogeriatric Evaluation and Treatment (INET) protocol

רשת ערים בריאות בישראל

מפגש למידה של חברי רשת ערים בריאות
בנושא קידום הגיל השלישי / זקנה פעילה /עיר ידידותית גיל

משמעות-

- אינדיבידואליות –רפואית

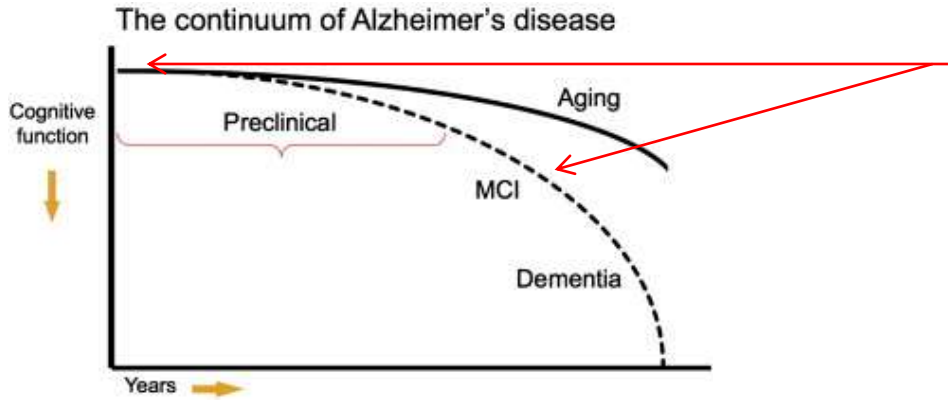
- תפקוד אישי וקהילתי – עצמאי + תובנה

- אוכלוסייתית pre-clinical/MCI

-שיעור גבוה

-רוורזיביליות MCI

-זהירות מאפקט "דיור מוגן"



רשת ערים בריאות בישראל

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אינדיבידואלי –לעומת סטטיסטי

מטרה -

-חייבת להיות משולבת-

-פסיכוסוציאלית

-סביבתית-פסיכולוגית

-רפואית

-כללית

-קוגניטיבית- התנהגותית- תפקודית

B.המרכיב הפסיכולוגי -לא נבדק

מודל Ryff ל- psychological successful aging

1. Autonomy
2. Self-acceptance
3. Positive relations
4. Environmental mastery
5. Purpose in Life
6. Personal growth
7. Second order factor

(מרכיב Well-being)

contentment, satisfaction with the past,
optimism for the future
and happiness in the present (McNulty,2012)

(Ryff,1995; van Dierendonck2008)

C. מחקרי המרכיב הרפואי +

-גורמי סיכון וסקולרי

Vol. 41

Epidemiological Approaches to Heart Disease: The Framingham Study*

THOMAS R. DAWBER, M.D., GILCIN F. MEADORS, M.D., M.P.H., AND FELIX E. MOORE, JR.

National Heart Institute, National Institutes of Health, Public Health Service, Federal Security Agency, Washington, D. C.

1948-51

-הפעלה מוחית

מחקר Framingham
תוצאות 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Incidence of Dementia over Three Decades in the Framingham Heart Study

Claudia L. Satizabal, Ph.D., Alexa S. Beiser, Ph.D., Vincent Chouraki, M.D., Ph.D., Geneviève Chêne, M.D., Ph.D., Carole Dufouil, Ph.D., and Sudha Seshadri, M.D.

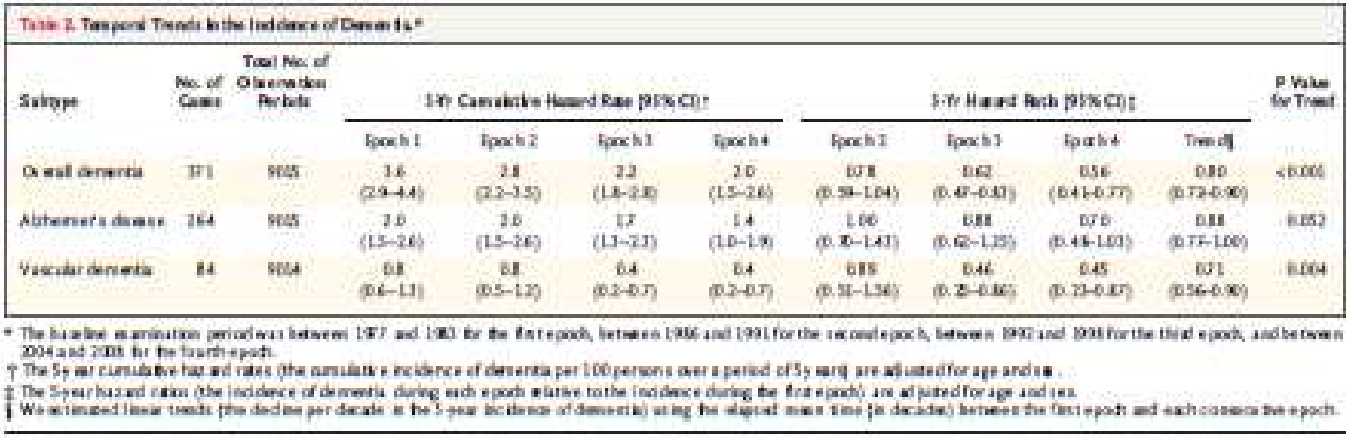


Table 2. Temporal Trends in the Incidence of Dementia.*

Subtype	No. of Cases	Total No. of Observation Periods	5-Yr Cumulative Hazard Rate (95% CI)†				5-Yr Hazard Ratio (95% CI)‡				P Value for Trend
			Epoch 1	Epoch 2	Epoch 3	Epoch 4	Epoch 2	Epoch 3	Epoch 4	Trend§	
Overall dementia	371	9025	3.6 (2.9–4.4)	3.8 (3.2–3.5)	2.2 (1.8–2.8)	2.0 (1.5–2.6)	0.78 (0.59–1.04)	0.62 (0.47–0.82)	0.56 (0.41–0.77)	0.80 (0.72–0.90)	<0.001
Alzheimer's disease	264	9025	2.0 (1.5–2.6)	2.0 (1.5–2.6)	1.7 (1.3–2.2)	1.4 (1.0–1.9)	1.00 (0.70–1.43)	0.88 (0.62–1.25)	0.70 (0.48–1.03)	0.88 (0.77–1.00)	0.052
Vascular dementia	84	9054	0.8 (0.6–1.3)	0.8 (0.5–1.2)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.85 (0.51–1.34)	0.46 (0.25–0.86)	0.45 (0.23–0.87)	0.71 (0.56–0.90)	0.004

* The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch.
† The 5-year cumulative hazard rates (the cumulative incidence of dementia per 100 persons over a period of 5 years) are adjusted for age and sex.
‡ The 5-year hazard ratios (the incidence of dementia during each epoch relative to the incidence during the first epoch) are adjusted for age and sex.
§ We estimated linear trends (the decline per decade in the 5-year incidence of dementia) using the elapsed mean time (in decades) between the first epoch and each consecutive epoch.

-אפקט AD ≠ אפקט VD

-לא מוסבר ע"י- Framingham Stroke Risk Profile

(כולל-לחץ דם סיסטולי,טיפול נוגד לחץ דם גבוה, סטטוס סכרת ,סטטוס עישון,
פרפור פרוזדורים ואירועים וסקולריים קליניים)

Table 3. Temporal Trends in the Incidence of Dementia, Stratified by Age, Sex, Educational Level, and Apolipoprotein E ε4 Status.*

Variable	No. of Cases of Dementia	Total No. of Observation Periods	P Value for Interaction	5-Yr Hazard Ratio (95% CI)†				P Value for Trend
				Epoch 2	Epoch 3	Epoch 4	Trend‡	
Age at entry (yr)			0.82					
60–69	42	4418		0.43 (0.18–1.00)	0.36 (0.15–0.89)	0.38 (0.15–0.93)	0.65 (0.47–0.89)	0.008
70–79	133	3229		0.91 (0.59–1.42)	0.67 (0.42–1.07)	0.64 (0.36–1.11)	0.83 (0.68–1.00)	0.047
≥80	196	1368		0.86 (0.56–1.33)	0.72 (0.48–1.09)	0.68 (0.44–1.06)	0.86 (0.74–1.01)	0.06
Sex			0.27					
Female	234	5173		0.70 (0.50–1.00)	0.52 (0.36–0.74)	0.53 (0.36–0.78)	0.77 (0.67–0.89)	<0.001
Male	137	3842		0.96 (0.59–1.57)	0.89 (0.55–1.43)	0.64 (0.38–1.08)	0.85 (0.71–1.02)	0.08
Educational level			0.031					
No high school diploma	130	1831		1.46 (0.94–2.26)	0.97 (0.58–1.61)	1.66 (0.87–3.15)	1.11 (0.89–1.39)	0.34
High school diploma	228	6948		0.54 (0.36–0.81)	0.55 (0.38–0.79)	0.46 (0.31–0.67)	0.77 (0.67–0.88)	<0.001
APOE ε4 status§			0.15					
Any genotypic information	246	6304			0.96 (0.70–1.30)	0.83 (0.60–1.16)	0.89 (0.74–1.08)	0.25
Negative for APOE ε4	169	5000			0.95 (0.65–1.37)	0.75 (0.50–1.13)	0.84 (0.66–1.06)	0.14
Positive for at least one APOE ε4 allele	77	1304			1.01 (0.58–1.75)	1.09 (0.61–1.93)	1.05 (0.75–1.47)	0.76

- חינוך-

- APOEϵ4-

- הסברים נוספים !!!

מחקר CFAS

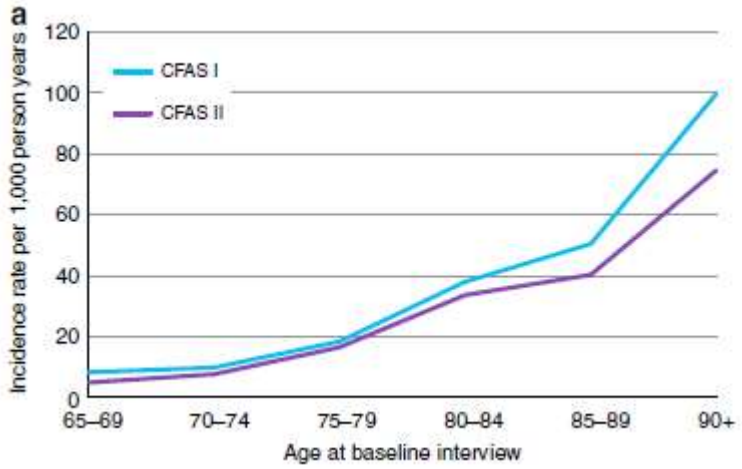
תוצאות -2016

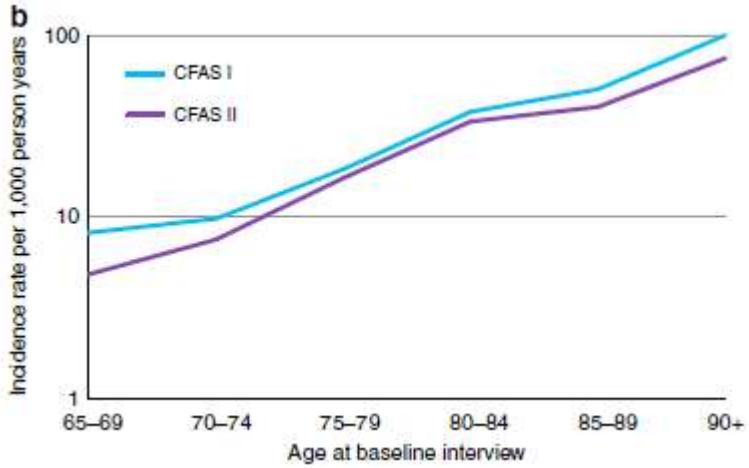
1989-1994-CFAS I-

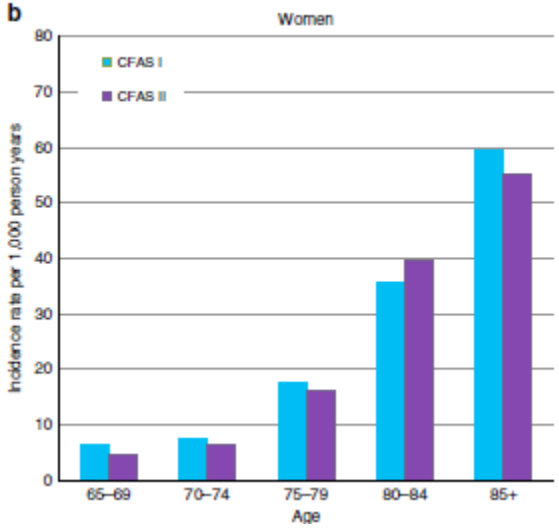
2008-2011- CFAS II-

ירידה ב-20%

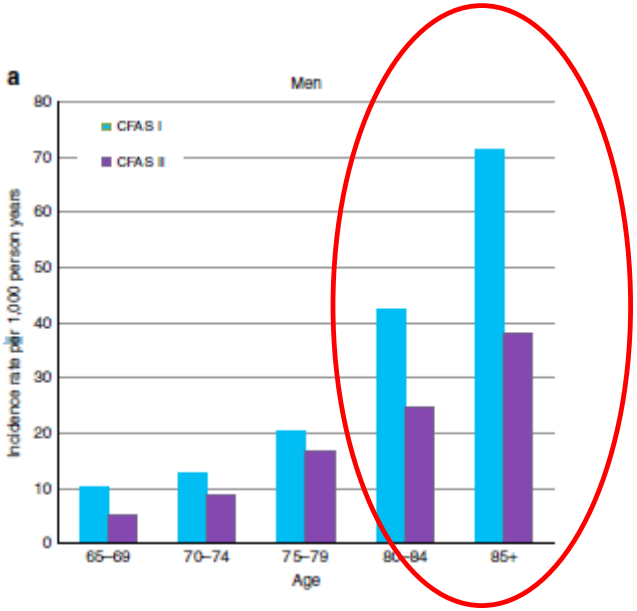
ב-incidence !!!






b
Women
CFAS I
CFAS II
Incidence rate per 1,000 person years
0
10
20
30
40
50
60
70
80
65–69
70–74
75–79
80–84
85+
Age

נשים


a
Men
CFAS I
CFAS II
Incidence rate per 1,000 person years
0
10
20
30
40
50
60
70
80
65–69
70–74
75–79
80–84
85+
Age

גברים

-

CFAS I

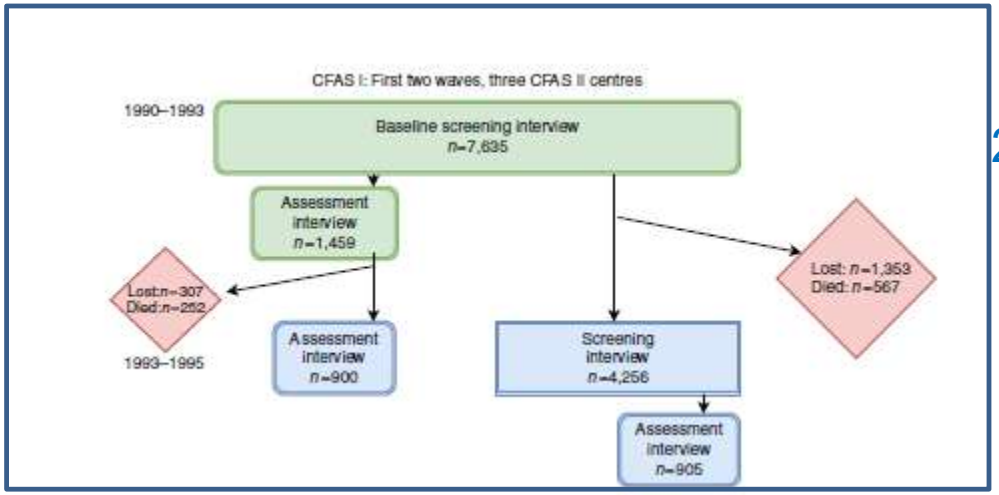
-לפני סריקה-

-24%-refusals

-אחרי סריקה

-אבדו- 1660

-נפטרו-819



CFAS II

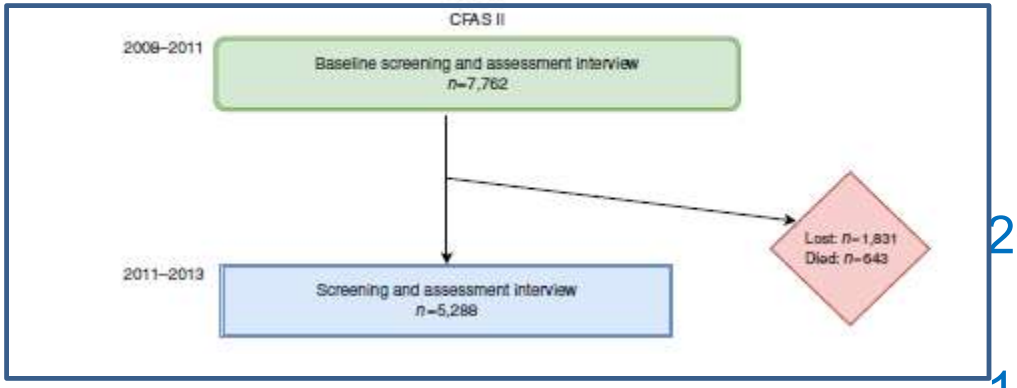
-לפני סריקה-

-26%-refusals

-אחרי סריקה

-אבדו- 1831

-נפטרו-643



מחקר ה- PreDIVA

(PREvention of Dementia by Intensive VAscular care)

(Moll van Charante et al., 2016)

-משתתפים-

-קב' התערבות- 1853

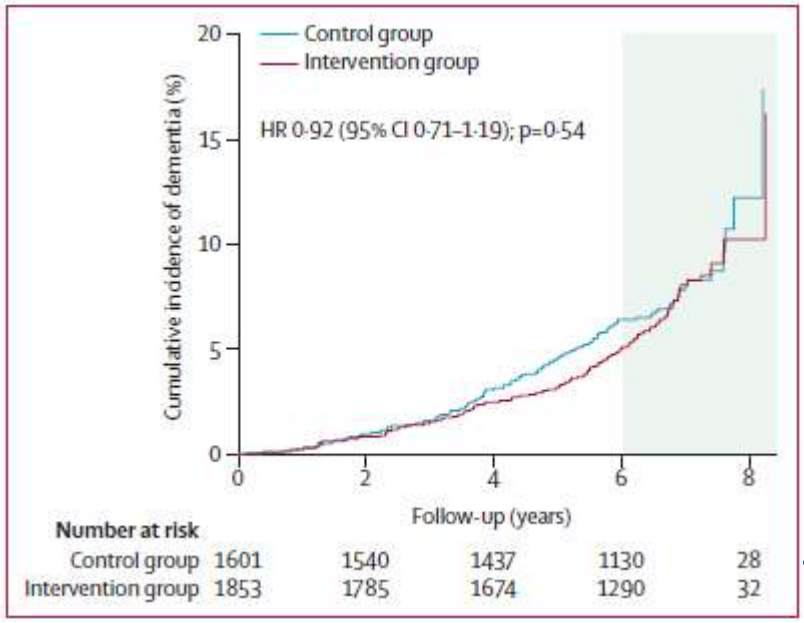
-קב' בקורת- 1601

-ההתערבות-

- multidomain cardiovascular

-למשך 6 שנים

אפקט-



א. -שיעור התפתחות דמנציה
ב-6 השנים-
7%-
-אין אפקט

-גורמים אפשריים
-רמת טיפול בסיסית טוב
-הטיות גיוס חולים

ב.אפקט נמצא-
-יתר לחץ דם לא מטופל
-שכיחות D- קב' התערבות- 4% ,קב' בקורת- 7% (HR-0.54)
-נעדרי עבר קרדיווסקולרי-
-שכיחות D -קב' התערבות- 5% קב' בקורת- 7% (HR- 0.64)

אינדיבידואלי !!!

מחקר בסיס- FINGER

התערבות משך שנתיים

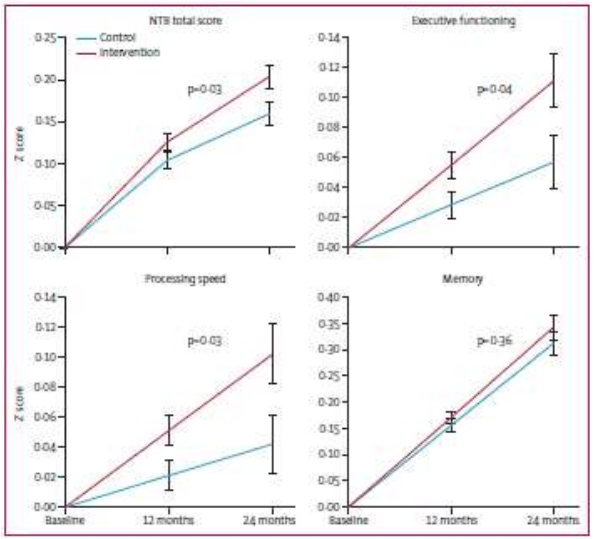
-דיאטה-פעילות גופנית-אימון קוגניטיבי- ניטור גורמי סיכון וסקולריים

-משתתפים-

-1260

-גיל - 60-77שנים (69.5 ± 4.6 שנים)

-תוצאות-



1.המדגם- משמעות לשיפור

א. CAIDE Dementia Rosk Score-

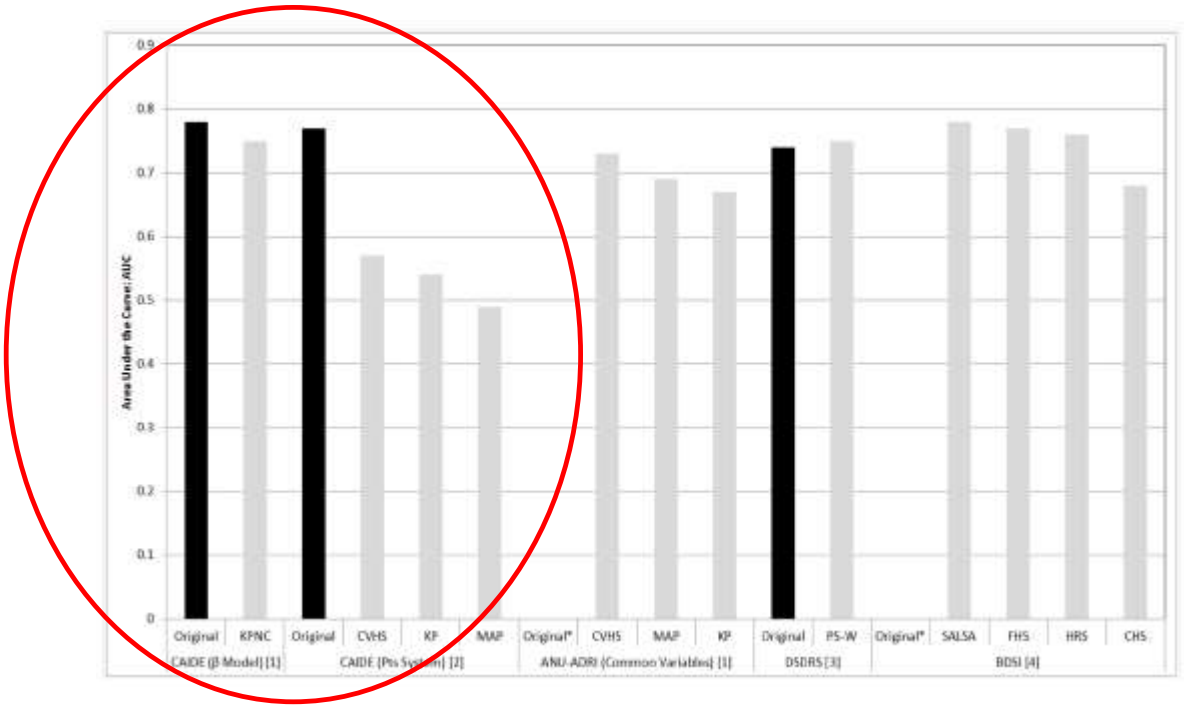
CAIDE- Cardiovascular Risk Factors ,Aging and Dementa-

(Kivipelto et al, 2006)

-מודל מותאם לגילאי 39-65 למעקב 20 שנה לגורמי midlife

-איננו מתאים לגילאים מבוגרים יותר- (Tang et al., 2015)

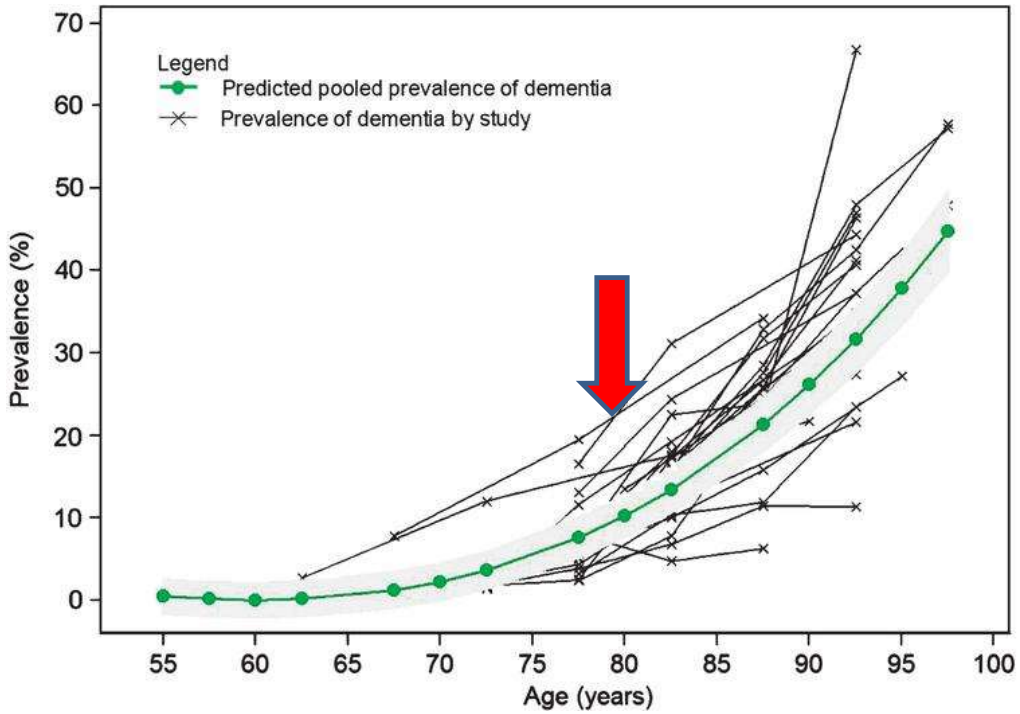
משקף השפעה שונה של גורמים ספציפיים



1. המדגם- משמעות לשיפור

ב.השפעת גיל המדגם

-גיל - 60-77שנים (69.5 ± 4.6 שנים)



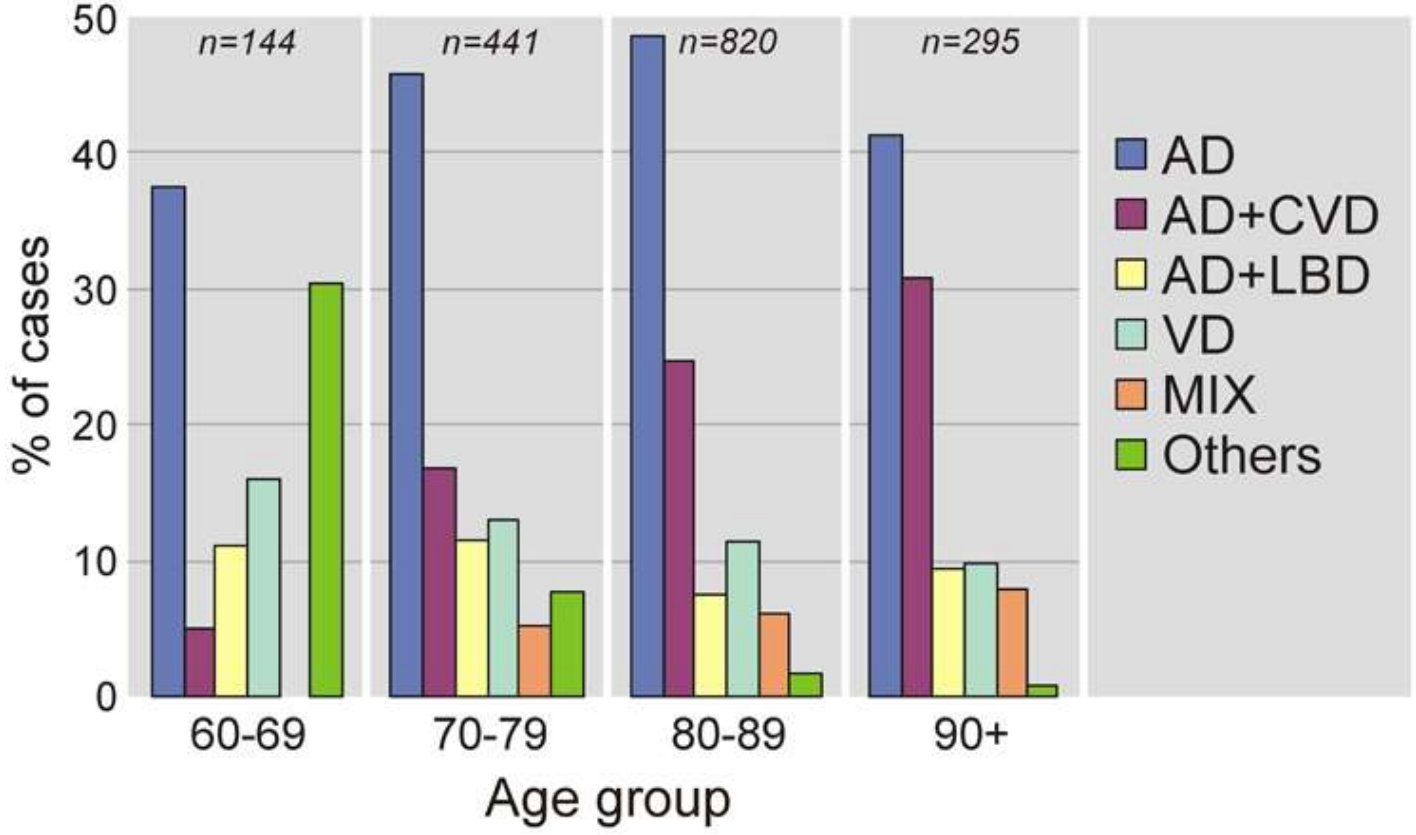
(Alexander et al., 2015)

*הגיל לבדיקת מניעה-

-מעל 75

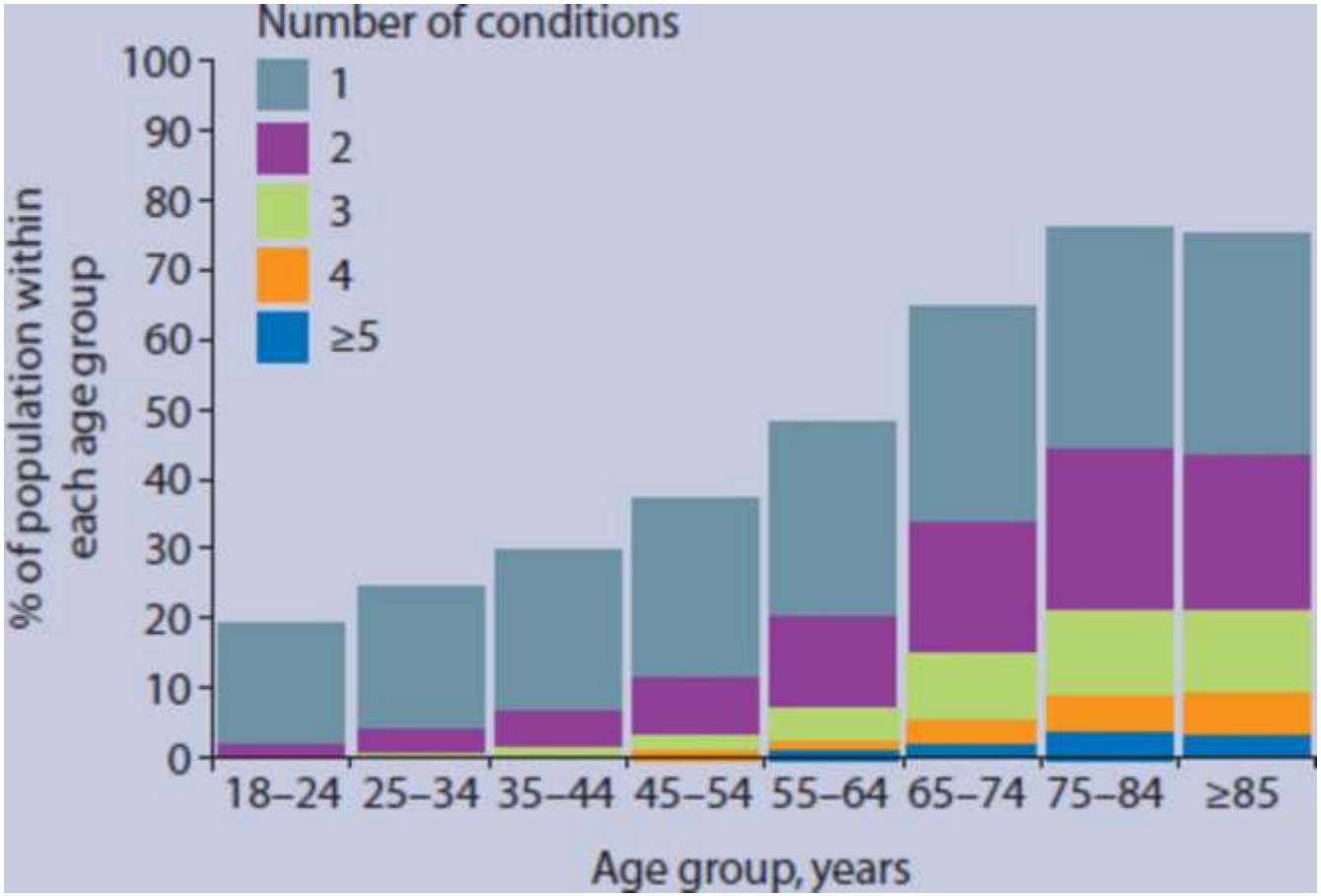
*פתולוגיה מוחית משמעותית בגיל המדגם-

-מניעה שניונית !!!

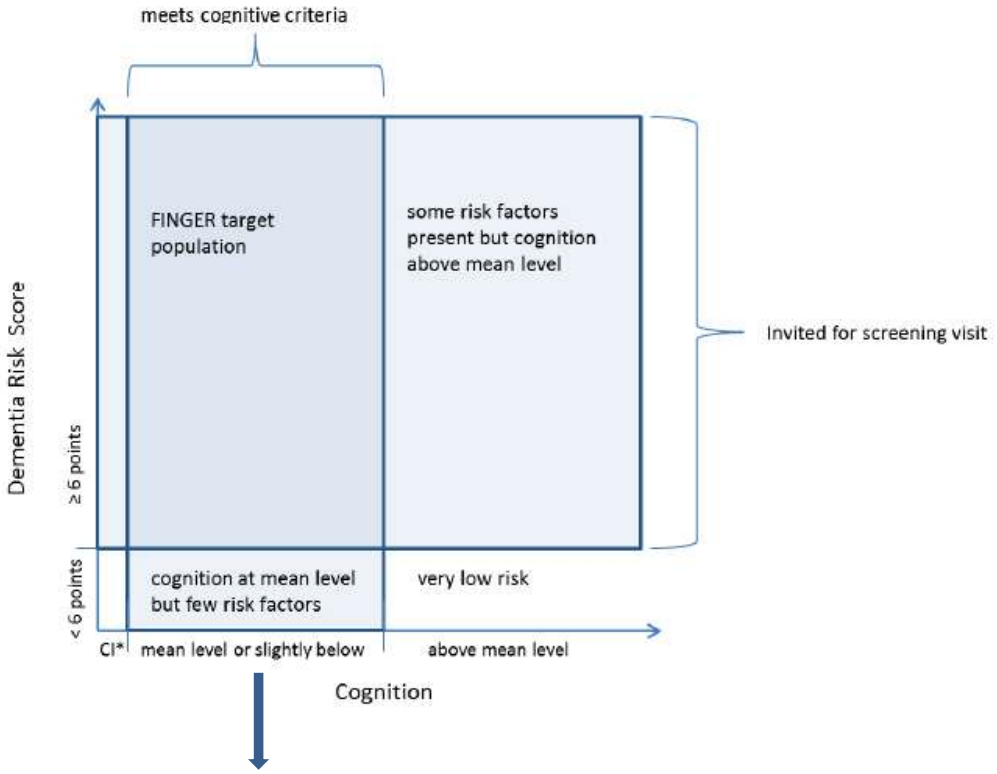


Jellinger)

Multimorbidity* -לפי גיל



(Salisbury et al., 2011)



1. המדגם- משמעות לשיפור

ג. הגדרת המדגם-

סטטוס קוגניטיבי

-

פחות מ- 0.5 SD

(Ngandu et al., 2014))

Table 4. Cognitive performance of the randomized participants and formation of the cognitive outcome modified Neuropsychological Test Battery (mean (SD)).

Characteristics at Baseline	n	All n = 1260	Intervention n = 631	Control n = 629	p-Value
Memory					
WMS-R Logical Memory (immediate)	1258	11.0 (3.7)	10.9 (3.8)	11.1 (3.6)	0.37
WMS-R Logical Memory (delayed)	1257	9.3 (3.9)	9.2 (4.0)	9.5 (3.8)	0.17
CERAD Word List Learning	1257	18.4 (3.2)	18.3 (3.2)	18.6 (3.3)	0.08
CERAD Word List Recall	1255	5.5 (1.7)	5.5 (1.7)	5.6 (1.7)	0.46
WMS-R Visual Paired Associates (immediate)	1239	9.1 (3.8)	8.9 (3.8)	9.3 (3.8)	0.08
WMS-R Visual Paired Associates (delayed)	1237	3.4 (1.8)	3.3 (1.8)	3.4 (1.8)	0.38
Executive function					
CERAD Category Fluency	1257	21.6 (5.7)	21.3 (5.6)	21.8 (5.8)	0.13
WMS-R Digit Span (total)	1258	11.5 (2.9)	11.5 (2.9)	11.4 (2.9)	0.64
CST (condition C) *	1157	65.2 (40.6)	64.3 (37.2)	66.1 (43.7)	0.44
TMT shifting score (B-A) *	1180	107.7 (65.7)	110.8 (66.9)	104.6 (64.4)	0.10
Stroop test interference score (3-2) *	1240	34.6 (18.0)	34.8 (18.1)	34.4 (17.8)	0.69
Processing speed					
Letter Digit Substitution Test	1253	22.0 (6.0)	21.7 (5.9)	22.2 (6.0)	0.14
CST (condition A) *	1256	33.1 (9.5)	33.3 (8.9)	32.8 (10.0)	0.33
Stroop test (condition 2) *	1251	29.5 (6.4)	29.6 (6.3)	29.3 (6.5)	0.55
Mini Mental State Examination	1257	26.7 (2.0)	26.7 (2.0)	26.8 (2.0)	0.55

* Timed task where smaller number indicates faster performance/better test result. In other tasks bigger number indicates better result. WMS-R: Wechsler Memory Scale-Revised, CERAD: Consortium to Establish a Registry for Alzheimer's Disease, CST: Concept Shifting Test, TMT: Trail Making Test.

איננו יודעים-

-מצב התלונות

-המצב האפקטיבי

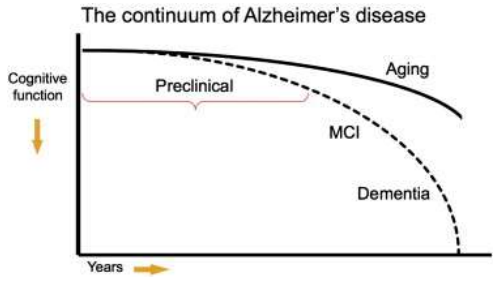
-המצב התפקודי

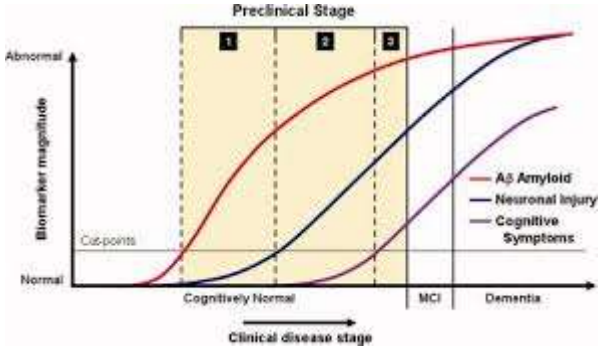
-לכן איננו יודעים האם-

MCI- -SCI - pre-clinical- נורמה

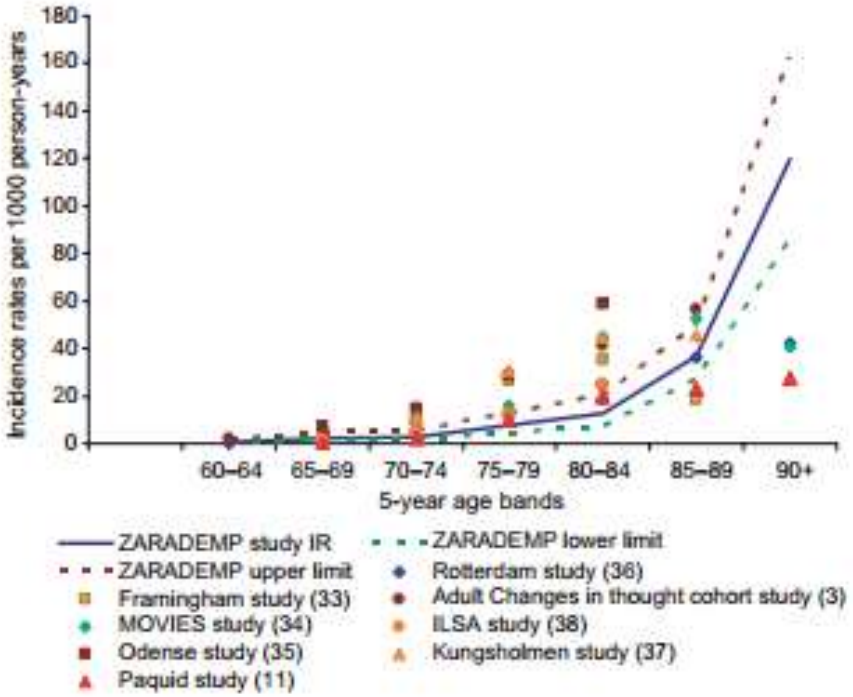
-קריטי לידיעת מידת הסיכון

(Kozauer & Katz, 2013)





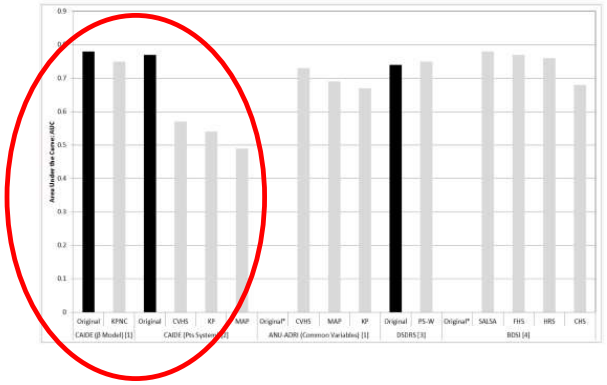
ללא מקרים חדשים של דמנציה משך שנתיים !!!



	Total dementia				Alzheimer's disease		
	Person-years at risk	No. of dementia cases	Incidence rate	95%CI	No. of Alzheimer's disease cases	Incidence rate	95%CI
Total							
55–59	673	0	0.0	0–5.5	0	0.0	0–5.48
60–64	3609	1	0.3	0–1.5	0	0.0	0–1.02
65–69	3516	8	2.3	1–4.5	2	0.6	0.07–2.06
70–74	3174	9	2.8	1.3–5.4	4	1.3	0.34–3.23
75–79	2109	16	7.6	4.3–12.3	9	4.3	1.95–8.10
80–84	1352	17	12.6	7.3–20.1	10	7.4	3.55–13.60
85–89	1251	46	36.8	26.9–49.1	30	24.0	16.2–34.2
90+	342	41	119.7	85.9–162.6	32	93.5	63.9–131.9
All ages	16 025	138	8.6	7.2–10.2	87	5.4	4.35–6.70

(Lobo et al., 2011)

לא ברורה מידת הסיכון באוכלוסיה זו!!!



1.המדגם- משמעות לשיפור

ד.הקונטקסט הקליני –

-גורמי הסיכון הוסקולריים –

-נכלל ב--CAIDE

-לחץ דם סיסטולי, BMI, tCHOL, פעילות גופנית

-לא נכלל-

-פרפור פרוזדורים, אי ספיקת לב,סכרת ועוד

-גורמי סיכון קריטיים !!!

-לכן-הסיכון הוסקולרי- לא נראה שנמדד כראוי

-גורמים סיסטמיים-

-אין בדיקה לגבי המצב הסיסטמי

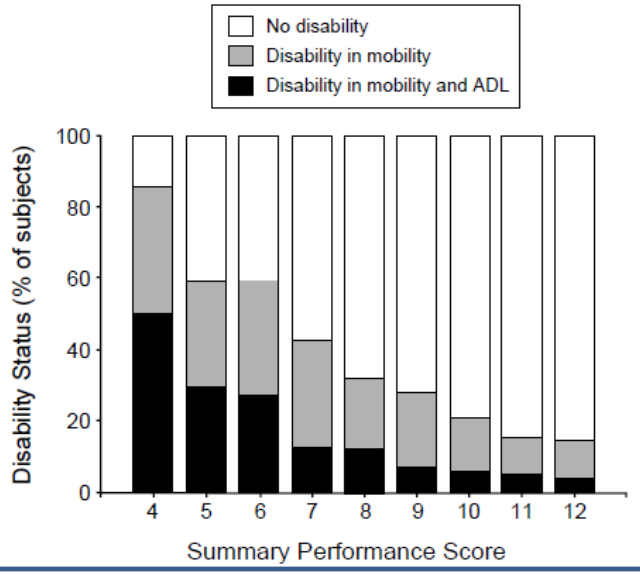
-המצב התפקודי

Short Physical Performance Battery score-
-כולל- שווי משקל היררכי, הליכה , קימה מכסא

Journal of Gerontology: MEDICAL SCIENCES
1994, Vol. 49, No. 2, M85-M94

A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission

Jack M. Guralnik,[1] Eleanor M. Simonsick,[1] Luigi Ferrucci,[2] Robert J. Glynn,[3] Lisa F. Berkman,[4] Dan G. Blazer,[5] Paul A. Scherr,[6] and Robert B. Wallace[7]



FINGER population

Characteristics at Baseline	n	All n = 1260	Intervention n = 631	Control n = 629	*p*-Value
Short Physical Performance Battery score	1178	10.8 (1.5)	10.8 (1.5)	10.8 (1.5)	0.96

2.ההתערבות

facilitating lifestyle changes. Participants were advised to consume a diet with 10–20% of daily energy from proteins, 25–35% daily energy from fat (<10% from saturated plus trans fatty acids, 10–20% from monounsaturated fatty acids, and 5–10% from polyunsaturated fatty acids [including 2·5–3 g/day of omega-3 fatty acids]), 45–55% daily energy from carbohydrates (<10% from refined sugar), 25–35 g/day of dietary fibre, less than 5 g/day of salt, and less than 5% daily energy from alcohol. Energy intake facilitating 5–10% reduction in bodyweight was recommended only if necessary after taking into account BMI, health status, age, and diet of the participant. These goals were achieved by recommendation of high consumption of fruit and vegetables, consumption of wholegrain cereal products and low-fat milk and meat products, limiting of sucrose intake to less than 50 g/day, use of vegetable margarine and rapeseed oil instead of butter, and fish consumption at least two portions per week.

The physical exercise training programme followed international guidelines[22] and represented a modified version of the Dose Responses to Exercise Training (DR's EXTRA) study protocol.[23] Training was guided by study physiotherapists at the gym and consisted of individually tailored programmes for progressive muscle strength training (1–3 times per week) and aerobic exercise (2–5 times per week), including exercises to improve postural balance. The strength training programme was standardised to include exercises for the eight main muscle groups (knee extension and flexion, abdomen and back muscles, rotation, upper back and arm muscles, and press bench for lower extremity muscles). Individual aerobic training included activities preferred by each participant. Aerobic group activities were also provided. Individualisation of strength and aerobic training was based on repetition maximum measurements (done at baseline and at 1, 3, 6, 9, 12, 18, and 24 months after the start of the exercise intervention).[24] Cognitive training

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תזונה ומשקל

פעילות גופנית

קוגניטיבית

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חברתית

(shape match task). Social activities were stimulated through the numerous group meetings of all intervention components. Management of metabolic and vascular

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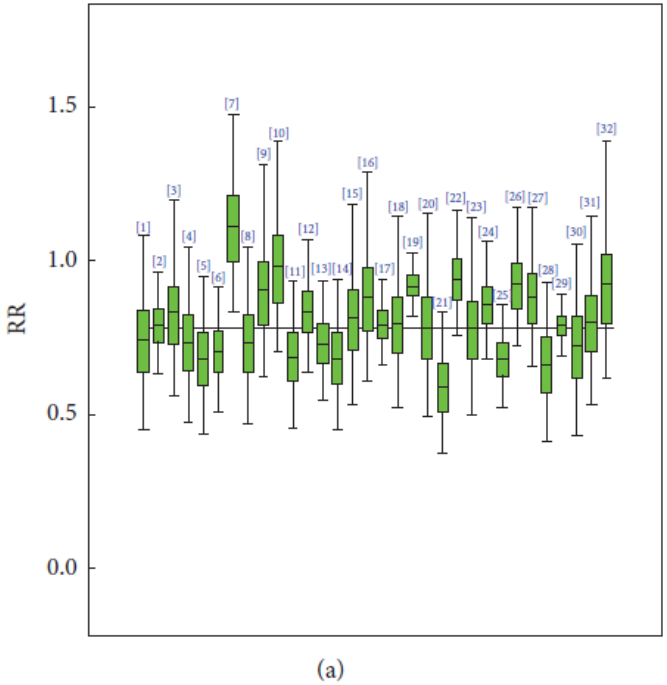
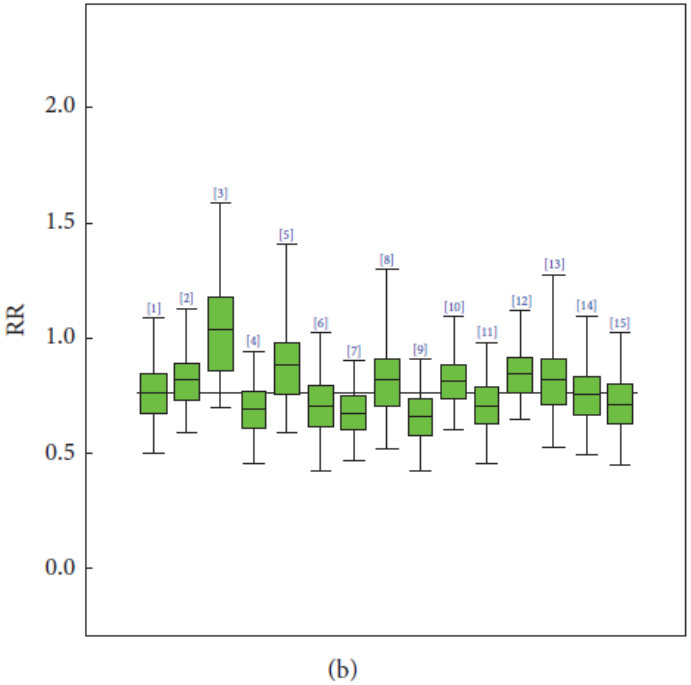
פעילות גופנית והשפעה למניעת דמנציה

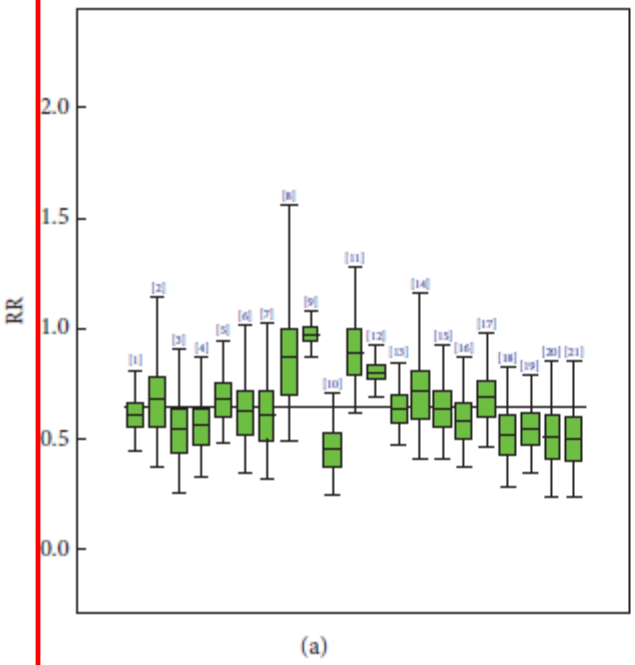
(Guure et al., 2017)

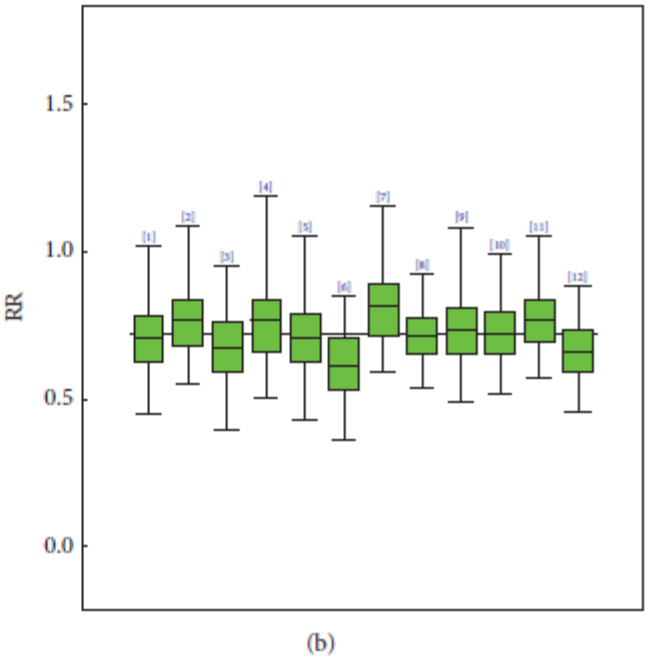




רבה **בינונית** רמת פעילות

Alzheimer's





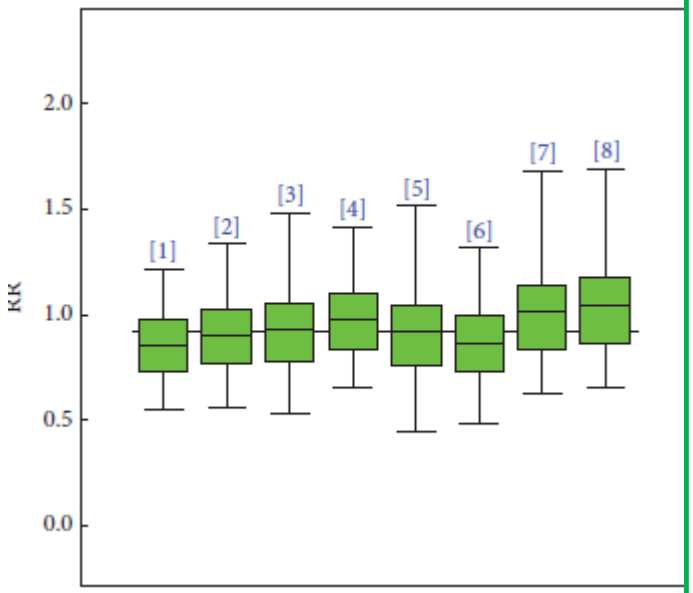
רמת פעילות

רבה

בינונית

דמנציה וסקולרית

אין אפקט !!!



2.ההתערבות

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השפעת אימון קוניטיבי על פעילות המוח-fMRI

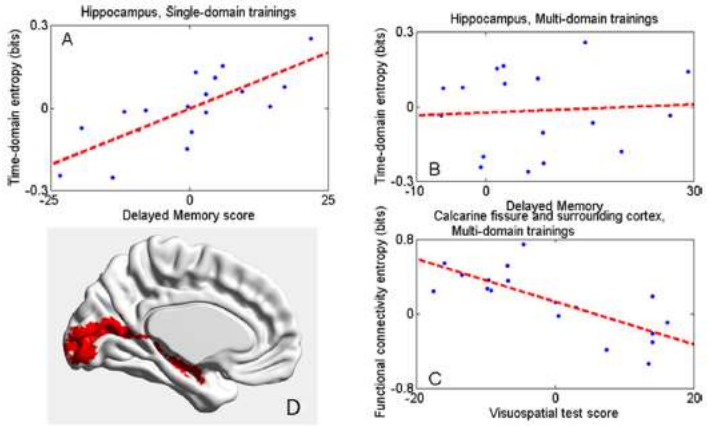


Fig. 6 The correlation between cognitive capacity and resting state fMRI. Panel (**a**) and (**b**): Regional time-domain entropy for the hippocampus was significantly and positively correlated with delayed memory in the single-domain group ($r = 0.760$, $p = 2.56 \times 10^{-4}$) and positively (but not significant) correlated with delayed memory in the multi-domain group. Panel (**c**): In the multi-domain group, regional functional entropy of the calcarine fissure and the surrounding cortex was significantly negatively correlated with the visuospatial test ($r = -0.758$, $p = 2.72 \times 10^{-4}$).

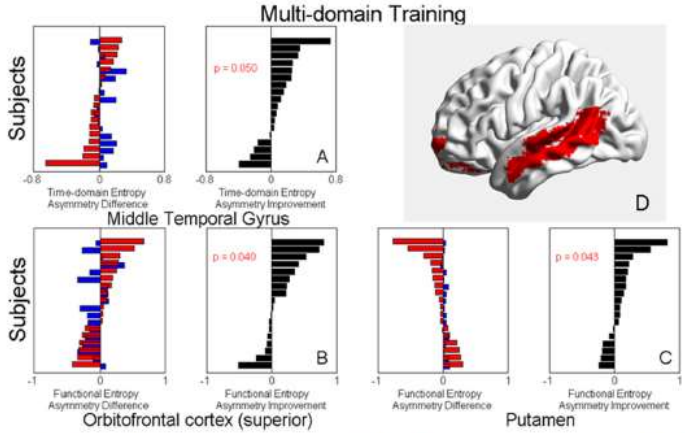
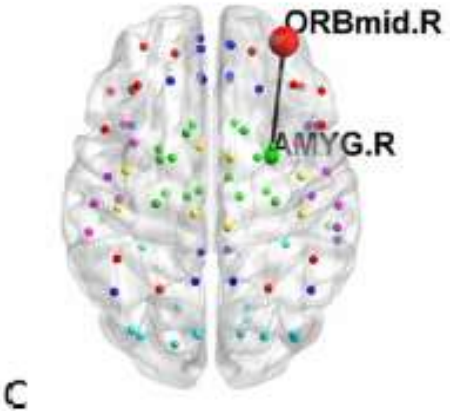


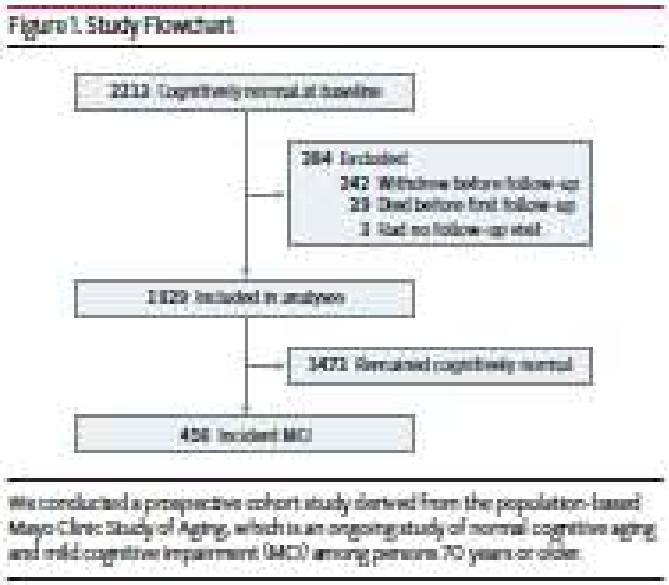
Fig. 5 Entropy asymmetry change in multi-domain CogTr group. Panels (**a**), (**b**) and (**c**): Compared to controls, the amount of entropy asymmetry was significantly reduced in the middle temporal gyrus ($t = 1.72$, $p = 0.050$). **a** the orbital part of the superior frontal gyrus ($t = 1.86$, $p = 0.040$) (**b**) and the putamen ($t = 1.82$, $p = 0.043$). **c** of the multi-domain CogTr group. Panel (**d**): These regions found in (**a**), (**b**) and (**c**) are represented. Subjects are ranked according to the entropy values

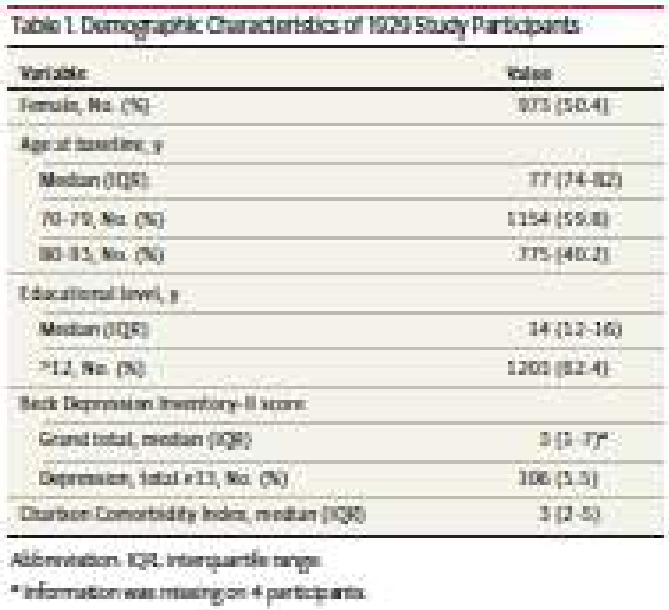


(Li et al, 2017)

פעילות פנאי –חשוב

הקשר בין mental stimulating activities ל-MCI





(Krell-Roesch et al., 2017)

פעילות בשנה לפני איסוף הנתונים

Table 2. Mentally Stimulating Activities and Risk of Incident Mild Cognitive Impairment (MCI)*

Variable	No. at Risk	No. With Incident MCI	Median Follow-up, y	HR (95% CI)†	P Value	HR (95% CI)‡	P Value
Reading books	1083	240	4.1	0.83 (0.68-1.01)	.06	0.86 (0.71-1.05)	.14
Playing games	1108	245	4.1	0.78 (0.65-0.95)	.01	0.83 (0.69-1.01)	.06
Craft activities	502	104	4.1	0.72 (0.57-0.90)	.004	0.78 (0.62-0.98)	.03
Computer use	1027	193	4.1	0.70 (0.57-0.85)	< .001	0.74 (0.61-0.90)	.002
Social activities	787	154	4.1	0.77 (0.63-0.94)	.009	0.79 (0.64-0.96)	.02

Abbreviation: HR, hazard ratio.

* No. at Risk refers to the number of participants (of the total sample size of 15203) who reported mentally stimulating activities performed at least 1 to 2 times per week. No. With Incident MCI refers to the number of participants (of the total sample size of 15203) who developed incident MCI.

† The model was adjusted for sex, age (scale), and educational level.

‡ The model was also adjusted for medical comorbidity, depression, and APOE ε4 carrier status.

Table 3. Mentally Stimulating Activities and Risk of Incident Mild Cognitive Impairment (MCI) Stratified by APOE ε4 Carrier Status*

Variable	No. at Risk	No. With Incident MCI	Median Follow-up, y	HR (95% CI)†	P Value	HR (95% CI)‡	P Value
APOE ε4+							
Reading books	283	77	3.4	0.91 (0.63-1.29)	.59	1.02 (0.71-1.46)	.94
Playing games	288	75	3.5	0.72 (0.51-1.01)	.06	0.78 (0.55-1.10)	.15
Craft activities	123	33	3.0	1.02 (0.69-1.51)	.93	1.08 (0.73-1.61)	.70
Computer use	270	61	3.7	0.65 (0.46-0.92)	.01	0.73 (0.50-1.06)	.05
Social activities	194	45	3.9	0.62 (0.43-0.89)	.009	0.64 (0.45-0.92)	.02
APOE ε4-							
Reading books	732	162	4.2	0.81 (0.64-1.02)	.07	0.82 (0.64-1.04)	.09
Playing games	815	169	4.2	0.81 (0.64-1.02)	.07	0.85 (0.68-1.06)	.18
Craft activities	378	71	4.5	0.65 (0.49-0.85)	.002	0.67 (0.51-0.88)	.004
Computer use	735	132	4.2	0.73 (0.58-0.93)	.01	0.75 (0.59-0.95)	.02
Social activities	571	108	4.2	0.83 (0.66-1.06)	.13	0.86 (0.68-1.09)	.23

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APOEε4 +

APOEε4 -

ריקוד ומוזיקה

משתתפים-
261-
עם MCI-
גיל-
76 ± 4.5 -

התערבות -
40- שבועות

(Doi et al., 2017)

Values for Cognitive Function Outcomes

Variables	Group	Baseline*	Differences†	*P* value (vs control)‡
Primary outcomes				
Story memory	Control	5.1 (2.0)	0.01 (1.9)	-
	Dance	5.1 (2.1)	0.73 (1.9)	.011
	Music	5.3 (2.1)	0.35 (1.7)	.123
Word memory	Control	3.4 (2.1)	0.27 (1.7)	-
	Dance	3.1 (2.1)	0.06 (1.6)	.213
	Music	3.5 (2.2)	0.21 (1.6)	.773
Secondary Outcomes				
MMSE	Control	25.8 (2.4)	−0.36 (2.3)	-
	Dance	26.0 (2.6)	0.29 (2.6)	.026
	Music	25.9 (2.6)	0.46 (2.1)	.008
TMT-A	Control	22.2 (5.9)	1.57 (6.0)	-
	Dance	21.8 (6.0)	−0.01 (5.2)	.052
	Music	21.9 (5.4)	0.19 (4.2)	.094
TMT-B	Control	42.0 (13.7)	1.5 (11.8)	-
	Dance	41.1 (14.2)	−0.02 (11.2)	.339
	Music	42.4 (13.7)	0.5 (11.6)	.390

2.ההתערבות

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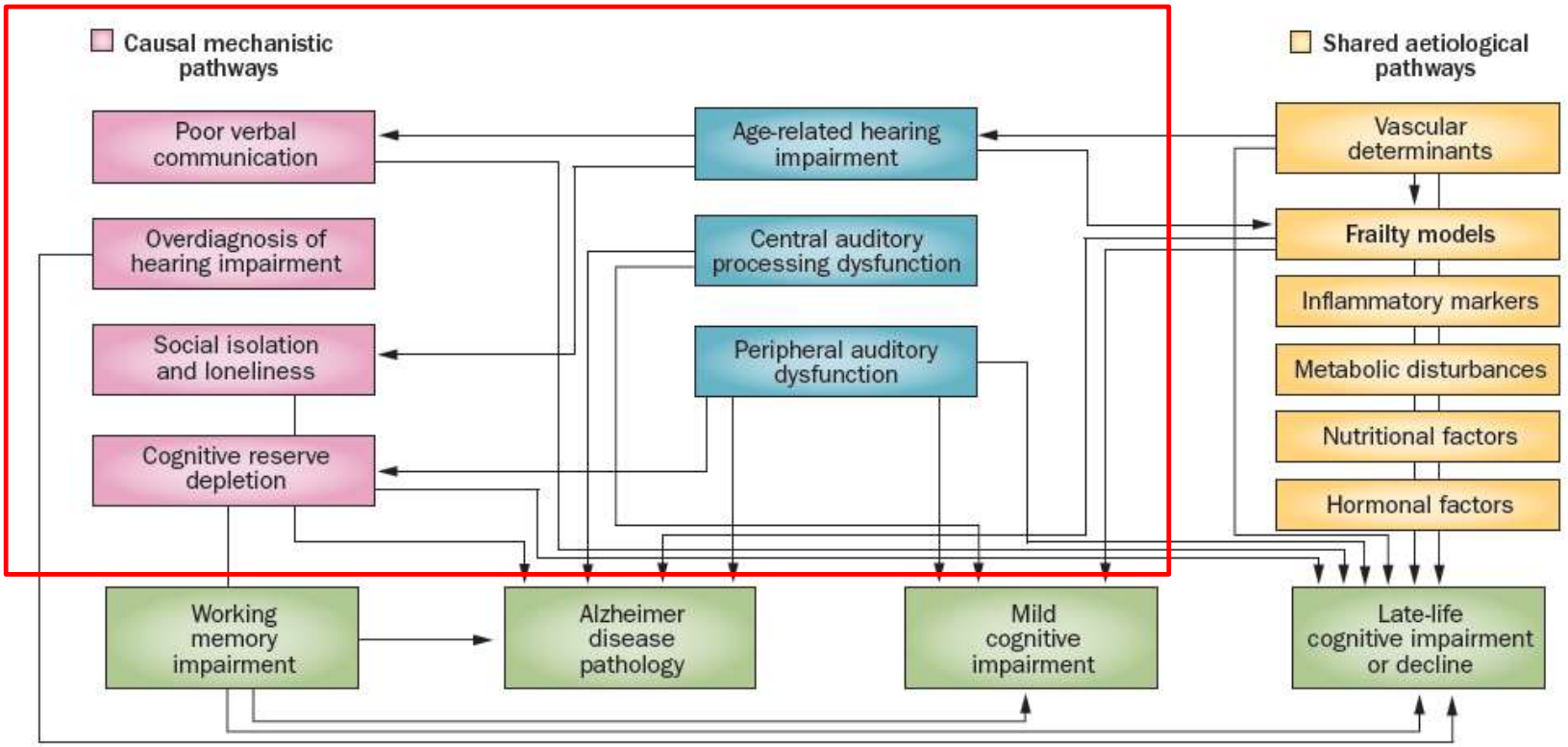
- **הפרעת שמיעה**



- (Panza et al., 2015)

2.ההתערבות

facilitating lifestyle changes. Participants were advised to consume a diet with 10–20% of daily energy from proteins, 25–35% daily energy from fat (<10% from saturated plus trans fatty acids, 10–20% from monounsaturated fatty acids, and 5–10% from polyunsaturated fatty acids [including 2·5–3 g/day of omega-3 fatty acids]), 45–55% daily energy from carbohydrates (<10% from refined sugar), 25–35 g/day of dietary fibre, less than 5 g/day of salt, and less than 5% daily energy from alcohol. Energy intake facilitating 5–10% reduction in bodyweight was recommended only if necessary after taking into account BMI, health status, age, and diet of the participant. These goals were achieved by recommendation of high consumption of fruit and vegetables, consumption of wholegrain cereal products and low-fat milk and meat products, limiting of sucrose intake to less than 50 g/day, use of vegetable margarine and rapeseed oil instead of butter, and fish consumption at least two portions per week.

The physical exercise training programme followed international guidelines[22] and represented a modified version of the Dose Responses to Exercise Training (DR's EXTRA) study protocol.[23] Training was guided by study physiotherapists at the gym and consisted of individually tailored programmes for progressive muscle strength training (1–3 times per week) and aerobic exercise (2–5 times per week), including exercises to improve postural balance. The strength training programme was standardised to include exercises for the eight main muscle groups (knee extension and flexion, abdomen and back muscles, rotation, upper back and arm muscles, and press bench for lower extremity muscles). Individual aerobic training included activities preferred by each participant. Aerobic group activities were also provided. Individualisation of strength and aerobic training was based on repetition maximum measurements (done at baseline and at 1, 3, 6, 9, 12, 18, and 24 months after the start of the exercise intervention).[24] Cognitive training

הרגלי חיים

תזונה ומשקל

פעילות גופנית

קוגניטיבית

start of the exercise intervention).[24] Cognitive training included group and individual sessions. The ten group sessions were led by psychologists: six sessions with educational content on age-related cognitive changes, memory, and reasoning strategies applied to everyday activities, and four sessions for checking progress in individual computer-based training plus a visit to the local Alzheimer Association. Individual sessions consisted of computer-based training at home or at study site, conducted in two periods of six months each. Each period included 72 training sessions (three times per week, 10–15 min per session). The training programme was a web-based in-house developed computer program including several tasks adapted from protocols previously shown to be effective in shorter-term randomised controlled trials:[25] executive processes (updating spatial, updating letter, updating number, and mental set shifting tasks), working memory (maintenance task), episodic memory (relational and spatial tasks), and mental speed (shape match task). Social activities were stimulated

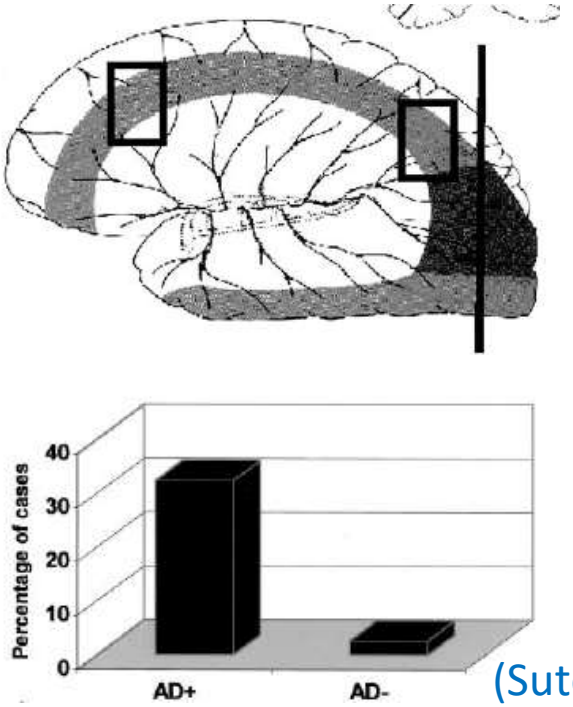
חברתית

(shape match task). Social activities were stimulated through the numerous group meetings of all intervention components. Management of metabolic and vascular

רפואית

components. Management of metabolic and vascular risk factors was based on national evidence-based guidelines.[26–27] It included additional meetings with the study nurse (at 3, 9, and 18 months), and the study physician (at 3, 6, and 12 months) for measurements of blood pressure, weight and BMI, and hip and waist circumference, physical examinations, and recommendations for lifestyle management. Study physicians did not prescribe medication, but strongly recommended participants to contact their own physician or clinic if needed.

2.ההתערבות



(Suter et al.,2002)

components. Management of metabolic and vascular risk factors was based on national evidence-based guidelines.[5-7] It included additional meetings with the study nurse (at 3, 9, and 18 months), and the study physician (at 3, 6, and 12 months) for measurements of blood pressure, weight and BMI, and hip and waist circumference, physical examinations, and recommendations for lifestyle management. Study physicians did not prescribe medication, but strongly recommended participants to contact their own physician or clinic if needed.

רפואית---

-תדירות

-נתוני לחץ דם -אורתוסטטיזם

-ויסות תרופות -ועוד

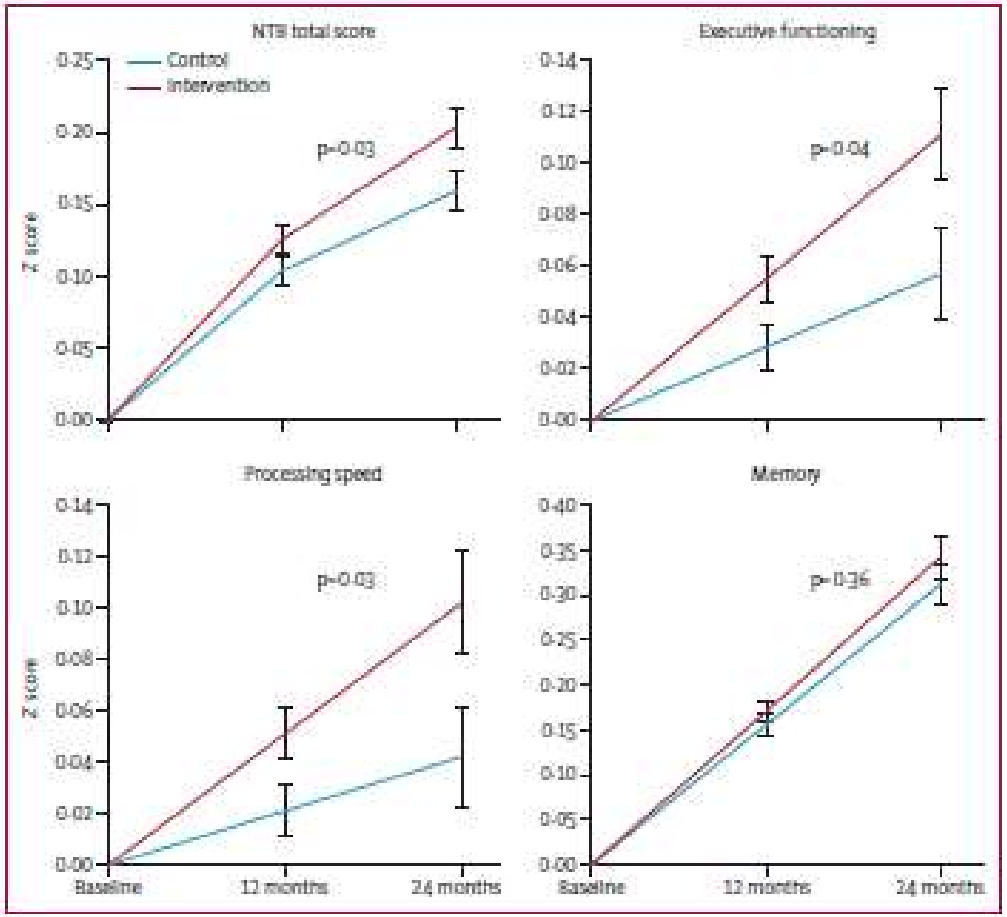
נתוני FINGER

-לחץ דם מאוזן –

-יתר לחץ דם מדווח-

	Participants with information available	Intervention group (n=591)	Control group (n=599)
Demographic characteristics			
Age at the baseline visit, years	1190	69·5 (4·6)	69·2 (4·7)
Number of women	1190	267/591 (45%)	284/599 (47%)
Education, years	1179	10·0 (3·4)	10·0 (3·4)
Married or cohabiting	1189	436/590 (74%)	454/599 (76%)
Vascular factors			
Systolic blood pressure, mm Hg	1179	140·1 (16·7)	139·8 (15·7)
Diastolic blood pressure, mm Hg	1179	80·5 (9·6)	80·1 (9·3)
Serum total cholesterol, mmol/L	1186	5·2 (1·0)	5·2 (1·0)
Fasting plasma glucose, mmol/L	1188	6·1 (0·8)	6·1 (1·0)
2 h oral glucose tolerance test, mmol/L	1031	7·0 (2·1)	7·0 (2·2)
Body-mass index, kg/m^2	1179	28·3 (4·5)	28·1 (4·9)
Lifestyle factors			
Physical activity two or more times per week	1180	410/585 (70%)	427/595 (72%)
Current smokers	1186	58/588 (10%)	48/598 (8%)
Alcohol drinking at least once per week	1182	265/588 (45%)	265/594 (45%)
Fish intake at least twice per week	1183	316/587 (54%)	304/596 (51%)
Daily intake of vegetables	1187	360/589 (61%)	374/598 (63%)
Self-reported medical disorders			
Hypertension	1177	392/585 (67%)	387/592 (65%)
Hypercholesterolaemia	1180	389/587 (66%)	414/593 (70%)
Diabetes	1180	76/586 (13%)	74/594 (12%)
History of myocardial infarction	1184	29/589 (5%)	31/595 (5%)
History of stroke	1181	32/587 (5%)	34/594 (6%)
Cognition*			
NTB total score	1190	−0·03 (0·55)	0·03 (0·59)
Executive functioning	1189	−0·03 (0·66)	0·03 (0·69)
Processing speed	1190	−0·02 (0·78)	0·05 (0·84)
Memory	1190	−0·03 (0·68)	0·03 (0·66)
Mini mental state examination	1187	26·7 (2·0)	26·8 (2·0)

3. האפקט במחקר FINGER



-מדדי אפקט -

-קב' התערבות- 0.23 SD

-קב' בקורת- 0.19 SD

(טיפול סטנדרטי והסברה)

-הבדל אבסולוטי-

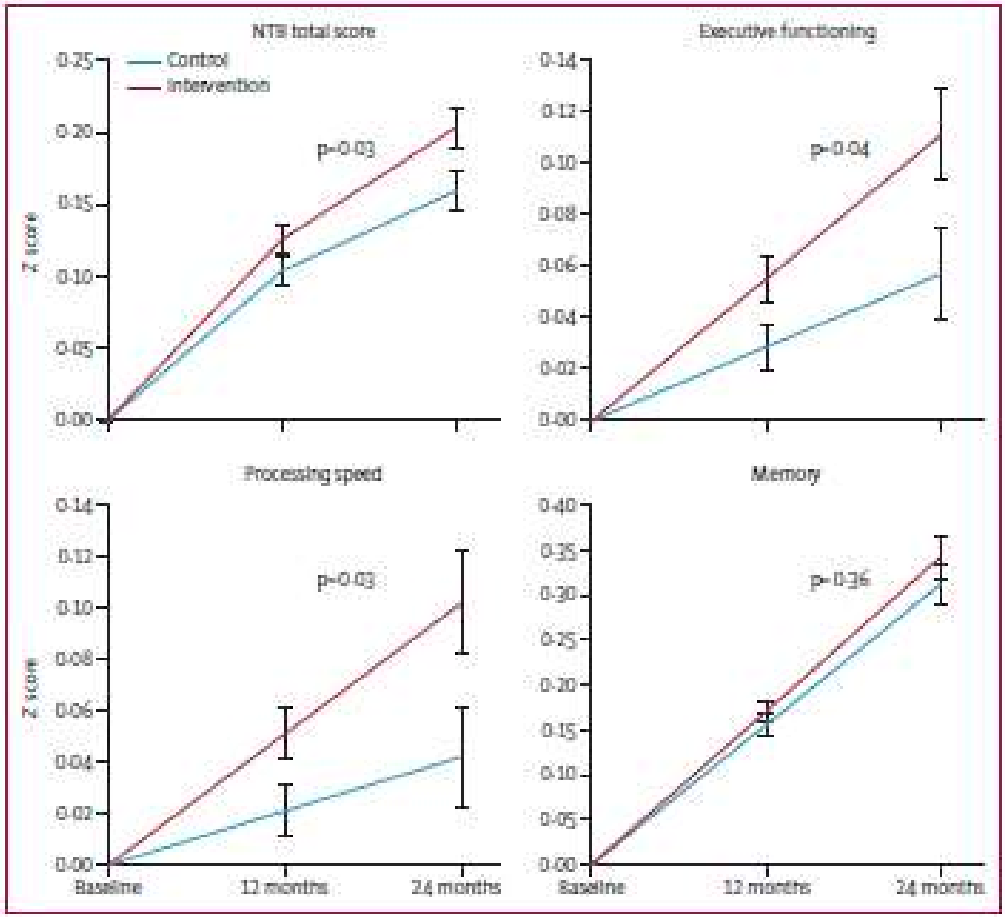
-קבוצתי 0.02 SD -0.04

-אינדיבידואלי- 0.13

(Cohen's d)

-

3. האפקט במחקר FINGER



-קשיים –

-יש שיפור (!) קב' בקורת !!!

-אין מהלך ירידה טבעי

-אין מעבר ל-MCI/D

-אפקט צנוע מאד

-עקרונית

- learning effect

-NTB- יתר התפקודים

- additivity

-drop- 12% -

-לא ודאי-

-קריטריוני FDA לטיפול מניעתי

לתשומת לב-

-גיל

-קבוצה קוגניטיבית

-מרכיב חברתי

-אין psychological successful aging

-איזון בין המרכיבים להתערבות

-התערבות רפואית

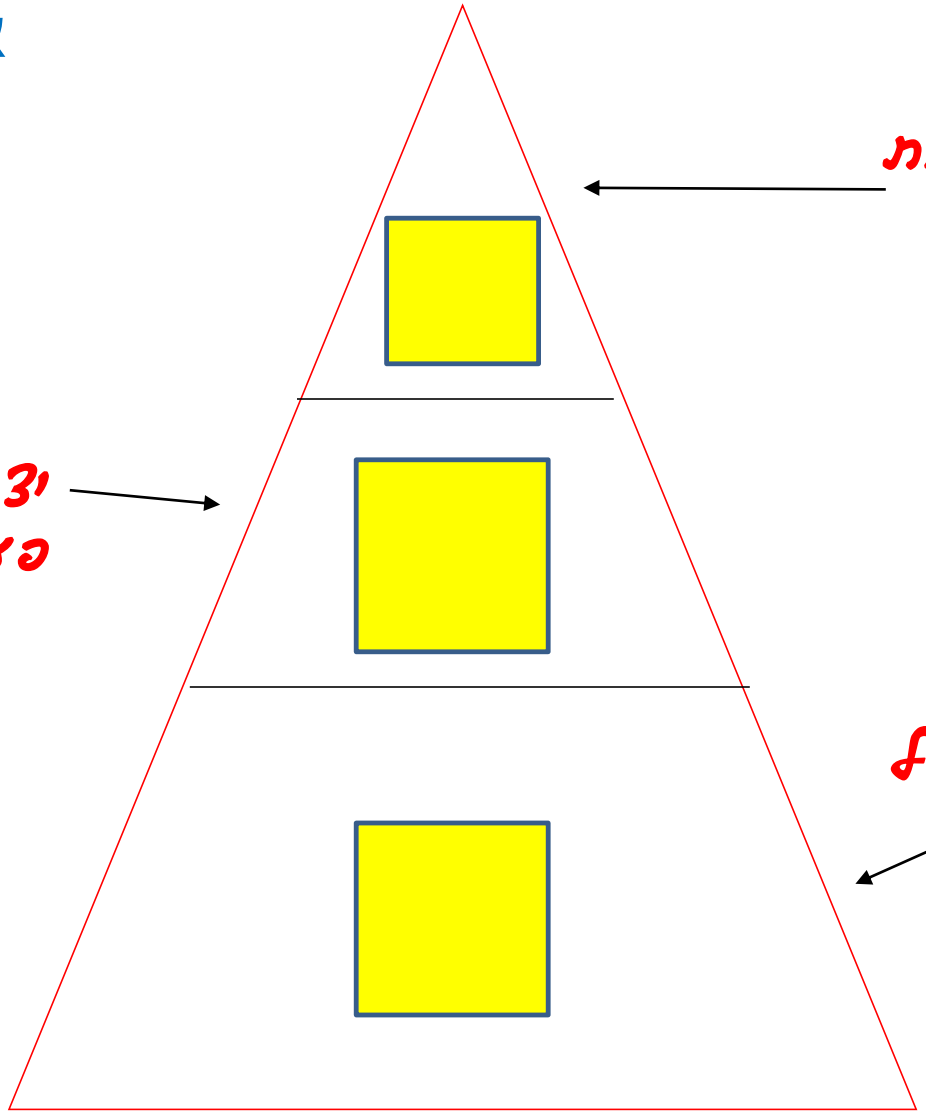
-העדר אינדיבידואליות

-ועוד

ניתן כנראה להשיג הרבה יותר אם מדייקים

סיכום עקרוני

שכרון יכולות קוגניטיביות



יכול יכולות עיסוק פעיל בחיים (ריפוי בעיסוק, תפקוד פסיכוסוציאלי, תנועתיות, הסברת self, הסברה חברתית)

יכול אופטימלי של רקמת המוח

אינדיבידואלי !!!

(גיל, סטטוס קוגניטיבי, תחלואה, וכו')