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NATIONAL INSTITUTE FOR HEALTH AND WELFARE

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The real potential to prevent Alzheimer's disease

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CAHS FORUM ON DEMENTIA, September 17, 2015

Are there ways to prevent cognitive impairment and dementia/AD?

- **State of the art**

- **Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability**

FINGER

- **Future directions: Multi-domain, multinational studies and pragmatic prevention programs**

EDPI European Dementia Prevention Initiative

HATICE

MIND-AD

Dementia as a public health priority

47 million: number of people living with dementia worldwide in 2015; this number is expected to almost **double by 2030** and more than **triple by 2050**.

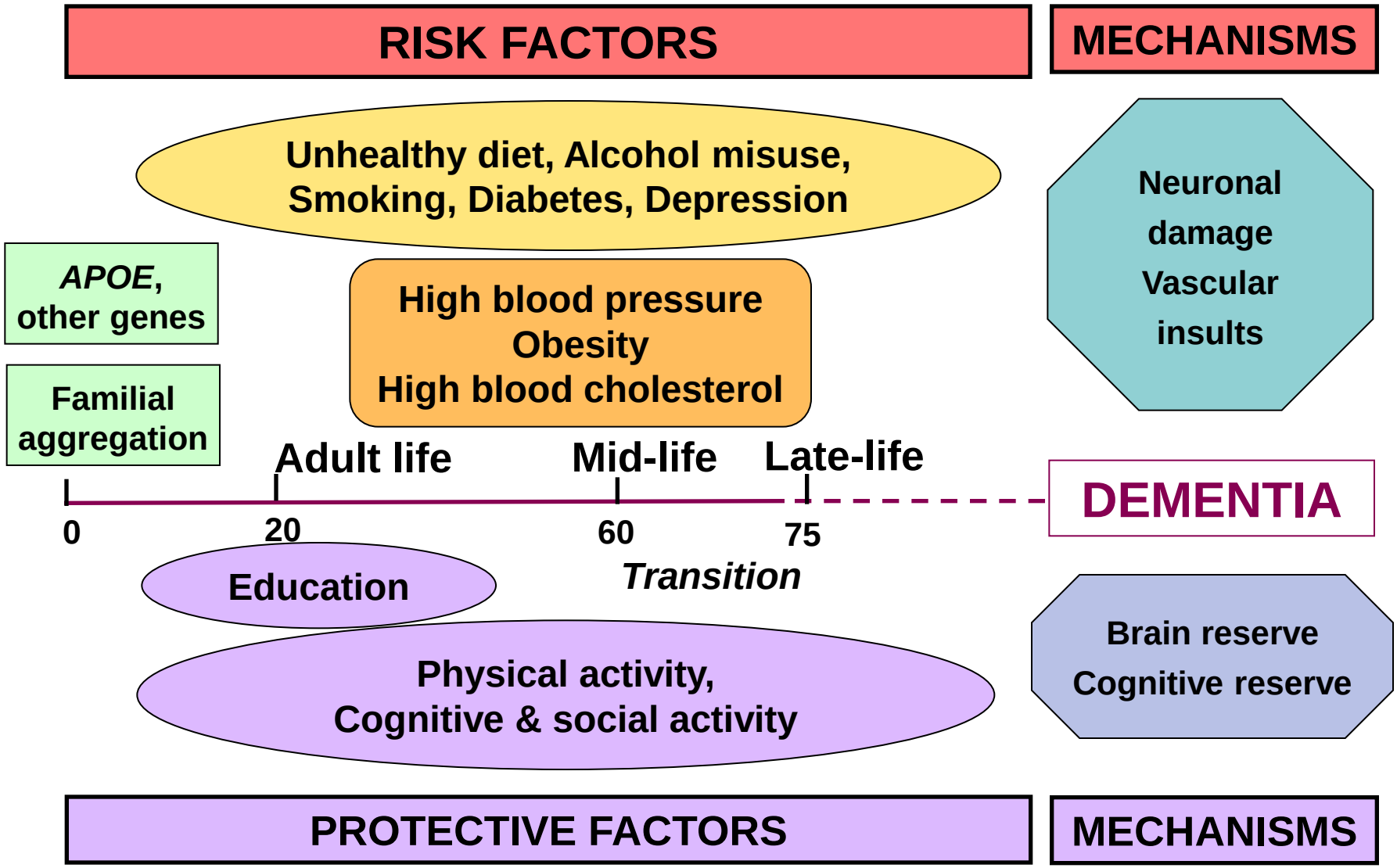
US $818 billion: global cost of dementia estimated in 2014.

AD prevention and adequate care: worldwide priorities

AD drug development: major political, academic and industrial effort

WHO 2012 report; Alzheimer Disease International 2015; G8 Dementia Summit, Health Ministers, 2013; WHO Ministerial Conference on Global Action Against Dementia, 2015

Dementia and Alzheimer disease: importance of life-long exposure to multiple factors



Kivipelto, Mangialasche et al., Oxford Ger Text Medicine 2015, in press

Trends of reduced dementia occurrence

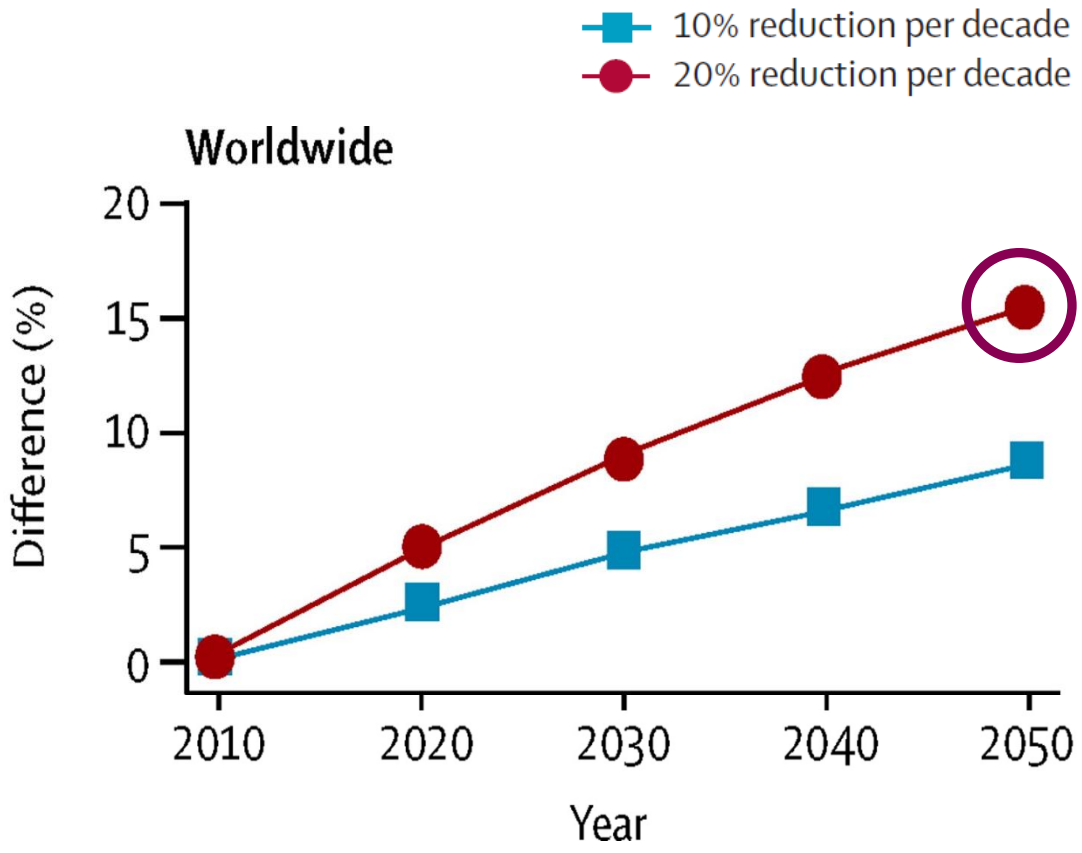
Selected Recent Studies of the Dementia Epidemic.

Study	Outcome	Data Source	Key Findings	Factors
Manton et al. (United States)[1]	Prevalence of severe cognitive impairment	National long-term care survey interviews, 1982–1999	Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)	Higher educational level, decline in stroke incidence
Langa et al. (United States)[2]	Prevalence of cognitive impairment	Ongoing population-based survey of people ≥51 yr of age	Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)	Higher educational level; combination of medical, lifestyle, demographic, and social factors
Schrijvers et al. (Rotterdam)[3]	Incidence of dementia	Population-based cohort ≥55 yr of age in 1990, extended in 2000	Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)	Higher educational level, reduction in vascular risk, decline in stroke incidence
Qiu et al. (Stockholm)[4]	Prevalence of DSM-III-R dementia*	Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004	Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence	Favorable changes in risk factors, especially vascular risk; healthier lifestyles
Matthews et al. (England)[5]†	Prevalence of dementia in 3 regions	Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)	Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)	Higher educational level, better prevention of vascular disease

Larson et al., NEJM 2013

To what extent can Alzheimer dementia be prevented?

Risk factor	PAR
Diabetes mellitus	2.9%
Midlife hypertension	5.1%
Midlife obesity	2.0%
Physical inactivity	12.7%
Depression	7.9%
Smoking	13.9%
Low education	19.1%
Combined PAR*	28.2%



PAR=population-attributable risk.
*Adjusting for non-independence of the risk factors.

Norton et al., Lancet Neurol, 2014; Kivipelto and Mangialasche, Nature Neurol Rev, 2014

Randomize  **led trials**

The pre-FINGER framework

- **Long tradition in risk factor monitoring: The FINRISK Study**

CAIDE

- **Intervention studies: North Karelia Project, Finnish Diabetes Prevention Study, Dose-Responses to Exercise Training**

- **Integrating multidomain intervention to prevent cognitive impairment into the existing framework**

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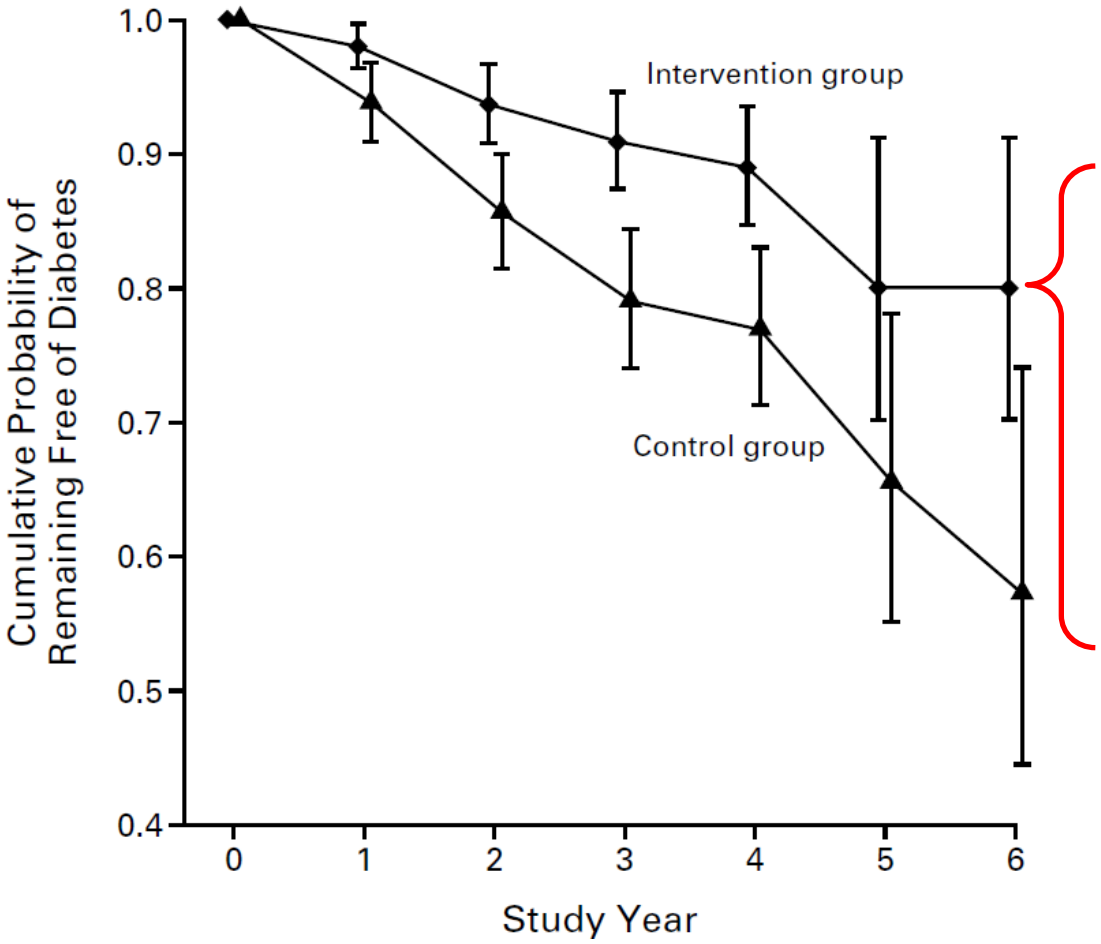
The Finnish Diabetes Prevention Study (DPS): Diabetes incidence was decreased by 58%



Goals:

- Weight reduction ≥5%
- Moderate fat <30 E%
- Low saturated fat <10 E%
- High fibre ≥15g/1000kcal
- Physical activity ≥30 min / day

Tuomilehto et al. N Engl J Med 2001

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Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

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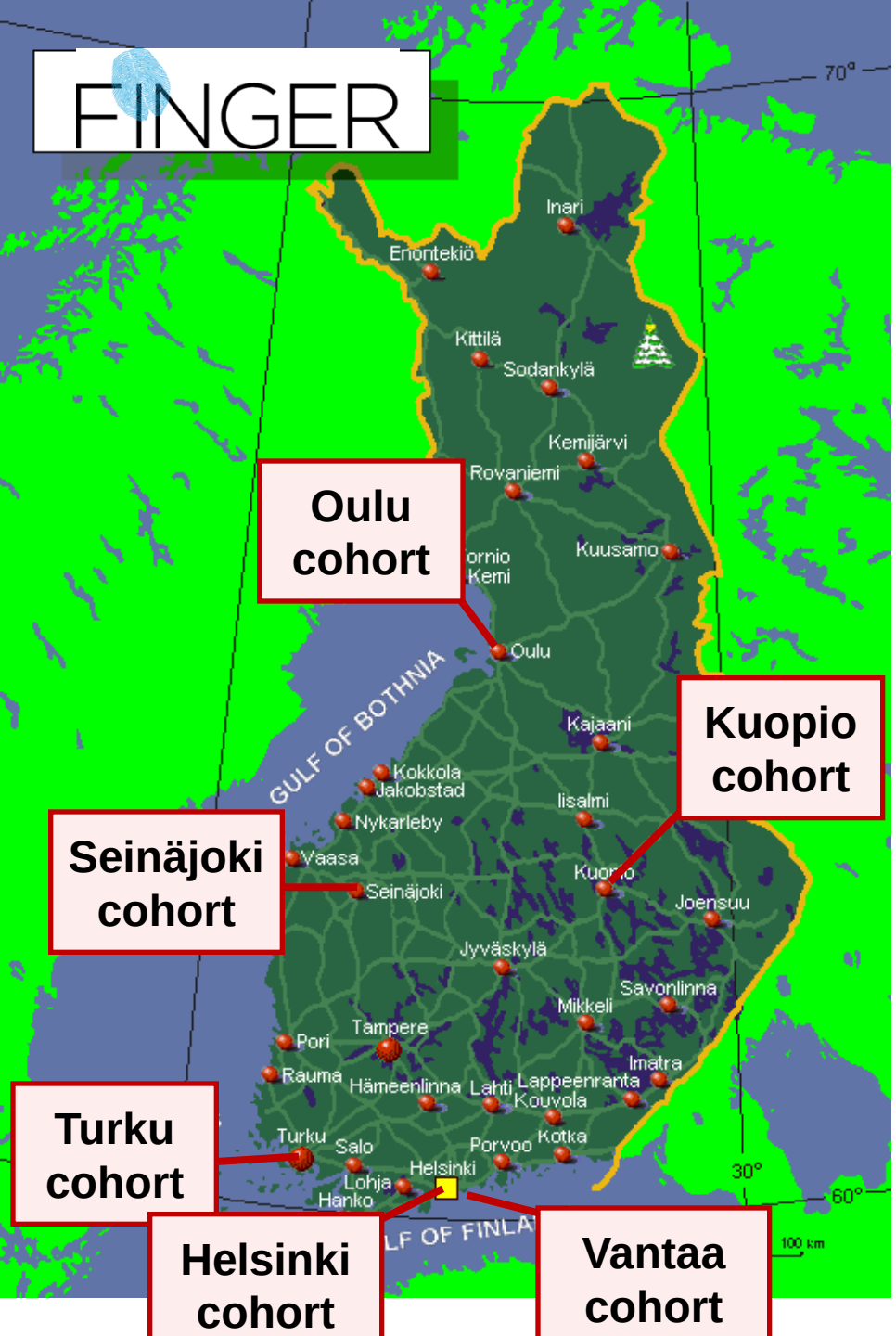
- **Proof-of-concept trial - multidomain approach to cognitive decline prevention**
- **At-risk segment of the general elderly population (not patients)**

- **2-year multi-domain lifestyle intervention:**
  - → Nutritional guidance
  - → Physical activity
  - → Cognitive training and social activities
  - → Monitoring of metabolic and vascular risk factors: hypertension, dyslipidemia, obesity, impaired glucose tolerance

Clinicaltrials.gov NCT01041989

Protocol in *Kivipelto, Solomon et al., Alzheimer & Dementia 2013*



Principal Investigator:
Prof. Miia Kivipelto

Participants:

- **Previous national surveys (FINRISK)**
- **N=1260**
- **Age 60-77y**
- **Randomized into 2 groups (1:1)**

Time schedule:

- **Intervention completed February 2014**
- **Extended 5-year follow-up starts April 2015**
- **Extended 7-year follow-up planned**

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INCLUSION CRITERIA: persons at risk of dementia/cognitive decline

- **Dementia Risk score ≥ 6 points**

  Based on risk factors assessed in earlier population surveys: Age, Education, Sex, SBP, Cholesterol, BMI, Physical Activity (Kivipelto et al., Lancet Neurology 2006)

AND

- **Cognitive performance at mean level or slightly lower than expected for age**
  (based on CERAD test battery)

Protocol in Kivipelto et al., Alzheimer & Dementia 2013

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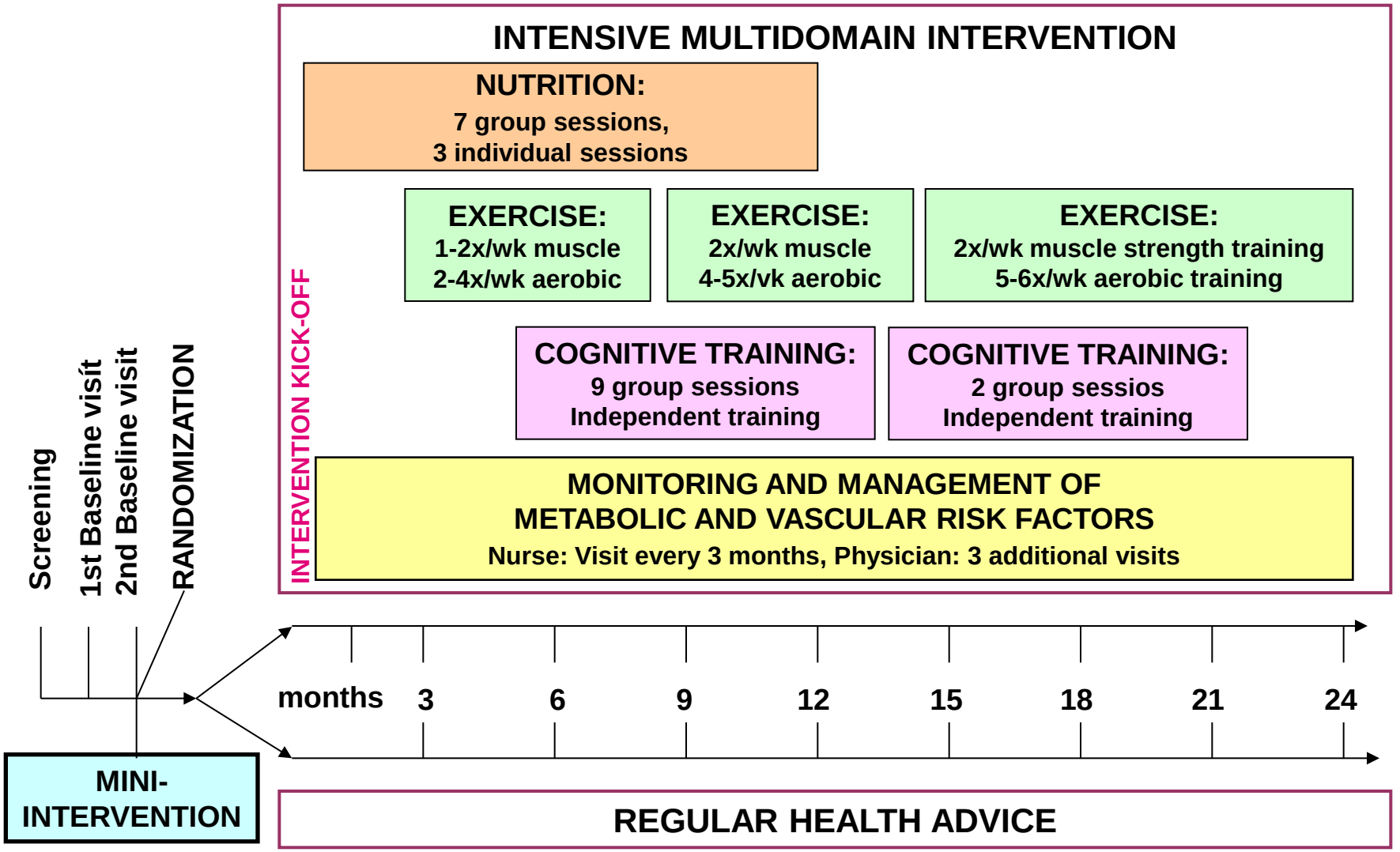
INTERVENTION SCHEDULE



Kivipelto et al., Alzheimer & Dementia 2013

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OUTCOMES

- **Primary:**
  - →**Neuropsychological Test Battery (NTB) total z score (cognitive change)**
- **Secondary:**
  - **Dementia/AD (after 7 years)**
  - →**Depressive symptoms (Zung scale)**
  - →**Vascular risk factors, morbidity and mortality**
  - →**Disability (questionnaire, ADL + IADL)**
  - →**Quality of life (RAND-36, 15D)**
  - →**Utilization of health resources**
  - →**Blood markers (i.e. inflammation, redox status, lipid and glucose metabolism, telomere length)**
  - →**Brain MRI measures (n=200) and PET (n=60)**

Kivipelto et al., Alzheimer & Dementia 2013

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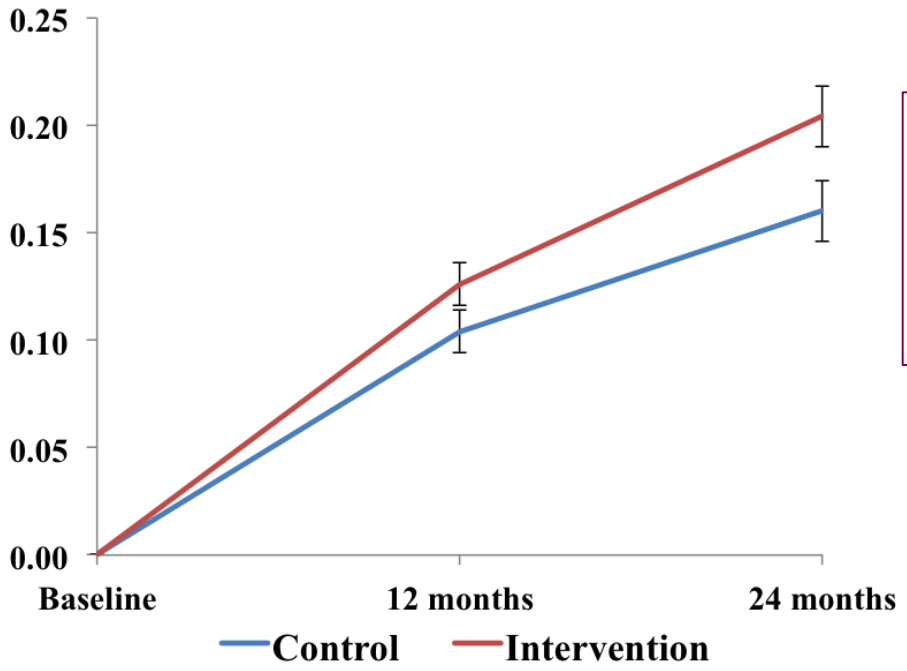
Results

Primary efficacy outcome: global cognition

(NTB composite Z score)



Intervention group: 25% higher improvement

Difference between intervention and control groups per year:

Estimate (95% CI) = 0.022 (0.002-0.042)

p=0.03

Lines = estimates for cognitive change from baseline to 12 and 24 months
Higher scores = better performance
Error bars = standard errors
P-values = difference in trajectories over time between groups

Kivipelto, Ngandu, Mangialasche et al., Lancet 2015

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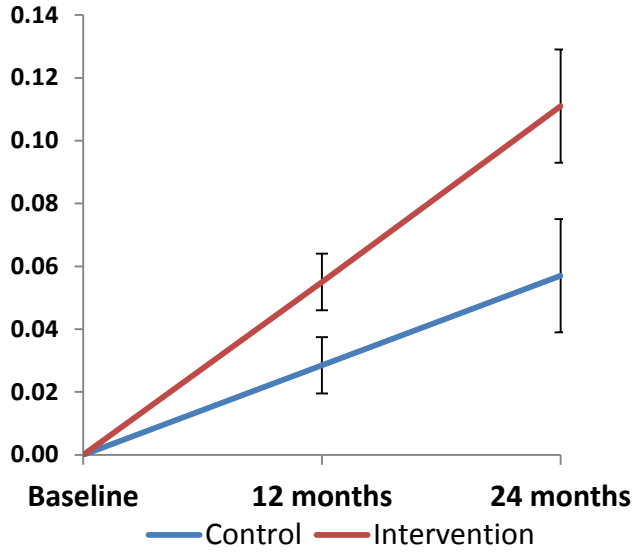
Results

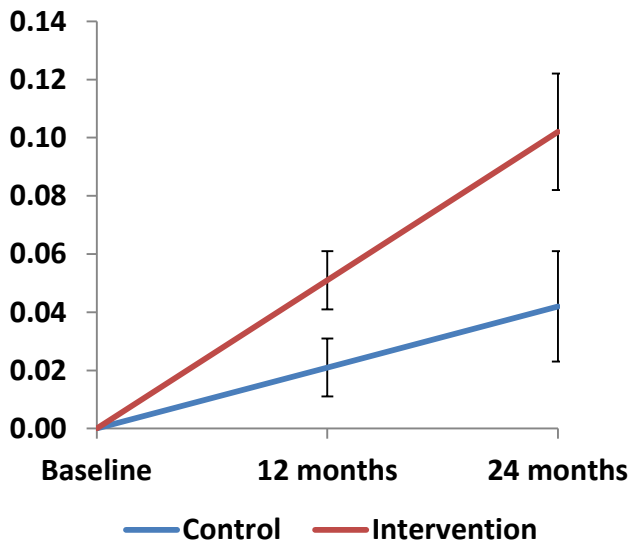
Intervention effects on various cognitive domains (secondary outcomes)

Executive functioning



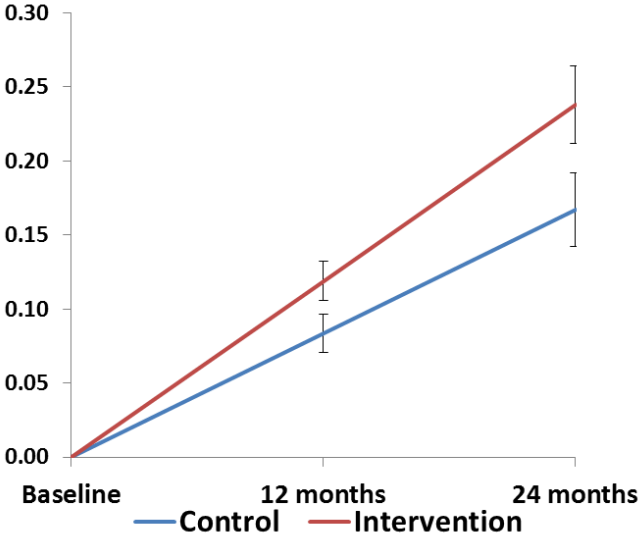
83% higher improvement

Processing speed



150% higher improvement

Memory (abbreviated score)



40% higher improvement

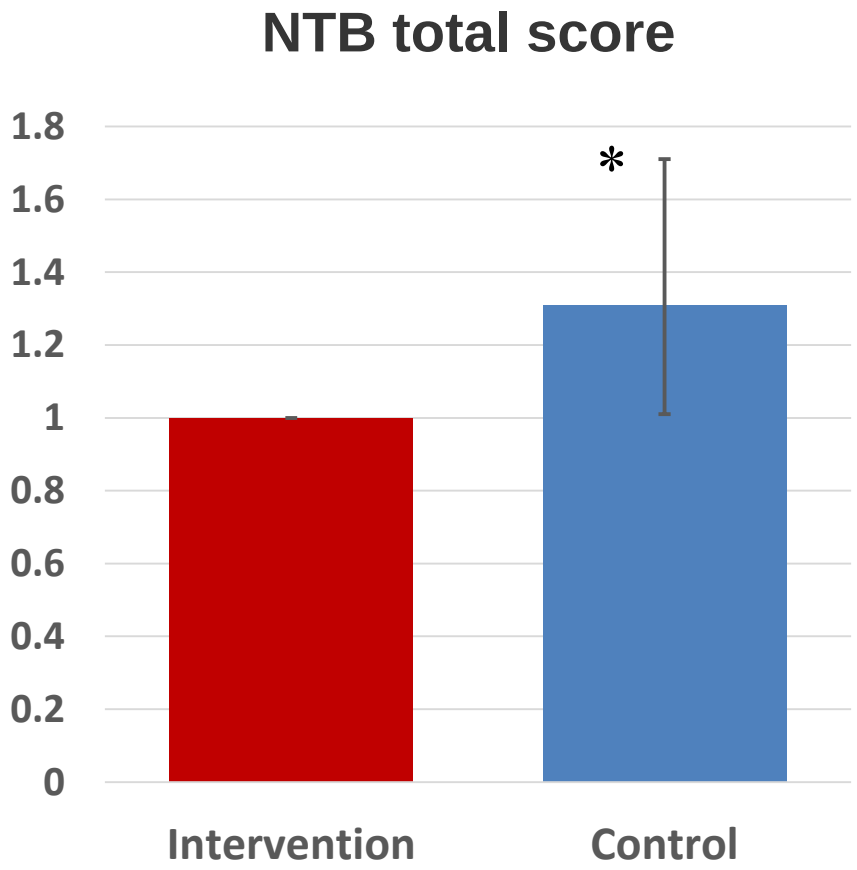
Difference between intervention and control groups per year:

Estimate (95% CI), p-value

0.027 (0.001-0.052)	0.030 (0.003-0.057)	0.038 (0.002-0.073)
p=0.04	**p=0.03**	**p=0.04**

Kivipelto et al., Lancet 2015

Risk for cognitive decline



Control group:
30% increased risk
Cognitive decline

* p<0.05

Kivipelto, Ngandu, Mangialasche et al., Lancet 2015

Intervention effects on secondary outcomes

	Control	Intervention	Difference between intervention and control groups per year	
	Mean change (SE)	Mean change (SE)	Estimate (95% CI)	P value
Vascular factors				
Body mass index (kg/m2)	-0·33 (0·05)	-0·49 (0·05)	-0·077 (-0·149 - -0·006)	0·02
Lifestyle factors **				
Fish intake at least twice/week (%)	+0·8	+11·0	10·2	<0·001
Daily intake of vegetables (%)	-1·0	+2·9	3·9	0·023
Physical activity ≥2 times/week (%)	-2·1	+7·0	9·1	<0·001

Mixed-model repeated-measures analyses

*** Multinominal logistic regression (change in % units between baseline and 24 months)*

Kivipelto et al, Lancet 2015

Self-reported adverse events during the study and health care register follow-up

Event	Total (n=1260)	Intervention (n=631)	Control (n=629)
Self-reported adverse events or negative experience of the study			
All	52	46	6
Slight musculoskeletal pain	32	32	0
Stress	8	6	2
Time-consuming	4	1	3
Other*	8	7	1
Dead during the study	10	5	5
Health care register information			
Myocardial infarction	6	1	5
Stroke	8	4	4

No serious adverse events

Kivipelto et al, Lancet 2015

Self reported adherence

Domain	Any participation, %
Nutrition	99.7%
Exercise	90.3%
Cognitive training	84.9%
Risk factors monitoring	87.0%

No of domains	Any participation, %
1	1.4%
2	6.2%
3	20.8%
4	71.6%

Kivipelto et al, Lancet 2015

Prevention of dementia: Future?

Necessary of multi-national studies and pragmatic prevention programs

European Dementia Prevention Initiative

www.edpi.org

- **FINGER** Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
- **Pre-DIVA** Prevention of Dementia by Intensive Vascular Care
- **MAPT** Multidomain Alzheimer Preventive Trial

Data pooling and joint analyses
> 6000 participants

Healthy Aging Through Internet Counseling in the Elderly

- **Main goal**: prevention of dementia and cardiovascular diseases in the elderly
- **Strategy:** motivate and support lifestyle changes to improve management of vascular risk factors
- **Tool:** new easily accessible, interactive internet platform, with readily available nurse-support

www.HATICE.eu

JPND research
EU Joint Programme – Neurodegenerative Disease Research

- Pilot Studies on Preventive Strategies related to Neurodegenerative Diseases

Multimodal preventive trials for Alzheimer's Disease: towards multinational strategies (MIND-AD)

Alzheimer's Disease International

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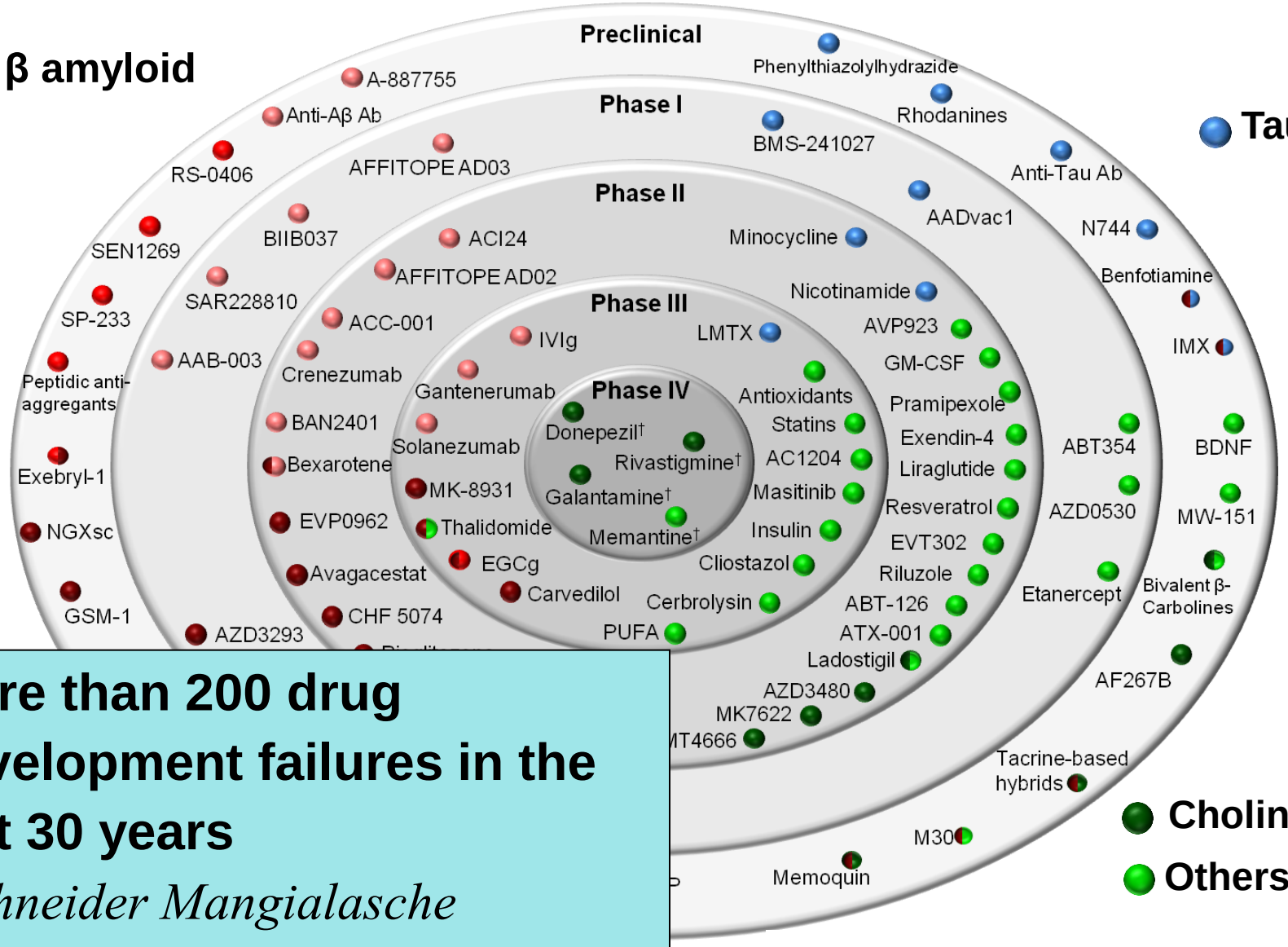
Ongoing clinical trials in Alzheimer disease (AD)



More than 200 drug development failures in the last 30 years

(Schneider Mangialasche Kivipelto et al., JIM 2014)

† ialasche , Kivipelto et al, modified 2013 from Lancet Neurology, 2010

Take home points: how to prevent dementia

1. Timing: starting early, at-risk persons

2. Multi-factorial aetiology – multi-domain interventions effective for several cognitive domains

3. FINGER: a pragmatic model that can be tested and adapted in various settings and populations

4. Future: Multi-national prevention RCTs & Pragmatic prevention programs, integrated interventions

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Life matters!