The role of nutrition in maintaining cognitive function in older people

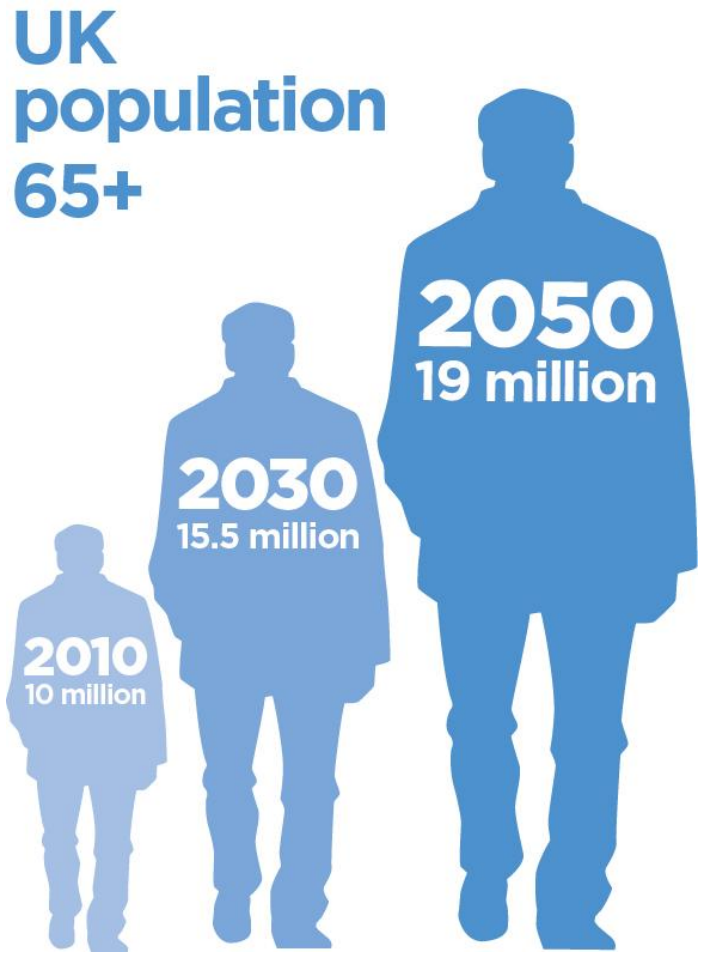
Jayne Woodside

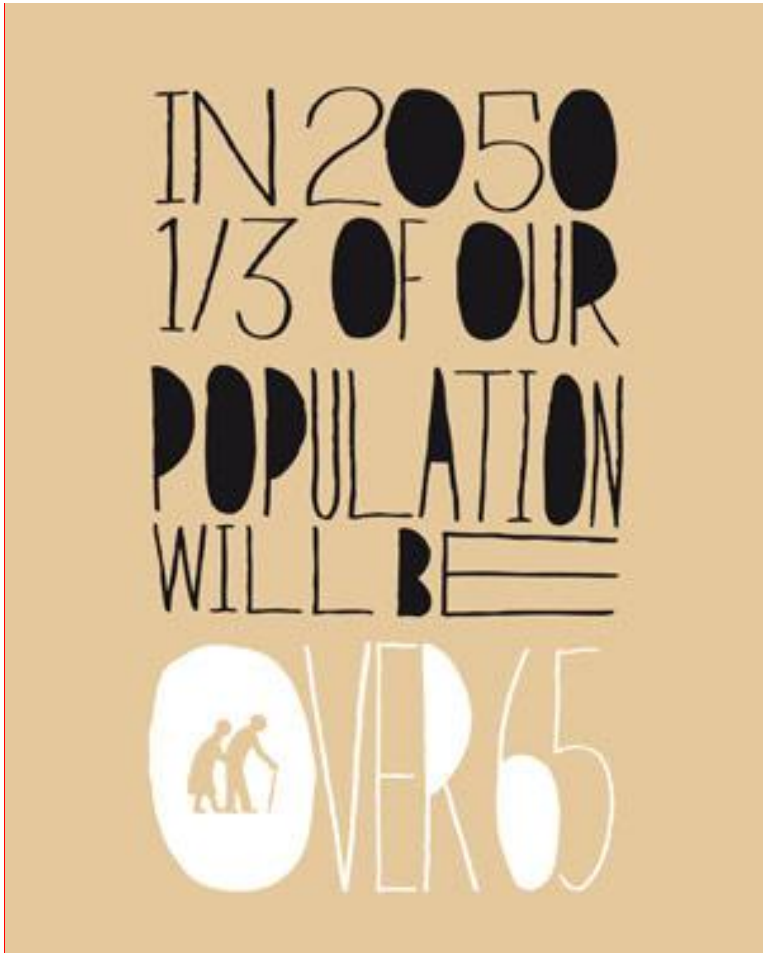
Centre for Public Health

Queen's University Belfast

Nutrition and Health – What's New?; The Dairy Council for Northern Ireland; 9th May 2014

Proportion of older adults increasing





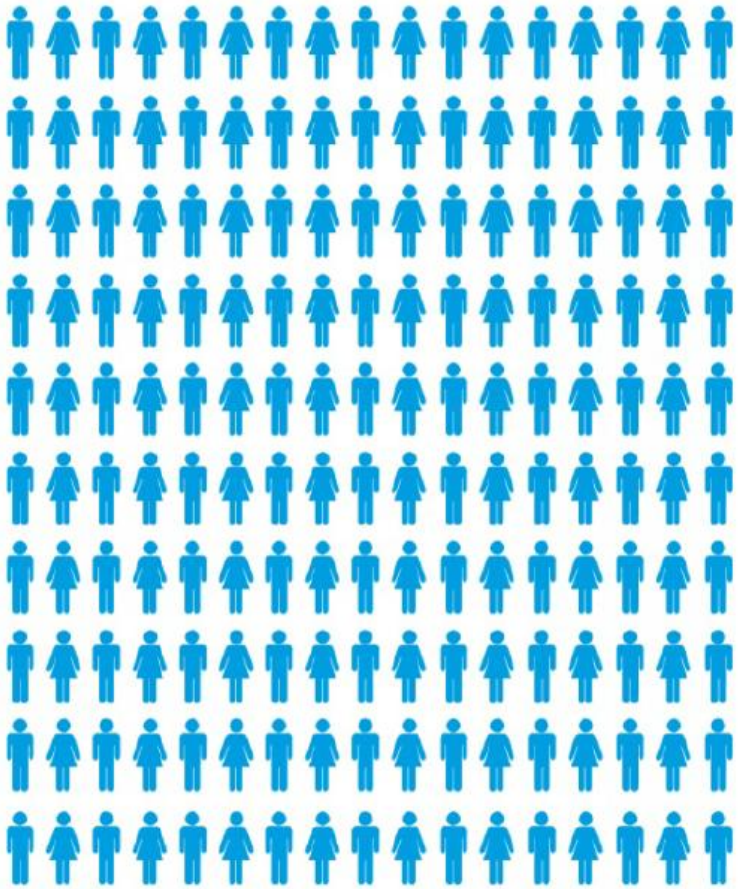
Future projections

The number of people in the UK with dementia will double in the next 40 years.

= 10,000 people

800,000 people with dementia in **2012**

1,000,000 people with dementia in **2021**



1,700,000 people with dementia in **2051**

Source: Alzheimer's Society, 2013

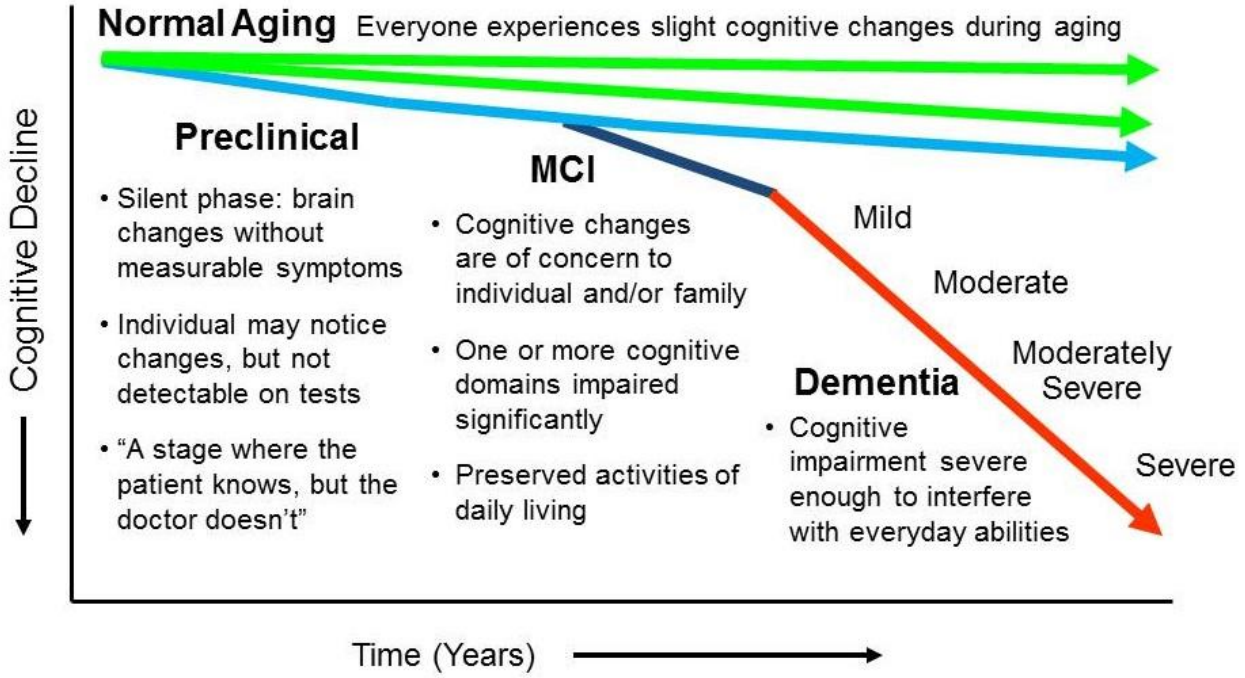
alzheimers.org.uk

Cost to society

Some of the cost of dementia is hidden by the work done by family carers supporting people at home.

Source: Alzheimer's Society, 2013

Progression from normal aging to Alzheimer's disease or another dementia



- Mild Cognitive Impairment (MCI) - memory and/or other cognitive difficulties disrupt everyday life and are noticeable to the person affected and/or others, but are not severe enough to interfere with basic living skills
- An individual with MCI will score significantly lower than others of the same age on neuropsychological measures of particular cognitive domains
- Some studies suggest that up to 10-20% of older adults age > 65 y have MCI

http://www.alz.uci.edu/alzheimers-disease/

Nutrition and healthy ageing

- As proportion of older people increases, so will incidence of chronic diseases and proportion of the population with disability
- Strategies that reduce age-related morbidity and reduce chronic disease prevalence are therefore important for healthy ageing
- ***Good nutrition contributes to health of older people and their ability to recover from illness***
- May help **lessen the burden of health costs** by enabling older people to remain independent for as long as possible and improve QoL

Talk overview

1) Nutrition and cognitive function

   Alcohol intake; B-vitamin intake; Fish intake; Mediterranean diet

2) Conducting dietary intervention studies

3) Conducting dietary intervention studies in older people

Queen's University Belfast

Nutrition and cognitive function

Systematic Review: Factors Associated With Risk for and Possible Prevention of Cognitive Decline in Later Life

Brenda L. Plassman, PhD; John W. Williams Jr., MD, MHSc; James R. Burke, MD, PhD; Tracey Holsinger, MD; and Sophiya Benjamin, MD

Table 3. Summary of Findings on Potential Risk Factors and Interventions for Cognitive Decline

Direction of Association and Factors	Quality of Evidence
Increased risk	
Apolipoprotein E ε4 genotype	Low
Low plasma selenium level	Low
Depressive disorder	Low
Diabetes mellitus	Low
The metabolic syndrome	Low
Current tobacco use	Low
Decreased risk	
Cognitive training*	High
Vegetable intake	Low
Mediterranean diet	Low
ω-3 fatty acids*	Low
Physical activity*	Low
Noncognitive, nonphysical leisure activities	Low
No association	
Vitamin C, vitamin E, and β-carotene*	High
Conjugated equine estrogen*	High
HMG-CoA reductase inhibitors (statins)*	High
Aspirin*	Moderate
Dehydroepiandrosterone*	Moderate
Cholinesterase inhibitors*	Moderate
Multivitamin*	Moderate
Vitamins B_6 and B_{12} and folic acid*	Moderate
NSAIDs*†	Low
Alcohol intake	Low
Antihypertensives*	Low
Homocysteine	Low
Hyperlipidemia	Low
Anxiety disorders	Low
Hypertension	Low
Obesity	Low
Early childhood factors	Low
Higher levels of education	Low
Social network or social support	Low
Inadequate evidence to assess association	
Trace metals	–
Fat intake	–
High caloric intake	–
Ginkgo biloba*	–
Memantine	–
Sleep apnea	–
Resiliency	–
Occupational level	–
Traumatic brain injury	–
Toxic environmental exposures	–
Agent Orange exposure or the Gulf War syndrome	–
Genetic factors other than apolipoprotein E genotype	–

Direction of Association and Factors	***Quality of Evidence***
Decreased risk	
Mediterranean diet	Low
N-3 fatty acids	Low
No association	
Vitamins B6, B12, folic acid	Low
Alcohol intake	Low

"On the basis of observational studies, evidence that supported the benefits of selected nutritional factors...was limited."

Plassman et al., 2010

ONLINE FIRST

Risk Factors and Preventive Interventions for Alzheimer Disease

State of the Science

Martha L. Daviglus, MD, PhD; Brenda L. Plassman, PhD; Amber Pirzada, MD; Carl C. Bell, MD; Phyllis E. Bowen, PhD, RD; James R. Burke, MD, PhD; E. Sander Connolly Jr, MD; Jacqueline M. Dunbar-Jacob, PhD, RN; Evelyn C. Granieri, MD, MPH, MSEd; Kathleen McGarry, PhD; Dinesh Patel, MD; Maurizio Trevisan, MD, MS; John W. Williams Jr, MD

Background: Numerous studies have investigated risk factors for Alzheimer disease (AD). However, at a recent National Institutes of Health State-of-the-Science Conference, an independent panel found insufficient evidence to support the association of any modifiable factor with risk of cognitive decline or AD.

Objective: To present key findings for selected factors and AD risk that led the panel to their conclusion.

Data Sources: An evidence report was commissioned by the Agency for Healthcare Research and Quality. It included English-language publications in MEDLINE and the Cochrane Database of Systematic Reviews from 1984 through October 27, 2009. Expert presentations and public discussions were considered.

Study Selection: Study inclusion criteria for the evidence report were participants aged 50 years and older from general populations in developed countries; minimum sample sizes of 300 for cohort studies and 50 for randomized controlled trials; at least 2 years between exposure and outcome accepted diagnostic cri

Data Extraction: Incl eligibility and data were dence for each factor v ate, or high.

Data Synthesis: Diab midlife, and current tob creased risk of AD, and M intake, low or moderate ties, and physical activity were associated with decreased risk. The quality of evidence was low for all of these associations.

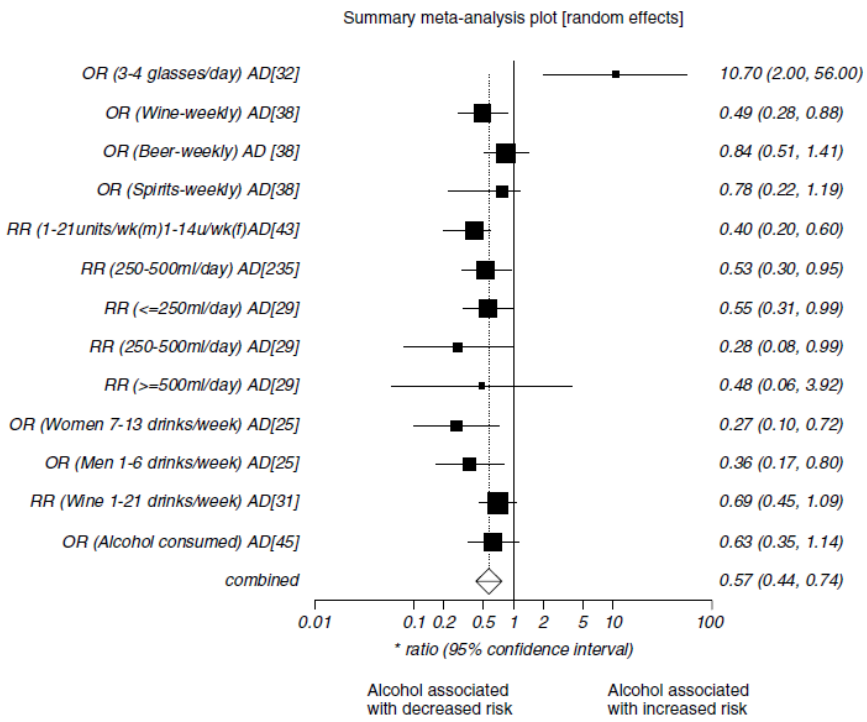
Conclusion: Currently, insufficient evidence exists to draw firm conclusions on the association of any modifiable factors with risk of AD.

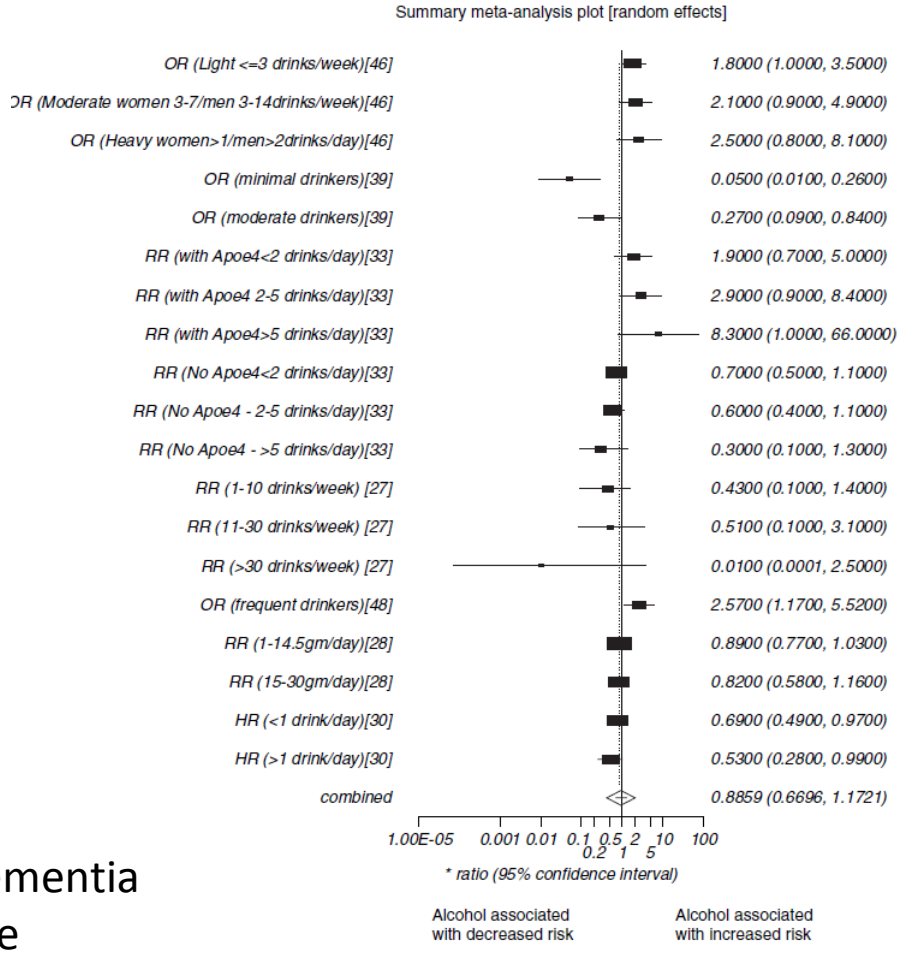
Arch Neurol. 2011;68(9):1185-1190. Published online May 9, 2011. doi:10.1001/archneurol.2011.100

Mediterranean-type diet, folic acid intake, low or moderate alcohol intake...were associated with decreased risk. The quality of evidence was low for all of these associations.

Daviglus et al., 2011

Alcohol – meta-analyses





- Association with reduced risk of AD and dementia
- No association with risk of cognitive decline

Peters et al., 2008; Anstey et al., 2009

Alcohol

- Evidence strongest for wine but not conclusive
- Studies varied, with differing lengths of follow up, measurement of alcohol intake, inclusion of true abstainers and assessment of potential confounders
- Interventions not feasible; best evidence comes from longitudinal studies
- Alcohol proposed to have CV and/or haematological effects, but also potential direct “neuroprotective” actions

Peters et al., 2008; Collins et al., 2009

B-vitamins

- Data from cohort studies of dietary or supplemental B-vitamin intake contradictory
- High serum B vitamins related to lower AD risk and better cognitive function
- Intervention studies conflicting – lower doses may be more beneficial
- Effects may depend on stage of disease

Otaegui-Arrazola et al., 2014

THE COCHRANE COLLABORATION®

Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people

Malouf et al., 2009

The small number of studies which have been done provide no consistent evidence either way that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer's disease to cholinesterase inhibitors. In another, long-term use appeared to improve the cognitive function of healthy older people with high homocysteine levels. More studies are needed on this important issue.

Effect of Folic Acid, with or without Other B Vitamins, on Cognitive Decline: Meta-Analysis of Randomized Trials

David S. Wald, MA, MRCP, MD, Anuradhani Kasturiratne, MD, Mark Simmonds, PhD

Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine, Queen Mary University of London, London, UK.

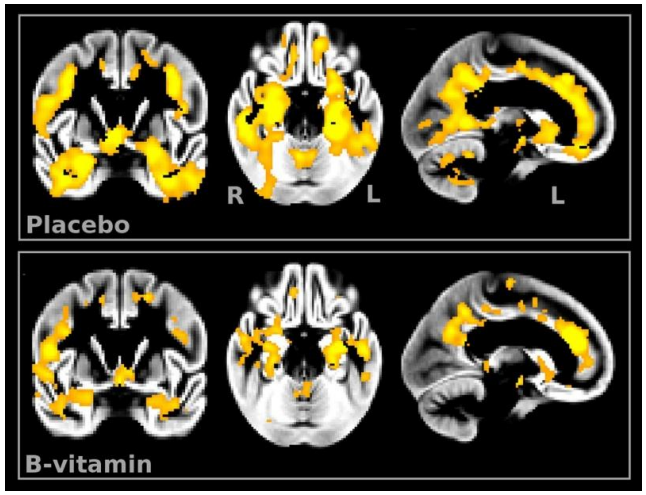
CONCLUSION: Randomized trials show no effect of folic acid, with or without other B vitamins, on cognitive function within 3 years of the start of treatment. Trials of longer duration, recording the incidence of dementia, as well as cognitive decline, are needed.

Wald et al., 2010

CLINICAL SIGNIFICANCE

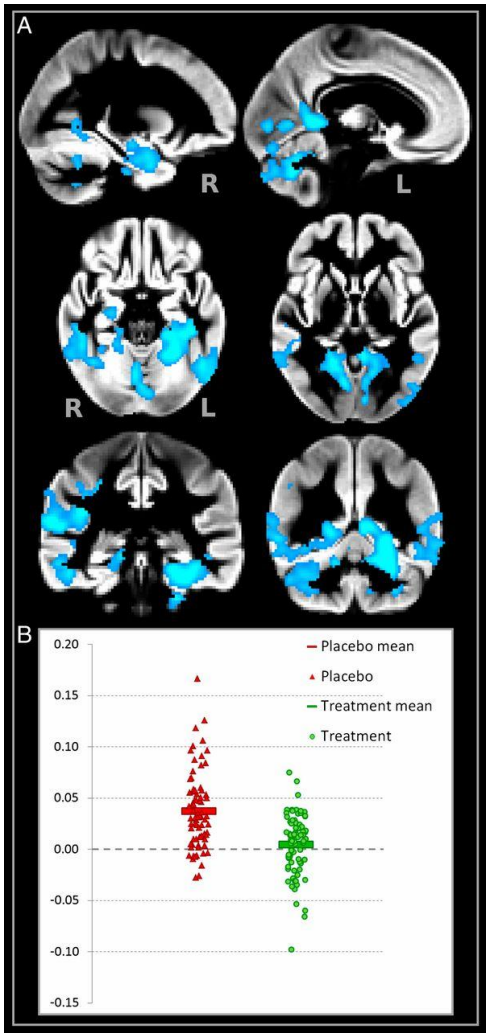
- The synthesis of data from randomized trials indicates no effect of folic acid on the prevention of age-related cognitive decline within 3 years of the start of treatment.
- The lack of effect is consistent across different elements of cognitive function: memory, language, processing speed, and decision making.
- Trials have generally been of short duration (about 6 months). Long-term trials recording the incidence of dementia and cognitive function are needed.

Regional loss of grey matter volume in placebo and B-vitamin groups

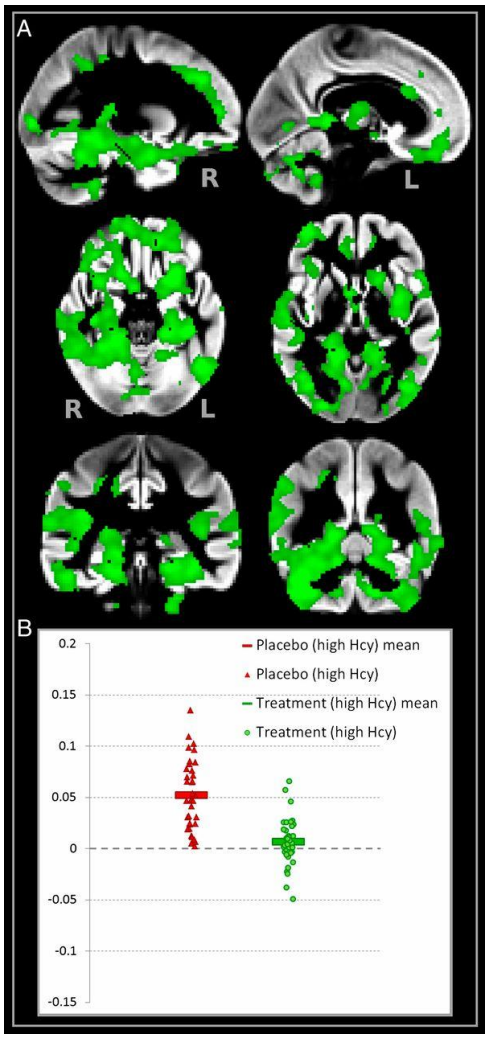


- Folic acid 0.8 mg/d, vitamin B12 0.5 mg/d, vitamin B6 20 mg/d in MCI patients over two years
- Previously shown to preserve brain volume

B-vitamin treatment significantly reduces regional loss of GM



B-vitamin treatment is only effective in participants with higher tHcy levels



Douaud G et al. PNAS 2013;110:9523-9528

PNAS

Fish/n-3 fatty acids

- Consumption of n-3 PUFA from diet has been associated with decreased risk of AD, MCI and better cognitive ageing
- High levels of n-3 PUFA biomarkers related to better cognitive function and higher brain volumes
- Intervention studies have not demonstrated a positive effect of n-3 PUFAs in AD or healthy subjects
- Effect on very early stages of AD, such as MCI or subjective memory complaints, is promising
- Acting through vascular or direct neuroprotective mechanisms

Otaegui-Arrazola et al., 2014

THE COCHRANE COLLABORATION®

Omega 3 fatty acid for the prevention of cognitive decline and dementia

Sydenham et al., 2012

Direct evidence on the effect of omega-3 PUFA on incident dementia is lacking. The available trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people. Omega-3 PUFA supplementation is generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.

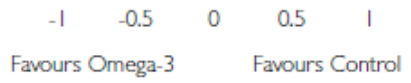
Further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 PUFA supplementation in preventing cognitive decline in older people.

Study or subgroup	Control N	Mean(SD)	Omega-3 N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dangour 2010	363	28.3 (2.2)	365	28.2 (1.8)		35.3 %	0.10 [-0.19, 0.39]
Geleijnse 2011	627	27.56 (2.45)	1866	27.73 (2.17)		64.7 %	-0.17 [-0.39, 0.05]
Total (95% CI)	**990**		**2231**			**100.0 %**	**-0.07 [-0.25, 0.10]**

Heterogeneity: $Chi^2 = 2.12$, $df = 1$ ($P = 0.14$); $I^2 = 53\%$

Test for overall effect: $Z = 0.85$ ($P = 0.40$)

Test for subgroup differences: Not applicable



MMSE Score

The Mediterranean diet

Emphasizes a diet that is

- high in fruits, vegetables, bread, other forms of cereals, potatoes, beans, nuts, and seeds
- includes olive oil as an important fat source and dairy products, fish, and poultry consumed in low to moderate amounts
- eggs consumed zero to 4 times weekly, and little red meat
- wine is consumed in low to moderate amounts
- dietary pattern based on food patterns typical of many regions in Greece and southern Italy in the early 1960s

Kris-Etherton, Circulation 2001

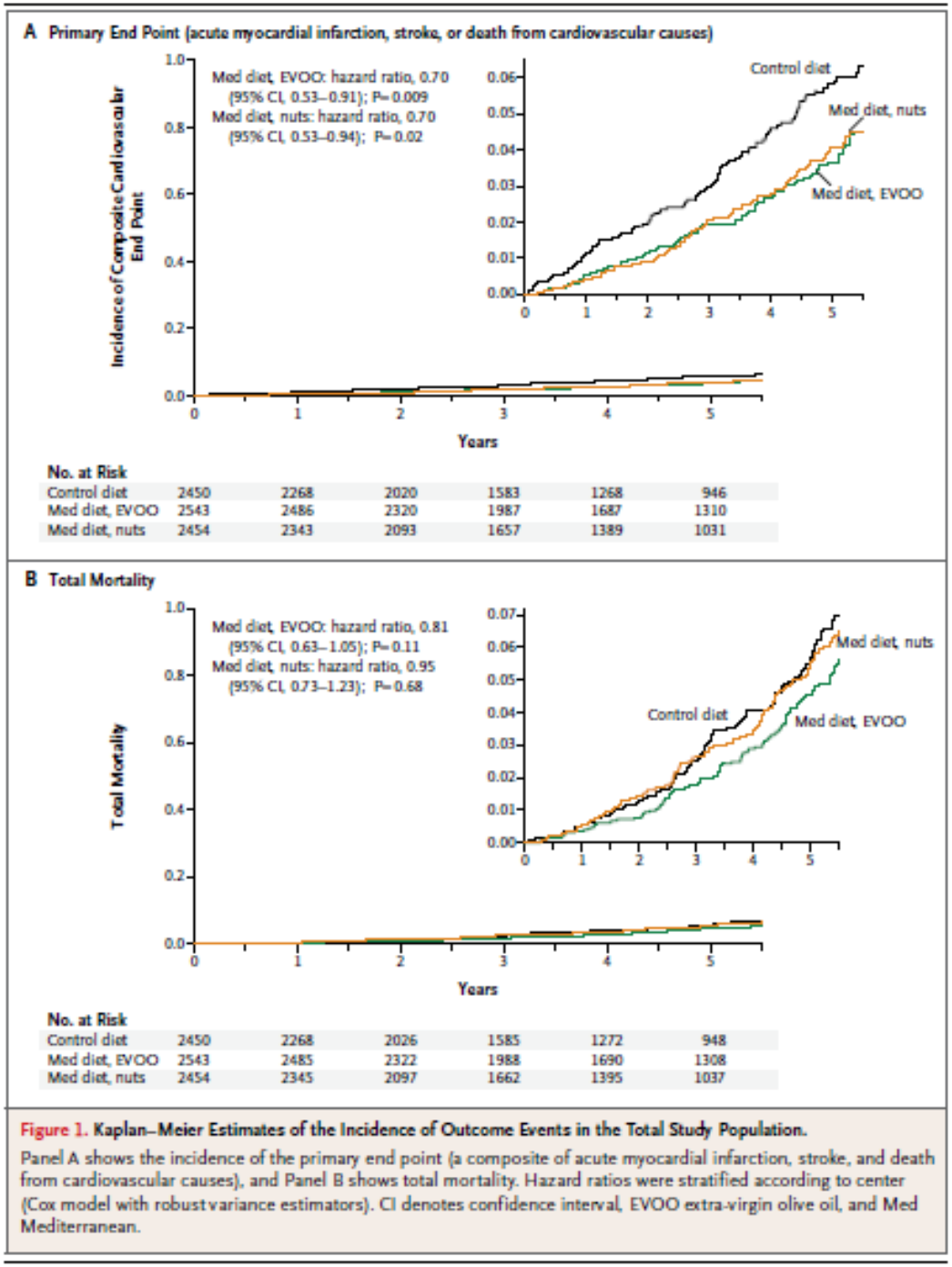


Figure 1. **Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.**
Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, and death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.

Primary endpoint: acute MI, stroke or death from cardiovascular causes

Med diet olive oil HR 0.70 (0.53-0.91); P=0.009

Med diet nuts HR 0.70 (0.53-0.94); P=0.02

Secondary endpoint: total mortality

Med diet olive oil HR 0.81 (0.63-1.05); P=0.11

Med diet nuts HR 0.95 (0.73-1.23); P=0.68

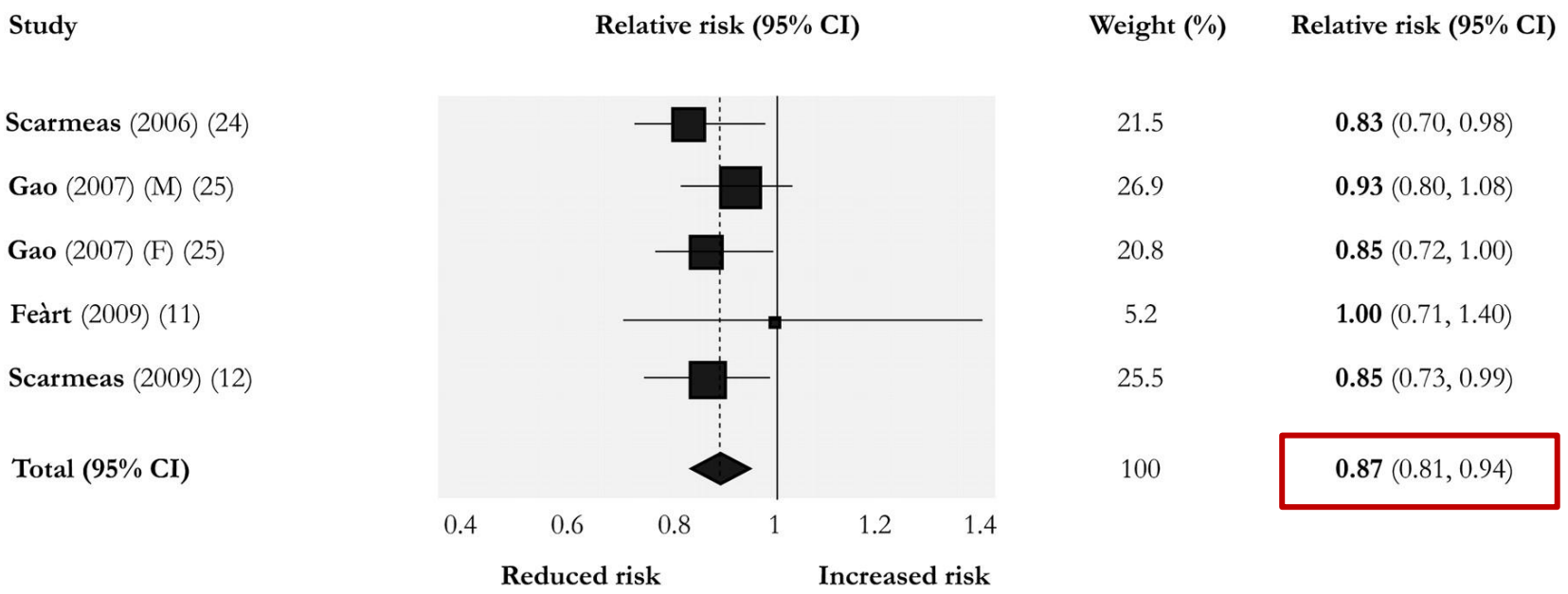
PREDIMED study

Estruch et al., NEJM, 2013

Evidence linking a Mediterranean diet with cognitive decline - *observational*

Association between a 2-point increase of adherence score to the Mediterranean diet and the risk of incidence of neurodegenerative diseases

The American Journal of Clinical Nutrition



Sofi F et al. Am J Clin Nutr 2010;92:1189-1196

Mediterranean Diet, Cognitive Function and Dementia
A Systematic Review

- Twelve eligible papers (11 observational studies and one randomised controlled trial)
- Seven unique cohorts
- Methodological heterogeneity and limited statistical power in some studies
- Reasonably consistent pattern of associations
- Higher adherence to MD associated with better cognitive function, lower rates of cognitive decline and reduced risk of AD in 9/12 studies
- Results for MCI were inconsistent

Lourida et al., 2013

Evidence linking a Mediterranean diet with cognitive decline - *intervention*

RESEARCH PAPER

Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial

Elena H Martínez-Lapiscina,[1,2] Pedro Clavero,[3] Estefania Toledo,[1,4] Ramon Estruch,[4,5] Jordi Salas-Salvadó,[4,6] Beatriz San Julián,[1] Ana Sanchez-Tainta,[1] Emilio Ros,[4,7] Cinta Valls-Pedret,[4,7] Miguel Á Martinez-Gonzalez[1]

Table 4 Multivariable-adjusted means after a 6½-year follow-up and differences versus control (95% CIs) in each intervention group

	MedDiet+EVOO (n=224)		MedDiet+Nuts (n=166)		Control (low-fat diet) (n=132)
	Mean (95% CI)	p Value (vs control)	Mean (95% CI)	p Value (vs control)	Mean (95% CI)
MMSE	27.73 (27.27 to 28.19)		27.68 (27.20 to 28.16)		27.11 (26.61 to 27.61)
Adjusted diff. versus control (95% CI)	+0.62 (+0.18 to +1.05)	0.005	+0.57 (+0.11 to +1.03)	0.015	0 (reference)
CDT	5.31 (4.98–5.64)		5.13 (4.78–5.47)		4.80 (4.44–5.16)
Adjusted diff. versus control (95% CI)	+0.51 (+0.20 to +0.82)	0.001	+0.33 (+0.003 to +0.67)	0.048	0 (reference)

General Linear Models. The PREDIMED-NAVARRA trial.
CDT, Clock Drawing Test; EVOO, extra virgin olive oil; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination.
Adjusted for sex, age, education, family history of cognitive impairment or dementia, *ApoE4* genotype, hypertension, dyslipidaemia, diabetes, smoking status, alcohol intake, body mass index, physical activity and total energy intake.

Global cognitive performance assessed by MMSE and Clock Drawing Test after 6.5 years

Secondary outcome: incidence of dementia and MCI in PREDIMED-NAVARRA RCT

After 6.5 years of nutritional intervention, 60 cases of incident MCI (18 in MedDiet+EVOO; 19 in MedDiet+Nuts; 23 low-fat) and 35 cases of incident dementia (12 in MedDiet +EVOO; 6 in MedDiet+Nuts; 17 in low-fat) were diagnosed in the PREDIMED-NAVARRA centre.

To cite: Martínez-Lapiscina EH, Clavero P, Toledo E, *et al. J Neurol Neurosurg Psychiatry* 2013;**84**:1318–1325.

Conducting dietary intervention studies

Single nutrient supplements which can be placebo-controlled are relatively straightforward

Guidelines for the Design, Conduct and Reporting of Human Intervention Studies to Evaluate the Health Benefits of Foods

Robert W. Welch[1], Jean-Michel Antoine[2], Jean-Louis Berta[3], Achim Bub[4], Jan de Vries[5], Francisco Guarner[6], Oliver Hasselwander[7], Henk Hendriks[8], Martin Jäkel[9], Berthold V. Koletzko[10], Chris C. Patterson[11], Myriam Richelle[12], Maria Skarp[13], Stephan Theis[14], Stéphane Vidry[13] and Jayne V. Woodside[11]

Intervention: selection of control
Blinding
Compliance

ILSI Europe
International Life Sciences Institute

Table 1. Factors and recommended standards for human intervention trials evaluating health benefits of foods. Modified from Welch et al. [1]

Phase	Factor	Recommended standard
Design	Hypothesis	Clear hypothesis
	Study design	Appropriate design
	Duration	Appropriate to design, intervention and outcome measures
	Intervention	Test and control foods suitably matched
	Amount	Appropriate to outcome measures and to practical usage
	Outcome assessment	Define primary outcome and method of measurement
		Define all secondary outcomes and methods of measurement
	Eligibility criteria	Define all eligibility criteria
	Statistical considerations	
	Randomisation	Use randomised design; ensure appropriate allocation, sequence generation and concealment
	Blinding	Ensure double blinding if feasible, single blinding if not
	Size of study	Conduct power calculation based on primary outcome measure
Conduct	Study protocol	
	Ethical approval and trial registration	Obtain approval, register trial, comply with Declaration of Helsinki
	Recruitment	Define recruitment strategy and process, including settings and dates
	Data collection	
	– Demographics, lifestyle, background health status and diet, and diet changes	Define relevant measures, select suitable methods for assessment, collection and analysis
	– Adverse events and unintended effects	Use suitable methods to record, and respond appropriately
	Compliance	Define acceptable level, strive to maximise, assess
Analysis and inter-pretation	Statistical analysis	Devise appropriate analysis methods, based on study design and outcome measures
	Discussion and interpretation	Consider study limitations and generalisability of findings
	Conclusions	Relate directly to hypothesis, study design, food and participants

Welch et al., 2011; Woodside et al., 2013

Conducting dietary intervention studies in older people

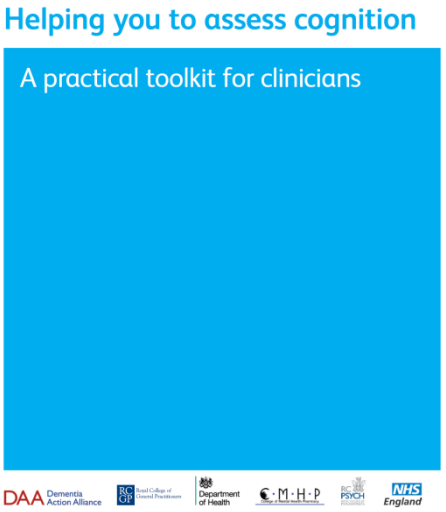
1. Efficacy studies
2. Studies to encourage behaviour change

Design of clinical trials/efficacy studies to test effect of dietary change on cognitive function

	Think…
Participants	Baseline level of cognitive function Baseline dietary intake
Design issues	Duration of intervention Outcomes measured (consider likely mechanisms) Control group Blinding Increase in adherence to be achieved How to encourage, monitor and measure compliance Monitor other lifestyle behaviours Effect of genetic background?

Outcomes

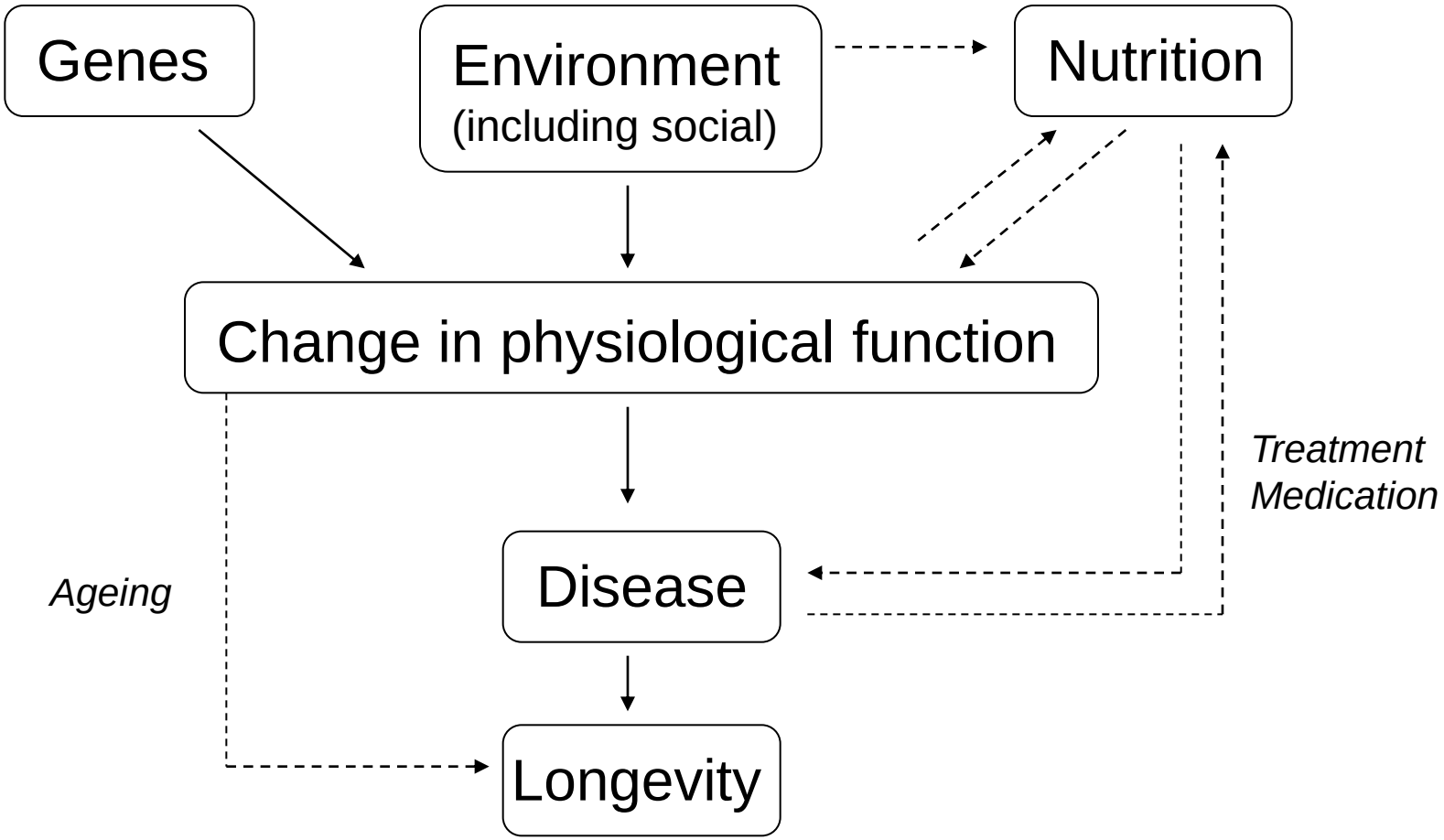
- Must be responsive to dietary change during study duration
- Could be:
  - Neuropsychological
  - Imaging
  - Biological sample based
  - A combination
- Study team should include a specialist



Conducting intervention studies in older people

Studies to encourage behaviour change

Nutrition, ageing and disease



One example...change in eyesight

- Deteriorating eyesight can affect:
  - Buying food
  - Getting to supermarket (inability to drive)
  - Reading food labels
  - Counting money
  - Preparing food

Ageing-related social and emotional considerations

- Whether or not a person lives alone
- How many daily meals are eaten
- Who does shopping and cooking
- Adequate income to purchase appropriate foods
- Alcohol and medication use

ALL of these factors may interfere with appetite or affect ability to purchase, prepare or consume an adequate diet

Need to consider when designing interventions to encourage behaviour change

Memory

- Most interest has focused on effect of nutrition on cognitive function
- Cognitive decline likely to affect eating behaviour as condition progresses
- In a cross-sectional study in acute care subjects with cognitive decline had
  - significantly lower frequency of being well-nourished (MCI=10%, dementia=8%, NoCI=22%, $p<0.05$)
  - higher frequency of being malnourished (MCI=47%, dementia=62%, NoCI=19%, $p<0.001$)
- Those with more severe MCI had alterations in eating behaviour

Lee et al., 2008; Orsitto et al., 2012

Initial work examining attitudes to dietary change in MCI patients

Encouraging behaviour change in mild cognitive impairment patients: development of educational material

CARDI
Centre for Ageing Research and Development in Ireland

Objectives

- To explore attitudes of mild cognitive impairment (MCI) patients and health professionals regarding diet and lifestyle and its relationship with cognitive health

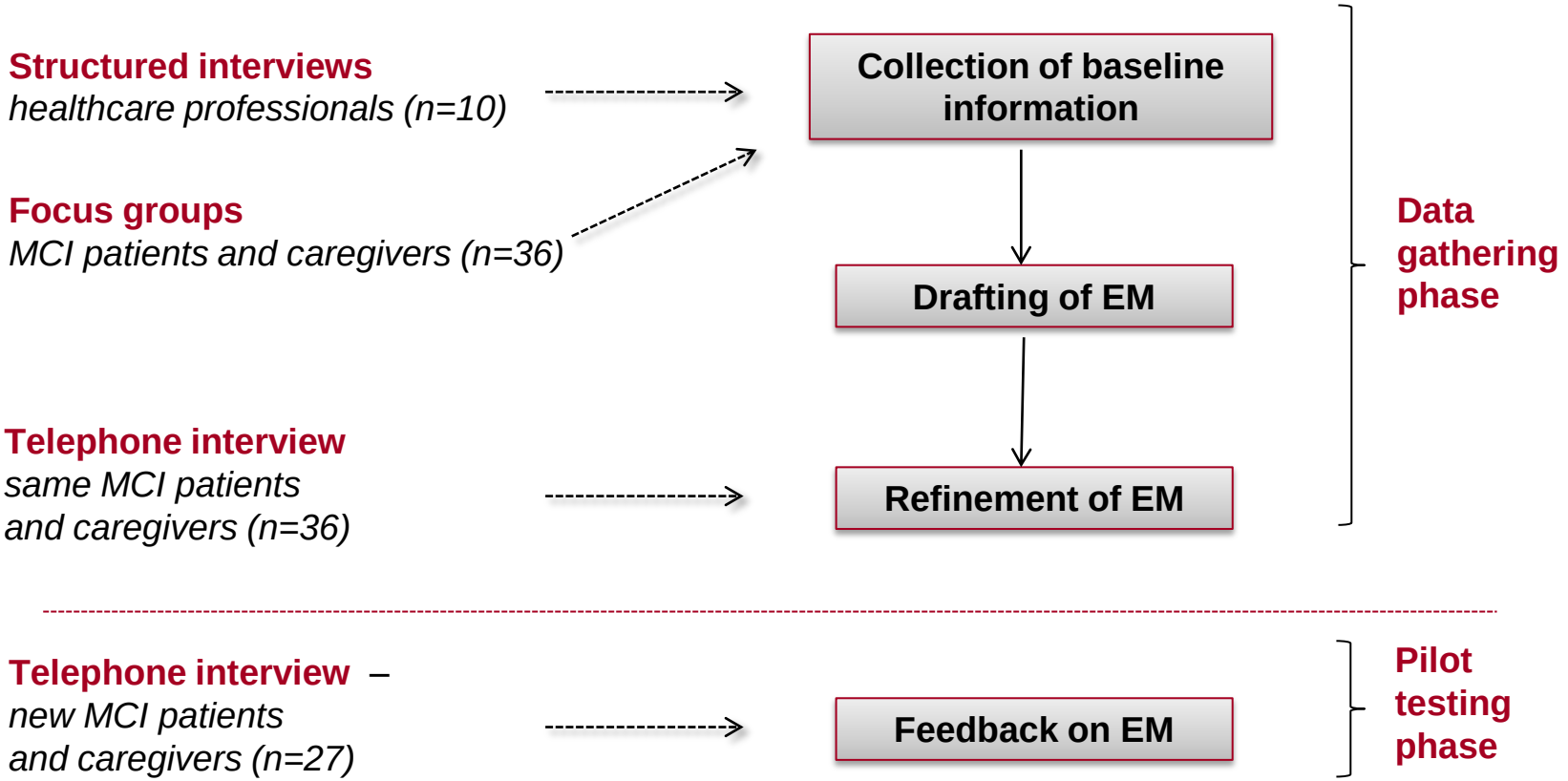
- To design, develop and pilot test educational material (EM) to help encourage lifestyle behaviour change in these patients

Methods

- Healthcare professionals, MCI patients and their caregivers were recruited from Belfast and Dublin

- Focus groups and structured interviews conducted

Study design



Draft educational material developed

Conclusions

- HPs alluded to the lack of clinical trial evidence for the link between lifestyle and MCI risk
- Lifestyle-related discussions tended to be patient-driven
- MCI patients lacked awareness of the lifestyle-cognition link
- MCI patients preferred EM to be concise, eye-catching and in written format, with personal delivery of information preferred
- A staged or gradual approach to delivery of information needed to maintain patient motivation and help with retention of information
- MCI patients approved of the EM but were heterogeneous in terms of lifestyle, willingness to change and support needed to change
- Tailored EM are potentially useful tool for use in interventions but will require further refinement and formal evaluation

Neville et al., Aging & Mental Health, 2013

NICOLA study design

- Stratified random sample of ~8500 men/women aged 50+ in Northern Ireland
- Longitudinal : Repeated measures every 2-4 yrs for a period of >10 yrs
- CAPI home interview - data on social, behavioural, economic and environmental aspects of ageing
- Health Assessment - Biomedical tests / collection of biological samples

NICOLA

Measurements - Wave 1

Health Assessment:

Computer Assisted Personal Interview:

COGNITIVE TESTS

Mini Mental State Examination
Sustained attention response time
Picture memory test
Visual reasoning
Choice reaction time
Colour trails 1 & 2
Montreal cognitive assessment
CES-D

NICOLA

Summary

- Strategies to encourage healthy ageing are increasingly important to global public health
- Dietary change may be important in preventing cognitive decline
- Reasonable observational evidence base for benefits of alcohol, fish, B-vitamins and Med diet
- Randomised trial data more limited
- Careful consideration given to study design when planning future efficacy studies and interventions to promote behaviour change

Nutrition and Metabolism Group, Centre for Public Health, QUB