PILLS VS. FOOD: WHAT WE KNOW ABOUT NUTRITION AND DELAYING THE PROGRESSION OF DEMENTIA

Dementia Cares 2014

Heather H Keller RD PhD
Schlegel Research Chair, Nutrition & Aging, University of Waterloo

RESEARCH | EDUCATION | PRACTICE

Enhancing the quality of life and care of older adults through partnerships in *research*, *education* and *practice*.

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Narrative Review:

Keller, H., Bocock, M.A. (2011). Nutrition and dementia: clinical considerations for identification and intervention. *Neurodegenerative Disease Management* 1(6):513-22.

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Prevention of Dementia with Diet

- A lifecourse perspective is required…
  - Long latency period; pathology begins decades before symptoms
  - Accumulation of risks
  - Sensitive periods in development e.g. 35- 40 wks of gestation
  - Brain reserve- for same level of pathology, different expressions and severity
- Means that ‘definitive’ intervention studies are elusive

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So why is diet of interest?

- Those with a healthier diet, less likely to have cognitive impairment (X-sectional studies)
- Deficiencies of key nutrients increase with age
- Nutrients involved in development, function and survival of neurons

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Brain ⟺ Diet Connections

- Antioxidants
- Glucose + glycation end products
- Alcohol
- Dietary Fat; cholesterol, PUFA, omega-3
- Obesity, hypertension, metabolic syndrome
- Trace mineral accumulation
- General nutrition; essential nutrients needed for function
- B vitamins- folate, B12 (via homocysteine?)
- Weight loss …. ? Brain atrophy

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Nootropics

Definition: agents that improve brain function; protect neurons

- Do not act like classical antipsychotics, tranquilizers etc
- Have limited side effects
- Combined into “memory cocktails”

Ginko Biloba, phospatidyl serine, vinpocetine, acetyl-L-carnitine, choline-related nutrients, antioxidants, alpha-lipoic acid

B vitamins

Folate, B12 and homocysteine→ amyloid, tau

- Deficiency increases with age
  - ~10% B12 at 75+
- 7/21 cohort studies showed an association between dementia and B12 deficiency (O'Leary et al., 2012)
- Less evidence for B6 and folate
- Few consider underlying nutrient status
- Yet hyperhomocysteinemia is consistently associated with cognitive decline (Zhou et al., 2011)

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Trials with B vitamins

- B6 (3-50mg), folate (0.75-15 mg) and B12 (0.05-1mg) in combination to reduce tHcy
  - 19 studies (Zhoug et al., 2011)
  - Any level of supplementation of these three nutrients reduced tHcy
  - No effect on cognitive function in health or cognitively impaired
- A few more recent studies suggest mixed findings (Hankey et al., 2013; Douaud et al., 2013; Walker et al., 2013; deJager et al, 2011; Kwok et al., 2011)
  - Potential improvements in cognitive decline in those who had high tHcy
  - Those with B vit deficiency benefit

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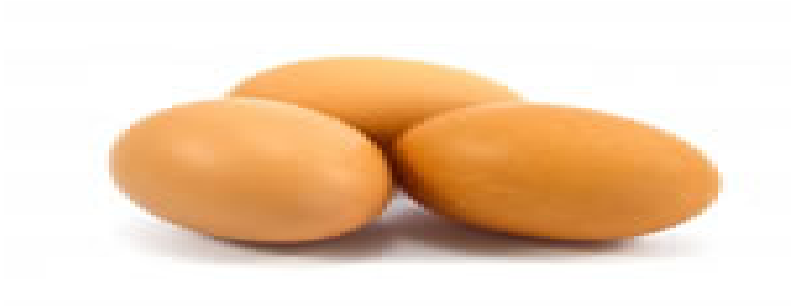
Food Sources of B Vits

- B6: bread, eggs, fish, milk, peanuts, potatoes, pork, poultry, soya beans, vegetables [1.7 (M), 1.5 (F) mg/d]
- Folate: asparagus, broccoli, brown rice, brussels sprouts, chickpeas, liver, peas, spinach [0.4 mg/d]
- B12: cheese, cod, eggs, meat, milk, salmon [0.0024 mg/d]



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What Are Antioxidants?

Definition: any substance that delays or prevents oxidation

Endogenous: peroxidases, metal chelating proteins, repair enzymes

Exogenous: vitamins C, E, B-carotene, flavonoids, trace minerals, Ginko Biloba, phytochemicals, co-enzyme Q10, DHA, zinc, selenium, ginseng, etc.

- Believed to be nootropic; neutralize FR thus limiting neuron death

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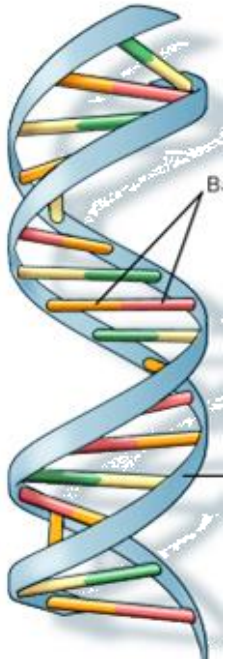
How FR Affect the Brain

- Changes in cell structure, DNA damage
- Lipid peroxidation; cell membranes damaged
- B amyloid accumulation; leads to further lipid peroxidation

Neuron death

Decreased brain volume

Decreased brain function (neurotransmitters)



In AD, lack of adaptation or upregulation of antioxidant systems

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Best Epidemiological Evidence - Food

Study	Vitamin A/ Carotenoids	Vitamin E	Vitamin C
Honolulu-Asia Study (HAAS)	- No effect	- Modest trend	- No effect
Paquid (blood levels)	+ association	+ association	
Rotterdam Study	- No effect	+ association	+ association
Nurses Health Study		- No effect	- No effect

Antioxidant Food Sources

- Vitamin E: nuts, seeds, plant oils, wheat germ [15 mg/d]
- Vitamin C: blackcurrants, broccoli, brussel sprouts, oranges/jc, red and green peppers, potatoes, strawberries [90 (M), 75 (F) mg/d]
- Flavonoids: dark chocolate, dry beans, fruit, grains, herbs, soy, tea, vegetables and wine (no recommendation)

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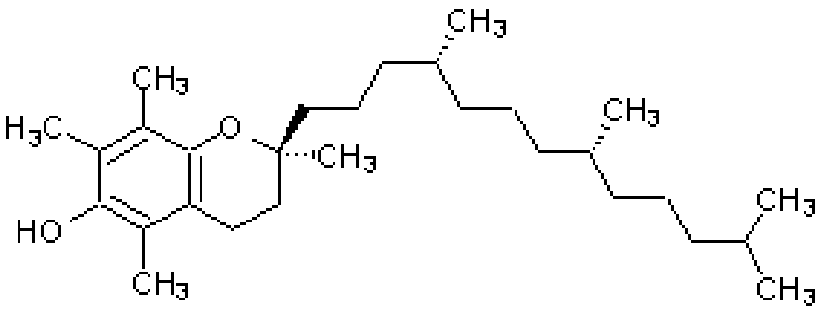
RCT in Persons with Dementia

(2000IU Vitamin E + Selegiline; Sano, 1997)

Evidence:

- 2 year follow-up
- Decreased mortality, institutionalization, level of dependence
- No effect on cognitive tests



Criticism:

- Already have dementia, too late to see effects
- Death can occur for other reasons
- Crudeness of memory tests
- Increased falls with vitamin E supplementation
- Natural form not used
- 1/d administration may not be best method
- Very high dose

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MCI Study (2005 NEJM)

Protocol:

- Mild cognitive impairment + Apo E-4 +ve
- # 769 at 69 sites
- Three year follow-up
- Donepezil (10 mg/day), vitamin E (2000 IU/day), or placebo
- Daily multivitamins

Findings:

- 212 developed AD
- First year donepezil had benefit
- No benefit by year 3
- Increased benefits in those with Apo E-4
- No benefit for vitamin E at any time point

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Antioxidant Pills

- Cochrane review confirms no benefit of Vit E on cognition (Farina et al., 2012)
- Meta-analysis of 19 studies on vitamin E
  - suggests pharmacologic doses increase mortality ~1000 mg/d (Miller, 2005)
  - benefits occur near recommended levels
- Trial of flavonols at different doses, no effect (Desideri et al., 2012)
- Beta carotene, vitamin E (500 mg), no effect (Grodstein et al., 2013)
- Ginkgo biloba, no effect for 5 yrs (Vellas et al., 2012)

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Omega 3

- DHA the most abundant omega-3 in the brain
- Primary source: oily fish (salmon, mackerel, herring, sardines, tuna, swordfish); DHA/EPA eggs/meat of fed animals [ALA requirement is 1.6 (M) 1.1 (F) g/d]
- Mechanisms:
  - CVD protection e.g. antithrombotic
  - Decrease cytokine synthesis, reduces inflammation
  - Membrane integrity
  - May promote clearance of B amyloid

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Relationship to Dementia

- Low omega-3 intake in those with dementia
- Risk appears to be reduced with fish consumption in some studies (Morris et al., 2003), but not others (Laurrieu et al., 2004); confounding effect of SES
- Cochrane review on supplementation of omega-3, no effects in healthy individuals (Syndenham et al., 2012)

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What about a modest amount of nutrients?

- Mulitvitamin/mineral preparation
- 12 months
- Minimal effect
  - Those over 75 showed some improvement
  - Suspected undernutrition in this group which was being reversed with treatment

(McNeill et al., 2007)

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Conclusions on Nutrient Treatment

- There is no silver bullet cure
  - No clear or consistent evidence for
    - B6, B12, vitamins C or E, folate, or omega-3
- Recommendation for supplementing with single dose nutrients is premature
- Supplements can not replace a *healthy* diet
- Some potential for negative effects with pharmacological doses
- Studying supplements is a problem…
  - Need long follow ups

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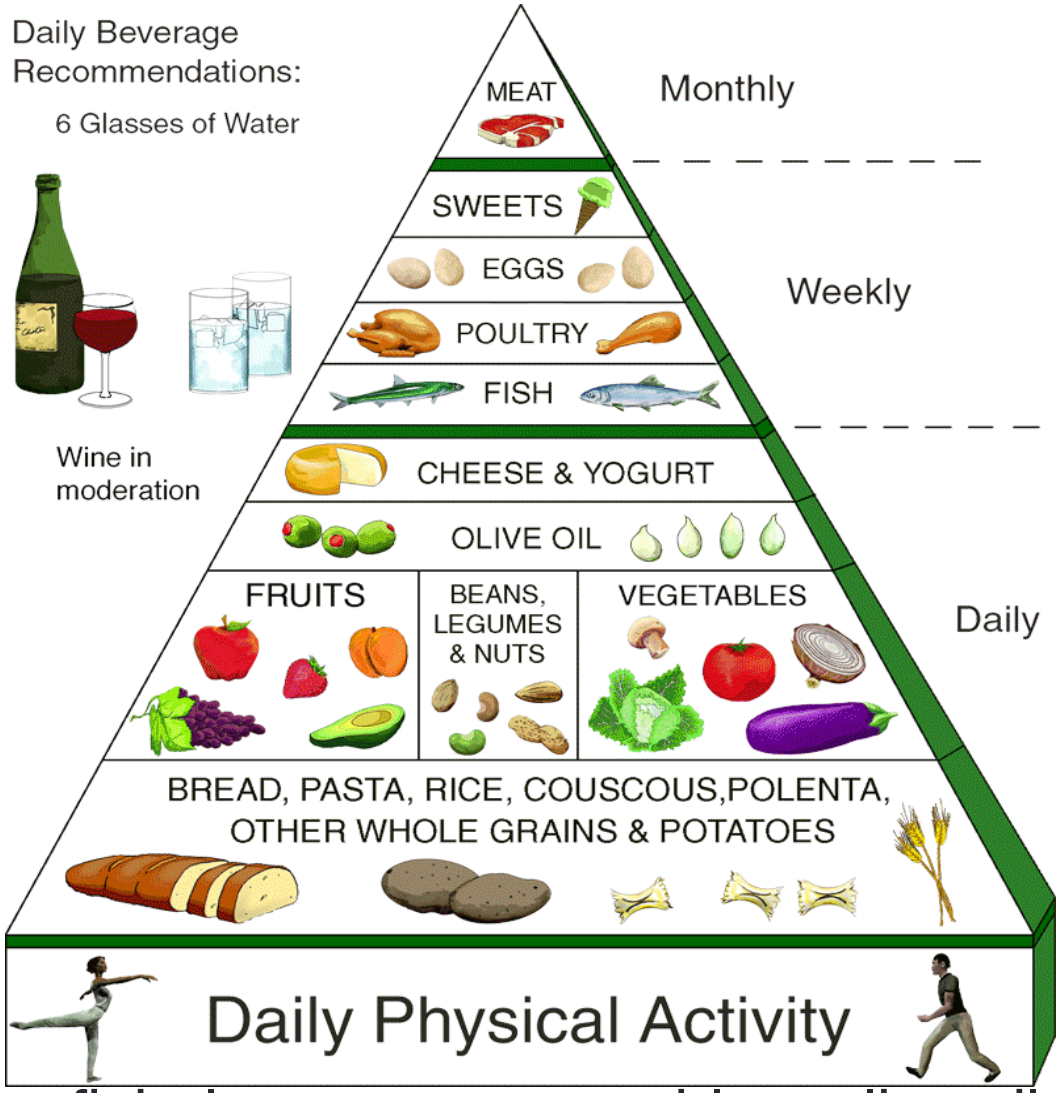
WHAT ABOUT DIET OVERALL?

Mediterranean diet:



- cereals, fruits, fish, legumes, vegetables, olive oil, low to moderate dairy (cheese, yogurt), moderate alcohol at meals

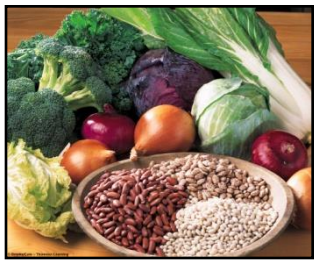
What is the Evidence?

- Primarily long term cohort studies
  - Improved CVD, DM, cancer, overall mortality
  - 9 studies on cognitive decline
    - 7 studies showed effect of diet

- One RCT, PREDIMED-NAVARRA (Martinez et al., 2013)
  - N=285 Tx: diet + olive oil/mixed nuts Placebo: low fat diet; 6.5 years
  - Protective, but needs to be replicated

Recommendations for Brain Health

- Balanced, high quality diet; lots of fruit, vegetables, whole grains, nuts, fish
- The earlier the better!
- Maintain body weight
- Multivitamin supplementation if concerned about potential poor diet
- Don’t smoke, exercise, decrease stress and avoid exposure to free radicals in the environment



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THE ISSUE OF BODY WEIGHT AND DEMENTIA

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Obesity and Cognitive Decline

- A high BMI in mid-life may be a risk factor for dementia (Gorospe & Dave, 2007; Beydoun et al., 2008; Anstey et al., 2011)
  - Insulin resistance, hyperinsulineamia, advanced glycosylation end products
  - Metabolic and inflammatory cytokines released by adipose tissue
  - Cardiovascular risk factors such as hypertension
  - Accumulation of risk factors, increased risk
- Greater evidence for fat pattern, truncal fat

(Whitmer et al., 2008; Gustafson et al., 2009)

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What do we know about weight loss and AD?

- Weight loss seems to predominate, part of Alois Alzheimer's profile of Ms August D
- Weight loss precedes dementia (Barrett-Connor, 1996; Knopman et al, 2007).

  - 11-20 years prior in women but not men (Knopman et al., 2007)
    - apathy, lack of interest in cooking/eating

- Weight loss is a signal event in AD diagnosis (Nourhashemi, 2003)

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Research Indicates:

- Weight loss continues after diagnosis
  - approximately 1 lb, 0.8% or 0.5 decrease in BMI is seen each year after diagnosis (White et al., 1998; Cronin-Stubbs et al., 1997)
  - however the variability is great; weight fluctuations in general are greater in AD than in nondemented controls (Wang et al., 1997 & Shatenstein et al, 2001)

- Estimate of 15-22% malnutrition (Irving et al, 1999)
- Weight loss associated with cognitive loss (Guyonnet et al. 1998)

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Mortality in AD

- A modest weight gain of 5% of body weight is associated with significantly decreased mortality (Keller, 1995)
- The risk of death associated with undernutrition was found to be of greater importance than typical risk factors (Keller & Ostbye, 2000)
- How?
  - Infections
  - Loss of lean body mass→ falls
  - Decreased function→ pressure sores
  - Increased hospitalization→ increased comorbidity

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WHY DOES WEIGHT LOSS OCCUR?

Multi factorial and complex causes

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Hypothesis for Weight Loss

Reduced Intake

1) Changes in olfactory function
2) Changes in satiety/feeding drive (limbic & hypothalmic changes, atrophy)
3) Malabsorption
4) Changes in orexigenic factor concentrations
5) Depression, apathy
6) Initiative for cooking/eating- social link
7) Self-feeding and assisted feeding difficulties
8) Dysphagia, dental health
9) Wandering, increased waking hours

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Factors Influencing the Early Stage

- appetite
- motivation
- self-neglect
- forget to eat
- changes in taste and smell
- depression
- disorientation
- inability to adapt to new situations
- difficulty shopping
- difficulty cooking

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Factors Influencing the Middle Stage

- lack of food choice
- increased agitation
- aggression
- aphasia, agnosia
- relocation trauma

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Factors Influencing the Late Stage

- appetite (physiologic)
- apraxia, agnosia, aphasia
- loss of communication skills
- loss of motor skills
- refusal to eat
- distractability
- loss of sequencing skill
- dysphagia

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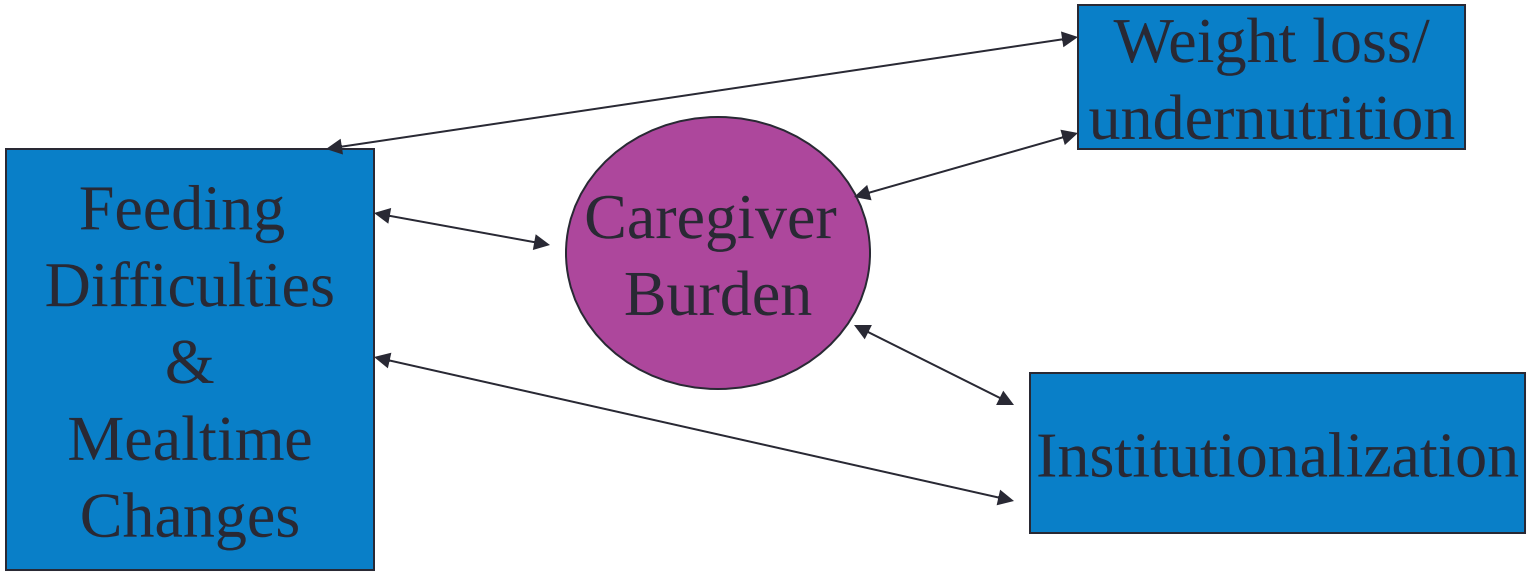
Family Caregivers



Potentially greater benefit for earlier intervention.

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CAN WEIGHT LOSS BE REVERSED?

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- There is some indication that weight loss promotes impaired cognition and that weight gain slows the progression of AD

(Barrett-Connor, 1996; White et al., 1998)

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Things that have been tried

- Appetite stimulants
- Flavour enhancements
- Nutritional supplements (shakes, puddings, soups)
- Care partner training
- Mealtime environment

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Supplements

(Lauque et al., 2004)

- Geriatric wards and day centres, France
- 46 received 3 months of nutritional supplements
  - 400 kcal/d in addition to food
- 45 received usual care
- 6 month follow-up

Supplements: increased protein, energy intake; increased weight and FFM

No changes in dependence, cognitive function

Maintained weight after discontinuation

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Training Care Partners

Care Aids

- Eating assistance skills training – 4 hrs (Chang et al 2005)
  - Improved attitudes, knowledge and behvaiours but no change in body wt
- Assessing and monitoring nutrition status, how to intervene- 24 hrs (Suominen et al 2007)
  - 21% increase in food intake but no change in nutritional status

Family

- 3 studies, group sessions conducted by health professional; focused on knowledge around nutrition and managing behaviours
  - NutrALZ largest study (Salva et al., 2011)
    - No effect on body weight
  - Brazil + supplements (Pivi et al., 2011)
    - Increased body weight, most in supplemented group
  - 3 cities in Europe (Riviere et al. 2001)
    - No effect

Mealtime Interventions

- Lots of suggestions, ideas, very little empirical research
- Family style dining, incorporates many ideas (e.g. small #, few distractions, food on table, sensory stimulation, staff sit with residents) (Nijs et al., 2006)
  - Improved food intake, body weight, quality of life and physical performance

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Summary

- Potential bi-directional relationship between nutrition and dementia
- Answers are elusive… healthy diet for prevention and delaying of progression
- Prevent weight loss, promote dignity and support meals as an event
- Oral nutritional supplements and mealtime interventions are most likely to promote weight maintenance

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