Multi-domain Interventions to Prevent Cognitive Impairment and Alzheimer’s Disease: The Role of the Gut Microbiome

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Disclosures

- **Advisory boards**: Combinostics, Swedish Care International, Roche

- **Speaker**: Biogen

- Guidelines development group: WHO
- Governance Committee member: Global Council on Brain Health

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Alzheimer’s & Dementia: Complex, Heterogeneous, and Multifactorial

Multiple disease mechanisms
Genes x Environment

Birth → Old age

Prevention potential ≈ 30% AD cases
Norton et al, Lancet Neurol 2014

Kivipelto, Mangialasche and Ngandu, Nature Neurology 2018
Hara et al, Neurology 2019

Diabetes | Depression
Hypertension | Smoking
Obesity | Low education
Physical inactivity | ...

LBD

Lipid metabolism
Glucose metabolism
Mitochondrial dysfunctions

 Proteostasis & autophagy deficits
 Oxidative Nitrosative stress
 Vascular damage
 β-amyloid accumulation
 Tau aggregation
 TDP-43 inclusions

Neuronal death
Microbiome???

Inflammation
Epigenetic changes
Microbiome & Aging

• The microbiome has bidirectional links to the CNS, with evidence from psychiatric conditions and Parkinson’s disease

(Cerovic et al., 2019; Cryan et al., 2016; Scheperjans 2016)

• With aging, both the GI tract epithelium and the Blood Brain Barrier undergo significant restructuring and become permeable (both become more ‘leaky’)

(Hill 2015; Zhao 2015; Shoemark 2015; Tran 2013; Marques 2013; Oakley 2014; Blanco 2012)

• Greater microbiome inter-individual variability among older adults compared to young adults (Claesson, 2011)

• Microbiome is associated with frailty, nutritional status, comorbidities & inflammatory markers (Claesson, 2012)

• Diversity of one’s diet is associated with greater microbiome diversity and better health outcomes (Claesson, 2012)
Microbiome-Derived Amyloid?

- Several hypotheses on the role of the microbiome in AD pathogenesis
  - Transgenic AD mouse models have shown that the microbiome is altered (review: Cryan et al., 2019).
Evidence in Humans:
3 small cross-sectional studies showed that in AD patients compared to controls:

• Pro-inflammatory bacterial taxa are elevated, while anti-inflammatory bacteria are reduced (Kang et al., 2017)

• A decrease in microbiome diversity and richness (Vogt et al., 2017)

• Differing levels of various bacteria types (Zhuang et al., 2018)

A small double blind RCT (6, men, 24 women) using probiotics among AD patients showed an increase in MMSE scores, blood lipid profile and carbohydrate metabolism, but fecal samples were not collected (Akbari et al., 2016)
Total 10 studies
• 6 are classified as ‘Interventional’ ‘Clinical Trial’
• Only 3 are randomized controlled trials, of which:
Sample sizes range between 30-200 (10-50 per arm)

Interventions include:
1) Fecal microbiota transplant in healthy adults and AD patients (n=30) (Pilot)
2) Multidomain intervention in a heterogenous sample (Mild AD or MCI or SCI +
    beta-amyloid (PET) (n=60)
3) Multimodal lifestyle intervention + epigallocatechin gallate (tea extract) in
    Subjective Cognitive Decline (n=200)

None specifically use the Prodromal AD criteria, nor combine the intervention with
medical food
“….a substantial lack of human data, both from observational and intervention studies, preventing to formulate any clinical recommendation on this topic.

….a promising area of research for identifying novel preventive and treatment strategies against dementia.”

(Ticinesi et al., 2018)
CHALLENGE: One size does not fit all
Precision-based multi-domain approaches

- Multidomain interventions: several simultaneous targets
- Tailor interventions to the individual’s specific risk profile
- Heterogeneity in phenotype and response
- Optimal time windows
<table>
<thead>
<tr>
<th>Evidence review</th>
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<tbody>
<tr>
<td>Physical activity</td>
<td>Overweight</td>
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<tr>
<td>Tobacco</td>
<td>Hypertension</td>
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<td>Alcohol</td>
<td>Dyslipidemia</td>
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<td>Diet</td>
<td>Diabetes</td>
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<td>Cognitive Training</td>
<td>Depression</td>
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<tr>
<td>Social Activity</td>
<td>Hearing loss</td>
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**Multidomain interventions?**

Guidelines launched May 14th, 2019
Alzheimer’s disease and dementia prevention: From single domain to complex multi-domain trials

Pharmacological
- Antihypertensives
  - Statins
- Hormone replacement therapy
- NSAIDs

Dietary
- Nutraceuticals
  - Vitamin B12
  - Folate
  - Vitamin E
  - Vitamin C
  - Ginkgo Biloba

Lifestyle
- Physical Activity
- Cognitive Training
- Mediterranean diet & olive oil

Multidomain
- LipiDiDiet
- FINGER
- MAPT
- Pre-DIVA
- MIND-AD

Solomon, Mangialasche, Schneider, Kivipelto JIM 2014, Ngandu, Mangialasche, Kivipelto, Nature Neurology 2018
A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial


<table>
<thead>
<tr>
<th>Factors</th>
<th>Points</th>
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<tbody>
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<td>Age years</td>
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<td>&gt;53</td>
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<td>Inactive</td>
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Dementia Risk Score (midlife)

Kivipelto et al., Lancet Neurology 2006
Alzheimer’s and Dementia 2011

N = 1260
Age 60-77 years
At risk general population

MULTIDOMAIN INTERVENTION
Nutrition
Exercise
Cognitive training
Vascular risk monitoring

REGULAR HEALTH ADVICE

Extended 5- & 7-year follow-up finished
10-year follow-up
Multidomain intervention

Group & individual training
High adherence
No SAEs
Summary of primary findings

**Primary: NTB total score**
*(Composite z-score)*

- **Improvement**: + 25%

**Executive functioning**

- **Improvement**: + 83%

**Processing speed**

- **Improvement**: + 150%

**Memory**
*(complex tasks)*

- **Improvement**: + 40%

- Lower risk for cognitive decline
- 30% lower risk for functional decline *(Kulmala, Kivipelto et al., JAGS 2019)*
- Better health related quality of life *(Strandberg, Kivipelto et al., Eur Ger Med 2017)*
- 60% lower risk of other chronic diseases *(Marengoni, Kivipelto, JAMDA 2017)*
APOE4 carriers - clear beneficial effects

JAMA Neurology  |  Original Investigation  |  April 2018  |  Volume 75, Number 4

Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention
A Subgroup Analysis of a Randomized Clinical Trial

Alina Solomon, MD, PhD; Heidi Turunen, BM; Tiia Ngandu, MD, PhD; Markku Peltonen, PhD; Esko Levälahti, MSc; Seppo Helisalmi, PhD; Riitta Antikainen, MD, PhD; Lars Bäckman, PhD; Tuomo Hänninen, PhD; Antti Jula, MD, PhD; Tiina Laatikainen, MD, PhD; Jenni Lehtisalo, MSc; Jaana Lindström, PhD; Teemu Paajanen, MA, Psy; Satu Pajala, PhD; Anna Stigsdotter-Neely, PhD; Timo Strandberg, MD, PhD; Jaakko Tuomilehto, MD, PhD; Hilkka Soininen, MD, PhD; Miia Kivipelto, MD, PhD

Telomere length: FINGER intervention counteracts shortening of telomeres among the ApoE4 carriers (Sindi, Solomon, Kivipelto et al., submitted)
New research area

Microbiome Gut-Brain Axis: Interdisciplinary Study

KI Center for Alzheimer Research

Dept: Microbiology, Tumor and Cell Biology (MTC)

Dept: Neurobiology, Care sciences and Society (NVS)

KI Gastrocentrum

SCI Lifelab

Karolinska Institutet

KAROLINSKA Universitetssjukhuset
MIND-AD
Microbiome Gut-Brain Axis – Sub-Study

Baseline:
• Does the microbiome of prodromal AD patients differ from healthy controls?
• Is it associated with relevant biomarkers?

Biomarkers
- Beta-amyloid
- Tau
- MRI
- Inflammatory
- APOE4

Post-intervention:
• Does the multidomain lifestyle intervention impact microbiome profiles?
• Is the change in microbiome associated with relevant biomarkers?

Target group: prodromal AD + vascular + lifestyle risk factors
Participants receive a **home self-sampling kit (Ziploc bag stool collection tube)** and mail it back to the clinic

(It does not need to be placed in the refrigerator/freezer)

The sampling procedure takes ≈5 min, without health risk/pain

The sample may be kept at room temperature until sending it by post

Once samples arrive to the clinic, the samples are stored at -20°C
Microbiome analyses

Analyses will be performed at The Centre for Translational Microbiome Research (CTMR), Karolinska Institute/ Science for Life Laboratory
PI: Professor Lars Engstrand

Analysis method: Shotgun Metagenomic Sequences
### Data harmonization

**WW-FINGERS biorepository**

**Translational bioinformatics**

- Master protocol designed to accommodate trials across the **entire continuum** from at-risk states to biomarker-defined preclinical/prodromal AD

- Designing the first multimodal lifestyle + pharmacological preventive intervention

### COGNITIVE

### CLINICAL

### LIFESTYLE

### BLOOD MARKERS

- AD biomarkers
- Omics in clinical trials

### GENETICS

- GWAS in clinical trials

### BRAIN IMAGING

- Novel in-vivo pathology imaging

### CSF MARKERS

### MICROBIOME
Future: The AD precision prevention / treatment cocktail

- Neurotransmitter modulators
- Neuroprotection
- Dietary interventions/ Medical food
- Risk factors intervention
- ApoE Structure Correctors
- Amyloid & Tau lowering molecules
- Microbiome?

Personalized Medicine

FINGER 2.0
## Take home action points

**Multi-factorial aetiology!**
- Multidomain interventions effective & feasible
- Importance of understanding novel mechanisms eg. microbiome

**One size does not fit all!**
- Precision prevention: tailored interventions for specific at-risk profiles
- Combination Therapy: Non-pharma + pharma

**Global collaboration!**
- Sharing experiences & data, joint projects
- Harmonization of methods, long-term follow-up
- Implementation, pragmatic prevention programs

**Multimodal interventions for various settings and populations**
Acknowledgements


All teams
- FINGER
- US-POINTER
- SINGER
- UK-FINGER
- MIND-CHINA
Prevention matters!