

# Multidomain Interventions for the Prevention of Late in Life Alzheimer's disease and Dementia

**Francesca Mangialasche**  
**MD, Geriatrician, PhD**

Karolinska Institutet, Division of Clinical Geriatrics, Center for Alzheimer Research  
Karolinska University Hospital, Theme Inflammation & Aging, Stockholm, Sweden

## **Dementia and Alzheimer (AD) prevention**

The multidomain approach: the FINGER model

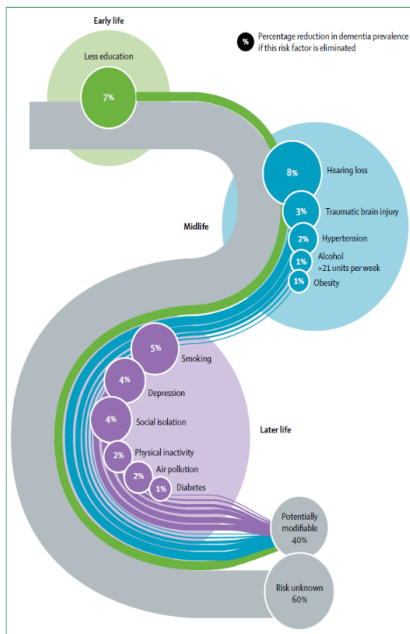
## **From FINGER to World-Wide FINGERS**

## **Prevention at the time of the COVID-19 pandemic?**

**Future!**

# Prevention of Alzheimer's disease and dementia

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission



**Modifiable risk factors for dementia**

**Prevention Potential  $\approx$  40%**

**Multidomain & tailored interventions**

Livingston et al, Lancet Commission 2020

## RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

### WHO GUIDELINES

#### EVIDENCE PROFILES

Physical activity interventions  
Tobacco cessation interventions  
Nutritional interventions  
Interventions for alcohol use disorder  
Cognitive interventions  
Social activity  
Weight management  
Management of hypertension  
Management of diabetes  
Management of dyslipidaemia  
Management of depression  
Management of hearing loss



World Health Organization

WHO 2019 (update ongoing)



Karolinska Institutet



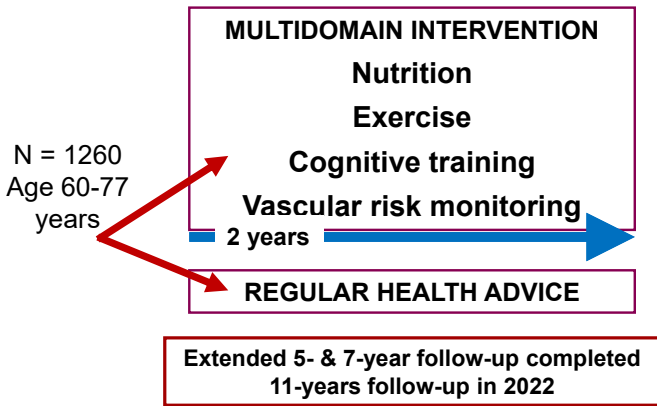
UNSW SYDNEY

## FROM KNOWLEDGE ABOUT RISK FACTORS TO CLINICAL TRIALS AND SUSTAINABLE IMPLEMENTATION

- **Multidomain interventions: several simultaneous targets**
- **One size does not fit all! Tailor interventions: maximize the individual's prevention potential**
- **Mechanistic foundation**
- **Optimal time windows**

# The FINGER model

FINGER



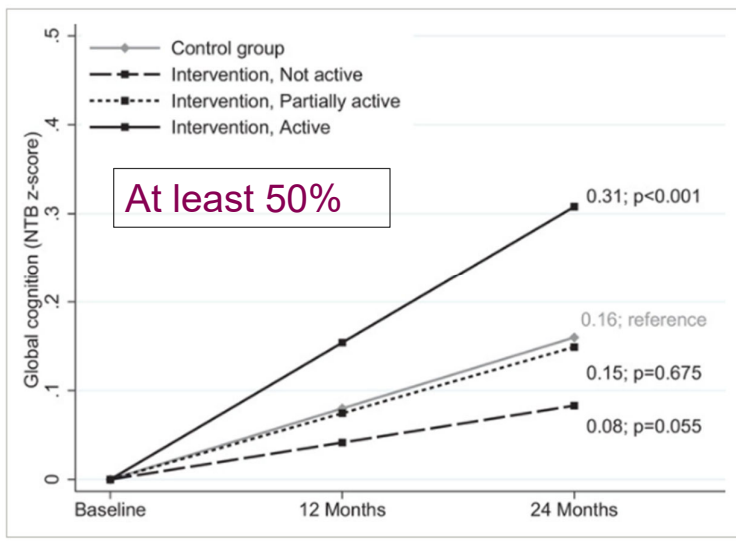
- Cognitive benefits
- 20% lower risk cardiovascular events
- 30% lower risk for functional decline
- 60% lower risk of chronic diseases
- Better health related quality of life
- Health-economical benefits

Lancet 2015; JAMA Neurology 2018, Eur Ger Med 2017, JAMDA 2017, JAGS 2019; Alzheimer's Dementia 2021; European J Cardiology 2022

# The FINGER model

FINGER

## The effect of adherence on cognition



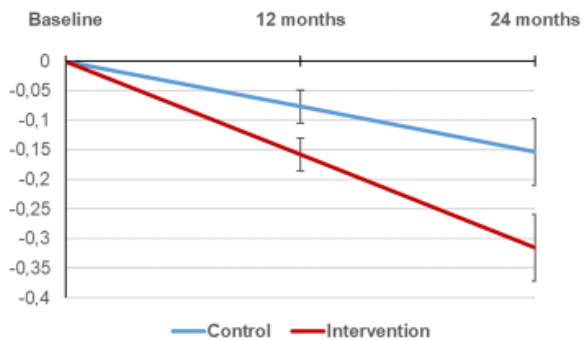
- Active participation is associated with better cognition
- Supporting adherence is essential!

## DEMENTIA RISK REDUCTION:

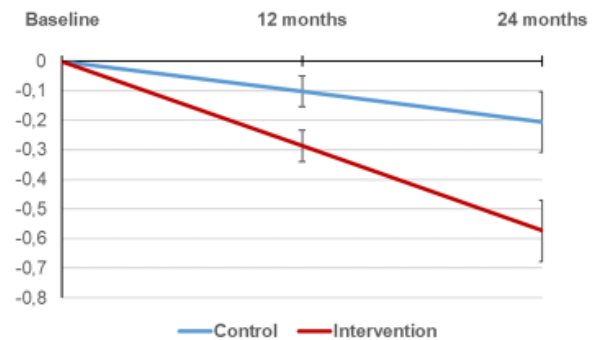
Intervention effects on change in Dementia Risk Scores



### CAIDE score



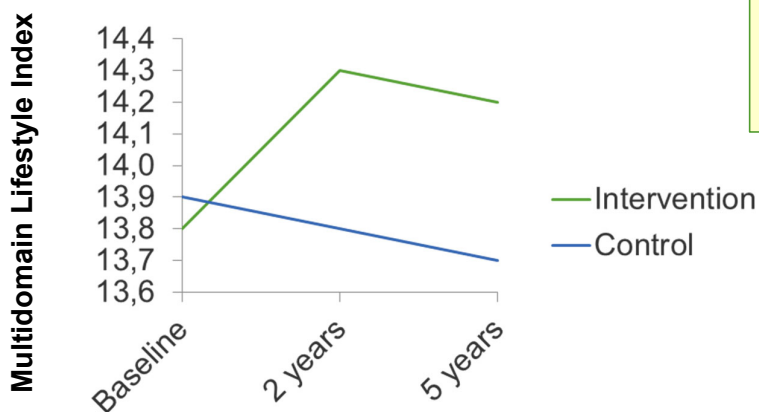
### LIBRA score



**The FINGER multidomain lifestyle intervention reduced the overall dementia risk**

Solomon, Kivipelto, Ngandu et al., *J Alz Dis* 2021, Deckers et al., *Alz & Dem* 2021

## Long-term beneficial effects of the multidomain intervention ?



**DEMENTIA RISK REDUCTION:**  
Improved lifestyle changes were maintained at 5 years

Rissanen, Kivipelto et al, in preparation

# Mechanisms and mediating pathways?

## 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 Levälähti, MSc; Seppo Helisalmi, PhD; Riitta Antikainen, MD, PhD; Lars Bäckman, PhD; Tuomo Hämmänen, 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; Hilikka Soininen, MD, PhD; Miia Kivipelto, MD, PhD



## Higher AD polygenic risk score (PRS) - clear beneficial effects (prel. results)

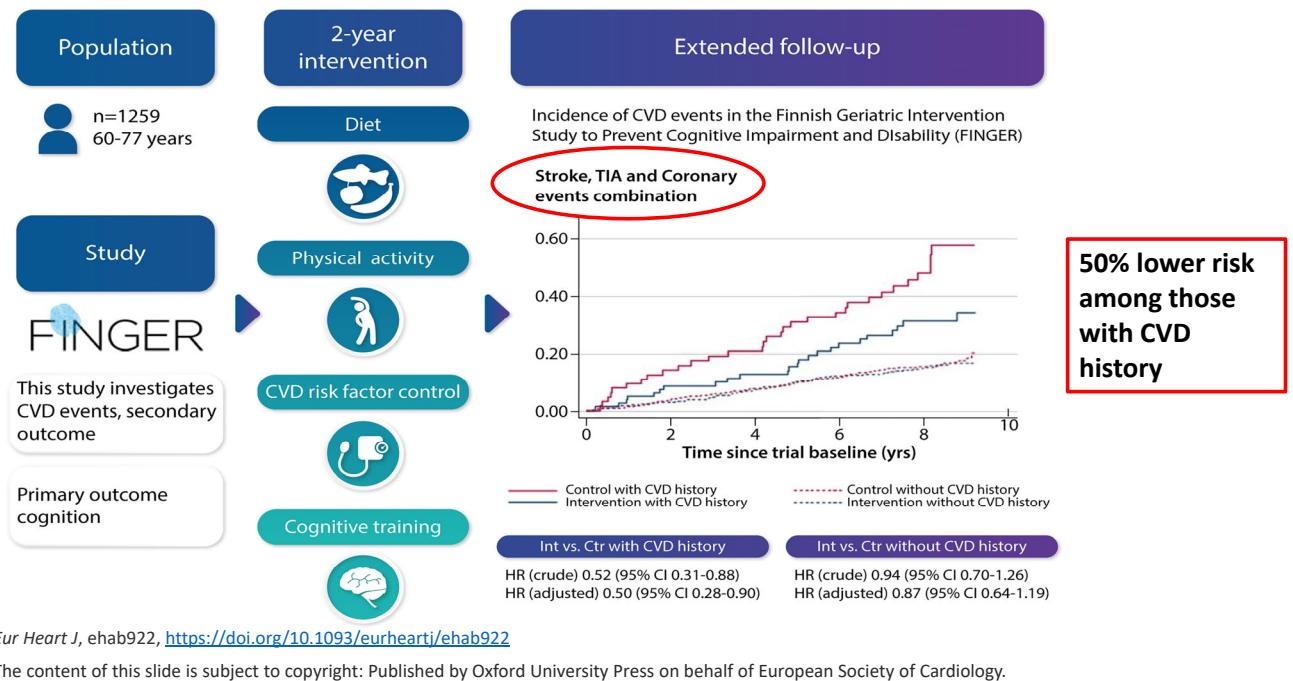
Cognitive end point	PRS	PRS without APOE			PRS with APOE		
		Difference between intervention and control groups per year		PRS*intervention*time interaction	Difference between intervention and control groups per year		PRS*intervention*time interaction
		Estimate (95% CI)	p-value	p-value	Estimate (95% CI)	p-value	p-value
NTB total score	< median	0.009 (-0.018 - 0.037)	0.515	0.093	0.008 (-0.019 - 0.035)	0.560	0.331
	> median	<b>0.038 (0.010 - 0.067)</b>	<b>0.009</b>		<b>0.042 (0.013 - 0.071)</b>	<b>0.005</b>	
NTB complex memory	< median	0.014 (-0.037 - 0.066)	0.582	0.047	0.003 (-0.047 - 0.053)	0.894	0.031
	> median	<b>0.069 (0.019 - 0.119)</b>	<b>0.006</b>		<b>0.086 (0.035 - 0.137)</b>	<b>0.001</b>	

Mixed effects regression models with maximum likelihood estimation; change in cognition analyzed as a function of randomization group, time, PRS, and their interactions (group\*time, PRS\*time, PRS\*group, PRS\*group\*time). Adjusted for study site, age at baseline, sex, age\*time and sex\*time interactions. For PRS without APOE, analyses additionally adjusted for APOEε4 and APOEε4\*time interaction. p-value for PRS\*intervention\*time shown from models with continuous PRS.

Solomon, Hiltunen, Kivipelto et al., manuscript

PRS description: <https://doi.org/10.1101/19012021>

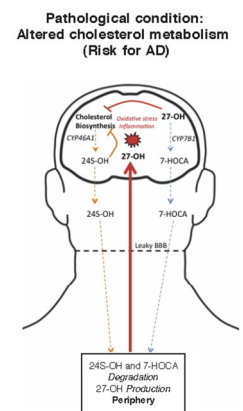
# Incidence of cardiovascular events in the FINGER trial after a 2-year multidomain lifestyle intervention and extended follow-up stratified by the cardiovascular event history.



## Other (emerging) mechanisms

### • Cholesterol and lipids

- **27-hydroxycholesterol (27-OH)**, a possible link between peripheral hypercholesterolemia and AD
- Higher 27-OH in the periphery is associated to poorer cognition and reduced cortical volumes
- Improved cognition from FINGER intervention was associated with reduced 27-OH (Matton, Kivipelto et al., *Alz Research Therapy* 2021)



### • Metabolomics, Proteomics, Inflammatory markers, P-Tau, amyloid, NFL etc

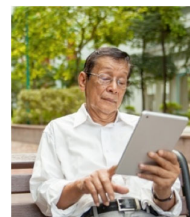
- Ongoing analyses

# From FINGER To



Launched 2017 PI: Miia Kivipelto

- Urgent need to expand FINGER work to test the **generalizability, adaptability, and sustainability** in diverse populations worldwide
- **Harmonize** research methods in prevention trials
- **Share** experiences and data and plan joint dementia prevention initiatives



Lancet 2015

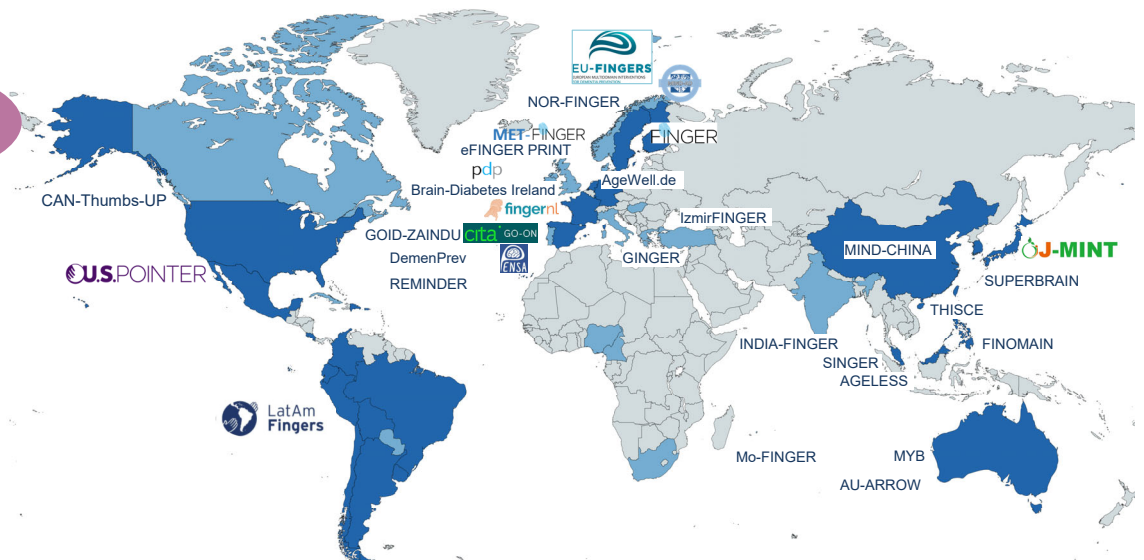


## WW-FINGERS Network



Covid-19 related methodological challenges

- Countries with studies in planning stage
- Countries with ongoing studies



Participating countries 2022: 45+



# SARS-CoV-2 (COVID-19) pandemic and brain health



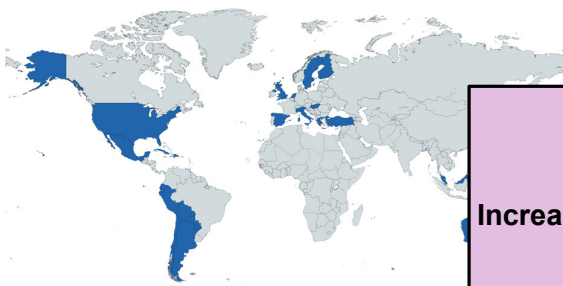
## Pandemic direct and indirect effects on cognition:

- infection effects on CNS
- infection effects on organs and systems
- disruption of regular healthcare
- effects of physical distancing measures



**WHO collaboration:  
Neurology and COVID-19  
global forum**

## World-Wide FINGERS-SARS-CoV2 survey



To assess the indirect effects of the pandemic on :

- Lifestyle and risk factors
- Medical care of chronic conditions
- Mental wellbeing

**Less physical activity**  
~30%

**Increased intake of unhealthy snacks**  
~25%

**More sleeping problems**  
~25%

**Experience of loneliness**  
~ 40%

**Memory decline (self reported)**  
~ 15-25%

Country	Subjects N	Female %
USA	109	49%
UK	193	71%
Germany	100	67%
France	15	NA
Spain	11	NA
Italy	735	47%
Canada	380	56%
Japan	100	NA
China	394	65%
India	600	61%
South Korea	90	NA
Sweden	100	51%
Denmark	82	54%
Poland	215	61%
Belgium	152	70%
Spain	7272	58%
Netherlands	4036	75%
Turkey	222	64%
UK	7752	53%
USA	1011	74%
<b>Total</b>	<b>23569</b>	



**WHO collaboration:  
Neurology and COVID-19  
global forum**

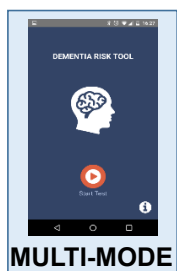


# New technology & Digital solutions: Personalized, Effective and Feasible, Scalable Interventions and Implementation

## E-Health & M-Health tools

## Machine learning and AI

## Clinical decision support



## eFINGER PRINT



**E-FINGERS**

**AI-FINGERS**

# Secure Data Sharing and Harmonization to accelerate discovery

COGNITIVE

CLINICAL

LIFESTYLE

BLOOD MARKERS

AD biomarkers  
Omics in clinical trials

GENETICS

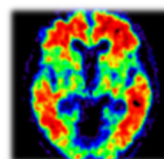
GWAS in clinical trials

BRAIN IMAGING

Novel in-vivo pathology imaging

CSF MARKERS

MICROBIOME



**ADDI**  
Alzheimer's Disease  
Data Initiative

# Next generation of clinical trials: Combine updated FINGER lifestyle model + drugs

## FINGER 2.0

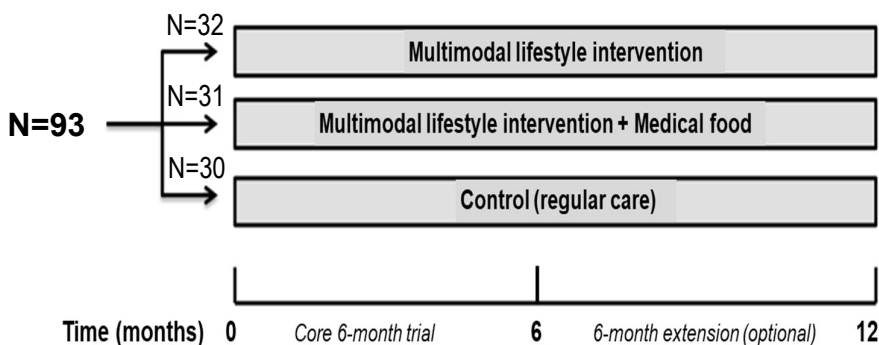


## Implementation



## Multimodal preventive trial for Alzheimer's Disease: MIND-ADMINI

Target group: prodromal AD + vascular + lifestyle risk factors



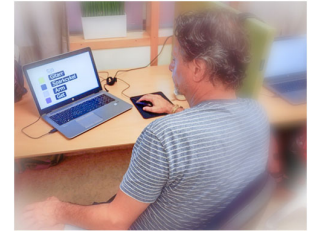
- Trial completed Dec 2019
- Electronic data entry and processing completed in Dec 2020 (delays due to Covid-19).
- Mean age 72.9 years
- MMSE 27.6 points
- Vascular and lifestyle-related risk factors were common



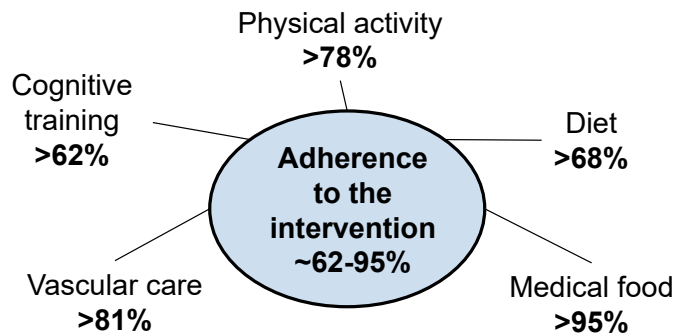


# MIND-AD preliminary results

Target group: Prodromal AD  
+ lifestyle + vascular risk factors



## Preliminary compliance data



Importance of **social component** and adapting the intervention to the target population

Sindi, Kivipelto et al., JPAD 2022

LipiDiDiet: Lancet Neurol 2017; Alz & Dem 2020

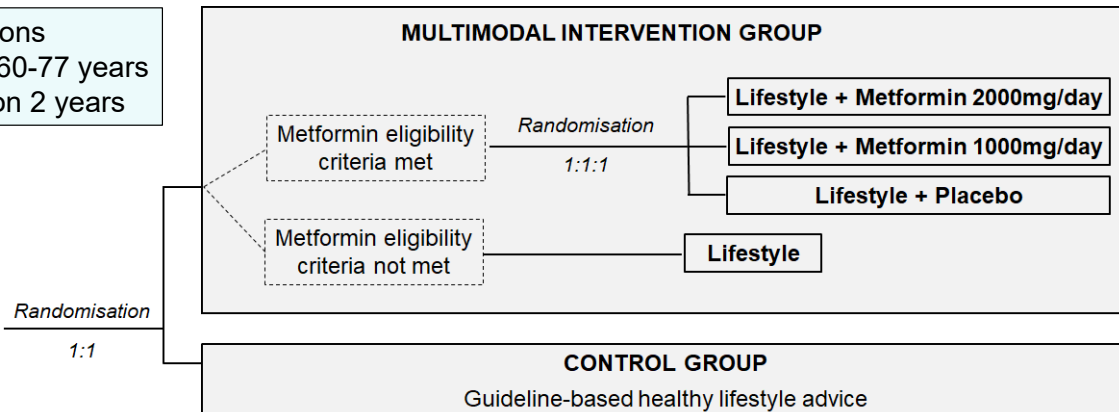
## MET-FINGER

### MET-FINGER study diagram

Phase 2b proof of concept trial

Diabetes medicine metformin  
Repurposed drug approach

At risk persons  
Age range 60-77 years  
Trial duration 2 years



**Outcomes:**  
memory and cognition  
Brain scans  
Alzheimer related biomarkers

*Lifestyle domains: nutrition, exercise, cognitive and social activities, cardiovascular / metabolic risk factors*

## Can Dementia and Alzheimer (AD) be prevented?

- YES, a significant portion of cases can be prevented or at least delayed. Importance of the multidomain approach.
- It is never too early or too late!

## From FINGER to World-Wide FINGERS

- The FINGER multidomain preventive model was feasible and effective. The model is being adapted and optimized globally to develop sustainable interventions in different settings

## Prevention at the time of the COVID-19 pandemic?

- It is even more important! Requires innovative approaches and collaboration.

## Future!

- Precision prevention: tailored interventions for specific at-risk profiles.
- Combination Lifestyle + Pharma + E-FINGERS.
- Implementation

Thank you for your attention!

## Acknowledgements



IMJA. ID !, IDIK@GJ



Thank you all WW-FINGERS countries and member teams!



**Grant support:** Swedish Research Council, CIMED, Wallenberg Clinical grant, Alzheimerfonden, Hjärnfonden, Academy of Finland Alzheimer's Research and Prevention Foundation, EU 7<sup>th</sup> framework, JPND, IMI, EiT-Health, Stiftelse Stockholms Sjukhem, ALF grants, FORTE, KI-Janssen Strategic Collaboration, Imperial College ITMAT, Gates Ventures/ADDI, Alzheimer's Drug Discovery Foundation, Part the Cloud