ANNAKAISA HAAPASALO (ED.)

7th Kuopio Alzheimer Symposium

From mechanisms to prediction and intervention of Alzheimer’s disease

Kuopio, Finland, June 11-13, 2015

Program and Abstracts
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ABSTRACT

The 7th Kuopio Alzheimer Symposium is organized by the University of Eastern Finland, Institute of Clinical Medicine – Neurology, the Doctoral Program in Molecular Medicine, and the Finnish Alzheimer’s Disease Research Society. The symposium brings together the current leaders in clinical and basic research for exchanging new ideas on neurodegeneration, diagnosis, prediction, novel biomarkers, imaging, technology-supported diagnosis and care, and clinical treatment of Alzheimer’s disease. The Finnish program of the Memory Day (Muistipäivä) concentrates on memory problems in individuals in the working age and prevention and rehabilitation of memory diseases.

This book contains the program and abstracts of the 7th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 11-13, 2015.

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Yleinen suomalainen asiasanasto: muisti; muistihäiriöt; muistisairaudet; dementia; Alzheimerin tauti; aivot; diagnostiikka; kuvantaminen; merkkiaineet; markkerit; proteomiikka; genomiikka; ehkäisy; ennaltaehkäisy; hoito; hoitomenetelmät; ravitsemus; alkolohinkäyttö; liikunta; lääketieteellinen tekniikka
Welcome to 7th Kuopio Alzheimer Symposium

Dear Friends and Colleagues,

It is my great pleasure to welcome you to the 7th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 11-13, 2015, and organized by University of Eastern Finland, Institute of Clinical Medicine, Neurology, The Doctoral Program in Molecular Medicine, and The Finnish Alzheimer’s Disease Research Society.

Alzheimer’s disease has been identified as a global health priority, as the growing burden of the disease will challenge the current healthcare systems and national economies. Consequently, the disease mechanisms, prevention, early diagnosis and treatment of Alzheimer’s disease have been under intense research. In its 7th year, Kuopio Alzheimer Symposium provides an outstanding forum to meet and learn from highly respected top-level speakers, who will spotlight the most timely and significant advances in Alzheimer’s disease research. The 7th Kuopio Alzheimer Symposium will also be an excellent opportunity for the attendees to collaborate, network and exchange innovative ideas for future Alzheimer's disease research, treatment and prevention.

We are proud to present our exciting scientific program, which features new and inspiring research findings concerning new insights into neurodegeneration, diagnosis and prediction of Alzheimer’s disease: update on biomarker studies, new advances in imaging, technology-supported diagnosis and care, novel approaches towards prevention, population-based prevention studies, and novel approaches in clinical treatment studies. The program also includes a Finnish Session "Memory Day" targeted at health care personnel working with memory patients.

I warmly welcome you all to enjoy this inspirational scientific event and experience the Finnish early summer and the midnight sun!

Kuopio, June 8, 2015

Hilkka Soininen, MD, Ph.D.
Professor, Dean
Chair of the Organizing Committee
7TH KUOPIO ALZHEIMER SYMPOSIM

Organized by
University of Eastern Finland, Institute of Clinical Medicine – Neurology
The Doctoral Program in Molecular Medicine
The Finnish Alzheimer’s Disease Research Society

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7th Kuopio Alzheimer Symposium

Program and Abstracts

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7th Kuopio Alzheimer Symposium

PROGRAM IN BRIEF

Thursday, June 11

Memory Day - Finnish Session / Muistipäivä

12:00-14:00  I Haasteena työikäisen muistipulmat
14:00-14:45  Coffee break
14:45-17:00  II Muistisairauksien ehkäisy ja kuntoutus

Opening symposium

18:00-18:15  Welcome address
18:15-18:30  Address from Alzheimer Europe
18:30-20:00  Keynote lectures

20:15-22:30  Welcome reception (Technopolis Katri Antell Restaurant)

Friday, June 12

Main symposium

08:30-10:30  I New insights into neurodegeneration
10:30-11:05  Coffee break
11:05-13:10  II Diagnosis and prediction of Alzheimer’s disease: Update on biomarker studies
13:10-14:10  Lunch break
14:10-15:50  III New advances in imaging
15:50-16:20  Coffee break
16:20-17:10  IV Technology supported diagnosis and care

19:30-23:00  Get-together Party and Posters (Hotel Scandic Ballroom)

Saturday, June 13

Main symposium

08:30-10:10  V Novel approaches towards prevention
10:10-10:40  Coffee break
10:40-12:20  VI Population-based prevention studies
12:20-13:20  Lunch break
15:25-15:35  Closing remarks
7th Kuopio Alzheimer Symposium

PROGRAM – MEMORY DAY

Thursday, June 11
Memory Day - Finnish Session / Muistipäivä

The Finnish Session - Memory Day - program is targeted for nurses, doctors, psychologists and other personnel working with memory patients.
Muistipäivän ohjelma on suunnattu erityisesti perusterveydenhuollossa, kotihoidossa ja hoitokodeissa muistipotilaiden kanssa työskentelevälle hoitohenkilöstölle, psykologille ja lääkäreille.

I Haasteena työikäisen muistipulmat
Puheenjohtaja: Anne Remes

12:00-12:30 Muisti työssä
Teemu Paajanen, Työterveyslaitos, Helsink

12:30-13:00 Alzheimerin taudin erityispiirteet nuorilla potilalla
Merja Hallikainen, Itä-Suomen yliopisto, Kuopio

13:00-13:30 Etenevä muistisairaus psykiksen oireilun taustalla
Anne Remes, Kuopion yliopistollinen sairaala, Kuopio

13:30-14:00 Alkoholi ja muisti
Ari Rosenvall, Mehiläinen Ympyrätalo, Helsinki

II Muistisairaauksien ehkäisy ja kuntoutus
Puheenjohtaja: Anne Koivisto

14:45-15:15 Voidaanko muistisairaauksia ehkäistä?
Miia Kiviipelto, Karoliininen Instituutti, Tukholma, Ruotsi

15:15-15:45 Ravitsemus ja muisti
Tiia Ngandu, THL, Helsinki ja Karoliininen Instituutti, Tukholma, Ruotsi

15:45-16:15 Liikunnan merkitys muistipotilaan kuntoutuksessa
Minna Raivio, Helsingin yliopisto, Helsink

16:15-16:45 Sopuutumisvalmennusta vai muuta tukea?
Anne Koivisto, Itä-Suomen yliopisto, Kuopio

16:45-17:00 Yhteenveto ja päättössanat
Anne Remes, Kuopion yliopistollinen sairaala, Kuopio
7th Kuopio Alzheimer Symposium

PROGRAM – OPENING AND MAIN SYMPOSIA

Thursday, June 11

Opening symposium

18:00-18:15 Welcome address
Hilkka Soininen, Dean, Professor, Chair of the Organizing Committee, University of Eastern Finland, Kuopio

18:15-18:30 Address from Alzheimer Europe: Making dementia a European priority
Jean Georges, Executive Director, Alzheimer Europe, Luxembourg

Keynote Lectures
Chairpersons: Mikko Hiltunen and Anne Remes

18:30-19:15 Do large databases provide answers to understanding of the pathogenesis and treatment of memory diseases?
Johannes Streffer, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium

19:15-20:00 Innovative approaches in treatment trials for AD (IMI-EPAD)
Miia Kivipelto, Karolinska Institutet, Stockholm, Sweden

20:15-22:30 Welcome Reception (Technopolis Katri Antell Restaurant)

Friday, June 12

Main symposium

I New insights into neurodegeneration
Chairpersons: Alberto Lleó Bisa and Annakaisa Haapasalo

8:30-09:00 New advances in neuropathology of neurodegenerative diseases
Alberto Lleó Bisa, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

09:00-09:30 Mechanisms of neurodegeneration in the co-morbidity of AD and diabetes
Paula Moreira, University of Coimbra, Coimbra, Portugal

09:30-10:00 Mechanism of action of the specific nutrient combination Fortasyn® Connect which is designed to enhance synapse formation and function in Alzheimer’s disease
Patrick Kamphuis, Nutricia Research, Utrecht, the Netherlands

10:00-10:30 A nutritional approach in early Alzheimer’s disease
David Wilkinson, Memory Assessment & Research Centre, Moorgreen Hospital, Southampton, UK

10:30-11:05 Coffee break
II Diagnosis and prediction of Alzheimer’s disease: Update on biomarker studies
Chairpersons: Ian Pike and Mikko Hiltunen

11:05-11:30  **Role of biomarkers in the NIA-AA and IWG criteria for prodromal AD**
Stephanie Vos, Maastricht University, Maastricht, the Netherlands

11:30-11:55  **Novel blood/CSF biomarkers as predictors of AD**
Kina Höglund, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

11:55-12:20  **High-throughput metabolic profiling – from focused studies to epidemiology**
Pasi Soininen, University of Eastern Finland, Kuopio, Finland

12:20-12:45  **Proteomics in prediction of AD**
Ian Pike, Proteome Sciences plc, Cobham, UK

12:45-13:10  **Genetic profiling in risk assessment**
Mikko Hiltunen, University of Eastern Finland, Kuopio, Finland

13:10-14:10  Lunch break

III New advances in imaging
Chairpersons: Juha Rinne and Wiesje van der Flier

14:10-14:35  **Genetic profiling and brain imaging**
Andy Simmons, Kings College, London, UK

14:35-15:00  **Molecular imaging**
Juha Rinne, University of Turku, Turku, Finland

15:00-15:25  **Revisiting the Cholinergic Hypothesis – New Evidence with Neuroimaging**
Harald Hampel, Pierre and Marie Curie University (Sorbonne), Paris, France

15:25-15:50  **Significance of microbleeds in Alzheimer's disease**
Wiesje van der Flier, VU University Medical Center, Amsterdam, the Netherlands

15:50-16:20  Coffee break

IV Technology supported diagnosis and care
Chairperson: Hilkka Soininen

16:20-16:45  **Decision making tools in memory diseases, PredictND**
Jyrki Löijönen, VTT Technical Research Centre of Finland, Espoo, Finland

16:45-17:10  **Harnessing big biomedical data for better clinical care, our efforts**
Richard Dobson, Kings College, London, UK

19:30-23:00  Get-together Party and Posters (Hotel Scandic Ballroom)
Saturday, June 13

Main symposium

V Novel approaches towards prevention
Chairpersons: Ingmar Skoog and Carol Brayne

8:30-8:55 Changing risk factors in changing societies – effect on dementia occurrence?
Ingmar Skoog, University of Gothenburg, Gothenburg, Sweden

8:55-9:20 To what extent AD can be prevented?
Carol Brayne, University of Cambridge, UK

9:20-09:45 Nutrition and brain health
Jussi Pihlajamäki, University of Eastern Finland, Kuopio, Finland

09:45-10:10 Vitamins in AD
Francesca Mangialasche, Karolinska Institutet, Stockholm, Sweden

10:10-10:40 Coffee break

VI Population-based prevention studies
Chairperson: Edo Richard

10:40-11:05 A Multidomain Two-Year Randomized Controlled Trial to Prevent Cognitive Impairment - the FINGER study
Miia Kivipelto, Karolinska Institutet, Stockholm, Sweden

11:05-11:30 Risk prediction models in dementia prevention
Alina Solomon, University of Eastern Finland, Kuopio, Finland

11:30-11:55 Multi-domain interventions to improve vascular risk management and prevent cognitive decline and dementia – the preDIVA and HATICE trials
Edo Richard, Academic Medical Centre, Amsterdam, and Radboud University Medical Centre, Nijmegen, the Netherlands

11:55-12:20 Lessons learned from prevention trials: the MAPT study
Sandrine Andrieu, INSERM, Toulouse, France

12:20-13:20 Lunch break

VII Novel approaches in clinical treatment studies
Chairpersons: Miia Kivipelto and Steen Hasselbalch

Heikki Tanila, University of Eastern Finland, Kuopio, Finland

13:45-14:10 Clinical trials in AD: pitfalls
Niels Andreasen, Karolinska University Hospital, Huddinge, Sweden

14:10-14:35 Health economic aspects in intervention studies
Anders Wimo, Karolinska Institutet, Stockholm, Sweden

14:35-15:00 Physical exercise as a disease-modifying approach in AD
Steen Gregers Hasselbalch, Danish Dementia Research Centre, Rigshospitalet, University of Copenhagen, Denmark
15:00-15:25  *A specific nutrition combination in prodromal Alzheimer's disease: the LipiDiDiet study*
Hilkka Soininen, University of Eastern Finland, Kuopio, Finland

15:25-15:35  *Closing remarks*
Hilkka Soininen, Chair of the Organizing Committee, University of Eastern Finland
Abstracts for invited talks


ALZHEIMERIN TAUDIN ERITYISPIIRTEET NUORILLA POTILAILLA

Merja K. Hallikainen
Itä-Suomen yliopisto, Kuopio


AT voi alkaa myös kielellisin oirein, jolloin sairaus voidaan virheellisesti tulkita otsa-ohimolohkorappeuman kielelliseksi muodoksi. Potilailla on vaikeuksia sanojen löytämisessä, nimeämisessä ja lauseiden toistamisessa ja puheen tuotto voi olla työlästä ja pysähtelevään, mutta kielellisesti puhe on normaalia. Näillä potilaililla muistioireet ilmaantuvat kuitenkin usein jo muutan vuoden sisällä puheongelmien ilmaannuttua, kun taas otsa-ohimolohkorappeumaa sairastavilla afasiapotilailla muut tiedonkäsittelyn osa-alueet säilyvät pidempään normaaline.

Aivojen etuosien vaurioihin pintottuvissa AT:n varianteissa voi olla mukan noaks otsalohkodementilla tyyppillisitä käytösoireita, kuten aloitteettomuutta tai estottomuutta, mutta muistioireet tulevat mukaan oirekuvaan varsin nopeasti, usein muutan vuoden kulussa.

Työikäisten AT:n tunnistaminen on haasteellista kuormittavan ja kiireisen työelämän mukaan taumien muistiongelmien sekä monenlaisten psykkisten ja käyttäytmisoireiden taustalta. Poikkeavat oirekuvat tuovat lisäähuastetta AT:n tunnistamiseen ja varhaisen diagnostiikan sekä erotusdiagnostiikan erityisesti työikäisiillä. Oirekuvat tulisikin tuntea ja oikean diagnosoin päästä mahdollisimman varhain, koska potilaat hyötyvät AT:n lääkehoidosta ja tukitoimista.
ETENEVÄ MUISTISAIRAUS PSYYKKISEN OIREILUN TAUSTALLA

Anne M. Remes
Itä-Suomen yliopisto ja Kuopion yliopistollinen sairaala, neurologia, Kuopio


Kirjallisuutta:
ALKOHOLI JA MUISTI

Ari Rosenvall
Mehiläinen Ympyrätalo, Helsinki


Oma erityinen kysymys on jälleen hyvin ääkköiden tai etenevää muistisairautta sairastavien alkoholinkäyttöä. Tällaisessa tilanteessa hyvinkin vähäiset alkoholimäärät (luokka 15 g eli 1 annos) voivat merkittävästi heikentää sekä kognitiivista että motorista toimintakykyä. Samaan haittaan voidaan myös päästä alkoholin ja keskushermostoa lamaavien lääkkeiden yhteiskäytössä ja tässä tulee erityisesti varoja.
II Muistisairauskielen ehkäisy ja kuntoutus

VOIDAANKO MUISTISAIRAUKSIA EHKÄISTÄ?

Miia Kivipelto, FINGER -tutkimusryhmän puolesta
Karolinska Institutet Center for Alzheimer Research, Stockholm, Sweden, Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland ja Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland

Etenevien muistisairauskien syynä on valtaosassa tapauksista joko Alzheimerin tauti (AT) tai aivoterveydenkierre sairaus (vaskulaarinen kognitiivinen heikentymä, VCI), tai näiden yhdistelmä. Viimeaikaiset tutkimukset ovat vahvistaneet käsitystä sitä, että myöhäisillä alkavia AT on monitekijäinen ja heterogeninen sairaus ja korkean iän ja geneettisten tekijöiden lisäksi useat vaskulaariset ja elintapatekijät vaikuttavat riskiin sairastumukseen. AT:n aivomuutokset voivat alkaa kehittyä jo 20–30 vuotta ennen kuin tauti voidaan kliinisesti diagnooida. Tästä syystä on alettu puhua yhä enemmän elintäkäisperpektiivistä muistisairauskielistä ja riskitekijöistä keski-ässä tai jo varhaisemmassa elämänvaiheessa ovat nousevat lisääntyvän huomion kohteeksi.

On vielä epäselvää kuinka paljon AT liittyi muokattavissa oleviin tekijöihin ja kuinka paljon tautia voidaan ennaltaehkäistä. Tuoreiden arvioiden mukaan noin 30 % AT:sta olisi yhteydessä muokattavissa oleviin elintapatekijöihin (matala koulutus, keski-iän korkea verenpaine, lihavuus, diabetes, vähäinen liikunta tupakointi, masennus). Tarvitaan kuitenkin kontrolloituja interventiotutkimuksia varmentamaan nämä arviot ja osittaan parhaat keinot tehokkaalle ennaltaehkäiseen.


Kahden vuoden interventio jälkeen tulokset osoittivat selvästi, että kognitiivisia toimintoja voidaan parantaa tai ylläpitää hallitsemalla niiden riskitekijöitä. Tavanomaista elintapaneuvontaa saaneella verrokkiryhmällä oli 31 % suurempi muistitoinnitoimien heikentymisen riski kuin tehostettua elintapaohjausta saaneella ryhmällä.

Tutkimustieto muistihäiriöiden ennaltaehkäisyn mahdollisuksista tulee täsmennyään lähivuosina. Yleisenä ohjeena väestötasolla voidaan jo tässä vaiheessa sanoa, että sydän- ja verisuonitautien ehkäisy, liikunta, monipuolinen aivojen käyttäminen kaikissa ikävaiheissa, terveellinen monipuolinen ravinto, tupakoinnittomuus ja aivojen suojaaminen vammoilta ovat suositeltavia preventiolle tai muistioireiden myöhemmässä. Lähivuosina tieto riskitekijöistä ja geenien ja ympäristötötekijöiden yhteisvaikutuksista tarkentuu, mikä voisi mahdollistaa tehokkaamman, kohdennetun intervention.
RAVITSEMUUS JA MUISTI

Tiia Ngandu
Kansantautien ehkäisy -yksikkö, Terveyden ja hyvinvoinnin laitos, Helsinki ja Karolinska Institutet Alzheimer’s Disease Research Center, Stockholm, Sweden


SOPEUTUMISVALMENNUSTA VAI MUUTA TUKEA?

Anne M. Koivisto
Neurokeskus, Neurologia, Kuopion yliopistollinen sairaala, Kuopio University Hospital ja Neurologia, Kliinisen lääketieteiden yksikkö, Itä-Suomen yliopisto, Kuopio

Viime vuosina Alzheimerin tautia (AT) sairastavan henkilön lääkkeettömän hoidon ja omaishoidon tukemisen vaikkattavuudesta on tullut runsaasti tieteellistä näyttöä. Tavoitteena muistasairaan kuntouttavassa hoidossa on käyttää sairauden eri vaiheissa yksilölliseen ja säännölliseen arviointiin perustuvia kuntoutus- ja tukimuotoja. Näillä pyritään hidastamaan AT:n etenemistä, vahvistamaan muistasairaan ja hänen läheistensä kotona selvitymistä sekä parantamaan heidän elämänlaatua.

Tieteellistä näyttöä on saatu aiemmin omaishoitotaitoja vahvistavasta valmennuksesta (mm. sopeutumisvalmennuksesta), muistikoodinaattori- ja yksilöllisesti suunnitelluista tukitoimista AT:a sairastavan henkilön ja hänen omaishoitajansa hyvinvoinnin ja toimintakyvyn sekä aktiivisista osallistumisen tuloksista. Viimeaikaiset tutkimustutkimukset tekevät ravitsemus- ja liikutuntoututusta. Myös toimintaterapeutin ohjauksesta ja sosiaalisen kuntoutuksen vaikkattavuudesta on näyttöä muistasairaan toimintakyvyn ylläpitämisessä.

Esityksessä käydään läpi myös muistikuntoutuksen strategioita sekä tuoreita tutkimustuloksia varhaisen, mutta pitkäkestoisen sopeutumisvalmennuksen vaikkattavuudesta Kuopio ALSOVA-tutkimuksen tuloksiin nojautuen. ALSOVA -tutkimus on antanut tietoa myös omaishoitajien tilanteesta AT:n edetessä ja omaishoitajariippuvaisista piirteistä, joiden tunnistaminen olisi keskeistä AT:a sairastavan kotihoidon onnistumiseksi ja heidän läheisensä tukemiseksi.


Thursday, June 11

Opening symposium

Address from Alzheimer Europe

MAKING DEMENTIA A EUROPEAN PRIORITY

Jean Georges
Executive Director, Alzheimer Europe, Luxembourg

In June 2006, Alzheimer Europe and its member organisations adopted the Paris Declaration of the political priorities of the European Alzheimer movement in which the associations called on the European institutions and national governments to make dementia a public health priority and to develop national action plans on dementia.

In his presentation, Jean Georges will present some of the achievements of Alzheimer Europe’s campaign at both EU and national level and pay particular attention to the continued development of national Alzheimer plans and dementia strategies and to the place of dementia in EU research programmes.

He will also present the organisation’s latest campaign which was launched at the Annual General Meeting of Alzheimer Europe in October 2014. In its Glasgow Declaration, Alzheimer Europe calls for the development of a European dementia strategy and for greater coordination with global initiatives at G7, WHO and OECD level.
Keynote Lecture

DO LARGE DATABASES PROVIDE ANSWERS TO UNDERSTANDING OF THE PATHOGENESIS AND TREATMENT OF MEMORY DISEASES?

Johannes Streffer
Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium

Progressive memory deficits and dementia are amongst the most urgent medical and societal needs. New therapeutic approaches are needed, but their development is hampered by a lack of understanding of a complex and multifactorial pathophysiology.

Alzheimer’s disease is the predominant disease, but rarely expected to be “pure”. We have good descriptions of the neuropathology and molecular composition of its lesions. Additional to the key proteins β-amyloid and tau, other proteins and pathways are involved, like α-synuclein. The multifactorial nature as well includes metabolic, vascular and genetic factors. The impact of these factors may range from a risk factor to a trigger or driver of the pathology.

Even in a given population with relative homogeneous genetic and cultural factors, there are obvious differences in different samples. Based on the selection of a given sample (specialised memory centre, general geriatric or psychiatric service, general practitioner or institutional care), the composition of risk profiles and shared pathology does vary significantly.

While the analysis of a small investigator-centric sample leads to successful hypothesis building, it is prone to false positive findings, enhanced by the positive publication bias of a “positive” finding. The era of these relatively small sample findings is now followed by successful biomarker-targeted multicentre cohorts (e.g. ADNI, AddNeuroMed), targeted data sharing (e.g. for large GWAS studies or selected biomarkers) as well as growing consortia (e.g. EMIF-AD). The power of these datasets needs multidisciplinary collaborations including e.g. basic science, epidemiology, clinical specialities, statistics and information technology to not only ask the right questions, but as well select the right cohorts, data sets, analysis methods and finally interpretations. The approach in the EMIF-platform is to enable access to data in a variety of formats (meta-data – fingerprinting; aggregated data – tranSMART; networked analysis). This enables access to more than 50,000 participants in AD research studies and more than 50,000,000 Europeans through electronic medical records (EMRs). Biomarker studies are underway with this approach, enabled by EMIF-AD at a scale and depth of data not previously possible. Additionally, there is huge potential for real-world data analysis, for post-marketing effectiveness studies and for research, such as repurposing of therapeutic approaches. In IMI-EPAD, this has been taken to the next step with a collaborative approach towards drug development itself.

In conclusion, we believe large databases will provide answers to the understanding of the pathogenesis and treatment of memory diseases. Even more so, we realize that if we do not succeed in utilizing large databases, we will not succeed in providing the urgently needed answers. The need for collaboration across diverse professional backgrounds as well as public-private partnerships is huge.
INNOVATIVE APPROACHES IN TREATMENT TRIALS FOR AD (IMI-EPAD)

Miia Kivipelto
Karolinska Institutet Center for Alzheimer Research, Stockholm, Sweden, Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland, and Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland

Rationale: The European Prevention of Alzheimer’s Dementia (EPAD) Initiative aims to improve the chance of successfully preventing Alzheimer’s dementia (AD). EPAD will develop an infrastructure that efficiently enables the undertaking of adaptive, multi-arm proof of concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations. The 5-year EPAD project is part of the Innovative Medicines Initiative Joint Undertaking (IMI JU) and includes about 35 partners from the private and academic sectors.

Methods: The project is divided into eight Work Packages - WP1 Scientific Challenges, WP2 Statistical/Methodology Engine Room, WP3 Parent Cohorts and EPAD Register, WP4 EPAD Cohort and EPAD Trials, WP5 Project Management, WP6 Dissemination, WP7 Business Model and Sustainability and WP8 Ethical, Legal and Social Implications (ELSI) - with four Scientific Advisory Groups. The trial will be delivered through approximately 30 Trial Delivery Centres (TDCs) within six country/regional areas.

Results: EPAD is currently establishing a European-wide register of 24000 participants. From this group, 6000 people will be asked to join a pan-European EPAD Cohort for consistent, longitudinal follow-up, and approximately 1500 of them will be invited to participate in a trial to test new treatments for AD prevention.

Conclusions: EPAD has numerous advantages over current approaches: detailed pre-trial characterisation of subjects to inform selection and reduce screening failure; establishment of the highest possible quality TDCs across Europe; rapid decision making on the likely success of a drug (or combination of drugs) in subsequent confirmatory trials and access to a shared placebo group.
NEW ADVANCES IN NEUROPATHOLOGY OF NEURODEGENERATIVE DISEASES

Alberto Lleó Bisa
Neurology Department. Hospital de Sant Pau. C/ Sant Antoni Mª Claret 167. 08025 Barcelona, Spain and CIBERNED (Center of Excellence in Neurodegenerative disease Research)

Studies from families with autosomal dominant Alzheimer’s disease (ADAD) have been critical to support the amyloid cascade hypothesis of Alzheimer disease (AD). However, whether the pathological changes in amyloid precursor protein (APP) processing in the CNS in ADAD are similar to those observed in sporadic AD (SAD) remains unclear.

In this talk, we will review the similarities and differences between the neuropathological aspects and APP processing patterns observed in ADAD and SAD. Our data suggest that the physiopathological events underlying the chronic Aβ production/clearance imbalance in SAD and ADAD are different. Neuroinflammation is another frequent process detected early in AD. Inflammation has drawn important attention recently due to the observation that some genetic factors involved in inflammation are also risk factors for AD. We will review new advances on neuroinflammation in AD and other neurodegenerative disorders during this session.
MECHANISMS OF NEURODEGENERATION IN THE CO-MORBIDITY OF AD AND DIABETES

Paula I. Moreira
Center for Neuroscience and Cell Biology and Faculty of Medicine, University of Coimbra, Coimbra, Portugal

A link between Alzheimer disease (AD) and type 2 diabetes (T2D) has been established, with patients with T2D at increased risk of developing AD and vice versa. The incidence of T2D is increasing at alarming rates worldwide, mainly due to poor lifestyle habits. In parallel, as the world population ages, the prevalence of AD, the most common form of dementia in the elderly, also increases. Growing evidence indicates that both diseases share several common features including insulin resistance, glucose dysmetabolism, mitochondrial alterations, oxidative stress, inflammation and amyloidogenesis.

I will discuss experimental pieces of evidence demonstrating the mechanistic links between T2D and AD. The similarities between both diseases suggest that a therapeutic agent effective against one disease can also be effective against the other. Under this perspective, experimental results demonstrating the efficacy of the antidiabetic drug liraglutide, a glucagon-like peptide 1 (GLP1) analogue, will be also discussed.

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MECHANISM OF ACTION OF THE SPECIFIC NUTRIENT COMBINATION FORTASYN® CONNECT WHICH IS DESIGNED TO ENHANCE SYNAPSE FORMATION AND FUNCTION IN ALZHEIMER’S DISEASE

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Synapse loss has been recognized to be the strongest structural correlate with memory impairment in Alzheimer's disease (AD) and is apparent already early in the disease process. Synapses and neurites consist of neuronal membranes largely composed of phospholipids. Synapse loss and synaptic dysfunction in AD are linked to neuronal membrane loss and altered membrane composition. The formation of new synapses requires the synthesis of new neuronal membranes. Dietary interventions that increase the availability of nutritional compounds, which support neuronal membrane formation and function, potentially counteract synaptic loss in AD.

In vitro and in vivo studies have demonstrated that supplementation with the phospholipid precursors DHA (docosahexaenoic acid) and/or EPA (eicosapentaenoic acid), UMP (uridine monophosphate), and choline not only increases the synthesis of membrane phospholipids, but also increases neurite outgrowth, levels of specific pre- or post-synaptic proteins, and the number of dendritic spines, all prerequisites for new synapse formation. Other nutrients, i.e. B-vitamins, vitamin C and E, selenium, and dietary phospholipids, were shown to act as cofactors by increasing the availability of membrane precursors or by directly affecting the neuronal membrane or membrane synthesis. Supplementation of combinations of these membrane precursors and cofactors was also shown to modulate membrane-related processes, such as neurotransmission, Aβ-related pathology, and ultimately cognitive performance.

Based on these insights, the specific nutrient combination Fortasyn® Connect (UMP, DHA, EPA, choline, phospholipids, folate, vitamins B6, B12, C and E, and selenium) was designed to enhance synapse formation and function in AD patients. Recent preclinical experiments with Fortasyn® Connect confirm the hypothesis that nutrients in Fortasyn® Connect act in concert to enhance synapse formation and functioning, and to ameliorate cognitive dysfunction. The medical food Souvenaid®, containing Fortasyn® Connect, is a nutritional intervention for the management of early AD. A clinical study program is investigating the efficacy of Souvenaid®. The clinical studies to date provide evidence that Souvenaid® has a beneficial effect on memory function in mild AD and support the hypothesis that enhancing synaptic function in the mild stage of AD may be related to improved memory performance.

Souvenaid® and Fortasyn® are registered trademarks of N.V. Nutricia.
A NUTRITIONAL APPROACH IN EARLY ALZHEIMER’S DISEASE

David G. Wilkinson  
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Alzheimer’s dementia, once synonymous, with Alzheimer’s Disease (AD) is increasingly seen as separate and not necessarily the inevitable corollary. Dementia is seen as a clinical syndrome driven by multiple factors, some genetic, environmental and lifestyle dependent. As such the accumulation of cerebral amyloid is less regarded as the single causal agent and more as a contributor to the inflammatory and oxidative stress that causes disruption of cell membranes and synapses, which are more closely linked to the onset of dementia symptoms. Consequently nutritional supplementation of the nutrients required for membrane replacement is seen as potentially beneficial in supporting neuronal function in early AD. Souvenaid\textsuperscript{®} containing the specific nutrient combination Fortasyn\textsuperscript{®} Connect, has been designed to that end. The nutrients in Fortasyn\textsuperscript{®} Connect are precursors and cofactors for the formation of neuronal membranes, and increasing their dietary intake can promote the synthesis of new brain synapses (Cansev et al., Alzheimers Dement, 2008; Kamphuis and Scheltens, J Alzheimers Dis, 2010). Souvenaid\textsuperscript{®} has been investigated in clinical trials and the results of a proof-of-concept study and two larger clinical trials in early and moderate AD will be presented.
II Diagnosis and prediction of Alzheimer’s disease: Update on biomarker studies

ROLE OF BIOMARKERS IN THE NIA-AA AND IWG CRITERIA FOR PRODROMAL AD

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In recent years, three sets of research criteria for diagnosis of Alzheimer’s disease (AD) in subjects with mild cognitive impairment (MCI) have been proposed: the International Working Group (IWG)-1, IWG-2, and National Institute of Aging-Alzheimer Association (NIA-AA) criteria. The criteria include biomarkers of AD pathology to increase the confidence that subjects with MCI have AD as underlying cause. However, they differ in the definition of MCI and biomarker abnormality.

In this presentation, I will compare the IWG-1, IWG-2, and NIA-AA criteria and show the prevalence and outcome of AD at the MCI stage according to these criteria. Furthermore, I will discuss the effect of neuronal injury marker and amnestic cognitive impairment on this prevalence and outcome. Also the prognosis of individuals with suspected non-Alzheimer pathophysiology (SNAP) and the overall utility of the three sets of criteria in clinical trials as well as in clinical settings will be discussed.
NOVEL BLOOD/CSF BIOMARKERS AS PREDICTORS OF AD

Kina Höglund

Institute of Neuroscience and Physiology, Department of Neurochemistry and Psychiatry, Sahlgrenska Academy, Gothenburg University and Department of Neurobiology, Care Sciences and Society, The centre for Alzheimer disease Research, Neurogeriatrics division, Karolinska Institutet

Changes in the cerebrospinal fluid (CSF) levels of total tau, phosphorylated tau and β-amyloid (Aβ) are biomarkers able to predict Alzheimer’s disease (AD) in patients with mild cognitive impairment (MCI) and they are now included as a research criteria for the diagnosis of AD. They reflect the underlying pathology of AD; neurodegeneration, tangles and plaques, respectively. However, these markers are fairly stable over time and there is a need for biomarkers reflecting disease progression. In addition, we need biomarkers to monitor concomitant pathology during disease development to further understand the temporal pattern of the underlying disease mechanisms. Neuropathological studies have shown that synaptic loss is evident already at the MCI stage of AD and synaptic degeneration is the neuropathological feature of AD with the strongest correlation to cognitive decline and may thus be a direct link to clinical symptoms. We also know that aggregation of Aβ may be an important player in disease progression based on its neurotoxic properties. Finally, inflammation is also suggested to be an early event in AD where reactive microglia and astrocytes may become involved in a vicious cycle producing Aβ.

Based on this knowledge, we are focusing on proteins important for neuronal integrity, such as structural proteins and synaptic proteins, on proteins involved in inflammation and on protein aggregates. Despite that many of these proteins are low abundant, we have been able to successfully identify and quantify proteins or fragments thereof in CSF and blood. Our data indicate that some proteins are degraded in brain in a disease-specific manner and that fragments or peptides are potential biomarkers as well as clues to underlying molecular events. In an effort to further understand the temporal pattern during disease progression, we also share initial data from the cross-sectional analyses of biomarkers of concomitant pathology in healthy elderly with plaque pathology who are being followed longitudinally.
HIGH-THROUGHPUT METABOLIC PROFILING – FROM FOCUSED STUDIES TO EPIDEMIOLOGY

Pasi Soininen

NMR Metabolomics Laboratory, School of Pharmacy, University of Eastern Finland, Kuopio, Finland and Computational Medicine, Institute of Health Sciences, University of Oulu, Oulu, Finland

Metabolic profiling (metabolomics) is increasingly used to provide insights into the molecular underpinnings of common diseases, such as diabetes and cardiovascular disease, and it holds also potential to improve current methods for risk assessment and prognostics. Yet metabolomics will be truly useful in epidemiology and genetics only if quantitative data on specific, identified metabolites are available

Towards these goals, we have set up an automated high-throughput platform for human serum NMR metabolomics that has been used to analyze over 250,000 samples during the past 6 years. At costs comparable to routine lipid analyses, our metabolomics platform offers robust quantification of >200 molecular measures, including 14 lipoprotein subclasses, various fatty acids, amino acids, glycolysis metabolites and ketones (www.computationalmedicine.fi/platform). The absolute metabolite concentrations can be analyzed with the standard medical statistics toolset, i.e., these data can be combined with other ‘omics and conventional clinical data. This eases interpretation of biological findings and clinical implications. The detailed metabolic profiling has provided insights to multiple biological pathways and metabolic functions in health and disease, and revealed biomarkers for cardiovascular disease, diabetes, and all-cause mortality. The metabolomics platform will be presented together with its applications in focused and epidemiological studies.

References:
PROTEOMICS IN PREDICTION OF AD

Ian Pike
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An early and accurate prediction of developing Alzheimer’s disease (AD) in individual patients has the potential to improve treatment outcomes by initiating treatment sooner and support better drug development through recruitment of trial cohorts enriched for rapid progressors. The rate of progression to AD within 12 months in patients with subjective memory complaints attending memory clinics is 10 – 15% (Alzheimer’s Society). Identifying these patients and prioritizing them for treatment or enrolment into clinical trials is thus challenging.

To deliver early biomarkers of AD and disease progression in readily available samples we, like others, applied a range of proteomic approaches to the analysis of blood plasma and cerebrospinal fluid. Over the last decade we have reported over 40 candidate biomarkers for early diagnosis and as surrogates of cognitive decline and hippocampal atrophy. Recently we have reported on the successful replication of our discovery results in a large cohort of over 1,100 individuals including patients with AD, MCI and appropriate controls. Based on changes in plasma concentration of 16 proteins we could classify AD severity and progression. Of greater significance was the finding that a panel of 10 proteins could predict conversion from AD to MCI within 12 months with an accuracy of 87%.

We have now turned our attention to novel proteomic workflows to find the earliest tissue-derived biomarkers in cerebrospinal fluid. With this enhanced mass spectrometry workflow we have been able to identify multiple candidate biomarkers of neuronal inflammation, synaptic dysfunction, altered metabolism and multiple other pathways reported to be affected in AD. These biomarkers have the potential to serve as very early diagnostic tests but require further validation in large cohorts.

During the presentation I will describe the various proteomics tools best suited to discovery and validation of AD biomarkers, show the results of our plasma and CSF studies and provide some future perspectives on how we can use the power of modern mass spectrometry methods to improve clinical management of AD.
Alzheimer’s disease (AD) is the most common neurodegenerative disorder in the world, which affects up to 50% of individuals above the age of 85. As the aging population continues to increase globally, treatment of AD and other age-associated neurodegenerative diseases is becoming increasingly important, not only from a human point of view, but also from an economic perspective.

In recent years, several attempts have been made to find novel susceptibility genes for AD. Particularly genome-wide association as well as whole genome and exome sequencing studies have identified several common and rare risk variants in different genes, which significantly associate with AD in different ethnic populations. Apart from APOE, approximately 22 common risk genes with low risk effect (~10-15%) have been confirmed based on the meta-analysis data from several independent genetic studies. Furthermore, different high-throughput sequencing efforts have identified rare variants with high risk effect (~200) in different genes, such as TREM2 and ABCA7. It is estimated that these already identified risk gene variations together with the established causative mutations account for more than 50% of the observed heritable aggregation of the disease. This indicates that additional susceptibility genes with low, intermediate and high effect size still exist, but their identification is getting more complex. Nevertheless, finding these novel risk genes and their subsequent functional characterization are extremely important tasks as these efforts may pave the way for the development of new biomarkers in the future. More specifically, it is likely that these new surrogate markers will be applied for risk, disease progression, and early diagnosis assessments.

Using particularly the polygenic risk score approach in combination with other biological endophenotype markers as well as clinical- and imaging-based outcome measures hold a great potential in the risk assessment and prediction of AD. It is also expected that the functional genetic approaches targeted to the risk genes will identify specific new molecular targets in AD pathogenesis underlying its clinical manifestations. This again may allow the development of new therapeutic strategies to slow down or even halt the progression of AD.
III New advances in imaging

GENETIC PROFILING AND BRAIN IMAGING

Andy Simmons
Kings College, London, UK
MOLECULAR IMAGING

Juha O. Rinne
Turku PET Centre and Division of Clinical Neurosciences, Turku University Hospital and University of Turku, Turku, Finland

Positron emission tomography (PET) is a functional imaging technique, which allows versatile investigation of various brain functions, such as blood flow, glucose metabolism, neurotransmitter function, neuroinflammation, and allows to visualize protein aggregations (such as β-amyloid and tau).

In Alzheimer’s disease (AD), PET can be used to help in the diagnostics and differential diagnostics of different dementing diseases, to investigate the pathophysiology, to follow-up possible changes during the progression, to identify individuals already at an asymptomatic stage and to help in the development of treatments and in monitoring the treatment effects.

Fluorodeoxyglucose (FDG) is an analogue of glucose, which is during the metabolism trapped into cells. FDG uptake reflects indirectly neuronal and synaptic functioning. In FDG-PET, patients with AD typically show symmetrical temporo-parietal hypometabolism. Similar kind of changes have been detected also in patients with mild cognitive impairment (MCI) and in healthy individuals carrying apolipoprotein E epsilon 4 (APOE4) allele, especially in those being homozygous for APOE4 and in healthy elderly individuals with familial history for AD. This hypometabolism in typically AD-affected areas in healthy elderly has been shown to predict future global cognitive decline. Frontotemporal degeneration shows predominantly frontal and anterior temporal hypometabolism, which aids in differential diagnosis from AD.

Dopamine transporter imaging either with PET or single photon emission tomography (SPET) is a sensitive method to visualize dopaminergic hypofunction for instance in PD. Also in dementia with Lewy bodies (DLB), there is a clear reduction in nigrostriatal dopaminergic function whereas in AD only mild or no changes have been found. Dopamine transporter imaging seems to be useful in the differential diagnostics between AD and DLB, which may sometimes be clinically challenging.

Nowadays it is possible to visualize in vivo typical protein aggregations in AD (β-amyloid and tau). Studies with several amyloid imaging ligands have shown that patients with AD show clear increase in tracer uptake in frontal, parietal, temporal cortices and in the posterior cingulate gyrus. In patients with MCI, positive amyloid imaging predicts further conversion to AD. Imaging tau aggregations in AD and various tauopathies might help in their diagnosis and differential diagnosis.

Studies regarding neuroinflammation have revealed controversial results. Increased astrocytosis has been found at MCI stage but not in AD, suggesting that astrocytosis is an early event in the pathophysiology of AD.

Longitudinal multi-tracer imaging could reveal the temporal relationship between the various pathological processes in AD.
REVISITING THE CHOLINERGIC HYPOTHESIS – NEW EVIDENCE WITH NEUROIMAGING

Harald Hampel
AXA Research Fund & UPMC Chair, Sorbonne Universités, Université Pierre et Marie Curie, Institut de la Mémoire et de la Maladie d’Alzheimer & INSERM U1127 and Institut du Cerveau et de la Moelle épinière (ICM), Département de Neurologie, Hôpital de la Pitié-Salpêtrière, 75013 Paris, France

Background: Post-mortem histopathological studies of human brain have provided evidence for basal forebrain cholinergic system (BFCS) changes in AD dementia. In vivo neuroimaging biomarkers of BFCS alterations would substantially facilitate the investigation of the cholinergic deficit during prodromal and preclinical stages of AD. The recent development of stereotactic cytoarchitectonic maps enables the indirect localization of the cholinergic BF in multimodal imaging approaches.

Methods: Using the BFCS cytoarchitectonic maps for automated morphometric analysis in high-resolution structural MRI scans, we assessed volumetric changes in this system in a large number (n > 800) of subjects, including AD patients, subjects with Mild Cognitive Impairment (MCI), as well as cognitively normal controls. Volumetric measures of the BFCS were evaluated for their diagnostic utility from preclinical to prodromal to clinically manifest dementia stages of AD and psychometric tests were implemented to assess cognitive correlates of BFCS degeneration. Using AV45- and FDG-PET scans from the ADNI2 database, we assessed associations between BFCS degeneration and cortical changes in amyloid deposition and hypometabolism, respectively, in the prodromal phase of AD.

Results: Our findings suggest that BFCS volume is particularly vulnerable to degeneration during advanced aging and the presence of prodromal AD provides an additional effect on BFCS volume loss. At clinically manifested dementia stages of AD, the diagnostic accuracy of BFCS volume is comparable to that of hippocampus volume, whereas in subjects with MCI hippocampus atrophy is more pronounced than BFCS atrophy. However, in the predementia phase of AD, BFCS volume is more closely associated with AV45-PET measured amyloid deposition, suggesting a higher specificity for AD pathology in premented subjects. BFCS atrophy correlates with performance decline in tests of both memory and attention/executive function in MCI. Regression analyses in FDG-PET scans indicate that the differential effect of BFCS atrophy on cognitive function is mediated by its association with hypometabolism in distinct cortical networks underlying these specific cognitive functions.

Conclusion: Through the wide availability of structural MRI scans, in vivo BFCS volumetry is well suited to complement laborious postmortem evaluations, especially facilitating the assessment of BFCS changes during predementia AD stages. Given the indirect nature of the measurement, histopathologic correlates of BFCS volume reductions remain to be elucidated in more detail.

Selected references:
Microbleeds are small dot-like lesions appearing as hyposignal on gradient echo T2* MR sequences. Microbleeds can have a deep and a lobar location. Deep microbleeds are presumed to be related to hypertensive vasculopathy, while lobar microbleeds supposedly are a radiological expression of cerebral amyloid angiopathy (CAA). Microbleeds are more prevalent in Alzheimer’s disease (AD) than in controls, and prevalence depends on field strength and other scan properties. In AD, microbleeds are of special interest as they may have a crucial role in the pathophysiology. They may be a missing link between two important theories on the neuropathogenesis of Alzheimer’s disease: the amyloid cascade hypothesis and the vascular hypothesis. Whilst presence of microbleeds has been associated with worse cognitive functioning in cognitively normal elderly, these associations are not as clear in patients with dementia. In AD, there are hardly any associations between presence or number of microbleeds and severity of cognitive impairment. However, microbleeds have repeatedly been shown to affect mortality, in a dose dependent manner.

We have shown that in AD, compared to no microbleeds, microbleeds in lobar locations were associated with an increased risk of stroke-related mortality (HR 33.9; 95%CI 2.5-461.7), whereas non-lobar microbleeds were associated with an increased risk of cardiovascular mortality (HR 12.0; 95%CI 3.2-44.7). In addition, lobar microbleeds were associated with an increased risk of incident stroke (HR 3.8; 95%CI 1.5-10.1) and non-lobar microbleeds with an increased risk of cardiovascular events (HR 6.2; 95%CI 1.5-25.0). Even higher risks for incident stroke and cardiovascular events were found in patients using antithrombotic medication. All 5 patients who suffered from an ICH had lobar microbleeds at baseline; 4 of them used antithrombotics. The clinical impact of microbleeds is especially relevant in the context of anti-amyloid therapies, where microbleeds and other amyloid related imaging abnormalities (ARIA) are frequent side effects.
IV Technology supported diagnosis and care

DECISION MAKING TOOLS IN MEMORY DISEASES, PredictND

Jyrki M.P. Lötjönen
VTT Technical Research Centre of Finland, Tampere, Finland

Rationale: Data from different sources are needed for making clinical decisions regarding memory disorders. The data include clinical and neuropsychological tests, imaging data, laboratory tests and demographic data. There is a need for tools helping to better exploit all information in the data and to form a comprehensive view of the patients status. Such tools may help in diagnostics and follow-up of disease progression.

Methods: The EU FP7 project PredictND develops a tool for helping clinicians both in differential diagnostics of memory diseases and in predicting progression to dementia. The work is based on the previous PredictAD-project and the ongoing VPH-DARE@IT-project. The core of the tool is the decision support module using disease-state index (DSI) and its graphical counterpart disease-state fingerprint (DSF) technologies. DSI measures the similarity of the patients data to data from previously diagnosed cases available in databases. As DSI alone would be a black box to users, DSF provides reasons behind by visualising how biomarkers from different sources contribute to the index. The PredictND tool has also multiple tools for quantifying MRI images. PredictND focuses on integrating the tool into clinical workflows and validating the use of the tool in a prospective clinical study. The prospective study with 800 memory clinic patients and 18-month follow-up is realised in four European hospitals (from Kuopio, Copenhagen, Amsterdam and Perugia). The study compares the diagnostic accuracy and the confidence about decisions with and without using the tool. In addition, the PredictND project develops a web-based portal for risk assessment. The idea is that web-based cognitive tests and games combined with other easily available measures, such as blood-based biomarkers, could provide a low-cost battery of tests for quantifying the risk and disease progression of memory diseases in the future.

Results: The PredictND prospective trial has started recently. However, results with retrospective data have already produced promising results. In differential diagnostics, we have obtained balanced classification accuracies up to 80 % with five classes: Alzheimer’s disease, frontotemporal dementia, Lewy body dementia, vascular dementia and subjective memory complaint.

Conclusions: Huge amounts of data are acquired in hospitals today but a lot of its potential remains still unexploited. Technologies for data-driven medicine help in revealing this hidden information. Tools that present all these data in an easily digestible form to clinicians may lead to major changes in clinical decision making in the future.

Acknowledgements:
EU FP7: VPH-DARE@IT (GA 601055) and PredictND (GA 611005) projects.
HARNESSING BIG BIOMEDICAL DATA FOR BETTER CLINICAL CARE, OUR EFFORTS

Richard J.B. Dobson
Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; and NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation, London, UK

In the modern digital era, we are generating huge amounts of biomedical data, with data sources including the electronic health record (EHR) itself, modern genomics and wearable devices. The challenge now is to integrate findings back into the electronic health record (EHR) to aid clinical decision making.

I will talk about some of our progress in this area that includes phenotyping of patients based on natural language processing of free text in the mental health EHRs (250k patients, 18 million documents), our work in generating genomic pipelines for processing of patient data that are efficient, portable, versioned and re-producible, and feasibility studies and infrastructure developed to enable remote monitoring of patients. Finally, I will describe the use of autonomous software multi-agents, which sit on live EHRs enabling trials in routine clinical practice and provide clinical decision assistance, through detection of adverse drug reactions for example. I will talk about some of the challenges we have faced when working with hospital IT and will provide details and links to our open source software.
Saturday, June 13

Main symposium

V Novel approaches towards prevention

CHANGING RISK FACTORS IN CHANGING SOCIETIES – EFFECT ON DEMENTIA OCCURRENCE?

Ingmar Skoog  
Centre for Ageing and Health AgeCap, Neuropsychiatric Epidemiology Unit, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Sweden

The population above age 80 will increase from 106 million in 2010 to almost 400 million in 2050. It is estimated that mean survival age in Europe will be 100 years in 2100. In Gothenburg, Sweden, we have conducted longitudinal population studies in the elderly since 1971. Thus, we are able to compare cohorts of elderly born from 1901-02 to 1930.

We found that the total prevalence of cardiovascular disorders declined among 75-year-olds between 1976 and 2005. However, there was a gender difference. While cardiovascular disorders were more common among women than among men in the 1970s, it was more common among men in 2000s. There were also different trends among cardiovascular disorders; the prevalence of obesity, diabetes and stroke increased, while hypertension and hypercholesterolemia decreased. This might be important, as vascular risk factors are related to dementia.

Other factors related to dementia were also affected. The prevalence of higher education, high social activity, high physical activity and risk-drinking increased, and the prevalence of ADL dependence decreased, in later-born cohorts. Lung function, cognitive function and gait speed become better.

Preliminary data suggests that the prevalence of dementia has decreased by almost one third in 85-year-olds 2008-2010 compared to 1986-87, despite an increase in the prevalence of stroke. This is probably due to the fact that elderly today are less vulnerable to different insults. Thus, elderly today differ to a large extent from elderly 30 years ago. This may have large implications for the occurrence of dementia.
TO WHAT EXTENT AD CAN BE PREVENTED?

Carol Brayne  
Cambridge Institute of Public Health, University of Cambridge, UK

This presentation will consider how the basic epidemiological approach to disease can inform what we understand by the terms "dementia" and "Alzheimer's Disease", what prevention is and why we are focused on this area of health and deviation from health at this point in our global history. Approaches and likely outcomes of different approaches will be explored and consideration of the contribution of contemporary evidence to debates about preventability. The challenges of providing an evidence base in this area and our attempts to develop this area will be expanded.
NUTRITION AND BRAIN HEALTH

Jussi Pihlajamäki
Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland, and Clinical Nutrition and Obesity Center, Kuopio University Hospital, Kuopio, Finland

Mounting evidence points to the important role of nutrition in the prevention of cognitive disorders. Furthermore, nutrition is a key component in maintaining health in individuals with Alzheimer disease (AD) who commonly present with reduced food consumption, food neglect, and changes in food preferences. In turn, the resulting compromised protein-energy status can contribute to decline in cognitive functions in patients with AD.

Prevention of the diseases in individuals at risk is the preferable approach in all common diseases, including e.g. diabetes, cardiovascular diseases and cancer. Overall, healthy diet during the whole life span, and even during the fetal period, have been associated with reduced risk. Importantly, the diet associating with brain health during aging is not different from the diet known to protect from other common diseases.

Based on the epidemiologic and longitudinal studies, the dietary components associating with brain health include vegetables, fruit and berries, vegetable fat, fish, low-fat dairy products, poultry, pulses, nuts, whole grain products and coffee. Importantly, the evidence from RCTs support the argument that healthy diet could promote brain health. Similarly than observed with other common complex diseases, it has been suggested that individuals at a very early stage of disease may benefit the most.

In experimental studies the maintenance of healthy neurons has been suggested to rely on adequate supply of individual nutrients that can be acquired from the diet. Following these reports some clinical studies have suggested that increased intake of these dietary compounds, or their combination, may slower cognitive decline in individuals at risk. Because no single dietary supplement has demonstrated beneficial effects with other common diseases, while changes in the whole diet has clearly been shown to decrease disease risk of common diseases, the interpretation of these results regarding individual nutrients should still be cautious.

In summary, the evidence for the role of nutrition in maintaining brain health is convincing. The important concept is likely to be healthy lifestyle as a whole, including healthy diet and exercise together. The avoidance of micro- and macronutrient malnutrition should always be the basis for all interventions. It remains to be proven whether substitution of individual nutrients in excess shows additional benefits. Since only the food that is consumed is the one that matters, multidisciplinary intervention approaches to support adequate food intake are an essential part of the solution.
VITAMINS IN ALZHEIMER’S DISEASE

Francesca Mangialasche (1,2), Babak Hooshmand (1), Patrizia Mecocci (2), Miia Kivipelto (1)
(1) Aging Research Center, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Stockholm, Sweden and (2) Section of Gerontology and Geriatrics, University of Perugia, Perugia, Italy

Nutrition can be central in the prevention or slowing of late-life cognitive impairment and Alzheimer’s disease (AD). Among essential nutrients, vitamins (e.g., vitamin E, B complex) have biological properties that are relevant for neuroprotection, and have been investigated in relation to age-related cognitive impairment, dementia and Alzheimer’s disease (AD). In general, several observational studies suggest a protective association between dietary intake or blood levels of these vitamins and late life dementia/AD. However, results from clinical trials (RCTs) are mostly negative, or at best, controversial.

Such inconsistency can be explained by different factors, including type and dosage of vitamin supplements used in the RCTs, as well as selection of the target population and the choice of the outcome measures. For instance, vitamin E includes four tocopherols and four tocotrienols, named α, β, γ, and δ. Most investigation of vitamin E in relation to AD has focused primarily only on α-tocopherol, with conflicting findings. However, increasing knowledge regarding the biological properties of vitamin E provides a strong rationale that other forms of vitamin E, beyond just α-tocopherol, may be important for AD prevention. Supplementation studies only tested α-tocopherol, often at very high dosage, which has been associated with increased risk of negative health outcomes.

B-complex vitamins (e.g., B12, folate) modulate plasma levels of homocysteine, which has been associated with cognition, structural brain changes and AD. Holotranscobalamin, the active form of vitamin B12, appears to be a more sensitive assay of B12 status. Recent findings from observational studies as well as RCTs on the impact of homocysteine/B-vitamins on the rate of brain tissue volume loss have been promising.

Overall, encouraging findings warrant further investigation of the role of vitamins in AD, to better define preventive strategies based on dietary recommendations. Adequately timed and powered randomized controlled trials are needed to determine the impact of vitamin supplementation on preventing cognitive decline and dementia-related pathology. Furthermore, since dietary supplements are often used by adults in the Western world, it is important to detect the potential benefits and/or harms associated to their use, not only in relation to late-life cognitive impairment and AD, but also on other relevant clinical outcomes.
VI Population-based prevention studies

A MULTIDOMAIN TWO-YEAR RANDOMIZED CONTROLLED TRIAL TO PREVENT COGNITIVE IMPAIRMENT - THE FINGER STUDY

Miia Kivipelto
Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland Karolinska Institutet Center for Alzheimer Research, Stockholm, Sweden Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland, and Aging Research Center, Karolinska Institutet-Stockholm University, Stockholm, Sweden

Rationale: The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a proof-of-concept randomised controlled trial for a multidomain approach to prevent cognitive decline in at-risk elderly from the general population.

Methods: FINGER included 1260 participants, aged 60-77 years, recruited from previous national surveys. Inclusion criteria were CAIDE Dementia Risk Score > 6 points, and cognition at mean level or slightly lower than expected for age. Participants were randomised to a 2-year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Primary outcome was change in cognition (neuropsychological test battery, NTB z-score). Analysis was by modified intention-to-treat (participants with at least one post-baseline observation). This trial is registered as NCT01041989.

Results: 2654 individuals were screened, and 1260 were randomised to the intervention (n=631) or control (n=629) group. 591 participants (intervention) and 599 (control) had at least one post-baseline assessment. Mean change (standard error) in NTB total z-score at 2 years was 0.20 (0.01) in intervention and 0.16 (0.01) in control group. Between-groups difference in change of NTB total score per year was 0.022 (95% CI 0-002-0-042), p=0.030. A significant effect was also observed for other cognitive outcomes (executive functioning, processing speed, abbreviated memory score), and risk of cognitive decline and other secondary outcomes (BMI, dietary habits, physical activity, quality of life). Dropout rate was 12.1%, and adverse events rare.

Conclusions: FINGER is the first large, long-term RCT showing that a multidomain intervention may improve/maintain cognitive functioning in at-risk elderly from the general population.

Acknowledgements:
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RISK PREDICTION MODELS IN DEMENTIA PREVENTION

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Rationale: In dementia research, the focus has shifted towards pre-symptomatic/pre-dementia disease stages and at-risk states when it may not be too late to intervene. The need for early identification of at-risk individuals who may benefit from preventive interventions has led to a growing interest in dementia risk prediction.

Methods: Published dementia risk scores were identified according to the following criteria: longitudinal studies with dementia as outcome, risk models including multiple health-related variables, and reporting AUC or C statistic.

Results: Risk scores emphasize several key issues: performance requirements should consider the purpose of a prediction model; performance comparisons can be difficult due to variability in reporting of prediction model studies; several predictive factors are common in risk scores for MCI, dementia, and vascular events; and there should be more focus on validating existing risk prediction models in multiple populations, not just on developing new models. External model validation and practical utilization are often missing. One exception is the CAIDE Dementia Risk Score used for selecting participants in the FINGER trial. Research is ongoing on computer-based methods for risk estimation, e.g. Disease State Index predicted dementia well in older participants in the CAIDE study.

Conclusions: Research on prognostic models for dementia prevention is still in its initial stages. A set of models will be needed for different purposes and contexts (e.g. midlife or late-life profiles, long-term or short-term prediction, public health, primary care, or specialized memory clinics). The potential utility of both pen-and-paper and computer-based risk profiling should be investigated.

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Background: Vascular and life-style related risk factors are associated with an increased risk of dementia. Whether treatment of risk factors reduces the risk of cognitive decline and dementia is not known. Multi-domain interventions to prevent cognitive decline and dementia are currently investigated in several RCTs, collaborating in the European Dementia Prevention Initiative (EDPI). Internet is increasingly considered as a powerful and scalable method of delivery of health care, including the treatment of vascular risk factors.

Methods: preDIVA is a cluster-randomised controlled trial among 3533 non-demented elderly (70-78 years), in which the effect of nurse-led vascular care is compared to care as usual. Intervention and follow-up are 6 years. Primary outcome is incident dementia. The HATICE-project consists of three phases. 1) explore, pool and analyse data from the recently completed preDIVA, MAPT and FINGER trials to define the optimal multi-domain intervention in different populations, 2) develop an interactive internet-intervention to improve cardiovascular risk management to prevent incident cardiovascular disease, cognitive decline and dementia, 3) Test the efficacy of this internet-intervention in an 18-months RCT among 4250 elderly in 3 countries at increased risk of cardiovascular disease and dementia. Primary outcome is cardiovascular risk profile. Main secondary outcomes are individual risk factors, dementia risk score, incident cardiovascular disease and cognitive function.

Results: All follow-up visits in preDIVA have been completed. Data analysis is ongoing. At baseline 87% of participants had risk factors amenable to treatment. Preliminary data show a complete follow-up for the primary outcome in over 97% of participants. Cumulative incidence of dementia is slightly lower than anticipated. The resulting loss of power is partly compensated for by extension of the RCT up to 8 years. In HATICE, aggregation of European guidelines for vascular risk management has resulted in a generic, widely implementable treatment-protocol. A pilot study among 40 persons showed good usability of the internet-platform. Recruitment is ongoing in three countries and expected to be completed in early 2016.

Discussion: The pragmatic primary outcome of preDIVA will allow for a firm conclusion if a treatment-effect is shown. Wide-scale implementation of dementia prevention strategies might be facilitated by the use of innovative approaches such as internet-based interventions. International collaboration increases the external validity of trial results and accelerates future implementation.
LESSONS LEARNED FROM PREVENTION TRIALS: THE MAPT STUDY

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NOVEL THERAPEUTIC STRATEGIES FOR AD – SUPPRESSION OF NEURONAL HYPERACTIVITY

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Alzheimer patients have been reported to carry an increased risk of epileptic seizures. We have conducted the hitherto only systematic study on the occurrence of epileptic seizures in common APP/PS1 AD model mice, and found that more than half of APP/PS1 mice displayed at least one seizure during a continuous 3-week video-EEG monitoring. Later on, seizures have been documented in practically all APP transgenic mouse lines to some extent. However, even more common is neuronal hyperactivity/hyperexcitability in the AD model mice. We have evidence that this can directly be induced by amyloid-β, although other APP cleavage products or enzymes may also contribute.

Interestingly, recent data suggest that neuronal hyperactivity in turn is a key factor in amyloid-β production. It may explain the peculiar accumulation of amyloid deposits first in the brain sites participating in the default mode network. Regional hyperactivity in the context of a cognitive task is a common finding in fMRI studies in MCI patients. This has usually been interpreted as compensatory recruitment of brain reserves to match the task requirements. However, there are also observations that neuronal hyperactivity may actually impair memory and account for fluctuations in cognitive functions in AD patients. In preclinical studies, the antiepileptic drug levetiracetam has proven to decrease epileptic spiking and improve spatial memory in APP transgenic mice at doses below the conventional anticonvulsive doses. In MCI patients, low-dose levetiracetam also decreased local hippocampal hyperactivity and improved performance in a demanding recognition memory task in a recent Phase 2 study. Drugs aimed at brain hyperactivity without sedative side effects may prove to be a new successful approach to AD treatment.
Clinical trials become more and more complicated both due to regulatory and company rules. Further, the use of CRO companies is frequently used. The CRO companies are competing for the contract and therefore trying to move as much job as possible to the investigator. The use of electronic CRF with mandatory training is implemented. Further, special companies for neuropsychological testing are engaged demanding extensive training of the investigator. When calculating the cost for the studies, these matters must be taken in consideration. These and other specific issues in clinical trials will be discussed.
HEALTH ECONOMIC ASPECTS IN INTERVENTION STUDIES

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Dementia disorders have a long duration, several years-decades if the early states are included. For cost effectiveness discussions, it is therefore not possible to conduct single studies that cover the whole duration. Several approaches can be used, such as open label follow up studies, registries, epidemiological data and economic modelling. When within trial data are in focus for economic evaluations, the issue of statistical power is important. Trials are powered for efficacy and not for analysis of resource use and cost effectiveness, for which such studies most often are under-powered. Data on resource use and costs are also more or less always very skewed where zero values are common, making conventional statistical methods problematic to use. The methods to obtain data on resource use also vary and it is important to use validated and standardized instruments.

In dementia, the contribution of informal care is substantial and it is important that methods for quantification and costing of informal care are transparent. Dementia shortens life and if disease modifying treatment is launched, the effects on survival by an intervention are crucial to analyze. Discussions of cost-effectiveness imply that not only costs are in focus. The selection of outcomes is crucial, particularly in discussions of cost effectiveness of interventions between different diseases. All these aspects will be discussed from a methodological viewpoint.
The number of people living with Alzheimer’s disease (AD) is growing and the effect of pharmacological treatment is limited. There is an urgent need for alternative treatments, including non-pharmacological approaches. Several longitudinal cohort studies show that physical activity in middle age protects against cognitive decline and dementia in old age and preserves the ability to perform activities of daily living (ADL) among older healthy subjects. Moreover, in healthy subjects higher levels of physical activity are associated with better cognitive performance.

Experimental studies in animal models of AD show an effect of physical exercise not only on central AD pathology, but also on neuroinflammation, brain plasticity and oxidative stress. It is therefore reasonable to suggest an effect of physical exercise on subjects with AD dementia, thus changing the focus from prevention to disease-modifying therapy.

Most studies of physical exercise in patients with mild cognitive impairment (MCI) demonstrate some positive effects on cognition, but due to methodological issues, interpreting findings in studies of dementia and AD can be difficult. Problems with small samples sizes, unsupervised exercise, and a lack of sufficient measures of exercise intensity indicate the need for more research in this area. Several new studies on physical exercise in AD are underway, including a large Danish multicenter study in mild AD, and results from this study will also be presented.
A SPECIFIC NUTRITION COMBINATION IN PRODROMAL ALZHEIMER’S DISEASE: THE LipiDiDiet STUDY

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Objectives: The specific nutrition combination Fortasyn® Connect is designed to support synapse formation and function in patients with Alzheimer’s disease (AD) by delivering specific nutritional precursors and cofactors for the formation of neuronal membranes. Two randomized controlled trials (RCTs) have shown that the nutrition combination improves memory performance in drug-naive mild AD patients (MMSE 20-26 and MMSE ≥20), indicating that it may have promising effects in (very) early AD as well. The LipiDiDiet study 1 is one of the first RCTs in prodromal AD, investigating the effects of the nutrition combination on cognitive functioning.

Methods: The LipiDiDiet study is a 24-month, double-blind, parallel-group, multi-centre, multi-country RCT in subjects with prodromal AD (criteria Dubois 2007), receiving the nutritional intervention or an isocaloric control product once daily. Primary outcome measure is cognitive functioning as assessed by a neuropsychological test battery.

Results: In total, 312 subjects have been randomized. By the end of 2014, 272 have completed the study. Four optional 12-month double-blind extension studies are ongoing. Baseline characteristics of the study population conform to the criteria for prodromal AD, with evidence for underlying AD pathology.

Conclusions: Further details on the progress of the study will be presented at the conference.

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Abstracts for poster presentations

Poster board numbers are the same as abstract numbers
CHARACTERIZATION OF ALZHEIMER’S DISEASE RISK GENE UBIQUILIN-1 IN HUMAN BRAIN AND IN IN VITRO AND IN VIVO MODELS

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Rationale: Ubiquilin-1 is genetically and functionally associated with Alzheimer’s disease (AD). It regulates the levels and trafficking of several AD-associated proteins and modulates stress conditions involved in neurodegeneration.

Methods: Here, we studied ubiquilin-1 function and interactions in human post-mortem brain tissue, in vitro in neuron-microglial cell co-cultures during neuroinflammation, and in vivo in the brain of adult AD model mice (APPswe/PS1dE9).

Results: We found that ubiquilin-1 expression decreased in human brain in relation to AD pathology. In addition, there was a correlation between the levels of ubiquilin-1 and BACE1, a key enzyme in AD pathogenesis, in the brain samples. Accordingly, BACE1 levels were increased in neuron-microglia co-cultures and hippocampi of mice overexpressing ubiquilin-1. Furthermore, neuronal viability was decreased in ubiquilin-1-overexpressing co-cultures. Mechanistic studies in neuronal cells suggested that ubiquilin-1 regulates the stability and subcellular localization of BACE1.

Conclusions: This study reveals a novel interaction between ubiquilin-1 and BACE1, which may affect the molecular pathogenesis, disease progression, and neurodegeneration in AD.

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SEPT5 AND ITS POTENTIAL ROLE IN THE MOLECULAR PATHOGENESIS OF ALZHEIMER’S DISEASE

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Rationale: Septins are a highly conserved family of guanosine triphosphate-binding proteins, which provide several candidates possibly involved in the underlying mechanisms of synaptic dysfunction in neurodegenerative diseases including Alzheimer’s disease (AD). Particularly SEPT5 has been shown to interact with syntaxin-1 of the SNARE complex and regulate synaptic vesicle (SV) localization at the presynaptic terminal. Furthermore, SEPT5 interacts with SEPT2/4/8, which all have been suggested to impact SV recycling. A central pathological feature in AD is amyloid-β (Aβ)-mediated synaptotoxicity. Thus, SEPT5 is an interesting target for further studies in the molecular pathogenesis of AD.

Methods: Here, we have investigated the possible alterations in SEPT5 mRNA expression and splicing in relation to the AD-related neurofibrillary pathology in the temporal cortex of human brain. Furthermore, we investigated whether the siRNA-mediated down-regulation of SEPT5 in human SH-SY5Y neuroblastoma cells impacts amyloid precursor protein (APP) processing and Aβ production.

Results: Our data suggest that the expression of SEPT5 is moderately decreased in relation to AD-related neurofibrillary pathology in the brain and that the down-regulation of SEPT5 reduces β-secretase (BACE1), soluble APP-β and Aβ levels in vitro.

Conclusions: Considering the known mechanistic functions and interactions of SEPT5, our results suggest that SEPT5 plays a role in the regulation of post-translational levels and activity of BACE1. Further characterizations of the potential role of SEPT5 in the early molecular pathogenesis of AD are currently undergoing.

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AMYLOID-β AND REGULATION OF THE TRIPARTITE SYNAPSE ACTIVITY

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Rationale: There is increased interest in the ways how the amyloid-β induced changes in astrocytes’ calcium waves and their ability to deliver nutrients to the brain (for example via glucose uptake from vasculature and delivery to neurons) contribute to AD pathology. The amyloid-β toxicity induced activation of astrocytes may eventually lead to neuronal dysfunction (initial hyperactivity followed by hypoactivity and death). Neuronal hyperactivity in its turn leads to excessive amyloid-β generation and concurrent astrocyte stimulation leading to increased glycogenolysis. Imbalance in glucose metabolism is likely to lead to impaired astrocyte-neuron interactions, which manifest as abnormal calcium signaling and defective transmitter release and reuptake in the tripartite synapse.

Methods: Fura-2AM calcium imaging studies show how simultaneous presence of amyloid-β and neurotransmitters glutamate and /or serotonin, causes changes in astrocytes’ calcium signaling.

Results: Neurotransmitters bind to their respective metabotropic receptors in both astrocytes and postsynaptic neurons, often followed by intracellular calcium transients. Amyloid-β alone causes increased calcium transients in astrocytes and these transients are further enhanced by serotonin and decreased by glutamate. In the presence of amyloid-β, astrocytes are converted to a reactive type, not able to function as a nutrient shunt for neurons or regulate the neuronal synaptic activity.

Conclusions: Astrocyte dysfunction contributes to AD pathology via effects on nutrient delivery and calcium waves in the brain. Impaired regulation of the neuronal microenvironment by astrocytes seriously affects the efficacy of synapses in the neural networks, causing cognitive decline seen in AD.
TBI INCREASES NOS1 EXPRESSION, Aβ CLEARANCE AND EPILEPTOGENESIS IN APP/PS1 MOUSE MODEL OF ALZHEIMER’S DISEASE

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Rationale: We hypothesized that genetic background, which causes the development of β-amyloid (Aβ) pathology, aggravates post-traumatic epileptogenesis, enhances somatomotor and cognitive impairment, and associates with long-term changes in the expression of genes involved in pathways affecting APP processing and Tau.

Methods: Mild (mTBI) or severe TBI (sTBI) was triggered using controlled cortical impact in APP/PS1 mice and wild-type (Wt) littermates. Gene expression profiling of the perilesional cortex, ipsilateral thalamus, and ipsilateral hippocampus was performed 16 wk post-TBI.

Results: Morris water-maze revealed a genotype effect on spatial learning and memory as APP/PS1-sTBI mice performed more poorly than Wt-sTBI mice (p < 0.05). Epileptogenesis was affected by genotype and TBI as 88% of APP/PS1-sTBI mice had epilepsy compared to 11% in Wt-sTBI (genotype effect p < 0.01) or 50% in APP/PS1-sham groups (TBI effect p <0.05). The higher the seizure frequency, the higher the cortical expression of Nos1 (r = 0.83, p < 0.001) and Mapk3 (r = 0.67, p < 0.001). Immunohistochemical analysis confirmed increased amount of NOS1 protein in neuronal somata and processes in the perilesional cortex in APP/PS1-sTBI mice as compared to APP/PS1-sham (p < 0.05) or Wt-sTBI mice (p < 0.01). Motor impairment at 2 days post-TBI correlated with increased cortical expression of genes encoding proteins related to Aβ clearance, including Clu (r = 0.83), Abca1 (r = 0.78), A2m (r = 0.76), Apoe (r = 0.70), and Ctsd (r =0.63). Immunohistochemical analysis revealed focal reduction in Aβ load lateral to lesion core in APP/PS1-sTBI mice as compared to APP/PS1-sham mice (p < 0.05).

Conclusions: The present study provides the first comprehensive evidence of exacerbated epileptogenesis and its molecular mechanisms in an AD-related genetic background after TBI.
THE TREATMENT OF EPILEPSY IN A MOUSE MODEL OF ALZHEIMER’S DISEASE

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Rationale: Patients with Alzheimer’s disease (AD) have an increased risk of unprovoked seizures. Seizures in AD are associated with a faster cognitive decline and a more severe neuronal loss. We investigated different treatments against AD-related epilepsy, including valproic acid (VPA) and supplementation with oxidative energy substrates (OES) in a mouse model of AD.

Methods: In experiment 1, 15-wk-old male APP/PS1 mice (n = 12) were injected (i.p.) with 30 mg/kg VPA (low dose) for one week. After a 3-wk wash-out, the same animals were treated with 300 mg/kg VPA (higher dose) for 1 wk. The control group was injected with saline. In experiment 2, 12- to 13-week-old APP/PS1 mice (n = 9) were fed with pyruvate and β-hydroxybutyrate enriched chow for 5 weeks, while the control group (n = 8) received regular chow. The antiepileptic action of treatments was evaluated using long-term (24/7) video-EEG monitoring. As outcome measures we assessed the occurrence of spontaneous seizures and epileptiform discharges (EDs).

Results: Occurrence of spontaneous seizures was reduced during the low-dose treatment with VPA (p < 0.05), but no longer after treatment discontinuation. The high-dose VPA, but not the low-dose, suppressed EDs during the treatment (p < 0.05), and for one week after treatment discontinuation (p < 0.05). OES diet reduced EDs during the dietary intervention and for 2 wk thereafter (p < 0.05).

Conclusion: Both VPA and OES diet reduced spontaneous epileptiform discharges in a mouse model of AD. OES diet was more efficient than low-dose VPA, while the efficacy of high-dose VPA was comparable to that of OES diet.
LONGITUDINAL CHARACTERIZATION OF CVN MOUSE FOR ALZHEIMERS DISEASE USING BEHAVIORAL, IMAGING AND BIOMARKER END-POINTS

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The CVN mouse model for Alzheimer’s Disease with mutated APP including Swedish, Dutch and Iowa mutations, crossed with NOS2 knockout line, exhibits wide range of AD hallmarks including increased insoluble Aβ and plaque formation, inflammation, tau phosphorylation, hippocampal neuronal death and behavioral deficits (Wilcock et al 2008). This longitudinal validation data from Charles River CVN mouse in-house testing colony shows reproducible AD defects described previously, and positions CVN mouse as the most comprehensive AD model available.

Wild-type and CVN mice were studied at 3, 6, 9 and 12 months of age. Behavioral testing battery included Open field, Barnes maze, Radial arm water maze and Contextual fear conditioning. Fine motor deficits were studied using Motorater. Electrophysiological measurements of the animals were performed. At each age point, MRI and MRS evaluation was performed before tissue, CSF and plasma collection for biochemical analysis. Immunohistochemical stainings for Aβ1-40, p-tau, microglia and astrocytes were performed, and neuronal number was evaluated by Cresyl fast violet histological staining.

CVN mice exhibited hyperactivity in open field already at 3 months of age. Significant behavioral deficits were seen at the age of 6 months in Barnes maze and in Radial arm water maze. Robust biochemical changes, including increased number of dense amyloid plaques in hippocampus, thalamus and cortex, were evident. Significant inflammatory response detected by Iba-1 immunoreactive microglia and CD45-positive monocyte/macrophage cells was heavily condensed around the plaques in all brain regions studied. The number of viable neurons in hippocampus was significantly decreased at 9 months of age. MRS showed significant AD-related changes in brain metabolites at 9 months of age.

The CVN mouse provides a more complete tool to study novel therapies targeted for treatment of AD. Several desired AD-related end-points are present in this mouse line making it a valuable model for drug development.
TRANSCRIPTOMICS AND MECHANISTIC ELUCIDATION OF ALZHEIMER’S DISEASE RISK GENES IN THE BRAIN AND IN VITRO MODELS

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**Rationale:** Several risk genes for Alzheimer’s disease (AD) have been identified, but their effects on AD pathogenesis remain elusive. Assessing the expression of these genes in the affected brain areas may help to identify their possible functions. Protein-fragment complementation assay (PCA) can reveal their effects on disease pathways.

**Methods:** The expression of genes involved in the pathogenesis or affecting the risk of AD was assessed in the post-mortem brain samples from 60 subjects with varying degree of AD-related neurofibrillary pathology. PCA was performed in HEK293T cells.

**Results:** Neurofibrillary pathology associated with altered expression of risk genes FRMD4A, MS4A6A, CLU and TREM2. Using PCA, we found that down-regulation of FRMD4A associated with increased amyloid-β40 secretion and altered phosphorylation of tau.

**Conclusions:** Taken together, we show that the expression of FRMD4A, MS4A6A, CLU, and TREM2 is altered in relation to increasing AD-related neurofibrillary pathology, and FRMD4A may be associated with amyloid-β and tau-related pathways in AD. In conclusion, studying the gene expression in the brain and the disease-associated pathways in vitro may provide mechanistic insights on how these genes contribute to AD pathogenesis.

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ENVIRONMENTAL AND GENETIC ANALYSIS OF VASCULAR FACTORS IN DEMENTIA

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Rationale: Dementia, particularly Alzheimer Disease (AD) and Vascular Dementia (VD), is a multifactorial idiopathic pathology caused by clinical, environmental and genetic factors, hence its unknown etiology. Our objective is to evaluate the main risks and protective factors associated with this disease.

Methods: Blood samples were collected from 98 patients and 160 controls for biological tests and DNA genotyping of six vascular polymorphisms (APOE-C122R, APOE-R158C, MTHFR-C677T, ACE-I/D, PON1-L55M, PON1-Q192R) using PCR-RFLP. Additional data were collected through clinical tests and a rigorous survey on lifestyle and dietary habits.

Results: Among the studied risk factors, those that appeared to be significant are: smoking (OR = 4.49; p = 0.001), hyperhomocysteinemia (OR = 5.47; p = 0.001), whereas subjects having a high education level (OR = 0.08; p = 0.002), an urban habitat (OR = 0.3; p = 0.032) and a currently or formerly active professional life (OR = 0.207; p = 0.016) seemed to be at a lower risk to develop dementia. Fish (OR = 0.06; p = 0.012), olive (OR = 0.01; p = 0.015), spices, especially curcumin (OR = 0.10; p = 0.026) and chocolate, especially black (OR = 0.04; p = 0.015) also appeared to be protective factors. After adjustment to the non-genetic factors presented above, risks associated with APOE-ε4 (OR = 3.98; p = 0.001), MTHFR-T (OR = 4.259; p = 0.007), ACE-I (OR = 3.35; p = 0.005) and PON1-55M (OR = 3.24; p = 0.021) alleles remained significant. Remarkably, when combined, APOE-ε4, ACE-I and PON1-55M alleles, presented a higher risk (OR = 8.44; p = 0.008), while the APOE-ε2 allele seemed to have a protective effect (OR = 0.15; p = 0.01).

Conclusions: The fact that five of the six vascular polymorphisms were associated with both Vascular Dementia and Alzheimer's Disease, suggests that the vascular component of AD is as important as the neurodegenerative one. Taking in consideration the multifactorial nature of dementia, a Mediterranean diet and a healthy active lifestyle are recommended, especially for APOE-ε4, ACE-I and PON1-55M allele-carriers since they showed an additive effect.
MONOCLONAL ANTIBODY AGAINST OXIDIZED LDL RECOGNIZES TRANSFERRIN IN HUMAN CEREBROSPINAL FLUID

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Rationale: Levels of oxidized proteins are increased in Alzheimer’s disease (AD) patients reflecting the increased oxidation in AD pathology. Germline encoded natural antibodies against oxidative modifications on low density lipoproteins (OxLDL antibodies) have been implied as a modifying factor in atherosclerosis. These antibodies also recognize epitopes on apoptotic cells and several bacterial strains. We have previously characterized OxLDL antibodies in cerebrospinal fluid in humans and hypothesized that they recognize oxidatively modified proteins in CSF.

Methods: We screened binding of several mouse monoclonal oxLDL antibodies against human CSF with western blotting and measured the intensity of binding in AD patients and controls. Proteins detected by the antibodies were further characterized by mass spectrometry. We also screened the antibody binding to oxidatively modified proteins in vitro with chemiluminescent immunoassay.

Results: Western blot showed that several natural monoclonal OxLDL antibodies recognize 70-80 kDa proteins in CSF. Mass spectrometry analysis revealed both of these proteins as human transferrin. The binding of antibody clone HMN_08_34 was further characterized and the clone demonstrated binding to transferrin in AD patients (n = 5) and controls (n = 4). Transferrin was modified in vitro to obtain malondialdehyde-acetaldehyde adducts (MAA-transferring) and we demonstrated that HMN_08_34 specifically bound to MAA-transferring, but not to native transferrin.

Discussion: Here we showed that monoclonal oxLDL antibodies also bind to human CSF transferrin. Binding is suggested to be due to modification of transferrin with lipid peroxidation end products. Further studies are needed to clarify the usability of oxidized transferrin as a biomarker in AD.
CHARACTERIZATION OF DIFFERENT MOLECULAR TAU ISOFORMS IN CSF

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**Rationale:** Unlike the characterization of tau in brain, the nature of tau in cerebrospinal fluid (CSF) is still controversial. Some studies demonstrated N-terminally truncated fragments by immunoprecipitation and different ELISAs, while others have sequenced C-terminal CSF-tau fragments (A384-K395; M348-K369) or quantified phospho-tau-S396/S404 using a bienzyme-substrate-recycle ELISA. Since the core of the paired helical filaments consists of the microtubule-binding domains and C-terminal truncation leads to faster tau aggregation, quantifying C-terminal tau fragments could improve our understanding CSF-tau.

**Methods:** We combined various tau monoclonal antibodies (mAbs), mapping in the N-terminal part of tau with affinities in the subnanomolar range and one C-terminal antibody with an affinity in the nanomolar range in different assay formats and quantified the tau forms in CSF samples with a range of CSF-tau levels.

**Results:** N-terminal fragments were readily quantified in all tested CSF samples with concentrations in the 10 to 1000 pg/ml range. While the nanomolar affinity of the C-terminal antibody allowed for a lower level of quantification in the 10 pg/ml range, C-terminal tau could not be measured in any of the CSF samples, even not those with CSF-tau levels above 1000 pg/ml.

**Conclusions:** Based on current estimates, the fraction of C-terminal tau in CSF is below 10% of the N-terminal tau levels. While this study is based on unselected CSF samples, it is worthwhile exploring the C-terminal tau fragment assay in other conditions with high tau levels (stroke, Creutzfeld Jacob Disease and AD with high CSF-tau levels).
DESIGN OF A MONOCLONAL ANTIBODY-BASED ELISA FOR NEUROGRANIN, C-TERMINALLY TRUNCATED AT POSITION 75


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Rationale: Neurogranin (Ng), part of the cerebrospinal fluid (CSF) proteome, circulates at higher levels in Alzheimer’s disease (AD). However, immuno-assays built to assess the value of neurogranin as AD biomarker involve at least one polyclonal antibody. Noteworthy, immuno-assisted mass spectrometry of CSF recently identified C-terminal fragments of neurogranin, truncated at proline 75 (P75) or serine 76 (S76), as more abundant than the full-length protein.

Methods: We describe the generation of two monoclonal antibodies (mAbs), and subsequent development of an ELISA, to quantify neurogranin species truncated at P75. The mAb ADxNGCl2 (IgG2a) maps to a C-terminally internal epitope (Ng57-Ng65), while the mAb ADxNGCT1 (IgG1) targets specifically neurogranin C-terminally truncated at P75 with a low nM range affinity. To complete the ELISA, a synthetic peptide is used as calibrator.

Results: In contrast to previously described assays where neurogranin could not be quantified in all samples of healthy individuals, combining these two mAbs enabled analysis of all CSF samples in initial experiments. Ongoing efforts are to refine the assay protocol while harmonizing the test set-up with other immuno-assays such as for total-tau and amyloid, and to further define the mAbs specificity by analyzing brain extracts. Additional (multicenter) clinical CSF studies are planned.

Conclusions: This straightforward mAb-based ELISA will allow larger clinical studies in many expert centers to define the full diagnostic and prognostic value of neurogranin species truncated at P75. It could also complement the core AD CSF biomarkers for efficient therapeutic trials with neurogranin levels as a surrogate for synaptic integrity.
DIFFERENCES OF CSF AND SERUM BIOMARKERS IN LITHUANIAN PATIENTS WITH ALZHEIMER’S AND OTHER DEMENTIA

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**Rationale:** The aim was to evaluate levels of main CSF and serum biomarkers in patients with Alzheimer’s disease (AD), other dementia, and healthy controls (HC) and to compare biomarkers levels among these three groups.

**Methods:** CSF and blood samples from 56 patients were taken. CSF Aβ42, t-tau, p-tau concentrations and Aβ40 serum levels were measured. Main group consisted of AD patients, second group of patients whom revealed other cognitive disease symptoms during the period of observation (from 6 to 24 months) and HC who matched AD group by sex and age. AD patients were grouped according to severity of dementia, age of dementia onset.

**Results:** Groups consisted of: 26 AD patients (age 68.69 ± 8.064 yrs, MMSE 20.50 ± 2.687 pts), 9 patients with other dementia (64.67 ± 9.987 yrs, 20 ± 3.937 pts) and 21 HC (67.14 ± 10.195 yrs, 28.48 ± 1.030 pts). All CSF and serum biomarkers differed significantly in AD group vs. healthy controls. T-tau, p-tau differed significantly comparing among all three groups. The lowest concentrations of t-tau, p-tau were found in other dementia group comparing among all three groups. We found significant difference in AD patients according to severity of disease onset, sex. There was no significant difference in CSF Aβ42 levels between AD and other dementia groups. T-tau, p-tau and Aβ40 biomarkers differed significantly in HC according to age.

**Conclusions:** AD patients have reduced CSF Aβ42 and increased t-tau, p-tau levels and serum Aβ40 comparing to HC. Patients with other dementia have lowest CSF p-tau and t-tau concentrations. Different levels of biomarker concentrations can be helpful differentiating type of dementia.
METABOLIC PROFILING OF CEREBROSPINAL FLUID AND BLOOD SERUM IN NEURODEGENERATIVE DISORDERS

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**Rationale:** Increasing evidence suggests that neurodegenerative disorders display a metabolic pathophysiology and abnormal molecular interrelationships during disease onset and progression. Hence our goal is to perform metabolic profiling of neurodegenerative diseases to map cerebral and systemic variations of metabolic measures in study cohorts. We envision that metabolic profiling of cerebrospinal fluid (CSF) and blood serum could reveal new insight regarding the molecular pathophysiology of neurodegenerative illnesses.

**Methods:** Patient CSF and blood serum metabolomes were quantified using two separate proton NMR spectroscopy platforms. Our current sample set consist of 798 CSF and blood serum samples extracted from patients in the following diagnostic cohorts: Alzheimer’s disease, Parkinson’s disease, vascular dementia, frontotemporal dementia, and a cognitively healthy control cohort.

**Results:** Our CSF metabolomics platform is currently capable of quantifying 32 abundant low-molecular-weight metabolites, including amino acids, short chain fatty acids, and energy metabolites. The serum metabolomics platform yields quantitative molecular data on lipoprotein subclasses, such as lipids, fatty acids, and apolipoproteins as well as on various low-molecular-weight metabolites, including amino acids, glycolysis-related metabolites, and ketone bodies.

**Conclusions:** We envision that quantitative CSF and serum metabolic profiling, combined with diagnostic and clinical biomarker data, can shed light upon molecular pathomechanisms of neurodegenerative diseases.

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VITAMIN B12, FOLATE, AND SULFUR AMINO-ACIDS IN RELATION TO THE RATE OF BRAIN ATROPHY IN SUBJECTS AT RISK OF DEMENTIA: A LONGITUDINAL POPULATION BASED STUDY

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Background and objective: Our aim was to investigate the association of vitamin B12, folate, and sulfur amino-acids with the rate of total brain volume loss over 6 years in a longitudinal population-based cohort of older adults.

Design: From the Swedish National Study of Aging and Care in Kungsholmen (SNAC-K), 501 dementia-free subjects at baseline aged 60-97 years with repeated structural brain magnetic resonance imaging (MRI) scans at 2-3 occasions over 6 years were recruited. The association of baseline RBC folate, vitamin B12, holotranscobalamin, homocysteine, methionine, cystathionine, cysteine, and glutathionine with the rate of total brain volume loss was examined with the use of linear mixed models.

Results: After adjusting for several potential confounders including age, sex, education, MMSE, creatinine, APOEε4 status, the use of vitamin supplements, and systolic blood pressure, higher baseline vitamin B12 and holotranscobalamin concentrations were associated with decreased rate of total brain tissue volume loss over 6 years: β coefficient and standard error (SE) were 0.0024 (0.001); p = 0.001 for B12 and 0.0043 (0.001); p = 0.003 for holotranscobalamin. Increased homocysteine was related to faster rates of decline: β (SE): -0.0901 (0.034); p = 0.008. These associations remained significant even after excluding 30 incident dementia cases. RBC folate levels and other sulfur amino-acids had no longitudinal relationship with total brain tissue volume.

Conclusions: Higher concentrations of vitamin B12 and lower levels of homocysteine are associated with decreased rate of brain volume loss in older adults, even in non-demented elderly.
UPDATE OF α-SYNUCLEIN PATHOLOGY IN THE POPULATION BASED VANTAA 85+ STUDY

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Rationale: Screening recommendations for α-synuclein pathology are based on selected samples. Former population-based studies have revealed that some α-synuclein pathology remains unclassified when following those guidelines. We aim to update our previously published data of α-synuclein pathology by analysing the complete population based sample of very elderly people (Vantaa 85+).

Methods: The prospective population-based Vantaa 85+ study includes all individuals who were living in the city of Vantaa aged at least 85 years 1st of April 1991. Of the 601 eligible subjects, a neuropathological examination was possible in 304 cases. In this study, eight brain areas (substantia nigra, hippocampus, amygdala, cingulate gyrus, spinal cord and frontal, temporal and parietal cortex) of all neuropathologically examined subjects are immunohistochemically stained with the novel antibody clone 5G4 (Kovacs et al 2012).

Expected results: This study completes the α-synuclein profile in the Vantaa 85+ cohort as all neocortical and amygdala samples are stained in all the neuropathologically examined individuals.

Conclusions: In this study, no hierarchical sampling strategy is used but instead every brain area is stained regardless of screening results from other areas. This is the first population-based study on α-synuclein pathology without former hypothesis or selection bias in the brains of very elderly people.
FUNCTIONAL MRI IN PATIENTS WITH THE C9ORF72 EXPANSION ASSOCIATE FRONTOTEMPORAL DEMENTIA

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Rationale: Functional MRI studies have revealed connectivity changes in several brain networks in patients with neurodegenerative diseases and imaging genomics is an emerging field to investigate the role of genetics in brain function. A hexanucleotide repeat expansion in open reading frame in chromosome 9 (C9ORF72) is a common cause of familial frontotemporal dementia. The aim of this study was to evaluate resting state networks in behavioral variant frontotemporal dementia (bvFTD) patients with the C9ORF72 expansion by using functional MRI.

Methods: Seven patients and matched healthy controls were examined. The group specific resting state networks were identified by independent component analysis and the dual regression technique was used to detect between-group differences in the resting state networks with p < 0.05 threshold corrected for multiple comparisons.

Results: Increased anti-correlation between bilateral thalamic parts of the salience network and anterior sub-network of the Default mode network (DMN) was found in patients with the C9ORF72 expansion. In addition, increased resting state connectivity was detected in the right-sided dorsal attention network.

Discussion: Functional connectivity changes were detected in several resting state networks. The changes in these cognitive networks may explain executive dysfunction as well as neuropsychiatric symptoms in patients with bvFTD.
CAIDE DEMENTIA RISK SCORE AND BIOMARKERS OF NEURODEGENERATION IN MEMORY CLINICA PATIENTS WITHOUT DEMENTIA

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The study’s aims were: 1) to explore the associations between CAIDE Dementia Risk Score and CSF and neuroimaging biomarkers of amyloid deposition, neurodegeneration and small vessel pathology and 2) to evaluate the scores capacity to predict dementia in a memory clinic population without dementia.

From a University Memory Clinic 724 patients (57.6% females), mean (SD) age 60.84 (8.46), MMSE score 27.70 (2.61) were included. Two versions of the CAIDE Dementia risk score were calculated: one based on age, gender, obesity, hyperlipidaemia, and hypertension; and one additionally including APOE e4 carrier status was calculated for 310 (42.8%) patients with available data on APOE genotype. CSF was analysed for β-amyloid (Aβ), total tau (t-tau), and phosphorylated tau (p-tau). 529 (73.1%) patients had MRI scans. Visual assessment of medial temporal lobe atrophy (MTA), global cortical atrophy-frontal (GCA-frontal), Koedam score for parietal atrophy (PA) and Fazekas scale for white matter changes (WMC) were performed.

A CAIDE Dementia Risk Score above 8 points (version without APOE) was significantly associated with higher total tau (β = 0.09, p = 0.04), more severe MTA (OR =1.47, 95%CI = 1.01-2.15), WMC (OR = 3.41, 95%CI = 2.20-5.27) and GCA-frontal (OR = 2.40, 95%CI = 1.11-5.10). A CAIDE Dementia Risk Score - version with APOE - above 9 points was associated with reduced Aβ (β = -0.27, p<0.001), more severe MTA (OR 2.71, 95%CI = 1.48-5.95) and WMC (OR = 3.91, 95%CI = 1.93-7.92). Version with APOE has a better prediction capacity than the version without APOE (area under curve = 0.659, 95%CI = 0.59-0.73).

CAIDE Dementia Risk Score is associated with biomarkers of neurodegeneration, amyloid deposition and small vessel pathology in memory clinic patients without dementia and the version with APOE has a better predictive capacity of dementia few years later.
BRAIN AMYLOID LOAD IS ASSOCIATED WITH IMPAIRED EXECUTIVE FUNCTIONING IN ELDERLY INDIVIDUALS AT-RISK TO DEVELOP DEMENTIA - FINGER: PET-SUB-STUDY

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Background: FINGER study is a randomized 2-year multidomain lifestyle intervention study in subjects at increased risk of cognitive decline. A sub-group of the study population participate in a PET study to investigate brain metabolism and amyloid deposition at baseline and at the end of intervention. At present, data from the baseline PIB scans is available and the association of PIB data to baseline characteristics and cognition are reported.

Methods: 48 elderly subjects underwent a \([1^{11}C]PIB\) PET scan, brain MRI and neuropsychological examination. Subjects were divided into two groups (PIB+ and PIB-) based on a visual PET scan analysis. Hippocampal atrophy and brain vascular changes were visually graded according to Scheltens and Fazekas scores. Between-groups differences in the cognitive function were analyzed.

Results: Twenty subjects (42%) were PIB positive. PIB- group performed better in executive functions than PIB+ group (Z-score difference \(p = 0.02\). PIB+ group showed a trend to higher amount of white matter lesions and hippocampal atrophy (Fazekas score 2-3: 50% in PIB+ vs. 29% in PIB-; Scheltens score 1-3: 40% right, 45% left in PIB+ vs. 29% and 21% in PIB-).

Conclusions: The high percentage of PIB positive subjects provides evidence of a successful recruitment process of the at-risk population in the FINGER trial. The results suggest an association between early brain amyloid accumulation and decline in executive functions, as well as a trend of increased vascular changes and hippocampal atrophy in amyloid positive subjects.

References:
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CAIDE DEMENTIA RISK SCORE AND CORTICAL THICKNESS ON BRAIN MRI IN FINGER TRIAL PARTICIPANTS

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Rationale: This study investigated associations between CAIDE Dementia Risk Score (validated tool for estimating 20-year dementia risk at midlife based on age, sex, education, hypertension, obesity, hypercholesterolemia and physical inactivity) and cortical thickness on brain MRI.

Methods: Participants of the Finnish Geriatric Intervention Study to prevent Cognitive Impairment and Disability (FINGER) were at-risk elderly without dementia or substantial cognitive impairment. They were derived from previous population-based non-intervention studies (FINRISK and D2D, used for calculating CAIDE Dementia Risk Score versions without and with APOE genotype). Brain MRI scans were available for 131 participants in the FINGER baseline visit. Cortical thickness in 33 regions was measured using Freesurfer software 5.0.3.

Results: Mean age (SD) was 52.5 (10.6) years at the FINRISK/D2D assessment, and 70.0 (4.6) years at the FINGER baseline visit. Mean (SD) time between FINRISK/D2D and FINGER baseline assessments was 18.1 (9.6) years. CAIDE risk score range was 2-13 (mean 6.8 points, version without APOE) and 2-15 (mean 8.0 points, version with APOE). Both CAIDE risk score versions were related to cortical thickness in several regions, particularly in the right hemisphere. After FDR correction, higher risk score (version without APOE) was related to lower right superior temporal gyrus thickness (coef. -0.02, corrected p 0.025); and higher risk score (version with APOE) was related to lower thickness in right superior temporal gyrus (coef. -0.02, corrected p 0.035) and right parahippocampal gyrus (coef. -0.03, corrected p 0.035).

Conclusions: Higher CAIDE Dementia Risk Score was associated with lower cortical thickness nearly two decades later.

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CARDIORESPIRATORY FITNESS AND BRAIN VOLUMES IN MEN AND WOMEN - THE FINGER SUB-STUDY

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Rationale: Structural magnetic resonance imaging studies have indicated a positive relationship between cardiorespiratory fitness (CRF) and brain volume in several cortical regions and in the medial temporal lobe (MTL). However, it is unknown whether sex modifies the association between CRF and brain structures. We investigated whether the association of CRF with total gray (GM) and white (WM) matter volumes as well as MTL and striatum volumes is different between men and women at increased risk for Alzheimer’s disease.

Methods: We used baseline data from the FINGER study in which inclusion criteria were elevated CAIDE Dementia Risk Score and cognitive performance at the mean level or slightly lower than expected for age according to Finnish population norms. Our sub-study included 68 randomly selected individuals (39 men and 29 women) aged 61-75 years. CRF was assessed as peak oxygen consumption (VO2peak) measured in a maximal exercise test on cycle ergometer. Brain structural imaging was performed using a 1.5-Tesla scanner.

Results: In men, VO2peak was positively associated with cortical (β = 0.59, P < 0.001) and total GM volume (β = 0.57, P < 0.001), but in women, no associations were found. VO2peak accounted for 23% and 1% of total variance of cortical GM volume in men and women, respectively. Of total variance of total GM volume VO2peak explained 25% and 4% in men and women, respectively. VO2peak was not associated with either WM, MTL or striatum volumes in men or in women.

Conclusions: CRF is associated with cortical and total GM volumes in elderly men at increased risk for Alzheimer’s disease.
OOPHORECTOMY, HYSTERECTOMY, AND RISK OF ALZHEIMER’S DISEASE: A NATIONWIDE CASE-CONTROL STUDY

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Objective: To assess whether oophorectomy, hysterectomy, and hysterectomy with bilateral oophorectomy are related to risk of Alzheimer’s disease (AD), and whether the possible indication for surgery and use of HT modifies this association.

Methods: Our nationwide register-based case-control (1:1) study included all women with clinically-verified AD diagnoses, residing in Finland on December 31, 2005 (n of cases = 19,043, n of controls = 19,043). AD cases, diagnosed according to NINCS-ADRDA and the DSM-IV criteria, were identified from Special Reimbursement Register. Information on HT use and surgery was collected from national prescription register and hospital discharge register respectively. Most of the women (91.8%) were over 51 years of age when the surgery was performed.

Results: Oophorectomy, hysterectomy, and hysterectomy with bilateral oophorectomy were associated with lower risk of AD (OR/95% CI: 0.85/0.75-0.97, 0.89/0.81-0.97 and 0.85/0.75-0.98, respectively) among women without the history of uterine/ovarian/cervical cancer irrespective of HT use. The association was not evident in women with uterine/ovarian/cervical cancer history (3.00 /0.20-44.87 for all surgeries). HT use >10 years was independently associated with reduced AD risk.

Conclusion: Our findings indicate that oophorectomy with or without hysterectomy after commencement of natural menopause is not an important determinant of AD risk in older age and support the critical window hypothesis for HT use.
MANAGEMENT OF VASCULAR AND LIFESTYLE-RELATED RISK FACTORS FOR ALZHEIMER’S DISEASE AND DEMENTIA IN OLDER ADULTS: A EUROPEAN PERSPECTIVE

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Rationale: As part of the Healthy Aging Through Internet Counselling in the Elderly (HATICE), a randomised controlled clinical trial was designed to test the efficacy of an internet-based intervention in improving cardiovascular and lifestyle-related risk-factors for dementia and Alzheimer’s disease (AD). 4600 subjects at risk of AD/dementia will be enrolled in Finland, France and The Netherlands and they will undergo a 18-month intervention, which must be consistently applicable in the three countries. Therefore, a comparative analysis of the existing Finnish, French, Dutch and European guidelines for the management of the cardiovascular risk-factors was carried out.

Methods: The guidelines were collected, summarised, and compared. Reference values for intervention, therapeutic goals, lifestyle and pharmacological recommendations, were evaluated. Risk-factors analysed were: blood pressure, dyslipidaemia, smoking, diabetes, obesity, physical exercise and diet. Main similarities and differences were examined to establish the feasibility of a uniform intervention.

Results: Major similarities were identified in the lifestyle management. Discrepancies were identified in the pharmacological management. Importantly, we found a substantial lack of specific guidelines for older adults, the group most at risk for AD/dementia. Hence, its management must be based on either single evidence from limited literature, and/or guidelines for populations that are similar but could still bear significant differences.

Conclusions: Uniform lifestyle guidelines to manage cardiovascular and lifestyle-related risk-factors were identified. Pharmacological guidelines are more heterogeneous and cannot be combined. Further research is needed to optimise specific management of these risk-factors in older adults and to understand their role in the onset of AD/dementia.
MIDLIFE CAIDE DEMENTIA RISK SCORE WITH UNHEALTHY-DIET INDEX FOR PREDICTING LATE-LIFE DEMENTIA RISK

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Rationale: Several vascular and lifestyle risk factors have been associated with dementia. We investigated the combined performance of the CAIDE Dementia Risk Score and CAIDE Healthy Diet Index in predicting the risk of late-life dementia among middle-aged people.

Methods: Data from the population-based Cardiovascular risk factors, Aging and the Incidence of DEmentia (CAIDE) study was used. Of 525 subjects randomly selected from population-based cohorts surveyed at midlife in 1982 or 1987, 351 had available data for CAIDE Dementia Risk Score and CAIDE Healthy Diet Index, and participated in a re-examination 14 years later. Unhealthy dietary patterns were assessed by reverse-scoring the CAIDE Healthy Diet Index, and the total score was added to the CAIDE Dementia Risk Score (total range 8-31 for version without APOE genotype, and 9-32 for version with APOE genotype).

Results: Occurrence of dementia during the 14 years of follow-up was 3.7%. The combined CAIDE Dementia Risk Score with unhealthy-diet index predicted dementia well: AUC (95% CI) was 0.76 (0.65-0.86) for the version without APOE, and 0.80 (0.71-0.90) for the version with APOE. In comparison, AUC (95% CI) was 0.66 (0.52-0.80) for the unhealthy-diet index alone, and 0.68 (0.55-0.82) for APOE genotype alone.

Conclusions: The combination of CAIDE Dementia Risk Score (including age, sex, education, hypertension, obesity, hypercholesterolemia, physical activity, and APOE genotype) and unhealthy-diet index (including multiple dietary components) predicted late-life dementia well among middle aged people.

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MODELING LATE-LIFE PREDICTORS OF DEMENTIA RISK USING THE DISEASE STATE INDEX

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**Rationale:** Early identification of at-risk individuals who may benefit from interventions is essential for dementia prevention. The objective of the study was to predict incidence of dementia seven years later in older individuals, using a computer-based method for modeling a wide selection of health-related variables.

**Methods:** Participants in the population-based Cardiovascular Risk Factors, Aging and Dementia study were assessed at midlife (baseline visit), after 20 years (1st re-examination), and after additionally 7 years (2nd re-examination). The present study focused on participants without dementia or MCI at the 1st re-examination (mean age 71 years). The main study population (n = 709) included participants/survivors who attended the 2nd re-examination (39 developed dementia). An extended population (n = 1009) was formed by adding dementia diagnoses from national registers for non-participants/non-survivors (151 developed dementia). The Disease State Index (DSI), a novel supervised machine learning method, was used for predicting subsequent dementia based on health-related variables assessed at the 1st re-examination.

**Results:** The composite AUC value (95%CI) was 0.75 (0.72-0.77) in the main population and 0.72 (0.71-0.74) in the extended population. Cognitive performance and cardiovascular risk factors were the most powerful predictors, followed by age and subjective memory complaints. APOE genotype predicted dementia less well. Biomarkers related to inflammation, oxidative stress or vitamin B12, and self-rated measures of health and depressive symptoms did not perform well as predictors in this population.

**Conclusions:** DSI performed well as a method for identifying comprehensive risk profiles to predict subsequent dementia development.
APPLYING THE DISEASE STATE INDEX IN STUDIES WITH NEURODEGENERATIVE DISEASES

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Rationale: The Disease State Index (DSI) is a statistical analysis method developed as part of a computer-assisted diagnosis tool. It integrates various data from patients and combines them for disease classification. The Disease State Fingerprint presents DSI data in a visual form, enabling quick evaluation of the patients’ status.

Methods: The DSI measures the similarity of patient data to previously diagnosed cases. It uses a fitness function, calculated from the false negative and positive error at classification threshold, and relevance, indicating the measurements ability to differentiate between populations. Patient data is combined into composite DSI values calculated from average fitness of measurements weighted by their relevance.

Results: The DSI has been investigated in the prediction of MCI progression to AD in several studies using different cohorts and also tested between cohorts. The AUC values for these classifications range from 0.75 in the ADNI cohort to 0.83 in AddNeuroMed. Differential diagnosis between AD and FTD has been looked at in two studies, where AUC increased from 0.78 to 0.89 by including additional variables. Additionally the DSI has been utilized to examine the effectiveness of NPH shunt treatment (AUC = 0.58-0.77) and using risk factors to predict dementia in a population-based cohort (AUC = 0.75).

Conclusion: The strengths of the DSI are that it can distinguish between clear and ambiguous cases, assess the severity of the disease, and also provide information on the effectiveness of different biomarkers. It has been tested in several different cohorts, and shown to be consistent with results from previous studies.

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CHARACTERIZATION OF PRODROMAL ALZHEIMER’S DISEASE PATIENTS AT MEMORY CLINIC AND IN CLINICAL TRIALS

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**Rationale:** Prodromal Alzheimer’s disease (AD) patients are a new target population of AD trials. However, little is known about this patient group. Knowledge about their characteristics is required for designing trials and assessing the generalizability of results. This study aims to characterize prodromal AD patients and assess the representativeness of clinical trial patients with prodromal AD.

**Methods:** Demographic and clinical data of drug trial participants at Karolinska Memory Clinic (n = 18), nutritional trial participants in Kuopio (n = 100) and Stockholm (n = 35), and patients in GEDOC database who were diagnosed with MCI at Karolinska Memory Clinic between 2007 - 2014 (n = 472), were collected from medical records and case report forms. Dubois criteria (2007) were used to identify prodromal AD patients among MCI patients.

**Results:** 31% of MCI patients met the prodromal AD criteria. They were older but had less comorbidities and medications than other MCI patients. Prodromal AD patients were more often APOEε4 carriers and had family history of dementia. Drug trial patients were similar to regular prodromal AD patients. However, nutritional trial participants were older, less educated and had poorer health. Comparison of Finnish and Swedish patients showed that Kuopio patients had lower MMSE and education, higher BMI and diastolic blood pressure, and more medications and comorbidities.

**Conclusions:** Trial participants at Karolinska Memory Clinic form a representative sample of the general prodromal AD population. However, the nutritional trial population is heterogeneous, which can complicate the demonstration of intervention effects. Different practices in diagnosing and recruiting patients should be considered in future trials.
THE FINNISH INFORMANT QUESTIONNAIRE IS USEFUL IN SCREENING ALZHEIMER’S DISEASE

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**Rationale:** The aim of this study is to determine the clinical utility of the Finnish Informant Questionnaire for screening Alzheimer’s disease.

**Methods:** 79 patients were assessed at Päijät-Häme Central Hospital memory clinic. Of these patients, 25 were diagnosed with Alzheimer’s disease. The control group consisted of 34 cognitively normal older adults. A collateral source rated the possible changes in memory of the patients and controls by completing the Finnish Informant Questionnaire. In addition, the participants were assessed with The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropsychological battery investigation as a part of a neuropsychological assessment.

**Results:** The memory ratings of the informants were significantly associated with the cognitive performance of the memory patients. Some informants of the cognitively normal controls reported mild memory impairment. However, no significant memory impairment was rated in the control group. The diagnostic accuracy of the Finnish Informant Questionnaire was studied with receiver-operating characteristic (ROC) analysis and the area under the ROC curve (AUC). The Finnish Informant Questionnaire significantly differentiated the Alzheimer patients from the control group and the total memory score of the questionnaire was the best predictor.

**Conclusions:** This study indicates that the Finnish Informant Questionnaire is a valid screening tool for Alzheimer’s disease.
INSULIN RESISTANCE IS ASSOCIATED WITH VERBAL FLUENCY DECLINE IN WOMEN IN THE HEALTH 2000 STUDY

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Rationale: Type 2 diabetes is an independent risk factor for cognitive decline. Insulin resistance precedes the onset of type 2 diabetes and insulin resistance in midlife may increase the risk of cognitive decline and dementia later in life. We evaluated the association of insulin resistance on cognitive functions in the Health 2000 Study, which is a nationwide, Finnish population-based study. (n = 5935, mean age 52.5 years, range 30-97 years).

Methods: A homeostasis assessment model (HOMA-IR) was used to measure insulin resistance. Cognitive functions were tested by a word list learning test, a word list delayed recall test, a categorical verbal fluency test and by simple and visual choice reaction time tests. Linear regression analysis was used to determine the association between HOMA-IR and the cognitive tests used. Previously acknowledged risk factors of cognitive decline were used as covariates in the analysis.

Results: Higher insulin resistance was associated with poorer verbal fluency for women (p < 0.0001), but not for men (p = 0.53) when other commonly acknowledged factors for cognitive decline were taken into account.

Conclusions: To our knowledge, no previous studies have reported that female gender impacts the association of insulin resistance and a decline in verbal fluency in a comprehensive population-based study, which included young adults. Our study is cross-sectional, so causal effects of insulin resistance on cognitive functions could not be evaluated. However, our results suggest that insulin resistance could be an early marker for an increased risk for cognitive decline and dementia in women.
FAMILIAL IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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Rationale: Idiopathic normal pressure hydrocephalus (iNPH) is a cause of gait, urinary and cognitive impairment with unknown origin but frequent concomitant Alzheimer’s disease (AD) related pathology. CSF shunt operation can alleviate symptoms. The aim of this study was to characterize a potential familial subgroup of iNPH in a nation-wide Finnish cohort.

Methods: Overall 393 iNPH-patients operated between 1993 and 2014 were questionnaired and phone interviewed. Family anamnesis of relatives with either diagnosed iNPH or disease-related symptomatology was determined. Genograms with multiple affected relatives were illustrated.

Results: Seventy patients (18 %) had potential familial iNPH and 21 of them had at least one relative shunted due to iNPH. Patients with familial iNPH reported complete triad of NPH-symptoms (p = 0.032) and memory problems more often than sporadic cases (p = 0.002). According to age-adjusted multinomial logistic regression analysis, diagnosed dementia (odds ratio [OR] 2.2; 95%, confidence interval [CI], 1.2-4.0) and venous thrombosis (OR, 3.5; 95% CI, 1.5-8.1) were more frequent in familial than sporadic group. Familial iNPH patients tended to have more frequently concomitant AD than sporadic cases (14 vs. 23 %; p = 0.066) but frequency of APOE e4 allele was similar in familial and sporadic patients (p = 0.455) as well as age and gender matched controls. Intermittent geographical alternation in the occurrence of iNPH was observed, the incidence being highest in Eastern Finland.

Conclusion: This study indicates a familial entity of iNPH inherited potentially in an autosomal dominant trait. Recognition of this familial subgroup offers a novel approach to discover the potential genetic characteristics of iNPH. Furthermore, these pedigrees offer an intriguing opportunity to conduct longitudinal studies focusing on potential preclinical signs of iNPH. AD comorbidity is frequent and should be taken into consideration in iNPH research.
WHICH SUBTESTS FROM THE CERAD NEUROPSYCHOLOGICAL TEST BATTERY WORK BEST IN MEASURING AD PROGRESSION?

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Rationale: In recent years, the emphasis of study concerning Alzheimer’s disease (AD) has been on early detection. However, measuring the progression of AD-related symptoms is needed in order to plan and evaluate the treatment and care. The CERAD Neuropsychological battery, which is developed for screening early AD, may be too time-consuming and stressful for persons with AD. On the other hand, the commonly used MMSE test is criticized. Thus, the aim of this study was to find out which subtests from the CERAD Neuropsychological battery could be used in a follow-up of cognitive performance of persons with mild AD.

Methods: The three-year follow-up data of 236 persons with recently diagnosed very mild or mild AD was analyzed. Subjects participated in the prospective, randomized rehabilitation study ALSOVA, and follow-up visits were arranged annually. 131 subjects participated in the last follow-up visit. Generalized Estimating Equations were used to analyze which tasks from the Finnish CERAD Neuropsychological battery were best related to the disease severity (Clinical dementia rating, CDR).

Results: The combination of the MMSE, verbal fluency, constructional praxis, and the clock drawing test, with commonly used covariates age, gender, and education, were best related to the disease severity during a three-year follow-up.

Conclusions: The combination of the MMSE, verbal fluency, constructional praxis, and the clock drawing test may be a good alternative as a follow-up method of cognitive symptoms in AD. Even memory deficits are the first signs of AD, measures of other cognitive domains may work better in follow-up.
LATE-LIFE CYNICAL DISTRUST, RISK OF INCIDENT DEMENTIA, AND MORTALITY IN A POPULATION-BASED COHORT

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Rationale: Psychosocial factors have been related to cognitive decline. Cynical distrust is associated with different adverse outcomes, but the association between cynical distrust and incident dementia has not been explored previously.

Methods: We investigated the association between late-life cynical distrust and incident dementia and mortality (the mean follow-up times 8.4 and 10.4 years, respectively) in the CAIDE study. Cynical distrust was measured basing on the Cook-Medley Scale and categorized to tertiles. Required data for the dementia analyses were available from 622 persons (46 dementia cases) and for the mortality analyses from 1146 persons (361 deaths). Age, sex, systolic blood pressure, total cholesterol, fasting glucose, BMI, socioeconomic background, smoking, alcohol use, self-reported health, and APOE genotype were considered as confounders.

Results: Cynical distrust was not associated with dementia in the crude analyses, but those with the highest level of cynical distrust had higher risk of dementia after adjusting for confounders (RR 3.13; 95% CI 1.15-8.55). Higher cynical distrust was associated with higher mortality in the crude analyses (HR 1.40; 95% CI 1.05-1.87) but the association was explained by confounders (adjusted HR 1.19; 95% CI 0.86-1.61).

Conclusions: Higher cynical distrust in late-life was associated with higher mortality, but this association was explained by socioeconomic position, lifestyle, and health status. Association between cynical distrust and incident dementia came evident when confounders were taken into account. This novel finding suggests that both psychosocial and lifestyle-related risk factors may be modifiable targets for interventions. We acknowledge the need for larger replication studies.
SUBJECTIVE MEMORY COMPLAINTS AND THEIR ASSOCIATION WITH NEUROPSYCHOLOGICAL PERFORMANCE IN OLDER ADULTS

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Rationale: The association between subjective memory complaints (SMC) and objective cognitive performance is not always clear. Aim of this study is to clarify the association between SMC (prospective memory, PM and retrospective memory, RM) and neuropsychological test performance in older adults at risk of cognitive decline.

Methods: This study is part of the FINGER study, a multicenter randomized, controlled trial aiming to lower the risk of cognitive decline in high-risk individuals. The cognitive assessment of participants was conducted at baseline using a modified neuropsychological test battery (NTB). SMC (sub-sample n = 560, men 50.7%, women 49.3 %, aged 60-77) were evaluated with the Prospective and Retrospective Memory Questionnaire (PRMQ).

Results: There were significant relationships between the self-reported PRMQ scores and NTB domains, after controlling for demographics. Subjective PM problems were associated with slower processing speed but not with other NTB domains. Subjective RM problems were associated with poorer function on NTB total, processing speed and memory domains. Executive function domain was not associated with any PRMQ ratings. Depressive symptoms and quality of life diluted the observed associations for NTB total and memory. However, the association between PRMQ and processing speed remained even after full adjustments.

Conclusions: Our results indicate that SMCs are associated with objective cognitive status. They also clarify the meaning of PM and RM memory as a part of that evaluation. In the future, we will investigate the importance of the subjective experience of PM and RM impairment to be used as an early messenger of objective cognitive decline.
COMPUTER-BASED COGNITIVE INTERVENTION FOR OLDER ADULTS - DETERMINANTS OF ADHERENCE

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Rationale: Computer-based cognitive training (CCT) may be an important tool in the prevention of dementia, but investigating its usability is crucial before implementation. Different individual characteristics may affect the participation and benefit from CCT.

Methods: This study is part of the FINGER study. FINGER is a multicenter RCT aiming to lower the risk of cognitive decline with an intensive 2-year multidomain intervention including CCT, diet, exercise and vascular risk factor monitoring. CCT included web-based exercises carried out independently at home three times a week for 2 x 6 months. The objective of this study was to explore the determinants of adherence to the CCT measured as number of completed training sessions. Predictor variables included demographics, health related factors, cognitive performance, and previous experience with computers. Multivariate zero-inflated negative binomial regression analyses were used.

Results: Participants, who trained, were younger, had higher education, better cognitive performance, less depressive symptoms, better subjective health, and they more often had experience with computers compared to those who did not train at all. In multivariate models previous experience with computers, better memory function and better subjective health were independently linked to greater probability to start the training. Among those who started training, previous experience with computers and male sex were associated with increased amount of training.

Conclusions: Our study showed that memory, previous computer use and perceived health predict adherence to CCT. Future analysis will clarify how the training affects cognition, who benefits the most and how much training is needed for optimal effect.
A CASE STUDY: ICT USE AS A DELAYING TOOL FOR ELDERLY PATIENT WITH MILD DEMENTIA

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Rationale: Aging, a major risk factor for dementia, is a serious issue in Japan with its older population rate continuing to grow until 2050 (26% in 2014). Although over 80% of the elderly prefer to receive homecare instead of hospital care, many professionals are skeptical about elderly patients with dementia living alone. The main challenges for such individuals are drug self-administration and maintenance of a safe environment.

Hypothesis: ICT can be an effective tool in enabling an individual with mild dementia to stay at home.

Purpose: The purpose of this study was to identify the issues of ICT use for dementia-afflicted homecare patients living alone.

Ethical consideration: The study plan was approved by the Sapporo City University ethics committee.

Method: For nine months, a subject (male, 75 yrs., living alone, FAST 3-4) used PC with a touch screen to communicate with hospital nurses (video chat) at regular intervals to ensure correct drug administration as well as confirming his safety. Patient also used the PC to send his B/P score to his nurse daily.

Results: The subject managed to stay home alone without any signs of dementia progression, and the nurse was able to assist the patient with correct drug administration and keeping his environment safe via PC (TV) monitoring. The patient stated that he felt secure and well after each session with a nurse.

Conclusions: If the correct ICT tool is employed, it can be effective in enabling dementia-afflicted elderly, even those without ICT experience, in staying at home.
THE DIAGNOSIS OF MEMORY DISEASES DOES NOT EQUAL DISABILITY TO WORK

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Rationale: Due to improvements in knowledge and diagnostic methods, people get the diagnosis earlier than before. The diagnosis of memory disease does not necessarily mean disability to work. People with early-onset memory disease should go through a proper evaluation of their ability to work and their need for rehabilitation, just as people with other diseases.

Methods: The Alzheimer Society of Finland collected perceptions of current praxis about the opportunities to continue to work of people with early-onset memory disease from 27 occupational health doctors and neurologist. The quantitative informed online survey was conducted during summer 2014.

Results: Results suggest that the diagnosis of memory disease is seen as an obstacle to the continuation of work: 70% of responders think that the employee wants to continue employment, while 60% assume that the employer is not ready to continue employment. 26% estimates that the assessment of rehabilitation is always done, 15% that it is not normally done. The main obstacles to work are difficulties in modifying the job descriptions and lack of support and rehabilitation. Support comes from suitable job description, adjustable work environment and rehabilitation.

Conclusions: Based on the results, there is a need for change in the attitudes of professionals and employers, as well as need for tailored information, support and materials. Rehabilitation plan should be made to every person with early-onset memory disease. At workplaces most of the actions are light and easy to incorporate. The Alzheimer Society of Finland recommends to develop good practices and models in working life.
SELF-RATED AND CAREGIVER-RATED QUALITY OF LIFE IN ALZHEIMER’S DISEASE: 5-YEAR PROSPECTIVE ALSOVA COHORT STUDY

Kristiina Hongisto (1,2), Saku Väätäinen (1,3), Janne Martikainen (3), Ilona Hallikainen (1,4), Tarja Välimäki (5,6), Sirpa Hartikainen (7), Jaana Suhonen (8), Anne M. Koivisto (1,9)

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Rationale: Examine and compare self-and caregiver-rated measures of Quality of Life (QoL) in relation to disease progression in patients with very mild or mild Alzheimer’s disease (AD) and at what disease stage patient’s ability to respond to QoL questionnaires with or without assistance begins to diminish.

Methods: 236 patients with very mild or mild AD and their family caregivers from three Finnish hospital districts participated in this prospective, longitudinal study with five years of follow-up. Three patient-reported wellbeing and life satisfaction instruments were used to assess health-related QoL- a generic 15D, the Quality of Life in Alzheimer’s Disease (QoL-AD), and the Visual Analogue Scale (VAS) as well as one caregiver-rated assessment of patient QoL (QoL-AD). AD severity was evaluated with the Clinical Dementia Rating Scale - Sum of Boxes (CDR-SOB).

Results: All self- and caregiver-rated QoL estimates correlated with AD severity. The self- and caregiver-rated QoL scores began to diverge even with very mild cognitive impairment after CDR-SOB reached 4, value that corresponds with a Mini-Mental State Examination (MMSE) score of 25-30. Patients also began to need assistance in responding to questionnaires at very early stages of AD (CDR-SOB 4-6). Furthermore, their ability to respond to QoL-questionnaires with or without assistance declined after CDR-SOB reached 11 points, value that correlated with an early moderate stage of AD and MMSE 11-20.

Conclusions: It is challenging to assess QoL in patients with AD, because even at very early stages of AD, patients have difficulty comprehending or communicating their health status.
FAMILY CAREGIVERS’ EXPERIENCES ON MEANING THEIR LIFE - ALZHEIMER’S DISEASE STUDY BASED ON THE LONGITUDINAL DIARIES

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Rationale: Our aim was to describe caregivers’ manifestations of meaning and explore how they find meaning in their life during the first year of caregiving after their family member was diagnosed with Alzheimer’s disease. The salutogenic approach, according to which meaning is considered a factor motivating individuals (Antonovsky 1987), was used as the theoretical framework in this study.

Methods: This is part of the ALSOVA follow-up study of persons with Alzheimer’s disease and their family caregivers (n = 240) (2002 - 2020). For this substudy, inductive content analysis was used to explore spousal caregivers’ unstructured, diaries (n = 57) written in two week period.

Results: The caregivers experienced meaning as a personal emotion, which was manifested as optimistic attitude, gratitude and hope. A good relationship between the caregiver and the care recipient, solitude time for themselves and ability to use supportive services were important elements in finding meaning.

Conclusions: The process of finding meaning in caregiving was powerful during the first year after Alzheimer’s disease diagnosis. Caregivers’ ability to find meaning in new life situation as primary carers, helps them to continue their life. Caregivers’ diaries have not been used widely as a research method. Diaries afford depth interpretations of caregivers’ life alongside of quantitative research. Further, diaries reveal a wide array of subjective aspects in caregiving.
SPOUSAL CAREGIVERS’ DEPRESSIVE SYMPTOMS PRODUCE PSYCHOLOGICAL STRESS UNRELATED TO THE SEVERITY OF ALZHEIMER’S DISEASE

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Rationale: To investigate family caregiver long-term psychological distress after Alzheimer’s disease (AD) diagnosis in a family member.

Methods: Family caregivers (n = 236) and persons with AD were prospectively followed up to 3 years after AD diagnosis. Caregivers’ psychological distress was assessed using the General Health Questionnaire (GHQ). Furthermore, caregiver depressive symptoms and sense of coherence, along with AD patient measurements were evaluated annually after baseline visit. General Estimation Equation models were applied to study associations of these baseline factors to caregiver GHQ.

Results: After 3-year follow-up period, spousal caregivers’ GHQ was significantly higher (P < .001) than in the non-spousal caregivers. The difference in GHQ scores was associated by depressive symptoms (P < .001) at baseline, and the depressed spouses suffered more severe distress than non-spousal caregivers over the observation period. Also, patient behavioral symptoms, caregivers’ sense of coherence at baseline predicted the trajectory of caregiver GHQ during follow-up.

Conclusions: Spousal and depressed caregivers of AD patients report higher and increasing psychological stress as compared to non-spousal and non-depressed caregivers. The current study highlights the need for evaluating AD caregiver mental health and level of coping.
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Parantaa todistetusti muistia varhaisista Alzheimerin tautiavauriissa

Souvenaid on ensimmäinen kliininen ravintovalmiste, jonka on todistettu parantavan muistia varhaisista Alzheimerin tautiavauriissa. Ainutlaatuinen, patentointu ravintoaine-yhdistelmä tukee synapsien muodostusta.


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Souvenaid on kliininen ravintovalmiste varhaisen Alzheimerin taudin ruokavaliohoitoon. Se on tarkoitettu käytettäväksi terveydenhuollon henkilöstön ohjauksessa.

BEKO\textsuperscript{®} STRONG
B\textsubscript{12}

UUTUUS

Tarvitsetko B-vitamiinin lisääntyvää?
B\textsubscript{12}-vitamiinin tarve lisääntyy mm. ikääntyessä, suoliston alueen imeytymishäiriöissä sekä kasvisruokavaliota noudattavilla.
Beko Strong B\textsubscript{12} 1 mg on pienikokoinen, helposti nieltävä B\textsubscript{12}-vitamiiniteippi.
B\textsubscript{12}-vitamiini edistää normaalitöytä, psychoLOGisia toimintoja, hermoston ja solujen normaalia toimintaa sekä vähentää väsymystä ja uupumusta.

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The 7th Kuopio Alzheimer Symposium is organized by the University of Eastern Finland, Institute of Clinical Medicine – Neurology, the Doctoral Program in Molecular Medicine, and the Finnish Alzheimer’s Disease Research Society. The symposium brings together the current leaders in clinical and basic research for exchanging new ideas on neurodegeneration, diagnosis, prediction, novel biomarkers, imaging, technology-supported diagnosis and care, and clinical treatment of Alzheimer’s disease. The Finnish program of the Memory Day (Muistipäivä) concentrates on memory problems in individuals in the working age and prevention and rehabilitation of memory diseases.

This book contains the program and abstracts of the 7th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 11-13, 2015.