Systemic low-grade inflammation and cognitive function

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Why should we care about cognitive function?
Table C. Percentage of total deaths, death rates, age-adjusted death rates for 2004, percentage change in age-adjusted death rates from 2003 to 2004, and ratio of age-adjusted death rates by race and sex for the 15 leading causes of death for the total population in 2004: United States

[Death rates on an annual basis per 100,000 population; age-adjusted rates per 100,000 U.S. standard population. The asterisks (*) preceding the cause-of-death codes indicate that they are not part of the International Classification of Diseases, Tenth Revision; see "Technical Notes".]

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of death (Based on the International Classification of Diseases, Tenth Revision, 1992)</th>
<th>Number</th>
<th>Percent of total deaths (%)</th>
<th>2004 crude death rate</th>
<th>2003 to 2004</th>
<th>Male to female</th>
<th>Black to white</th>
<th>Hispanic² to Non-Hispanic white</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diseases of heart (I00-I09,J11,J13,J20-J51)</td>
<td>652,486</td>
<td>27.2</td>
<td>222.2</td>
<td>217.0</td>
<td>-6.6</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>Malignant neoplasms (C00-C97)</td>
<td>553,888</td>
<td>23.1</td>
<td>188.6</td>
<td>185.8</td>
<td>-2.3</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>Cerebrovascular diseases (I60-I69)</td>
<td>150,074</td>
<td>6.3</td>
<td>51.1</td>
<td>50.0</td>
<td>-6.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>Chronic lower respiratory diseases (J40-J47)</td>
<td>121,987</td>
<td>5.1</td>
<td>41.5</td>
<td>41.1</td>
<td>-5.1</td>
<td>1.4</td>
<td>0.7</td>
</tr>
<tr>
<td>5</td>
<td>Accidents (unintentional injuries) (V01-X59,Y85-Y86)</td>
<td>112,012</td>
<td>4.7</td>
<td>38.1</td>
<td>37.7</td>
<td>1.1</td>
<td>2.1</td>
<td>0.9</td>
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<tr>
<td>6</td>
<td>Diabetes mellitus (E10-E14)</td>
<td>73,138</td>
<td>3.1</td>
<td>24.9</td>
<td>24.5</td>
<td>-3.2</td>
<td>2.2</td>
<td>1.5</td>
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<tr>
<td>7</td>
<td>Alzheimer’s disease (G30)</td>
<td>56,965</td>
<td>2.8</td>
<td>22.5</td>
<td>21.8</td>
<td>1.9</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>8</td>
<td>Influenza and pneumonia (J10-J19)</td>
<td>59,664</td>
<td>2.5</td>
<td>20.3</td>
<td>19.8</td>
<td>-10.0</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>9</td>
<td>Nephritis, nephrotic syndrome and nephrosis (N00-N07,N17-N19,N25-N27)</td>
<td>42,480</td>
<td>1.8</td>
<td>14.5</td>
<td>14.2</td>
<td>-1.4</td>
<td>1.4</td>
<td>2.3</td>
</tr>
<tr>
<td>10</td>
<td>Septicemia (A40-A41)</td>
<td>33,373</td>
<td>1.4</td>
<td>11.4</td>
<td>11.2</td>
<td>-3.4</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>11</td>
<td>Intentional self-harm (suicide) (U03,X60-X84,Y87)</td>
<td>32,439</td>
<td>1.4</td>
<td>11.0</td>
<td>10.9</td>
<td>0.9</td>
<td>4.0</td>
<td>0.4</td>
</tr>
<tr>
<td>12</td>
<td>Chronic liver disease and cirrhosis (K70,K73-K74)</td>
<td>27,013</td>
<td>1.1</td>
<td>9.2</td>
<td>9.0</td>
<td>-3.2</td>
<td>2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>13</td>
<td>Essential (primary) hypertension and hypertensive renal disease (I10,I12)</td>
<td>23,076</td>
<td>1.0</td>
<td>7.9</td>
<td>7.7</td>
<td>4.1</td>
<td>1.0</td>
<td>2.8</td>
</tr>
<tr>
<td>14</td>
<td>Parkinson’s disease (G20-G21)</td>
<td>17,989</td>
<td>0.8</td>
<td>6.1</td>
<td>6.1</td>
<td>-1.6</td>
<td>2.3</td>
<td>0.4</td>
</tr>
<tr>
<td>15</td>
<td>Assault (homicide) (U01-U02,X85-Y09,Y87)</td>
<td>17,357</td>
<td>0.7</td>
<td>5.9</td>
<td>5.9</td>
<td>-1.7</td>
<td>3.7</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>All other causes (Residual)</td>
<td>414,674</td>
<td>17.3</td>
<td>141.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The mortality rate of AD shows rapid increases.
Risk factors of cognitive decline

- Obesity
- The metabolic syndrome/Type 2 Diabetes
- Cardiovascular disease
- Physical inactivity
- Alcohol/smoking
- Depression

Among others….
(Genetics, trauma, nutrition, education/occupation, hormones….)
Sagittal abdominal diameter (SAD) in midlife is associated with the risk of dementia 3 decades later independently of BMI and T2D

N=6583 Americans

Whitmer et al, Neurology 2008
Individuals with diabetes have increased risk of reduced cognitive function

• The rate of cognitive decline due to ageing is increased 1.5-2.0 fold in individuals with type 2 diabetes

• Mild cognitive impairment are more likely to develop in individuals with type 2 diabetes: OR 1.4-1.8

Individuals with diabetes have increased risk of dementia

• Alzheimer’s disease: Relative risk 1.4-1.8

• Vascular dementia: Relative Risk 2.0-2.5

• Cerebral atrophy (brain imaging): OR 1.3-2.2

• Lacunar infarcts (brain imaging): OR 1.3-2.2

Physical activity is associated with better cognitive function in 18766 US women (age 70-81yrs) followed for 2 years

Weuve et al, JAMA 2004
Hypothesis

Domino effect:
Inflammation in one system affects other tissues and organs

Hansson, NEJM 2005
Hypothesis: Systemic low-grade inflammation accelerates neurodegeneration
Aging is associated with systemic low-grade inflammation

\[\text{TNF-}\alpha\]

\[\text{IL-6}\]

Bruunsgaard, J Gerontol 2000
Systemic low-level inflammation in elderly populations

Subjects at risk?
IL-6 predicts mortality risk in 333 80-year-olds independently of co-morbidity and other risk factors (5 years follow-up)

Cox regression

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Medium</td>
<td>1.69 (1.02-2.78)</td>
</tr>
<tr>
<td>High</td>
<td>2.88 (1.75-4.72)</td>
</tr>
</tbody>
</table>

Bruunsgaard, Clin Exp immunol 2003
IL6 -174C is associated with increased mortality risk in 234 80-year-old non-smokers (5 years of follow-up)

**Cox regression:**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>1.00</td>
</tr>
<tr>
<td>GC/CC</td>
<td>2.04; p=0.02</td>
</tr>
</tbody>
</table>

Adjusted for the effect of plasma IL-6, sex, BMI, CVD, and cancer

Bruunsgaard, Exp Gerontol 2003
Serum YKL-40 predicts mortality risk in 151 80-year-olds (5 years of follow-up)

Cox Regression Analysis:

<table>
<thead>
<tr>
<th>YKL-40</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Medium</td>
<td>1.22 (0.57-1.19)</td>
</tr>
<tr>
<td>High</td>
<td>2.52 (1.15-5.52)</td>
</tr>
</tbody>
</table>

Johanson 2007, Clin Exp Immunol
High plasma TNF is associated with near-term mortality independently of dementia and CVD in 126 centenarians

<table>
<thead>
<tr>
<th>Tertiles</th>
<th>HR(95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Medium</td>
<td>1.22 (0.79-1.88)</td>
</tr>
<tr>
<td>High</td>
<td>1.80 (1.13-2.84)</td>
</tr>
</tbody>
</table>

(Univariate analysis)

Bruunsgaard, Am J Med 2003
Inflammatory processes are involved in atherosclerosis from its initiation through to its thrombotic complications.

Hansson and Libby, Nat Rev Immunol 2006
Inflammation is associated with insulin resistance

TNF inhibits insulin receptor signaling

Hotamisligil, Nature 2006
85-year-olds from “The 1914-population”
Research Centre for Prevention and Health
Glostrup Hospital

• 119 people with:
  – DNA and plasma at age 85-years
  – Valid cognitive testing in investigations of 80-years-olds and 85 years-olds.

• WAIS IQ scores:
  – Performance subtests=Fluid intelligence =The current function of the brain
  – Verbal subtests=Crystallized intelligence=The life history of the brain

Krabbe, Neurobiology of Aging 2007
Plasma TNF, sTNFRI+II, and IL-6, are correlated with cognitive function (WAIS) in 85-year-olds from the 1914-population

IQ at age 85 years

TNF is divided by tertiles

Krabbe, Neurobiology of Aging 2007
Inflammatory Proteins in Plasma and the Risk of Dementia

The Rotterdam Study

Marianne J. Engelhart, MD, PhD; Mirjam I. Geerlings, PhD; John Meijer, MSc; Amanda Kiliaan, PhD; Annemieke Ruitenberg, MD, PhD; John C. van Swieten, MD, PhD; Theo Stijnen, PhD; Albert Hofman, MD, PhD; Jacqueline C. M. Witteman, PhD; Monique M. B. Breteler, MD, PhD

Background: Increased levels of inflammatory proteins have been found in the brains and plasma samples of patients with dementia. Whether the levels of inflammatory proteins in plasma samples are elevated before clinical onset of dementia is unclear.

Objective: To determine whether high levels of inflammatory proteins in plasma samples are associated with an increased risk of dementia.

Design and Setting: A case-cohort study within the Rotterdam Study, a population-based prospective cohort study in the Netherlands.

Participants: The source population comprises 67,133 subjects who, at baseline (1990-1993), were free of dementia and underwent venipuncture. From these, we selected both a random subcohort of 727 subjects and 188 cases who had developed dementia at follow-up.

Main Outcome Measures: The associations between plasma levels of α1-antichymotrypsin, C-reactive protein, interleukin 6, the soluble forms of intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 and the risk of dementia were examined using the Cox proportional hazards regression models.

Results: High levels of α1-antichymotrypsin, interleukin 6, and, to a lesser extent, C-reactive protein were associated with an increased risk of dementia; rate ratios per standard deviation increase were 1.49 (95% confidence interval, 1.23-1.81), 1.28 (95% confidence interval, 1.06-1.55), and 1.12 (95% confidence interval, 0.99-1.25), respectively. Similar associations were observed for Alzheimer disease, whereas rate ratios of vascular dementia were higher for α1-antichymotrypsin and C-reactive protein. Soluble forms of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 were not associated with dementia.

Conclusion: Plasma levels of inflammatory proteins are increased before clinical onset of dementia, Alzheimer disease, and vascular dementia.

Arch Neurol. 2004;61:668-672
High plasma TNF is associated with dementia in 126 centenarians

Medians and interquartile range

*, p<0.05

Bruunsgaard, J Gerontol 2000
Classification and prediction of clinical Alzheimer’s diagnosis based on plasma signaling proteins

120 proteins were measured with a proteomic multiplex Method.

40 patients with AD and 40 controls.

18 proteins were able to distinguish with almost 90% accuracy.

The 18 proteins identified also presymptomatic AD.

Patients with Alzheimer’s disease
Amyloid-β plaques

Neurofibrillary tangles

Microglial-cell activation and migration

Astrocyte

Microglial cell

CCL2, CCL3, IL-1, IL-6, ROS and TNF

Astrogliosis

ACT, CCL2, COX2, IL-1, IL-6, iNOS, ROS, S100B and TNF

Weiner and Frenkel, Nature Reviews 2006
Transgenic and KO studies in amyloid precursor protein (APP) mice reveal both beneficial and detrimental effects of immune and inflammatory factors.

Wyss-Coray, Nature Medicine 2006
Inflammation in Alzheimer disease: driving force, bystander or beneficial response?

Tony Wyss-Coray

Nature Medicine 2006
Conclusion

• Systemic low-grade inflammation is a biomarker of cognitive function and dementia.

• Driving force, bystander, or beneficial response?
Systemic low-grade inflammation and cognitive function

- Biomarker of the inflammatory burden?
Systemic low-grade inflammatory activity and cognitive function

- Biological driver?
Questions

• Does systemic low-grade inflammation affect cognitive function?

• Is systemic low-grade inflammation associated with neurotrophins such as BDNF?
Hypothesis

- Systemic infections and inflammation can cause acute exacerbations of symptoms and drive the progression of neurodegeneration in neurodegenerative diseases such as Alzheimer's disease
Routes of communication between peripheral inflammation and the brain

- Active transport or passive diffusion across BBB.
- Direct interaction with the brain endothelium.
- Communication with macrophages in the circumventricular organs that lack a BBB
- N.vagus
The cholinergic anti-inflammatory pathway

Tracey, J Clin Invest 2007
Sickness Behaviour

• **Systemic infections induce:**
  – Lethargy
  – Anhedonia
  – Apathy
  – Decreased social interaction
  – Poor concentration

• **Purpose:** The body makes condition suboptimal for microbial replication (altering body temperature, conserving energy, limiting exposure to more insults, and limiting the spread of infection)

• **Signals:** TNF, IL-1, IL-6

Perry, Nat Rev Immunol 2007
Immune cells may fend off AD

- Transgenic model of AD deficient in Ccr2, which recruits immune cells from the blood or within the brain
  - Microglia accumulation is impaired.
  - Early disease progression is accelerated
  - Increased mortality

Khoury et al. Nat Med 2007
Low-dose endotoxemia and human neuropsychological functions

Karen Suárez Krabbe a,*, Abraham Reichenberg c, Raz Yirmiya d, Annelise Smed e, Bente Klarlund Pedersen a, b, Helle Bruunsgaard a

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b Copenhagen Muscle Research Centre, Rigshospitalet, Faculty of Health, University of Copenhagen, Denmark
c Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA
d Department of Psychology, The Hebrew University of Jerusalem, Israel
e Neurological Clinic, Rigshospitalet, Denmark

Received 2 February 2005; received in revised form 4 April 2005; accepted 20 April 2005
Available online 15 June 2005

N=12
“Danger signals”
Pathogen-associated molecular patterns

Activation of innate immunity
“Pattern-recognition receptors”
(CD14, TLR, CD11b/CD18…)

Local inflammatory activity
Acute-phase response
Low-dose endotoxemia

No effect on:
Temperature, Cortisol, HR, BP
Low-grade inflammation improved declarative memory

Fig. 2. Performance in the learning condition of the word-list learning test assessing declarative memory following administration of 0.2 ng/kg E. coli endotoxin or saline. Means and 95% confidence intervals are shown.

Fig. 3. Correlation between IL-6 concentrations 4.5 h following endotoxin administration and declarative memory in the third testing period (5.5–6 h). (x-axis) Change in performance in word-list learning test following endotoxin administration compared to baseline—change in performance compared to baseline at the same point in time under saline conditions (see text for further details). (y-axis) Increases in levels of IL-6 in plasma.
Cognitive tests

The CERAD-test battery (The Consortium to Establish a Registry for Alzheimer's Disease)

Global cognitive function:
MMSE (Mini Mental State Examination): A brief 30-point questionnaire test that is used to assess cognition. It is commonly used in medicine to screen for dementia.

Selective cognitive test:
Verbal fluency test: (Frontal and temporal areas)

Modified Boston Naming test: essential language cortex, include both visual areas (occipital), Memory (temporal) and motor area (frontal lobe).

Word list memory: Test short time memory (Hippocampus)

Word list recall and saving: Delayed memory (Hippocampus)

Word list recognition: Recognition of the right objects (Hippocampus and maybe frontal region)

Constructional praxis and saving: Visuo-spatial and constructional ability (Non-dominant posterior hemisphere, motor cortex and cerebellum)

Clock draw: Test visuo-spatial neglect (Non-dominant posterior hemisphere, motor cortex and cerebellum)
Conclusion

• Low-grade increases in systemic inflammation are inversely associated with declarative memory performance independently of physical stress symptoms and the HPA axis (Krabbe 2005)

• Larger increases in circulating cytokines and activation of the HPA axis are associated with decreased declarative memory (Reicehnberg 2001)

• Limitation of studies: Acute versus chronic inflammation
Hypothesis

If inflammation is a causative factor in age-related cognitive decline, single nucleotide polymorphisms may also constitute risk factors.
Single nucleotide polymorphisms (SNP)

- Single base-pair mutations
- The variant is present in >1% of a normal population
- Constitute 90% of the human DNA variation with a frequency of 1-5 SNP/1-5 kbaser
The TNF $-308G>A$ promoter SNP

$-308A$ is a stronger transcriptional activator than the $G$ allele.

Hypothesis:

-308A is associated with high risk of dementia in centenarians
TNF –308GA is associated with the lowest prevalence of dementia in centenarians

OR=0.43, P=0.02

OR=1.23; P=0.8

Bruunsgaard, JAGS 2004
A balanced TNF response is optimal in neurodegeneration

- TNF is neurotoxic in acute models
- TNF contributes to the clearance of b-Amyloid
Genetic priming of a proinflammatory profile predicts low IQ in octogenarians

K.S. Krabbe\textsuperscript{a,\,*}, E.L. Mortensen\textsuperscript{b,c,1}, K. Avlund\textsuperscript{b,c,2}, H. Pilegaard\textsuperscript{d,3}, L. Christiansen\textsuperscript{e,4}, A.N. Pedersen\textsuperscript{f,5}, M. Schroll\textsuperscript{c,6}, T. Jørgensen\textsuperscript{c,6}, B.K. Pedersen\textsuperscript{a,7}, H. Bruunsgaard\textsuperscript{a,7}

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\textsuperscript{b} Institute of Public Health, University of Copenhagen, Denmark
\textsuperscript{c} Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark
\textsuperscript{d} The August Krogh Building, Institute of Molecular Biology, University of Copenhagen, Denmark
\textsuperscript{e} Department of Epidemiology, Institute of Public Health, University of Southern Denmark, Denmark
\textsuperscript{f} National Food Institute, Technical University of Denmark, Denmark

Received 8 May 2007; received in revised form 11 July 2007; accepted 21 August 2007
SNPs in cytokine genes and cognitive function in octogenarians

- TNF-308, IL18-137, IL18-607, IL6-174, IL10-592, IL10-1082

Krabbe, Neurobiology of Aging 2007
SNPs in cytokine genes and cognitive function in 119 octogenarians

• Criteria:
  – Common in the population
  – Effects in reporter assays or cell cultures
  – Associated with disease phenotypes
  – Circulating cytokine protein constitute risk factors
IL-18 SNPs are associated with cognitive function

<table>
<thead>
<tr>
<th>Carrier status</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>Full IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 80</td>
<td>Age 85</td>
<td>Change 80–85</td>
</tr>
<tr>
<td>TNF-308</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>94.4 ± 2.4</td>
<td>86.6 ± 2.5</td>
<td>-5.7 ± 1.3</td>
</tr>
<tr>
<td>GG</td>
<td>92.4 ± 1.7</td>
<td>90.5 ± 0.6</td>
<td>-1.9 ± 1</td>
</tr>
<tr>
<td>IL-6-174</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>91.8 ± 2.9</td>
<td>89.2 ± 2.7</td>
<td>-2.6 ± 1.3</td>
</tr>
<tr>
<td>GC</td>
<td>94.1 ± 1.8</td>
<td>90.1 ± 1.9</td>
<td>-2.7 ± 1.1</td>
</tr>
<tr>
<td>CC</td>
<td>94.7 ± 3.2</td>
<td>89 ± 3.4</td>
<td>-5.7 ± 1.8</td>
</tr>
<tr>
<td>IL-10-1082</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>91.9 ± 2.6</td>
<td>87.5 ± 2.9</td>
<td>-4.4 ± 1.5</td>
</tr>
<tr>
<td>GA</td>
<td>94.4 ± 2.0</td>
<td>90.4 ± 2.1</td>
<td>-4.0 ± 1.6</td>
</tr>
<tr>
<td>AA</td>
<td>92.4 ± 2.8</td>
<td>89.4 ± 2.8</td>
<td>-3.0 ± 1.5</td>
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<tr>
<td>IL-10-592</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>95.5 ± 1.9</td>
<td>89.6 ± 2.0</td>
<td>-5.9 ± 1.3</td>
</tr>
<tr>
<td>CA</td>
<td>89.2 ± 2.1</td>
<td>89.5 ± 2.3</td>
<td>0.3 ± 1.3</td>
</tr>
<tr>
<td>AA</td>
<td>91.3 ± 4.8</td>
<td>86.0 ± 4.0</td>
<td>-5.3 ± 3.5</td>
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<tr>
<td>IL-18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>91.8 ± 1.9</td>
<td>89.4 ± 2.4</td>
<td>-2.4 ± 1.2</td>
</tr>
<tr>
<td>Low</td>
<td>94.2 ± 1.9</td>
<td>89.3 ± 1.8</td>
<td>-3.7 ± 1.1</td>
</tr>
</tbody>
</table>

Values are mean absolute IQ scores at age 80 and 85 ± S.E.M. Change in IQ was calculated by subtracting IQ scores at age 85 from scores at 80. IL-18 high: carriers of two copies of the haplotype associated with high transcription: IL-18-607C in combination with IL-18-137G (N = 46). IL-18 low: rest (N = 60).

* P < 0.05 in multiple regression analysis using model: IQ/change in IQ = SNP + sex + education + MAP + BMI + cholesterol + smoking + alcohol intake (only for age 85) + comorbidity (not for decline). P < 0.1 in this model (Model 2) is highlighted. Further details on statistics in Table 2b.
**IL-18 SNPs are associated with plasma TNF**

Table 4  
**Associations between cytokine gene polymorphisms and inflammatory mediators in 112 85 year olds**

<table>
<thead>
<tr>
<th></th>
<th>TNF (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>sTNFR-I (pg/ml)</th>
<th>STNFR-II (pg/ml)</th>
<th>IL-18 (pg/ml)</th>
<th>CRP (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-308</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>3.2 (2.8–3.8)</td>
<td>2.1 (1.6–2.8)</td>
<td>1744 (1522–1999)</td>
<td>3382 (3071–3723)</td>
<td>238 (201–283)</td>
<td>4.0 (2.5–6.4)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GG</td>
<td>3.3 (3.0–3.6)</td>
<td>1.9 (1.7–2.3)</td>
<td>1687 (1556–1829)</td>
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<td>238 (206–274)</td>
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<td>1627 (1417–1868)</td>
<td>3040 (2441–3786)</td>
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</table>

Values are geometric means (95% confidence intervals). IL-18 high: carriers of two copies of the haplotype associated with high transcription: IL-18-607C in combination with IL-18-137G (N=46). IL-18 low: rest (N=60).

<sup>a</sup> P<0.05 in adjusted model: log(cytokine) = SNP/haplotype + sex + MAP + BMI + cholesterol + smoking.

<sup>b</sup> P<0.05 in unadjusted model: log(cytokine) = SNP/haplotype.
Interleukin 18 gene polymorphisms predict risk and outcome of Alzheimer's disease

Paola Bossù, Antonio Ciaramella, Maria Luisa Moro, Lorenza Bellincampi, Sergio Bernardini, Giorgio Federici, Alberto Trequattrini, Fabio Macciardi, Ilaria Spoletini, Fulvia Di Iulio, Carlo Caltagirone, Gianfranco Spalletta


Background and aim: Inflammation has been extensively implicated in the pathogenesis of Alzheimer's disease (AD). Although there is evidence of a key role for cytokines in neuroinflammation processes, so far the proinflammatory cytokine interleukin (IL)-18 has not been associated with AD. The aim of this study was to investigate the impact of two polymorphisms of the human IL-18 gene promoter at positions −607 (C/A) and −137 (G/C) on both susceptibility to and progression of AD.

Results: The results revealed that the genotype distribution of the −607 (C/A) polymorphism was different between patients with AD and control subjects (χ² = 7.99, df = 2, p = 0.0184). In particular, carriers of the CC genotype were at increased risk of developing AD (OR 2.33; 95% CI 1.29 to 4.22; p = 0.0052). The observed genotypes were in Hardy–Weinberg equilibrium, as for the −607 polymorphism, whereas the −137 polymorphism appeared in Hardy–Weinberg disequilibrium only in the patient group (p = 0.0061). Finally, in a 2 year follow-up study, the −137 CC genotype was strongly and specifically associated with a faster cognitive decline (F = 4.024; df = 4, 192; p = 0.0037 for time by IL-18 −137 G/C group interaction) with no interaction effect with the apolipoprotein E ε4/ε4 allele presence.

Conclusion: As IL-18 cytokine promoter gene polymorphisms have been previously described to have functional consequences on IL-18 expression, it is possible that individuals with a prevalent IL-18 gene variant have a dysregulated immune response, suggesting that IL-18 mediated immune mechanisms may play a crucial role in AD.
The 1905-cohort (K Christensen)
Aging Research Center, University of Southern Denmark

- 1600 90-year-old people examined in 1995
- 10 years of follow-up with repeated measurements of cognitive function.
- SNPs: TNF – 308G/A, -238G/A, TNFa2 microsatellit, IL6 – 174G/C, IL10 –1082A/G, IL18 –137G/C
- IL-18 –137 is weakly associated with cognitive function in men only.
- IL-10 –1082 is associated with cognitive function in women only.
- No association between cognitive function and SNPs in TNF and IL-6 genes.

Dato et al, unpublished 2009
Genetic linkage between inflammation and AD

• Individual reports sometimes show statistically significant genetic linkage of SNPs or haplotypes in case-control studies that needs to be confirmed.

• Meta-analyses of multiple such studies are helpful in assessing an overall genetic effect. This has been done for >100 genes: http://www.alzgene
### Inflammatory genes show only very modest effects on Alzheimer’s Disease risk

Table 1 Alzheimer disease risk associated with genetic polymorphisms in immune mediators.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>Allele; position in gene</th>
<th>Number of studies in meta-analysis</th>
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<tr>
<td>α1-ACT²</td>
<td>1.06</td>
<td>0.96–1.17</td>
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<tr>
<td>CCR2</td>
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<td>CCR5</td>
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<td>Δ32</td>
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<td>MCP-1</td>
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<td>Fas</td>
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<td>T/C; –509</td>
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<td>TNF-α</td>
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<td>A/G; –308</td>
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</table>

*α1-ACT, chemokine CC motif receptor; MCP, monocyte chemotactic protein; ICAM, intercellular adhesion molecule. ²All data were obtained from meta-analyses for the listed genes at AlzGene.org (Bertram, L., McQueen, M., Mullin, K., Blacher, D. & Tanzi, R. The AlzGene Database. Alzheimer Research Forum). ³More than one meta-analysis available on AlzGene; results in table are for polymorphisms with largest available number of studies. None of the other polymorphisms showed significant effects.

Wyss-Coray, Nature Medicine 2006
Common studied polymorphisms do not affect plasma cytokine levels upon endotoxin exposure in humans

S. Taudorf,* K. S. Krabbe,* R. M. G. Berg,* K. Møller,* B. K. Pedersen* and H. Bruunsgaard**
*Department of Infectious Diseases, Centre of Inflammation and Metabolism, †Intensive Care Unit and ‡Tissue Typing Laboratory, Clinical Immunology, Rigshospitalet, University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark

Accepted for publication 15 January 2008
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Summary

The aim of this study was to investigate to what extent single nucleotide polymorphisms (SNPs) in promoter regions of genes of Toll-like receptor (TLR)-4, tumour necrosis factor (TNF)-α, interleukin (IL)-18, interferon (IFN)-γ, IL-6 and IL-10 affect the cytokine response during a controlled low-grade inflammatory response in vivo. Two hundred healthy young male volunteers were genotyped, and cytokine levels were measured in response to a low-dose intravenous bolus of Escherichia coli endotoxin. No association was detected between SNPs (TLR-4299, TLR-4399, TNF-308, IL-18-137, IL-18-607, IFN-γ874, IL-6-174, IL-10-592 and IL-10-1082) and endotoxin-induced changes in plasma levels of TNF-α, IL-6 and IL-10. IL-18 levels were unaffected by endotoxin. In conclusion, the investigated SNPs did not affect endotoxin-induced low-grade cytokine production of TNF-α, IL-6, IL-18 or IL-10 in healthy young men. Previous reports of a major heritability factor in the inflammatory response may be due to other target genes or effects in older age groups or women.

Keywords: cytokine, human endotoxaemia, low-grade inflammation, single nucleotide polymorphism
Conclusion

• Meta-analyses of inflammatory genes show very modest effects on AD risk. It is possible that other SNPs or SNPs in other genes associated with inflammation might show stronger linkage to AD or in selected groups of affected individuals.

• There is a poor correlation between SNPs and circulating cytokine proteins.
Cognitive Function Over Time in the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT)

Results of a Randomized, Controlled Trial of Naproxen and Celecoxib

ADAPT Research Group*

**Background:** Observational studies have shown reduced risk of Alzheimer dementia in users of nonsteroidal anti-inflammatory drugs.

**Objective:** To evaluate the effects of naproxen sodium and celecoxib on cognitive function in older adults.

**Design:** Randomized, double-masked chemoprevention trial.

**Setting:** Six US memory clinics.

**Participants:** Men and women aged 70 years and older with a family history of Alzheimer disease; 2117 of 2528 enrolled had follow-up cognitive assessment.

**Interventions:** Celecoxib (200 mg twice daily), naproxen sodium (220 mg twice daily), or placebo, randomly allocated in a ratio of 1:1:1.5, respectively.

**Main Outcome Measures:** Seven tests of cognitive function and a global summary score measured annually.

**Results:** Longitudinal analyses showed lower global summary scores over time for naproxen compared with placebo (−0.05 SDs; P = .02) and lower scores on the Modified Mini-Mental State Examination over time for both treatment groups compared with placebo (−0.33 points for celecoxib [P = .04] and −0.36 points for naproxen [P = .02]). Restriction of analyses to measures collected from persons without dementia attenuated the treatment group differences. Analyses limited to measures obtained while participants were being issued study drugs produced results similar to the intention-to-treat analyses.

**Conclusions:** Use of naproxen or celecoxib did not improve cognitive function. There was weak evidence for a detrimental effect of naproxen.

**Trial Registration:** clinicaltrials.gov identifier: NCT00007189

*Arch Neurol.* 2008;65(7):896-905
Conclusion

• The effect of systemic low-grade inflammation is unresolved in relation to cognitive impairment.

• Dual role of cytokines/two edged sword?
Questions

• Does systemic low-grade inflammation affect cognitive function?

• Is systemic low-grade inflammation associated with neurotrophins such as BDNF?
Neurotrophin: Regulates the growth, differentiation, function and plasticity of neurons

The mature brain:
Long term memory storage
Neuronal survival during stress
Reduced BDNF in the brain:

- Increasing age
- Alzheimer’s Disease
- Parkinson
- Major Depression
- Huntington?
BDNF in the periphery

• Mice: Crosses BBB.
  high capacity saturable transport system INTO the brain (Pan et al, Neuropharmacology 1998)

• BDNF and its specific receptor, TrkB are expressed outside the CNS:
  – atherosclerotic vessels (Donovan et al. 1995),
  – endothelial cells (Nakahashi et al. 2000),
  – skeletal muscle cells (Wiedemann et al. 2005),
  – smooth muscle cells in the vascular wall (Donovan et al. 1995)
  – monocytes (Kerschensteiner et al. 1999),
  – macrophages (Barouch et al. 2001),
  – lymphocytes (Kerschensteiner et al. 1999),
Plasma levels of BDNF were decreased in diabetic subjects relative to non-diabetics ($P<0.0001$), and in obese relative to non-obese subjects ($P=0.02$)

Krabbe et al 2006
Hypotheses

- Low BDNF is a link between Type 2 Diabetes and cognitive decline.

- Systemic low-grade inflammation inhibits BDNF production.
Is low plasma BDNF associated with cognitive function in humans without dementia?
**Hypothesis:** Low plasma BDNF is associated with cognitive function in a general population.

**Population:** 684 men and 705 women aged 57-79 years. Random sample of Eastern Finnish people.

**Cognitive function:** The CERAD neuropsychological test battery.

**Plasma BDNF:** ELISA (R&D Systems)

**Logistic regression analysis** adjusted for age, education, depression, impaired glucose metabolism, cardiovascular disease, use of antihypertensive and lipid lowering medication, use of sex hormones, smoking and alcohol consumption.
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<th>Men (n=684)</th>
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<td>P-value</td>
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<td>0.60-1.16</td>
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Plasma BDNF is associated with cognitive function, obesity and T2D

Type 2 diabetes
Metabolic Syndrome

Low BDNF
Inflammation

Low BDNF
Inflammation

Dementia
Brain-derived neurotrophic factor predicts mortality risk in old women.

Karen S Krabbe, PhD*,†, Erik L Mortensen, MSc‡, Kirsten Avlund, DMSē‡, Agnes N Pedersen, PhD§, Bente K Pedersen, DMSē, Torben Jørgensen, DMSē, Helle Bruunsgaard, DMSē

- **Hypothesis:** Low plasma BDNF predicts all-cause mortality risk in old populations.
- **Population:** 188 85-year-old participants from the 1914-cohort, Research Centre for Prevention and Health. 5-6 years of follow-up
- **Measurements:** Plasma and serum BDNF at baseline
- **Statistics:** Survival analyses (Cox regression) with BDNF as a categorical variable or as a continuous variable adjusted for the effect of comorbidity and IL-6.

Krabbe et al, JAGS 2009
Low plasma BDNF is associated with brain disease and mortality in 117 85-year-old women (5 years of follow-up)

Krabbe et al, unpublished data
Serum BDNF is not associated with mortality

Krabbe et al, JAGS 2009
Conclusion

- Low plasma BDNF levels accompanies obesity and impaired glucose metabolism.

- Plasma BDNF is a biomarker of impaired memory and general cognitive function in ageing women.

- Low plasma BDNF is an independent biomarker of mortality risk in old women.
Correlation analyses (Pearson) in 188 85-year olds

<table>
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<th>Men</th>
<th>Men</th>
<th>Women</th>
<th>Women</th>
</tr>
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<tbody>
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<td>Plasma BDNF</td>
<td>Serum BDNF</td>
<td>Plasma BDNF</td>
<td>Serum BDNF</td>
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<tr>
<td>TNF-α</td>
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<td>R=-0.1</td>
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<td>R=-0.04</td>
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<td>IL-6</td>
<td>R=-0.2</td>
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<td>R=-0.04</td>
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<td>CRP</td>
<td>R=0.08</td>
<td><strong>R=-0.36</strong></td>
<td>R=0.08</td>
<td><strong>R=-0.21</strong></td>
</tr>
</tbody>
</table>
Plasma BDNF and acute inflammation *in vivo*

- 12 young (20-30yrs) and 7 elderly (60-70 yrs).
- A intravenous bolus of E.coli endotoxin 2 ng/kg
- (Human in vivo sepsis model)

Krabbe et al, unpublished data
Acute inflammation and plasma BDNF
Experimental findings - acute inflammation

BDNF levels in plasma relative to baseline

% of baseline

hours

control
Etox
Conclusion

- Low plasma BDNF levels accompanies obesity and impaired glucose metabolism.

- Plasma BDNF is a biomarker of impaired memory and general cognitive function in ageing women.

- Low plasma BDNF is an independent biomarker of mortality risk in old women.

- Low plasma BDNF is not associated with systemic low-grade inflammation.
Summary

• Systemic low-grade inflammation is associated with reduced cognitive function in population studies.

• It is unclear if systemic low-grade inflammation is a driving force, a bystander, or a beneficial response in cognitive decline.
  – Animal models show a dual role of cytokines in neurodegeneration.
  – Experimental human models of acute inflammation suggest dose dependent effects.
  – Modest effects of SNPs in inflammatory genes. Poor correlation between SNPs and circulating cytokine protein.
  – No convincing effect of anti-inflammatory drugs.

• There is no simple relation between systemic low-grade inflammation and plasma BDNF.
Acknowledgements

• CIM
  – Karen Krabbe
  – Maria Pedersen
  – Bente Klarlund Pedersen

• Aging Research Center, University of Southern Denmark
  – Kaare Christensen
  – Karen Andersen- Ranberg
  – Lene Christiansen
  – Serena Dato
  – Mikael Thingaard
  – Jakob v Hjelmborg

• Research Centre for Prevention and Health
  – Torben Jørgensen

• University of Copenhagen
  – Erik Lykke Mortensen
  – Kirsten Avlund

• Kuopio Research Institute of Exercise Medicine
  – Rainer Rauramaa
Questions

• How would you design a study to test how systemic TNF and IL-6 affect cognitive function?

• How would you design a study to test the hypothesis that inflammation in peripheral tissues accelerates neurodegeneration?