Vascular factors and Alzheimer’s disease
The importance of blood pressure

Ingmar Skoog
Director for Centre for Ageing and Health (AgeCap)
Neuropsychiatric Epidemiology (Epinep)
Institute of Neuroscience and Physiology
Sahlgrenska Academy
University of Gothenburg
Sweden
NEUROPSYCHIATRIC EPIDEMIOLOGY
THE GOTHENBURG H70 BIRTH COHORT STUDIES

• H70-study
• H85-study
• The 95+ Study
• The Prospective Population Study of Women (PPSW)

• Representative samples based on birth dates
Systematic samples of 70-year-olds living in Gothenburg sampled from the Swedish Population Register selected based on birth dates (e.g. 2, 5, 8, 12, 15, 18 etc)
H85 GÖTEBORG  
(Total N=1556)

<table>
<thead>
<tr>
<th>Age</th>
<th>85</th>
<th>88</th>
<th>90</th>
<th>92</th>
<th>95</th>
<th>97</th>
<th>99</th>
</tr>
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<tbody>
<tr>
<td>1901-02</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1923-24</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1930</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td></td>
<td></td>
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</table>

Systematic samples from the Swedish Population Register selected based on birth dates (e.g. 2, 5, 8, 12, 15, 18 etc)
# Prospective Population Study of Women in Gothenburg

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>1908</td>
<td>60</td>
<td>66</td>
<td>73</td>
<td>84</td>
<td>92</td>
<td>97</td>
<td>101</td>
<td>108</td>
</tr>
<tr>
<td>1914</td>
<td>54</td>
<td>60</td>
<td>67</td>
<td>78</td>
<td>86</td>
<td>91</td>
<td>95</td>
<td>102</td>
</tr>
<tr>
<td>1918</td>
<td>50</td>
<td>56</td>
<td>63</td>
<td>74</td>
<td>82</td>
<td>87</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>1922</td>
<td>46</td>
<td>52</td>
<td>59</td>
<td>70</td>
<td>78</td>
<td>83</td>
<td>87</td>
<td>94</td>
</tr>
<tr>
<td>1930</td>
<td>38</td>
<td>44</td>
<td>51</td>
<td>62</td>
<td>70</td>
<td>75</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>N</td>
<td>1462</td>
<td>661</td>
<td>580</td>
<td>450</td>
<td>250</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Year of examination and ages studied
General examinations

- Neuropsychiatric examination
- Key informant interview
- Medical examination (somatic disorders, alcohol, smoking)
- Functional ability (ADL, iADL)
- Anthropometry (length, weight etc)
- Social interview (social network, physical, social and cultural activities, life events, working life etc)
- Psychometric testings
- Personality (Eysenck, Five Factor, KASAM)
- Focus groups
- Gender
- Blood, serum, plasma
- Genetic analyses
- ECG, blood pressure
- Lung function
- Physical function (walking speed, hand grip, balance, chair stand etc)
- Audiology
- Ophtalmology
- Dietary examination, DEXA (bone, muscle, fat)
- CT and MRI of brain
- Lumbar puncture/ Neurochemistry
Background
- Prevalence of hypertension increases with age
- More than 50% of elderly populations have hypertension with current criteria (140/90)
- An emerging problem in low and middle income countries
End-organ damage

- The arterial tree
- Heart
- Kidney
- **Brain**
- Eyes
Hypertension and the brain

- Cerebral autoregulation
- Blood brain barrier dysfunction
- Decreased cerebral blood flow
- Stroke (hemorrhagic, ischemic)
- White matter lesions
- Alzheimer’s disease
A 15-year follow-up of blood pressure and Alzheimer’s disease

Skoog et al. Lancet 1996
LONGITUDINAL STUDIES ON BLOOD PRESSURE AND ALZHEIMER’S DISEASE

Previous high blood pressure

5-15 years

Alzheimer’s disease in late life

The H70-study in Gothenburg
Skoog et al. Lancet 1996

The Honolulu-Asia Aging Study
Launer et al. Neurobiol Aging 2000

The Rotterdam Study
Ruitenberg et al. Dissertation 2000

Kaiser Permanente, USA
Whitmer et al. Neurology 2005

Kuopio, Finland
Kivipelto et al. BMJ 2001

Kungsholmen Study
Qiu et al Arch Neurol 2003

Chinese Study
Wu et al Life Science 2003
HONOLULU-ASIA AGING STUDY

High midlife systolic blood pressure → Neuritic plaque ↑ in old age

Petrovitch et al. Neurobiology of Aging 2000
Higher late-life systolic blood pressure

↓

Neurofibrillary tangles ↑

in old age

Arvanitakis et al. Neurology 2018
The times they are a-changing
Time-trends in blood pressure
Important time points

• 1960s: Treatment of diastolic hypertension
• 1990s: SHEP trials. Treatment of systolic blood pressure
• 2000s: HYVET trial: Importance to treat hypertension above age 80
• Changing definitions of hypertension and when to treat
Life-courses of birth cohorts in the Western World during the 20th Century.

Increasing levels of education, better perinatal care, improved working conditions, access to healthcare and the welfare state

Widespread poverty, poor perinatal care  WWI famine  Great Depression  WWII Famines in Germany, Holland  Freezers, polio epidemics  Manned moon landings  Fall of Berlin Wall

Flu Pandemic  Penicillin  Treatment of hypertension  Treatment of cholesterol

Systematic samples of 70-year-olds living in Gothenburg sampled from the Swedish Population Register selected based on birth dates (e.g. 2, 5, 8, 12, 15, 18 etc)
Mean blood pressure among 70-year-olds 1971-2015

<table>
<thead>
<tr>
<th>Birth year</th>
<th>Exam</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mmHg</td>
<td>mmHg</td>
</tr>
<tr>
<td>1901-02</td>
<td>1971-72</td>
<td>161/95</td>
<td>173/98</td>
</tr>
<tr>
<td>1906-07</td>
<td>1976-77</td>
<td>161/87</td>
<td>161/88</td>
</tr>
<tr>
<td>1930</td>
<td>2000-01</td>
<td>156/87</td>
<td>154/85</td>
</tr>
<tr>
<td>1944</td>
<td>2014-15</td>
<td>140/80</td>
<td>140/79</td>
</tr>
</tbody>
</table>
Systolic blood pressure from age 70 to 79 in two birth cohorts

Joas et al J Hypertens. 2017;35(7):1424-1431
A 15-year follow-up of blood pressure and Alzheimer’s disease

Skoog et al. Lancet 1996
Systolic blood pressure from age 70 to 85 in relation to dementia onset between age 79 and 85 in two birth cohorts born 1901-02 and 1930

Skoog et al. Lancet 1996
Skoog et al. 2018
Has blood pressure as a risk factor for dementia disappeared?
Blood pressure trajectories in relation to late life dementia in women followed for 38 years

Joas et al. Hypertension 2012
Systolic blood pressure from age 70 to 85 in relation to dementia onset between age 79 and 85 in two birth cohorts born 1901-02 and 1930

Skoog et al. Lancet 1996
Skoog et al 2018
Is this a cause of changing frequency of dementia?
PREVALENCE OF DEMENTIA IN 85-YEAR-OLDS 1986-87 AND 2008-10

<table>
<thead>
<tr>
<th></th>
<th>1986-87</th>
<th>2008-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>494</td>
<td>571</td>
</tr>
<tr>
<td>%</td>
<td>31</td>
<td>24 *</td>
</tr>
</tbody>
</table>

Type of dementia in 85-year-olds examined in 1986-87 and 2008-9

<table>
<thead>
<tr>
<th></th>
<th>1986-87</th>
<th>2008-9</th>
<th>p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>14</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Has blood pressure as a risk factor for dementia disappeared?
The global perspective

- The example of blood pressure
Systolic blood pressure in men

Systolic blood pressure in women

Trends in systolic blood pressure world wide

The global perspective

Availability and affordability of cardiovascular disease medicines is lower in low and middle-income countries
(Khatib et al.. Lancet. 2016;387:61-9)
Time-trends in blood pressure

- Decrease in high income countries
- Not entirely due to increase in use of antihypertensive treatment
- Increase in low and middle income countries
- Time-trends show the importance of environmental factors
Trajectories of blood pressure
A 15-year follow-up of blood pressure and Alzheimer’s disease

Skoog et al. Lancet 1996
Blood pressure in relation to dementia in 85-year-olds

<table>
<thead>
<tr>
<th></th>
<th>1986-87</th>
<th>2008-10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dementia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>162</td>
<td>141</td>
<td>***</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>145</td>
<td>134</td>
<td>***</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>158</td>
<td>140</td>
<td>***</td>
</tr>
</tbody>
</table>

2008-10: Ribbe et al 2017
Lower blood pressure in persons with dementia

—

...but it is more complicated than so
Prevalence of hypertension (=blood pressure above 160/90) in 85-year-olds

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-demented (N=346)</td>
<td>63.9</td>
</tr>
<tr>
<td>Demented (N=147)</td>
<td>46.3 ***</td>
</tr>
<tr>
<td>Alzheimer disease (N=64)</td>
<td>42.2</td>
</tr>
<tr>
<td>Vascular dementia (N=69)</td>
<td>53.6</td>
</tr>
</tbody>
</table>
Hypertension accelerates cognitive decline in Alzheimer’s disease

- **Hypertension** at baseline was associated with **steeper cognitive decline** in Alzheimer patients below the age of 65. No effect of antihypertensive treatment (Bellew et al 2004)

- **Systolic hypertension** at baseline was related to **steeper cognitive decline** in Alzheimer patients from the Cashe County Study. Mainly among the elderly. Antihypertensive treatment was related to a slower decline (Mielke et al 2007)
BLOOD PRESSURE IN ALZHEIMER´S DISEASE

- Increased before onset
- Lower just before or after onset
Temporal ordering of the pathological processes of AD

Jack et al. Lancet Neurology 2013
Hypertension and the brain

- Cerebral autoregulation
- Blood brain barrier dysfunction
- Decreased cerebral blood flow
- **Stroke** (hemorrhagic, ischemic)
- White matter lesions
- Dementia and Alzheimer’s disease
The risk of dementia in relation to stroke in women followed over 44 years

Guo, Skoog et al Alz Dem 2018
Increased risk for dementia before stroke shows the importance of 'silent' vascular burden

- Silent infarcts
- Ischemic white matter lesions
- Co-occurrence of many different cerebrovascular disorders in the same individual (mixed cerebrovascular disorders)
- Shared risk factors
Hypertension and the brain

- Cerebral autoregulation
- Blood brain barrier dysfunction
- Decreased cerebral blood flow
- Stroke (hemorrhagic, ischemic)
- **White matter lesions**
- Dementia and Alzheimer’s disease
White matter lesions on CT and the development of dementia during a 10 year follow-up

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>(95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>3.8</td>
<td>(1.3-7.2)</td>
</tr>
<tr>
<td>Dementia</td>
<td>4.0</td>
<td>(1.2-11.8)</td>
</tr>
</tbody>
</table>

Gudmundsson et al. Eur J Neurol 2015
Blood pressure in relation to white matter lesions on CT in 2000. The Prospective Population Study on Women in Göteborg. OR per 10 mmHg increase in blood pressure

<table>
<thead>
<tr>
<th>Year</th>
<th>SBP OR (95% CI)</th>
<th>DBP OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968</td>
<td>0.9 (0.8-1.1)</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>1974</td>
<td>0.9 (0.8-1.1)</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>1980</td>
<td>0.9 (0.8-1.0)</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>1992</td>
<td>1.0 (0.9-1.1)</td>
<td>1.3 (1.0-1.6)</td>
</tr>
</tbody>
</table>

Guo et al Hypertension 2009
CONCLUSIONS

- Hypertension is very common in elderly populations
- Most cases are not detected and treated
- Treatment of hypertension reduces risk of stroke and cardiovascular death in all ages
- Higher blood pressure is related to later development of dementia and Alzheimer’s disease
- Antihypertensive treatment is related to lower risk of dementia in observational studies
- Hypertensives even in very old age need to be treated, irrespective of dementia, to prevent vascular disease including stroke
CONCLUSION

- Blood pressure decrease in high income countries
- Blood pressure increase in low income countries
- Mean blood pressure lower in persons with dementia
- We need to learn more about the trajectory of blood pressure in relation to preclinical and clinical AD
- A large proportion of Alzheimer patients has hypertension, which needs to be treated
EPINEP
Neuropsychiatric Epidemiology
Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
Sahlgrenska Academy
University of Gothenburg

Research Group Leader: Ingmar Skoog
www.epinep.gu.se

Senior Researchers
Margda Waern
Svante Östling
Anna Zettergren
Silke Kern
Hanna Falk
Elisabet Rothenberg
Kerstin Frändin
Tore Härlström
Ingvar Karlsson
Deborah Gustafson

Researchers with PhD
Pia Gudmundsson
Xinxin Guo
Helena Hörder
Lena Johansson
Jürgen Kern
Madeleine Mellqvist Fässberg
Simona Sacuiu
Robert Sigström
Stefan Wiktorsson
Daniel Jaraj

PhD students
Jenna Al-Najjar
Erik Joas
Isak Fredén Klenfeldt
Johan Nilsson
Mats Ribbe
Therese Rydberg
Johan Skoog
Felicia Nord
Hanna Wetterberg
Lina Rydén
Jessica Samuelsson

Scientific coordinator
Anna Zettergren

Administrative coordinator
Tina Jacobsson

Statisticians
Valter Sundh
Erik Joas
Yadi Nejad
Nazib Seidu
Neuropsychiatric Epidemiology
EPINEP
http://iagger2019.se

See you in Gothenburg!