World Stroke Academy

Stroke treatment gaps: men vs. women

This case study was created by Associate Professor Christine Kremer, University Hospital Malmö/Lund and Lund University, Sweden, for the World Stroke Academy.

Why are gender differences in stroke important?

- Differences in presentation
- Stroke etiology
- Risk factors in women, modifiable, non-modifiable, at what age?
- Outcome, Recurrency, prognosis?

Mortality stroke projected numbers of deaths

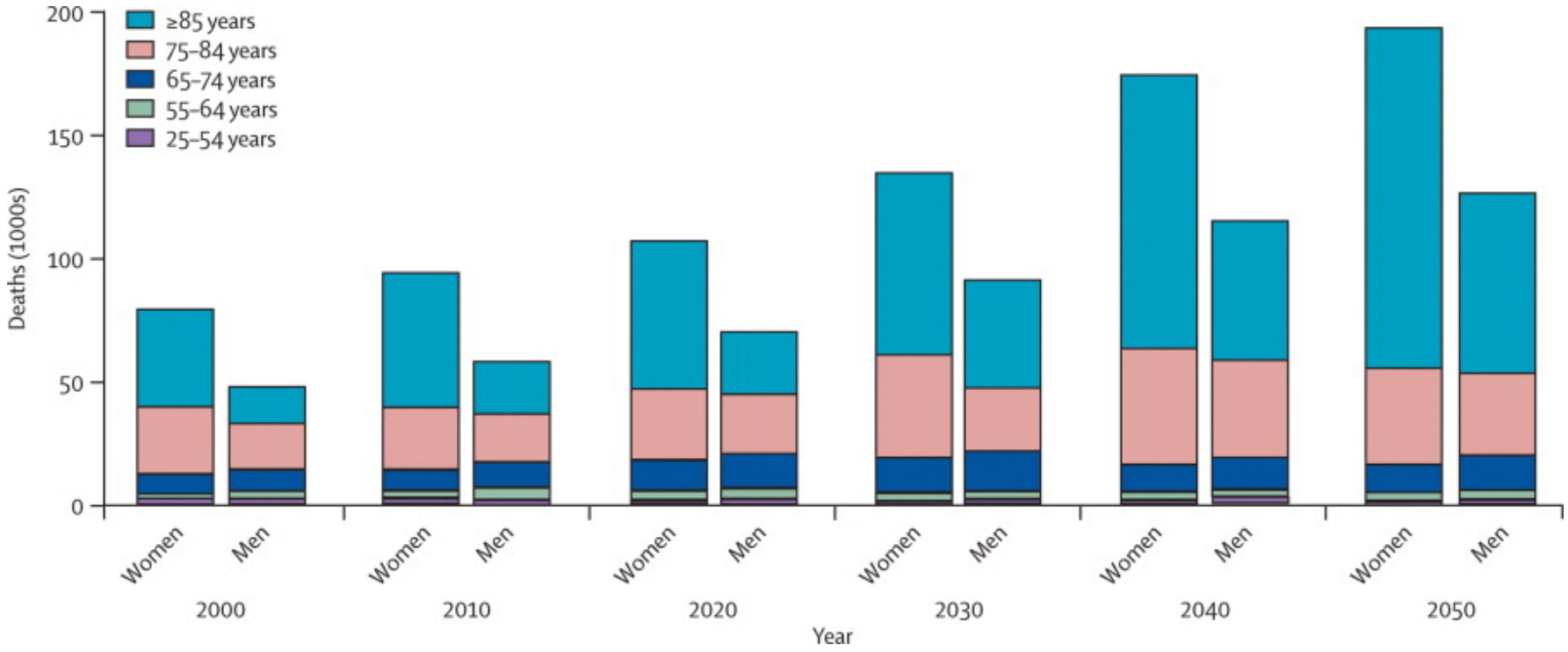


Figure 1. Reeves, J,Bushnell, C. Lancet Neurology 2008. 10: 915-926. Projected number of deaths from stroke among whites (USA, 2000–2050)

Gender-specific mortality-adjusted cumulative incidence (lifetime risk) of stroke.

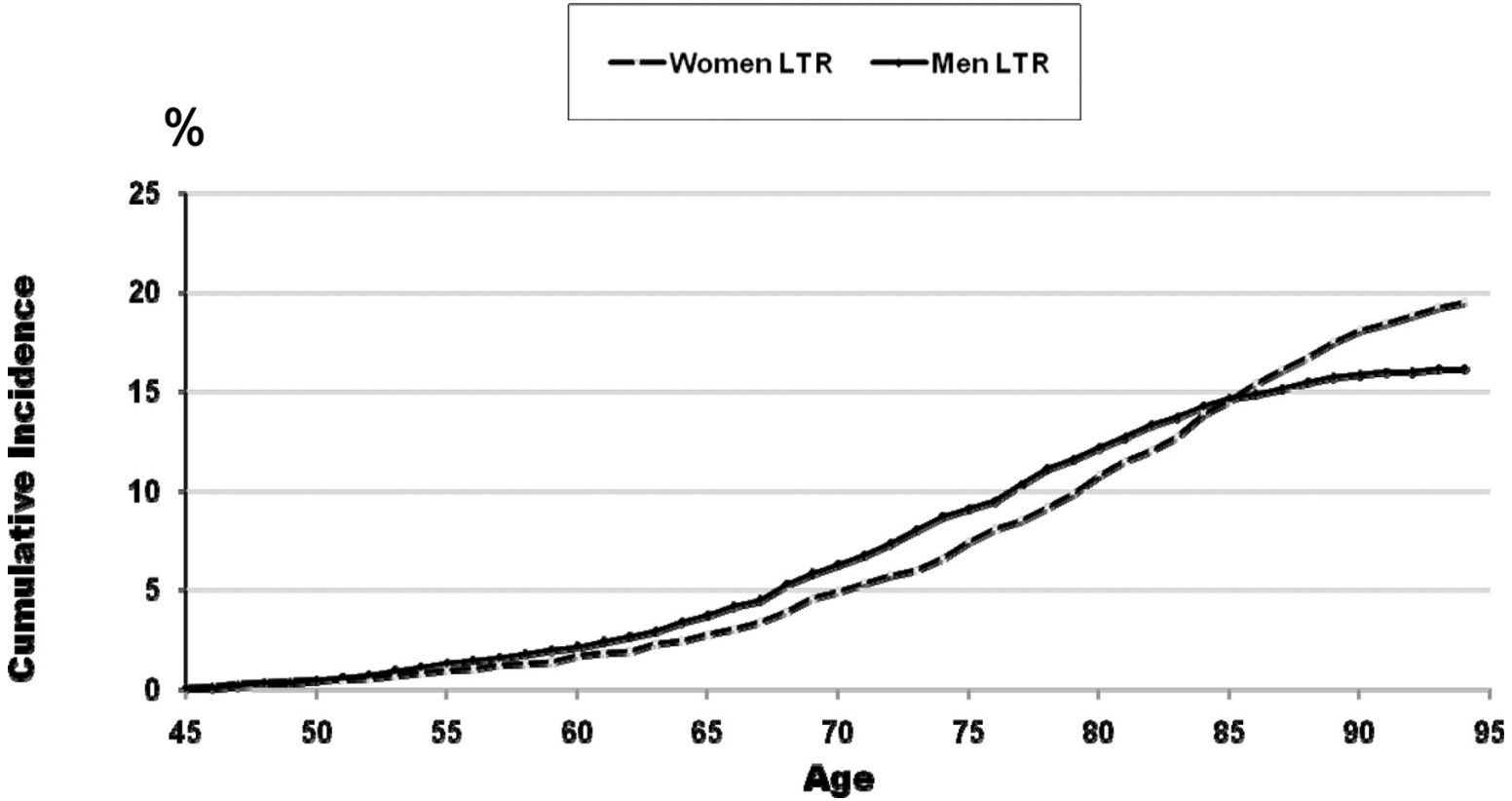


Figure 2. Rodica E. Petrea et al. Stroke. 2009;40:1032-1037

Presentation and admission

- Higher percentage of non-traditional stroke symptoms [1]
- More stroke mimics
- Treatment delay [2]

[1]Bushnell et al Lancet Neurology 2018, 17: 641-65

[2] Mainz et al Stroke 2020 Aug;51:2332-2338

Sex differences prevention and treatment

- Primary prevention ASA - ASA may be more effective
- Intravenous thrombolysis- higher mortality- lower rate of independence
- Endovascular therapy - lower rate of independence
- Stroke prevention in atrial fibrillation - lower mortality in women treatment with DOAC

Reference: Kremer et al. Sex differences in prevention and acute treatment of ischemic stroke- a systematic review and meta-analyses, unpublished, under review

Hemorrhagic stroke

- Men > women (< 80) (132 vs. 98)[1]
- Large global differences (asian > caucasian)
- Outcome comparable (Caucasian[2] , Asian[3])
- Tendency towards better outcome in women[4], perihematoma growth[5]?

Reversed in women >80

- Relative increase OAC related bleedings

[1]Suzanne Barker-Collo et al. Neuroepidemiology 2015;45:203–214;
[2] Arnstein Tveiten et al Eur Neurol 2012;67:240–245
[3] Shigematsu K et al. Acta Neurol Scand 2015: 132: 59–64;
[4] Justin T. Hsieh PLOS ONE | DOI:10.1371/journal.pone.0152945
[5]Wagner I et al. Eur J Neurol 2012, 19: 1477–1481

Subarachnoid hemorrhage

- Women > men (1,24 - nearly doubled) smoking/hypertension/excessive alcohol consumption
- Outcome comparable (adjusted data)[1;2]

Complications

- Delayed Ischemia tendency women > men [3](data limited)

[1] Ziemba-Davis M J Stroke and Cerebrovas Dis 2014; 5: 1073-1082;

[2] Hamadan A et al. J Neurosurg 2014.121:1367–1373;

[3] de Rooij et al. Stroke. 2013;44:43-54

Incidence of subarachnoid haemorrhage by age and gender.

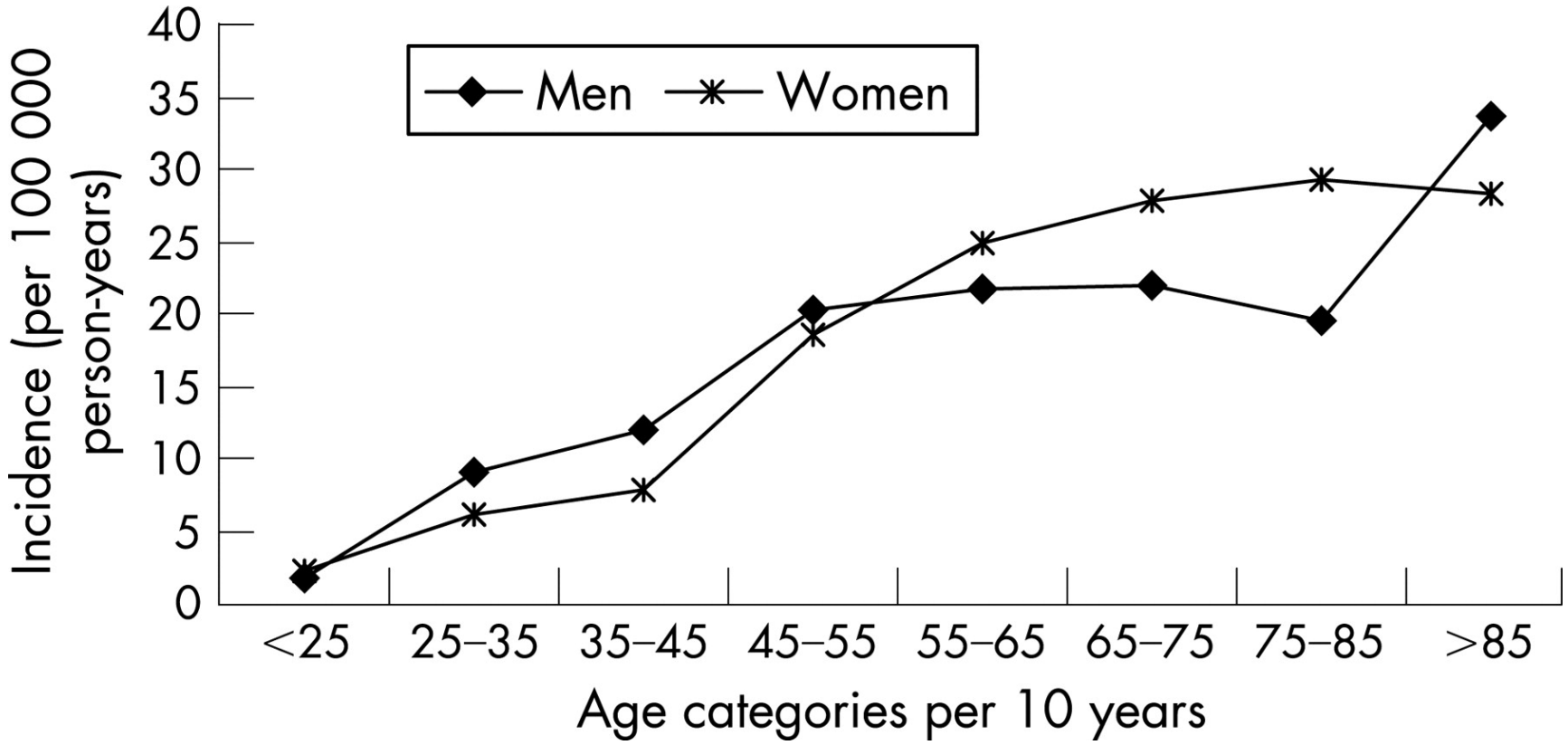


Figure 3. N K de Rooij et al. J Neurol Neurosurg Psychiatry 2007;78:1365-1372

Ischemic Stroke etiology age - dependent

- Older
- Cardioembolic ♀♀♂
- Large artery atherosclerosis ♂♂♀
- Lacunar ♂♂♂♀

- Younger pregnancy- related- hormonal therapy
- Cardioembolic ♂♀
- Large artery atherosclerosis ♂♀
- Unknown embolic source ♂♀
- Venous stroke ♀♀♀

Sex Differences in First-Ever Acute Stroke Roquer et al Stroke. 2003;34:1581-1585.

Stroke Etiology

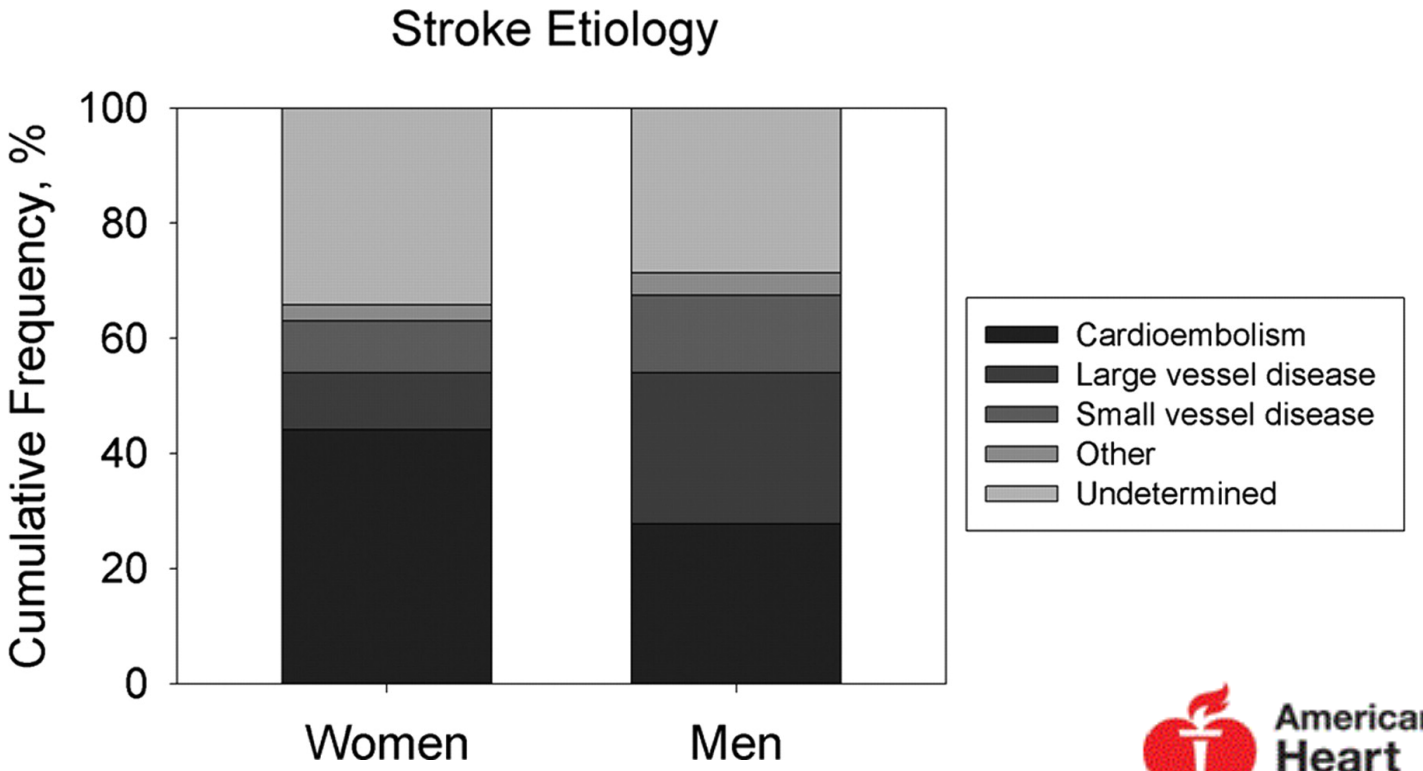


Figure 4. Alex Förster et al. Stroke. 2009;40:2428-2432

Younger vs. older women vs. men

- Hormonal (estrogen) therapy - dose-dependant [1](smoking/migraine)
- Cerebral venous thrombosis – Puerperium - obesity, hormonal therapy [2]
- Migraine with aura - migraineous stroke? [3] (posterior circulation)
- Reversible vasoconstriction syndrome (SAH/Stroke)

[1]Roach RE et al Cochrane Database of Systematic Reviews 2015;

[2]Zuurbier S et al JAMA Neurol. 2016 May 1;73(5):579-84.

[3] K. Laurell et al Eur J Neurol 2011;18: 1220–1226; Anne Ducros et al. Brain 2007, 130: 3091-3101.

Type of stroke

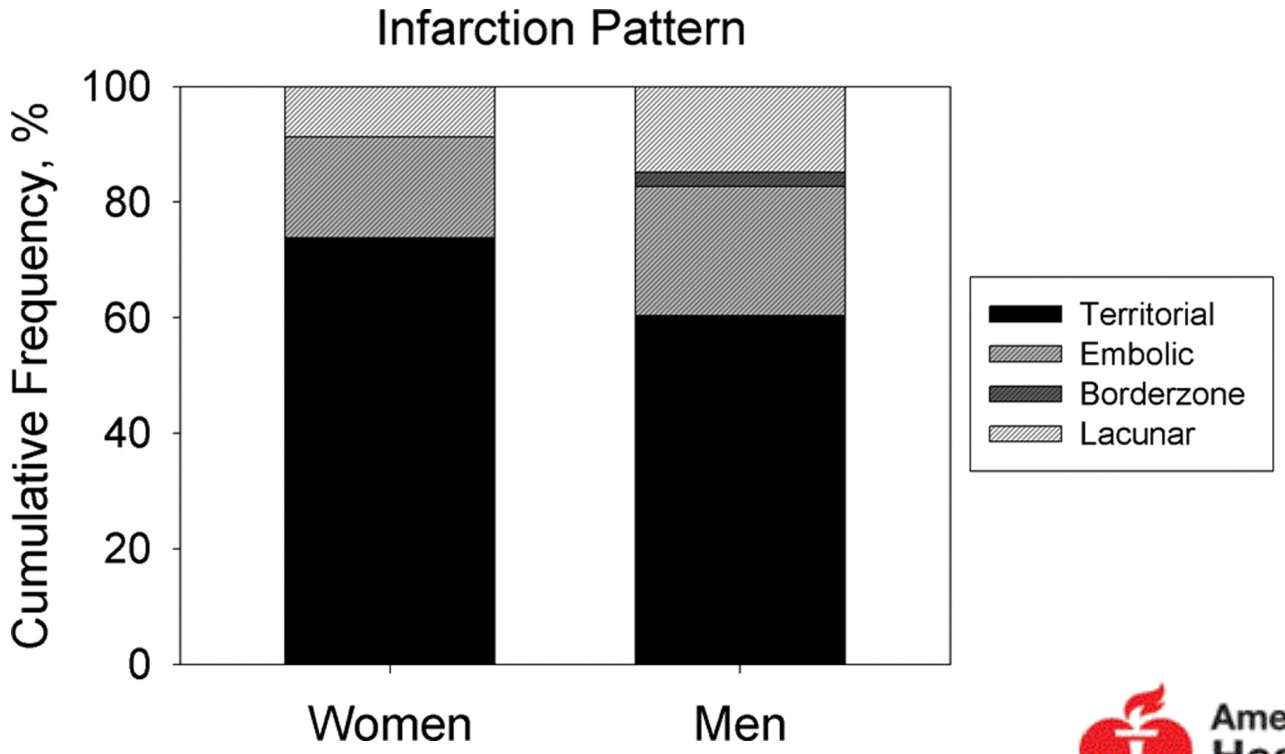


Figure 5. Alex Förster et al. Stroke. 2009;40:2428-2432

Women anterior vs. posterior circulation strokes

- Anterior circulation stroke (embolic)
  - Women > men

- Posterior circulation stroke(embolic/lacunar)
  - Men > women

Frid et al J Neurol. 2020 Mar;267(3):649-658

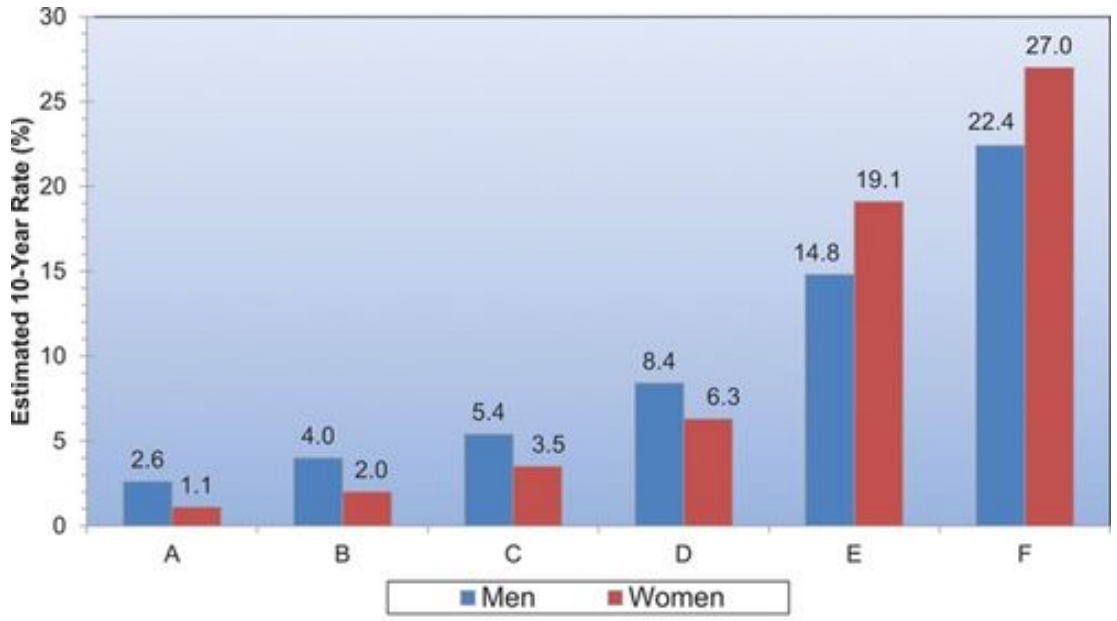
Stroke risk factors

- **Modifiable**
  - Blood pressure
  - Diabetes
  - Metabolic syndrome
  - Dyslipedemia
  - Smoking

Madsen et al, Focused update- Impact of conventional risk factors on stroke in women: an update Stroke 2018; 49, 3 : 536-542

- **Not-modifiable**
  - Pregnancy, post-partum
  - Migraine w/ aura
  - Atrial fibrillation
  - Post-menopausal - Hormonal replacement therapy

Stroke risk and co-morbidities



	A	B	C	D	E	F
Blood Pressure*	95-105	138-148	138-148	138-148	138-148	138-148
Diabetes	No	No	Yes	Yes	Yes	Yes
Cigarette Smoking	No	No	No	Yes	Yes	Yes
Prior AF	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

* - Closest ranges for women are : 95-104 and 115-124.

Figure 6. Dariush Mozaffarian. Circulation. Heart Disease and Stroke Statistics—2016 Update, Volume: 133, Issue: 4, Pages: e38-e360, DOI: (10.1161/CIR.0000000000000350)

Sex Differences in Risk Factor Prevalence, Associations, and Treatment Disparities, Women Compared With Men

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Risk Factor	Prevalence	Association With IS	Treatment Disparity
Hypertension	Lower in women (vs men) in younger age groups, higher in older age groups	Similar in women (vs men) in younger age groups, higher in older age groups	In younger age groups, women more likely to have BP controlled; in older age groups, women less likely to have BP controlled
Dyslipidemia	Data conflict; either similar between sexes or lower in women	Lower in women	Women less likely to be on statins and have LDL controlled
Atrial fibrillation	Higher in women	**Higher in women**	Women less likely to be prescribed oral anticoagulants, less likely to have cardiac ablation, and receive lower doses of NOACs
Migraine	Higher in women	**Higher in women**	Unknown if migraine treatment reduces stroke risk
Diabetes mellitus	Similar women vs men	**Higher in women**	Data conflict on sex differences in meeting HbA1c goal
Cognitive impairment	Higher in women	Unknown whether there is a sex difference	Women less likely to be treated with antidementia drugs

Madsen et al, Focused update- Impact of conventional risk factors on stroke in women: an update. Stroke 2018; 49, 3 : 536-542

Prognosis- Outcome

- Post-stroke depression
- Cognitive impairment
- Age
- Social factors, loneliness
- „unhappiness stroke“?
- Stress and vascular disease?

Gall S et al : Focused update in Patient Reported Outcome measures Stroke 2018;49:531–53

Outcome - Stroke Recurrency

- More severe strokes
- Higher recurrency stroke - atrial fibrillation [1]
- Less aggressive treatment in women
- „Underscreened“ ?

[1] Hong Y et al. Front Neurol.2017;8:166

Lack of evidence

- Underrepresentation of women in randomized clinical trials [1]
- Exclusion of older women
- Lack of sex –specific analysis [2]

[1] Tsivgoulis et al Ther Adv Neurol Disord. 2017;10(5):241-4.;

[2] Carcel et al Int J Stroke. 2019 Dec;14(9):931-938.

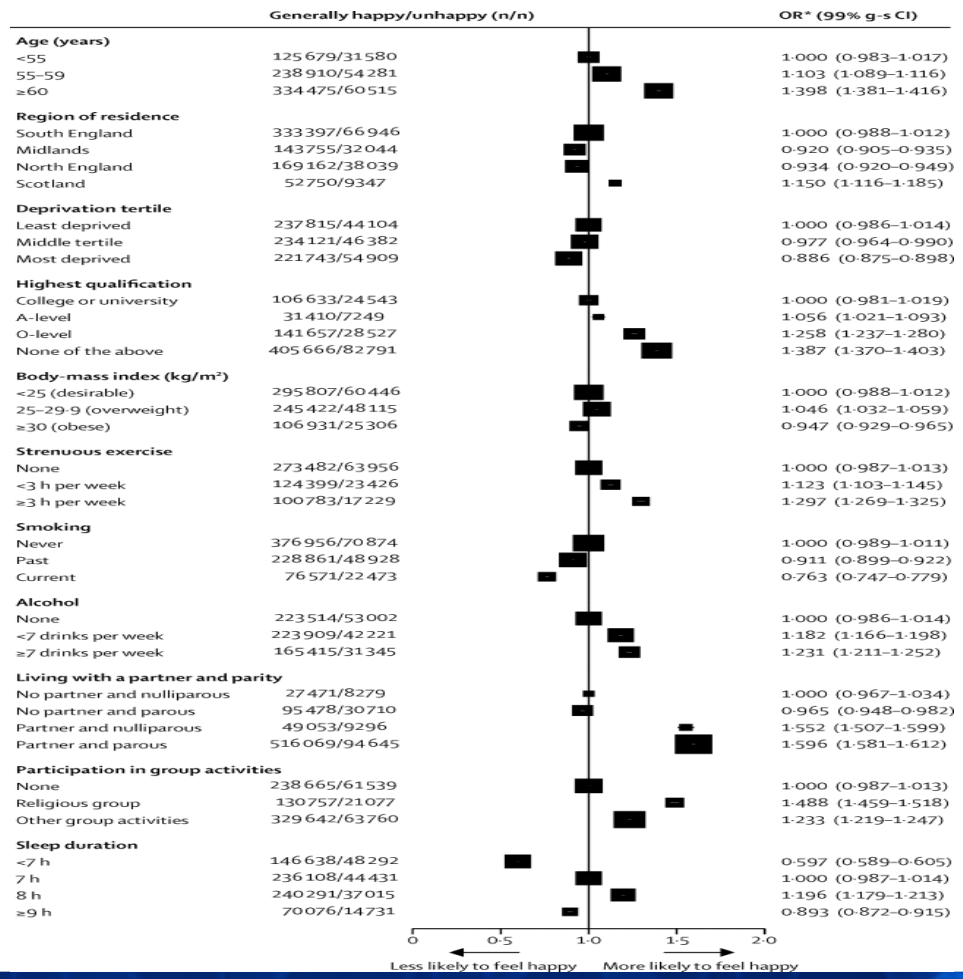
Future directions

- Sex as a variable prospectively [1]
- Sex-specific analysis
- Include females of all ages into trials
- Risk factors – screening- prevention- follow-up

[1] Azarpazhooh M et al Assess study J neurol sciences 2019;399:209-213

Does happiness itself directly affect mortality? The prospective UK Million Women Study

- COVID?



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Thank you for your attention!

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