

Stroke, gender and sex

Francesca Romana Pezzella¹, Valeria Caso²

¹Stroke Unit, AO S Camillo Forlanini, Roma; ²Stroke Unit, Santa Maria della Misericordia Hospital, University of Perugia, Italy

The question of gender in science may be addressed from different disciplines and perspectives. Londa Schiebinger, professor of history of science at Stanford University, California, USA, a leading international authority on gender and science is known to have said:

- Unconscious sex and gender bias can be socially harmful and expensive... gender should be included in all relevant phases of research: setting priorities, gathering and analysing data, evaluating results, developing patents and, finally, transferring ideas to markets.
- Science and technology should consider the biological and social needs of both women and men.
- Gender disparities are present at all levels of research, examples include the failure to use female cells, tissues and animals in basic biomedical research; women show an underrepresentation in clinical trials.
- Prejudices and preconceptions may act at different levels, osteoporosis is a clear and interesting example, this condition has long been defined as a disease mainly of post-menopausal women – an assumption that has shaped screening, diagnosis and treatment... Yet after the age of 75, men account for nearly one-third of osteoporosis – related hip fractures.

Research

In 1993, the NIH Revitalization Act required the inclusion of women in NIH-funded clinical research. However inclusion of women is not required at phases 1 and 2 of NIH-funded human subject trials when critical safety and dosage issues are addressed. Eighty percent of the drugs taken off the market between 1997 and 2000 “had disproportionately adverse effects on women”, starting a call for action for “Sex Balancing” in clinical and now pre-clinical studies.

“The over-reliance on male animals and cells in pre-clinical research obscures key sex differences that could guide clinical studies”. “And it might be harmful: women experience higher rates of adverse drug reactions than men do¹.”

Sex

Sex refers to biological qualities and characteristic of women (females) and men (males) in terms of reproductive organs and functions based on chromosomal complement and physiology. As such, sex is globally understood as the classification of living things as male and female, and intersex.

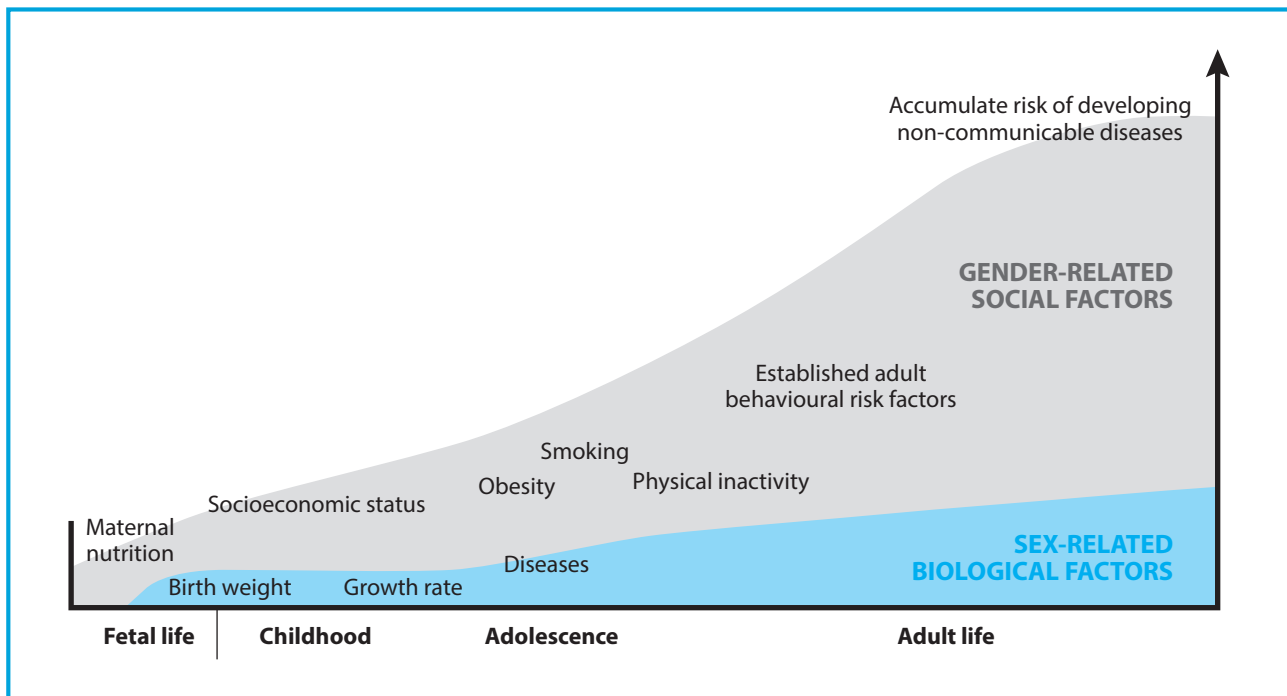
Gender

Gender is a socio-cultural process. It refers to cultural and social attitudes that together shape and sanction “feminine” and “masculine” behaviours, products, technologies, environments, and knowledge.

Sex and gender related differences in cardiovascular disease and stroke are issues of increasing interest. In terms of Stroke Epidemiology, population-based studies have shown that postmenopausal women (>65 years of age) have a higher risk of stroke than men. Stroke incidence is 33% higher in men. Stroke prevalence is 41% higher in women: women have been reported to have a higher lifetime risk of stroke compared with men, along with higher rates of post-stroke mortality, disability, depression, and dementia. Mortality after stroke is higher in women compared with men. We have a limited understanding of the factors that explain the disparity between survival of men and women after stroke.

In a recent study, Caso et al. review available data on stroke incidence and prevalence based on transition theory². The epidemiologic transition theory classifies countries into four stages according to their levels of industrialization and economy. To better understand how to prevent, treat, and manage stroke both in men and women it is critical to investigate availability on stroke epidemiology in women worldwide; if there are sex differences in stroke epidemiology, describe the nature of these differences and whether these are consistent across countries/groups of countries.

For countries that are placed, according to the transition theory, in the first and second stages, reliable regis-



Cumulative life course risk factors for non-communicable disease highlighting the influence of sex and gender-related factors. Modified from Darton-Hill et al, 2004.

tries and health certification are lacking; limited access to both emergency and general care for women; only 56% of stroke-related deaths occur in hospital in these two stages.

The incidences of stroke in women is on the rise due to the aging population. “The real numbers” are probably underestimated due to the lower access to care worldwide. Cultural and religious norms are important barriers in the access to health services for women in different countries.

Clinical issues

Women are reported to experience more aphasic disorders, visual field disturbances and dysphagia than men; while there have been no reported differences in either motor or sensory deficits, stroke in women is more frequently associated with anterior circulation ischemia, while men are more likely to have cerebellar and brain-stem symptoms and higher incidences of posterior circulation syndromes³.

Awareness and clinical outcome

Women have been reported to possess a better knowledge of major stroke symptoms and stroke risk factors and to learn from health behaviour and stroke cam-

paigns independently from educational level where for men it was found instead that the level of education influences their process of experiential learning. It has been demonstrated that the US knowledge of stroke warning signs is low among a nationally representative sample of women, especially among Hispanics. In contrast, the knowledge to call an emergency number when experiencing signs of stroke is high.

Recently Caso et al. demonstrated that the female sex is not a risk factor in the outcomes when a stroke unit treats the patient⁴. In this setting the clinical outcomes are undoubtedly influenced by the fact that all patients receive the best treatment available. Moreover, these are not limited by social conditions that could hinder the delivery of such treatment. Where these disparities have been addressed with effective programs, improvements in what once were worse outcomes for women have been turned around.

Principle risk factors

Women with diabetes mellitus have greater stroke risk compared to men. With metabolic syndrome: stroke risk doubles in women but not in men. Migraines: 2-fold increased risk of stroke in women even higher in women >45 years and those on an oral contraceptive pill. Atrial fibrillation (AF): women with AF have a two-fold greater risk of stroke than men with AF.

The burden of risk factors for vascular dysfunction increases in women after menopause, presumably because of the postmenopausal decrease in estrogen, a hormone with vaso-protective properties.

Some risk factors are unique to women, this is the case of combined hormonal contraception that increases the risk of stroke 2.47-fold (95% CI 2.04-2.99). The rate of stroke is increased by 9 fold at the time of delivery and 3 fold in the early postpartum period, with an increase in the risk of both ischemic and hemorrhagic stroke.

Prevention

Antiplatelet agents are claimed to be equally effective for both sexes in primary and secondary prevention of stroke, even though significantly fewer women have been studied in RCTs.

Aspirin has greater benefit in women for primary prevention of ischemic stroke without a significant increase of haemorrhage, while its benefit in men is prevalent for primary prevention of myocardial infarction, with a slight increase in the risk of hemorrhagic stroke.

References

1. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature* 2014; 509: 282-3.
2. Arnao V, Acciarresi M, Cittadini E, Caso V. Stroke incidence, prevalence and mortality in women worldwide. *Int J Stroke* 2016; 11 (3): 287-301.
3. Santalucia P, Pezzella FR, Sessa M, Monaco S, Torgano G, Anticoli S, Zanolì E, Maimone Baronello M, Paciaroni M, Caso V, Women Stroke Association (WSA). Sex differences in clinical presentation, severity and outcome of stroke: results from a hospital-based registry. *Eur J Intern Med* 2013; 24 (2): 167-71.
4. Caso V, Paciaroni M. Sex is not a risk factor in outcome when a stroke unit treats the patient. *Stroke* 2017; 48 (2): 250-51.

Correspondence to

Francesca Romana Pezzella

Stroke Unit

AO San Camillo Forlanini

Circonvallazione Gianicolense 87

00152 Roma, Italy

email frpezzella@gmail.com