Atherosclerosis 241 (2015) 208–210

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Invited commentary

Importance of sex and gender in atherosclerosis and cardiovascular disease

J. David Spence [a, *, 1], Louise Pilote [b]

[a] Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, Western University, London, Canada
[b] Division of General Internal Medicine, McGill University, Montreal, Canada

ARTICLE INFO

Article history:
Received 23 April 2015
Accepted 27 April 2015
Available online 29 April 2015

Keywords:
Sex
Gender
Atherosclerosis
Coronary
Cardiovascular

In this special issue of the journal, there are papers on bone health and coronary artery calcification, age and sex differences in the effect of parental stroke on the progression of carotid intima-media thickness, macrophage subsets in the adipose tissue by sex and by reproductive age of women, uric acid levels and metabolic syndrome, sex differences in cardiovascular risk factors and disease prevention, severity of stable coronary artery disease and its biomarkers, cardiovascular disease and autoimmune diseases genetics of cardiovascular disease, outcome after CABG; association of serum phosphorus with subclinical atherosclerosis in chronic kidney disease and relationship of uric acid levels to coronary disease. All these papers are about sex differences, yet even for this issue of the journal the authors of one of these papers mistakenly called them gender differences in their original submission.

There is unwarranted confusion about the use of the terms "sex" and "gender". Simply put, sex differences are biological differences, whereas gender differences are social differences. The definition used by the Canadian Institutes for Health Research Panel on Sex and Gender [1] is as follows: "Sex refers to a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed. Gender refers to the socially constructed roles, behaviours, opportunities, expectations, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman/femininity and boy/man/masculinity) yet there is considerable diversity in how individuals and groups understand, experience, and express it." (An online supplement amplifies the proper use of these terms.)

Some key biological differences between men and women relate to differences such as the size of the arteries. Women have smaller carotid arteries [2,3], with less plaque but more apparent stenosis [4] that may relate to differences in remodeling. Smaller coronary arteries in women may explain sex differences in diagnosis of acute coronary syndrome. However, apparent gender differences may interfere with decisions regarding investigation and revascularization of coronary arteries, and perhaps both sex differences and gender differences may affect outcomes after revascularization [5].

Given that sex and gender are different constructs, solely assessing one or the other cannot adequately account for variations in health [6]. Evidence that gender-related variables may help in explaining health-related sex differences includes the higher prevalence of cardiovascular diseases (CVD) in younger men than in women. The reason why men are at an increased risk may partly be explained by their gender-based propensity to engage in risk-taking behaviors such as smoking or excessive alcohol consumption. It has also been observed that the incidence of acute coronary

DOIs of original article: http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.030, http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.018, http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.025, http://dx.doi.org/10.1016/j.atherosclerosis.2015.04.797, http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.044, http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.048, http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.039, http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.013, http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.002, http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.032, http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.021, http://dx.doi.org/10.1016/j.atherosclerosis.2015.01.027.

* Corresponding author. Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, Western University, London, ON N6G 2V2, Canada.
E-mail address: dspence@robarts.ca (J.D. Spence).
[1] www.imaging.robarts.ca/sparc.

http://dx.doi.org/10.1016/j.atherosclerosis.2015.04.806

syndrome (ACS) in young adults, particularly women, is rising [7,8]. The increasing incidence of ACS in young adults may relate to changing family, social, and institutional roles and attitudes of men and women in the last decades [9,10]. Importantly, men and women may report gender-related characteristics traditionally attributed to the opposite sex. As such, the distribution of gender-related characteristics within populations of men and women is likely to influence health differently than biological sex.

According to the Global Gender Gap Report of 2012, the level of inequality (e.g. financial, educational, medical) between men and women in North America and Europe has decreased considerably since 2006 [9]. This phenomenon is likely related to the continual improvement in women's economic participation and opportunities, as well as educational attainment. In parallel, most women continue to retain major “feminine” responsibilities (e.g. child care) even when employed outside the home, and men whose wives work are also faced with increased demands to take charge of such responsibilities [11]. Gender-related characteristics, such as the care of children, housework responsibilities, employment characteristics and traits of personality are therefore likely to influence, among others, coping behaviors such as exercise or cardiac rehabilitation.

A recent study has reported a relationship between family roles and coronary heart disease (CHD) incidence, such that Japanese women living with both spouse and children had a 2.1-fold higher risk of CHD compared with women living with spouse but no children [12]. Another study suggested that personality traits and social roles traditionally ascribed to women, rather than biological sex, were explaining longer delays before diagnosis and treatment in both men and women with premature ACS [5]. Moreover, in the last decade, attempts to emphasize the importance of distinguishing gender from sex, as well as the important role gender may play in the incidence of CVD, have also multiplied [6,11–15]. For example, Ristvedt [15] and Krieger [13] aimed to highlight the differences and connections between gender and sex, and to stress the importance of considering both constructs in the context of health research. Both researchers presented some health studies in which gender and sex are relevant as independent or synergistic determinants of studies outcomes, and Krieger stressed that “The relevance of gender relations and sex-linked biology to a given health outcome is an empirical question, not a philosophical principle; depending on the health outcome under study, both, neither, one, or the other may be relevant as sole, independent, or synergistic determinants”.

Differences between the sexes may be overemphasized, at least with regard to therapeutic decisions. A recent guideline from the American Heart Association on prevention of stroke in women [16] emphasized sex differences, including reproductive and hormonal issues, migraine with aura, obesity, metabolic syndrome and atrial fibrillation. Not mentioned was paradoxical embolism via a patent foramen ovale; Ozdemir et al. reported [17] that 69.8% of such patients were women. Interestingly, mitral prolapse is significantly more common in patients with migraine [18], and both migraine and patent foramen ovale have in common activation of platelets [19]. However, most of these conditions would be treated the same in men and women, so focusing on getting it right for the things that are known to reduce by ~80% the risk of stroke in both sexes [20] is probably more important than focusing on differences.

One important and controversial difference is the issue of hormonal therapy, for both men and women. There is an abundance of evidence that in animal models estrogen is protective against atherosclerosis [21]. Similarly, there is ample evidence that testosterone deficiency increases the risk of atherosclerotic events [22,23]. Thus estrogen replacement for women, and testosterone replacement for men, ought to be beneficial. Yet both are widely regarded as being harmful. The issues are more complex than may be generally appreciated.

Although the Women's Health Initiative trial [24] is commonly thought to have put an end to postmenopausal hormone replacement therapy (HRT), a key issue for interpretation of this issue is the question of predisposition to estrogen-induced thrombosis by Factor V Leiden [25] or other thrombogenic disorders. It is possible that excluding women with Factor V Leiden may avoid many of the thrombotic complications related to estrogen.

Perhaps the best data on thrombogenic effects of estrogen come from a prospective study of oral contraceptive therapy in Denmark [26] that showed a statistically significant increase in the risk of stroke with preparations containing 30-40 mcg of ethinyl estradiol, with relative risks that seem rather high, ranging from 1.3 to 2.2 depending on the progesterone component of the preparation. However, the absolute risk was very small (0.02%). This is lower than the risk of stroke during pregnancy and the postpartum period (0.034%), so the risks of oral contraception may have been exaggerated. A California study [27] found that 1015 (0.06%) had a thrombotic event (248 strokes, 47 myocardial infarctions and 720 cases of venous thromboembolism). The risk was higher in the first six weeks postpartum than a year later.

Two large trials in women with vascular disease, the Heart and Estrogen/Progestin Replacement study (HERS) [28] and the Women's Estrogen for Stroke Trial (WEST) [29] showed no benefit or harm from HRT with regard to stroke.

The Women's Health Initiative study [24], a randomized trial of conjugated estrogen 0.625 mg daily vs. placebo in postmenopausal women with hysterectomy, found hazard ratios (95% confidence intervals) of 0.91 (0.75–1.12) for coronary disease, 1.39 (1.1–1.77) for stroke, 1.34 (0.87–2.06) for pulmonary embolism and a reduction of hip fracture: 0.61 (0.41–0.91). However, the excess risk was a “non-significant two events per 10,000 person-years”. Thus the hysteria over HRT (pun intended) seems unwarranted. Indeed, the Danish Osteoporosis Prevention Study (DOPS) [30], in recently menopausal healthy women age 45–58 at inception, found that after 10 years women receiving HRT had a significantly reduced risk of heart failure, myocardial infarction or death, with no apparent increase in the risk of cancer, venous thromboembolism or stroke.

There is a similar controversy about testosterone replacement in men. Health Canada recently released an advisory regarding testosterone therapy at http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/testosterone-eng.php. It seems to be based largely on a study by Vigen et al. [31] The totality of the literature [22,23] suggests that testosterone would probably improve quality of life and reduce cardiovascular risk. Page points out [32] that the primary data in the Vigen study actually showed a 50% reduction of cardiovascular risk with testosterone replacement before adjustment for some 50 variables.

The above data on hormonal differences between men and women illustrate the need for studies that include biological characteristics of both sexes as a first step. In addition, gender-related characteristics such care of children, housework responsibilities, employment characteristics and traits of personality should be taken into account, given the highly likely interplay between sex and gender.

Conflicts of interest

None.

Funding

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.04.806.

References

[1] Canadian Institutes for Health Research Definition of Sex Vs. Gender, 2015, 4-8-2015, http://www.cihr-irsc.gc.ca/e/32019.html.

[2] U.G. Schulz, P.M. Rothwell, Sex differences in carotid bifurcation anatomy and the distribution of atherosclerotic plaque, Stroke 32 (7) (2001 Jul) 1525–1531.

[3] J. Krejza, M. Arkuszewski, S.E. Kasner, J. Weigele, A. Ustymowicz, R.W. Hurst, et al., Carotid artery diameter in men and women and the relation to body and neck size, Stroke 37 (4) (2006 Apr) 1103–1105.

[4] F. Iemolo, A. Martiniuk, D.A. Steinman, J.D. Spence, Sex differences in carotid plaque and stenosis, Stroke 35 (2) (2004 Feb) 477–481.

[5] R. Pelletier, K.H. Humphries, A. Shimony, S.L. Bacon, K.L. Lavoie, D. Rabi, et al., Sex-related differences in access to care among patients with premature acute coronary syndrome, CMAJ 186 (7) (2014 Apr 15) 497–504.

[6] S.P. Phillips, Defining and measuring gender: a social determinant of health whose time has come, Int. J. Equity Health 4 (2005 Jul 13) 11.

[7] M. Izadnegahdar, J. Singer, M.K. Lee, M. Gao, C.R. Thompson, J. Kopec, et al., Do younger women fare worse? Sex differences in acute myocardial infarction hospitalization and early mortality rates over ten years, J. Womens Health (Larchmt) 23 (1) (2014 Jan) 10–17.

[8] F.B. Sozzi, G.B. Danzi, L. Foco, M. Ferlini, M. Tubaro, M. Galli, et al., Myocardial infarction in the young: a sex-based comparison, Coron. Artery Dis. 18 (6) (2007 Sep) 429–431.

[9] R. Hausmann, L.D. Tyson, Y. Bekhouche, S. Zahidi, The Global Gender Gap Report 2012, 2015. http://www3.weforum.org/docs/GGGR12/MainChapter_GGGR12.pdf. Accessed July 21, 2014.

[10] K. Kawase, A. Kwong, K. Yorozuya, Y. Tomizawa, P.J. Numann, H. Sanfey, The attitude and perceptions of work-life balance: a comparison among women surgeons in Japan, USA, and Hong Kong China, World J. Surg. 37 (1) (2013 Jan) 2–11.

[11] K. Marshall, Generational change in paid and unpaid work, Can. Soc. Trends. 2014 (August 20) (2011). http://www.statcan.gc.ca/pub/11-008-x/2011002/article/11520-eng.htm, 2014.

[12] A. Ikeda, H. Iso, I. Kawachi, K. Yamagishi, M. Inoue, S. Tsugane, Living arrangement and coronary heart disease: the JPHC study, Heart 95 (7) (2009 Apr) 577–583.

[13] N. Krieger, Genders, sexes, and health: what are the connections–and why does it matter? Int. J. Epidemiol. 32 (4) (2003 Aug) 652–657.

[14] J.L. Johnson, L. Greaves, R. Repta, Better science with sex and gender: facilitating the use of a sex and gender-based analysis in health research, Int. J. Equity Health 8 (2009) 14.

[15] S.L. Ristvedt, The evolution of gender, JAMA Psychiatry 71 (1) (2014 Jan) 13–14.

[16] C. Bushnell, L.D. McCullough, I.A. Awad, M.V. Chireau, W.N. Fedder, K.L. Furie, et al., Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (5) (2014 May) 1545–1588.

[17] A.O. Ozdemir, A. Tamayo, C. Munoz, B. Dias, J.D. Spence, Cryptogenic stroke and patent foramen ovale: clinical clues to paradoxical embolism, J. Neurol. Sci. 275 (1–2) (2008 Dec 15) 121–127.

[18] J.D. Spence, D.G. Wong, L.J. Melendez, P.M. Nichol, J.D. Brown, Increased prevalence of mitral valve prolapse in patients with migraine, Can. Med. Assoc. J. 131 (12) (1984 Dec 15) 1457–1460.

[19] J.D. Spence, Migraine, shear stress, and platelet serotonin, Headache 53 (3) (2013 Mar) 552.

[20] D.G. Hackam, J.D. Spence, Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study, Stroke 38 (6) (2007 Jun) 1881–1885.

[21] J.K. Williams, M.S. Anthony, E.K. Honore, D.M. Herrington, T.M. Morgan, T.C. Register, et al., Regression of atherosclerosis in female monkeys, Arterioscler. Thromb. Vasc. Biol. 15 (7) (1995 Jul) 827–836.

[22] P.M. Oskui, W.J. French, M.J. Herring, G.S. Mayeda, S. Burstein, R.A. Kloner, Testosterone and the cardiovascular system: a comprehensive review of the clinical literature, J. Am. Heart Assoc. 2 (6) (2013) e000272.

[23] M.J. Herring, P.M. Oskui, S.L. Hale, R.A. Kloner, Testosterone and the cardiovascular system: a comprehensive review of the basic science literature, J. Am. Heart Assoc. 2 (4) (2013 Aug) e000271.

[24] G.L. Anderson, M. Limacher, A.R. Assaf, T. Bassford, S.A. Beresford, H. Black, et al., Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial, JAMA 291 (14) (2004 Apr 14) 1701–1712.

[25] D.M. Herrington, E. Vittinghoff, T.D. Howard, D.A. Major, J. Owen, D.M. Reboussin, et al., Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease, Arterioscler. Thromb. Vasc. Biol. 22 (6) (2002 Jun 1) 1012–1017.

[26] O. Lidegaard, E. Lokkegaard, A. Jensen, C.W. Skovlund, N. Keiding, Thrombotic stroke and myocardial infarction with hormonal contraception, N. Engl. J. Med. 366 (24) (2012 Jun 14) 2257–2266.

[27] H. Kamel, B.B. Navi, N. Sriram, D.A. Hovsepian, R.B. Devereux, M.S. Elkind, Risk of a thrombotic event after the 6-week postpartum period, N. Engl. J. Med. 370 (14) (2014 Apr 3) 1307–1315.

[28] S. Hulley, D. Grady, T. Bush, C. Furberg, D. Herrington, B. Riggs, et al., Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group, JAMA 280 (7) (1998 Aug 19) 605–613.

[29] C.M. Viscoli, L.M. Brass, W.N. Kernan, P.M. Sarrel, S. Suissa, R.I. Horwitz, A clinical trial of estrogen-replacement therapy after ischemic stroke, N. Engl. J. Med. 345 (17) (2001 Oct 25) 1243–1249.

[30] L.L. Schierbeck, L. Rejnmark, C.L. Tofteng, L. Stilgren, P. Eiken, L. Mosekilde, et al., Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial, BMJ 345 (2012) e6409.

[31] R. Vigen, C.I. O'Donnell, A.E. Baron, G.K. Grunwald, T.M. Maddox, S.M. Bradley, et al., Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels, JAMA 310 (17) (2013 Nov 6) 1829–1836.

[32] S.T. Page, Testosterone, cardiovascular disease, and mortality in men: living in the dark, Lancet Diabetes Endocrinol. 2 (8) (2014 Aug) 609–611.