Practical guidelines for the consideration of the link between sex and gender in medical research and health: Cardiovascular

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CARDIOVASCULAR

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In 2014, the Inserm Ethics Committee set up a "Gender and Health Research" group (http://www.inserm.fr/qu-est-ce-que-l-inserm/l-ethique-a-l-inserm/les-groupes-de-reflexion-thematique-du-comite-d-ethique). As gender is often overlooked in biomedical research in France (unlike in Anglo-American and other European countries), one of the group's goals is to reflect on the ethical issues concerning the influence of social and cultural factors on the differences and inequalities between men and women when it comes to health and medical research practices.

It is important to encourage researchers to consider the differences between men and women - not just as a simple dichotomy between male and female, but as interaction between sex and gender (Fausto-Sterling 2000, 2012; Springer 2012; Krieger 2003). Such an approach provides a framework for improved research practices, and consequently increases knowledge about the origins of differences between women and men in health.

Recommendations for integrating sex and gender in research on cardiovascular disease

The link between sex, gender and cardiovascular disease

In 2008, the World Health Organization reported that cardiovascular disease was the leading killer of women in Europe - while only one in 26 European women died of breast cancer, one in three died of cardiovascular disease (World Health Organization 2008). Five years later, the situation has not evolved. Cardiovascular disease is still the number one killer of women in the world, breast cancer coming in at tenth place as an explanation for women's deaths (World Health Organization 2013). Women suffering from diabetes have a greater risk of developing heart disease or experiencing a stroke. Following a heart attack, women's prognosis is less encouraging than that of men in the same situation, and they also present greater risk of dying from such the attack (Regitz-Zagrosek 2011; Taylor 2011).

Women develop heart disease on average ten years later in their lives than men – the most commonly cited reason is the notion that menopause can lead to hypertension, diabetes, hyperlipidemia, obesity and other metabolic disorders. This hypothesis reinforces stereotypical views among doctors and researchers regarding the differences between men and women. However, studies relying on this hormonal hypothesis were seriously questioned (Wilson 1985). Indeed, the protective role of feminine hormones present before menopause as preventing cardiovascular disease in women is no longer a matter of consensus (Hulley 1988; Khan 2009; Springer 2012).

Numerous studies underline the fact that social representations linked to feminine and masculine gender roles have an impact on the attitude of patients as well as medical personnel. As a result, heart/coronary attacks are under-diagnosed among women. A woman who goes to see her doctor and expresses tightness and pain in her chest is more often than not prescribed anti-anxiety medication, whereas a man is almost immediately sent to a consult a cardiologist (Spring 2012; Klinge 2012; Krieger 2003).

Likewise, because cardiovascular disease is more often than not considered to be a man's disease, women are consequently underrepresented in research on cardiovascular disease, whether in clinical trials, intervention studies or biomedical research (Kim 2010; Gupta 2007; EMEA 2005, 2006).

These observations invite us to reconsider the differences between men and women relative to cardiovascular disease, not as a result of sole biological differences, but as the product of the imbrication between sex and gender. Such an approach allows us to formulate new questions, to analyze symptoms under a new light, improve diagnoses, and also develop new strategies for the prevention and treatment for all kinds of cardiovascular diseases.

These new approaches have already been integrated into research organizations of several other countries, notably by the National Institutes for Health in the United States, and have consequently led to an increase in the representation of women in clinical trials, as well as increased knowledge about the influence of sex and gender on cardiovascular disease. Another notable result of this initiative has been the launching of new public health campaigns that target women and men differently in an effort to provide more accurate information about risk factors and preventive measures.

Taking inspiration from the programs already underway not only in the United States, but in other countries as well (particularly in northern Europe), we make the following recommendations:

Recommendation 1: Include as many women as men in clinical trial and research protocols.

Studies carried out internationally as well as in France point to only approximately 33.5% of women making up all participants in research protocols. (http://genderedinnovations.stanford.edu/methods-sex-and-gender-analysis.html).
This under-representation is particularly noticeable in research on how to reduce cholesterol, the risk of ischemia and heart attacks.

Recommendation 2: Take different discourses expressed by women and men into account when evaluating symptoms so as to better establish diagnoses.

An international study of 26,755 patients with cardiovascular disease (only 29% of whom were women) demonstrated that the most common symptom in men (94%) and women (92%) is chest pain (Dey *et al*., 2009). However, significant differences between the sexes are observed for more "atypical" symptoms (Chen *et al*., 2005). Women in the study frequently complained of fatigue, nausea and jaw pain - three symptoms that are closely linked to cardiovascular disease, but do not necessarily raise red flags for cardiologists (Zbierajewski-Eischeid *et al*., 2009).

Recommendation 3: Adapt diagnostic tools to the specificities of cardiovascular pathologies experienced by women and men

It has long been believed that women suffer from the same cardiovascular diseases as men, namely coronary heart disease. However, recent research in the U.S. has found that ischemic heart disease is particularly prevalent among women (Shaw, *et. al*. 2009). Angiography, the most common technique used in the examination of patients complaining of chest pain, usually results in a diagnosis of coronary heart disease in men, but is not as effective at detecting the disease in women. Many women complaining of chest pain have "normal" angiograms, and are therefore left untreated. Many of these women have a heart attack or a stroke shortly thereafter (Robinson, *et. al.*, 2008).

It is therefore important to use different tools and diagnostic techniques for women, such as coronary reactivity testing (Von Mering *et.al*., 2004; Pepine *et al*., 2010), intravascular ultrasound (Khuddus et. al., 2010), cardiac MRI, cardiac spectroscopy (Ishimori *et. al*., 2011), myocardial scintigraphy, positron emission tomography (PET) (Johnson *et. al*., 2011), and stress echocardiography (Kaul, 2011).

Recommendation 4: Challenge assumptions and hypotheses regarding the role of estrogen in cardiovascular disease.

The decrease in estrogen rates has long been regarded as a causative factor for cardiovascular disease in women. As a result, hormone replacement therapy has often been recommended for female patients (Khan *et al*., 2009). However, large-scale studies have shown the opposite, namely a correlation between hormone replacement therapy and an increased risk of infarction in women (Wilson *et al*., 1985, Hulley *et al*., 1998). At present, the current status of research on the specific role of hormones on heart disease in women before and after menopause has yet to be confirmed.

Recommendation 5: Take sex and gender into account in cardiovascular research in order to better prevent and reduce the risk of developing heart disease.

The risk factors for cardiovascular disease are largely the same for men and women: age, hypertension, hyperlipidemia, diabetes, smoking, obesity, sedentary lifestyles, high-fat diets, and so on. However, the prevalence and impact of these factors differ according to gender (Mosca *et al*., 2012).

For example: habitual smoking is historically more common among men than women (WHO, 2010). However, in certain countries such as Sweden and Iceland, women now smoke more on average than men (Shafey *et al*., 2009). Women smoke less than men in the United States, Western Europe and other industrialized countries, but this is not the case in Central, Southern or Eastern Europe, nor in many emerging countries (Shafey *et al*., 2009). A recent study conducted on 3,587 people in five European countries has shown that smoking increases the risk of atherosclerosis in women as well as men. However, the adverse effects are twice as prevalent in women as in men (Tremoli 2010).

These studies on smoking have shown that that gender roles prevalent in specific geographic, economic, social, and cultural environments have a significant impact on the behavior of men and women who smoke, or decide to start smoking. In short, campaigns and programs that combat smoking should incorporate both sex and gender as factors to be taken into consideration.

Conclusion

For the last twenty years, the introduction of the factors of gender and sex into research on cardiovascular disease has undeniably improved knowledge surrounding diagnosis and treatment in North America. Prevention campaigns that take sex and gender into account have also helped to more accurately target at-risk populations and encourage them to adopt preventive behaviors.

In 2005, the European Society of Cardiology (http://www.escardio.org/) launched the "Women at Heart" initiative, which aims to improve awareness and understanding of cardiovascular diseases in women among both doctors and the general public. The European Medicines Agency has also made recommendations to include more women in clinical trials, and to collect data on gender in order to better assess the effectiveness of treatments for women and men (European Medicines Agency, 2006).

The medical research community in France is gradually becoming aware of the importance of including the factors of sex and gender in research on cardiovascular disease. The Foundation for Cardiovascular Research, for example, has recently launched the “At the Heart of Women” campaign (http://www.fondation-recherche-cardio-vasculaire.org/coeur-de- femmes/la-recherche-pour-le-coeur-des-femmes/lancement-programmes-de- recherche-coeur-de-femmes/), which aims to combat the under-representation of women in cardiovascular research.

While these initiatives are encouraging, there is still much work to be done, and Inserm researchers will have a key role in the future of cardiovascular research. Integrating the factors of sex and gender in research protocols in cardiovascular disease can only broaden and enrich the knowledge of these diseases, and benefit the health of both men and women.

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Bibliography

Chen, W., Woods, S., & Puntillo, K. (2005). "Gender Differences in Symptoms Associated with Acute Myocardial Infarction: A Review of the Research. Heart and Lung". *The Journal of Acute and Critical Care*, 34 (4), 240-247.

Dey, S., Flather, M., Devlin, G., Brieger, D., Gurfinkel, E., Steg, P., Fitzgerald, G., Jackson, E., & Eagle, K. (2009). "Sex-Related Differences in the Presentation, Treatment, and Outcomes among Patients with Acute Coronary Syndromes: The Global Registry of Acute Coronary Events". *Heart*, 95 (1), 20-26.

European Medicines Agency (EMEA). (2006). *Committee for Medicinal Products for Human Use (CHMP) Reflection Paper on Gender Differences in Cardiovascular Diseases*. London: EMEA.

EMEA. 2011. *Women at Heart: Scientific Material.Coronary Artery : Stenosis and Reversing Atherosclerosis*. Oxford: Oxford University Press.

Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B., & Vittinghoff, E. (1998). "Randomized Trial of Estrogen plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women". *Journal of the American Medical Association*, 280 (7), 605-613.

Ishimori, M., Martin, R., Berman, D., Goykhman, P., Shaw, L., Shufelt, C., Slomka, P., Thomson, L., Schapira, J., Yang, Y., Wallace, D., Weisman, M., & Bairey Merz, C. (2011). "Myocardial Ischemia in the Absence of Obstructive Coronary Artery Disease in Systemic Lupus Erythematosus". *Journal of the American College of Cardiology: Imaging*, 4 (1), 27-33.

Johnson, N., & Gould, K. (2011). "Positron Emission Tomography". In Thompson, P. (Ed.), *Coronary Care Manual 2E*, pp. 179-186. Chatswood: Elsevier Australia.

Khan, A., & Buscombe, J. (2009). "Nuclear Cardiology in Women". In Movahed, A., Gnanasergaran, G., Busombe, J., & Hall, M. (Eds.), *Integrating Cardiology for Nuclear Medicine Physicians*, pp. 287-297. Berlin: Springer Verlag.

Khuddus, M., Pepine, C., Handberg, E., Bairey Merz, C., Sopko, G., Bavry, A., Denardo, S., McGorray, S., Smith, K., Sharaf, B., Nicholls, S., Nissen, S., & Anderson, R. (2010). "An Intravascular Ultrasound Analysis in Women Experiencing Chest Pain in the Absence of Obstructive Coronary Artery Disease: A Substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE)". *Journal of Interventional Cardiology*, 23 (6), 511-519.

Mosca, L., Benjamin, E., Berra, K., Bezanson, J., Dolor, R., Lloyd-Jones, D., Newby, K., Piña, I., Roger, V., Shaw, L., & Zhao, D. (2012). "Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update: A Guideline from the American Heart Association". *Circulation*, 123, 1-22.

Pepine, C., Anderson, R., Sharaf, B., Reis, S., Smith, K., Handberg, E., Johnson, B., Sopko, G., & Bairey Merz, C. (2010). "Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia: Results from the National Heart, Lung, and Blood Institute (NHLBI) Women's Ischemia Syndrome Evaluation (WISE) Study". *Journal of the American College of Cardiology*, 55 (25), 2825-2832.

Prendre en charge le cœur des femmes, http://www.fondation-recherche-cardio-vasculaire.org/assets/Prendre-en-charge-le-coeur-des-femmes.pdf

Robinson, J., Wallace, R., Limacher, M., Ren, H., Cochrane, B., Wassertheil-Smoller, S., Ockene, J., Blanchette, P., & Ko, M. (2008). "Cardiovascular Risk in Women with Non-Specific Chest Pain (from the Women's Health Initiative Hormone Trials)". *American Journal of Cardiology*, 102 (6), 693-699.

Schafey, O., Eriksen, M., Ross, H., Mackay, J. (2009). *The Tobacco Atlas*. Atlanta: American Cancer Society.

Shaw, L., Bugiardini, R., & Bairey Merz, C. (2009). "Women and Ischemic Heart Disease: Evolving Knowledge". *Journal of the American College of Cardiology*, 54 (17), 1561-1575.

Springer, K., et. al., "Beyond a catalogue of differences: A theoretical frame and good practice guidelines for researching sex/gender in human health**",** *Social Science & Medicine***,** Volume 74, Issue 11, June 2012, Pages 1817–1824.

Taylor, K., Vallejo-Giraldo, C., Schaible, N., Zakeri, R., & Miller, V. (2011). "Reporting of Sex as a Variable in Cardiovascular Studies using Cultured Cells". *Biology of Sex Differences*, 2 (11), 1-7.

Tremoli, E., Veglia, F., Amato, M., Ravani, A., Sansaro, D., Tedesco, C., Discacciati, A., Frigerio, B., & Castelnuovo, S. (2010). "The Association of Tobacco Smoke with Subclinical Atherosclerosis and Atherosclerosis Progression is Stronger in Women than in Men". *Circulation*, 122, Abstract A20608.

Wilson, P., Garrison, R., & Castelli, W. (1985). "Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women over 50—The Framingham Study". *New England Journal of Medicine*, 313 (17), 1038-1043.

World Health Organization (WHO). (2013). "Women's Health. Fact Sheet". Consulted May 2016.

World Health Organization (WHO). (2011a). *Tobacco Free Initiative (TFI): Gender and Tobacco*. Geneva: WHO Press.

World Health Organization (WHO). (2010). *WHO Calls for Protection of Women and Girls from Tobacco*. Geneva: WHO Press.

World Health Organization (WHO). (2009). *Report on the Global Tobacco Epidemic: Implementing Smoke-Free Environments*. Geneva: WHO Press.

World Health Organization (WHO). (2008). *Causes of Death: 2008 Summary Tables*. Geneva: WHO Press.

Zbierajewski-Eischeid, S., & Loeb, S. (2009). "Myocardial Infarction in Women: Promoting Symptom Recognition, Early Diagnosis, and Risk Assessment". *Dimensions of Critical Care Nursing*, 28 (1), 1-6.