

Title: Beyond sex and gender: call for an intersectional feminist approach in biomedical research

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In recent years, a growing focus on the theme of gender has emerged in biomedical research. Inclusion of sex and gender dimensions is crucial to conduct “rigorous, reproducible and responsible science” (1), and to understand the sex and gender specificities in prevalence, clinical presentations and management and prognostic of diseases. Sex refers to individual’s biological attributes (chromosomes, gene expression, hormone function and anatomy) that serve the classification into male, female or intersex. Gender refers to the socially defined roles, behaviours and identities of men, women and gender-diverse people (2).

In the current issue of the *European Journal of Internal Medicine*, Alipour, Azizi *et al* (3) provide further evidence on the need to investigate the role of gender on health and disease, in their case on the development of metabolic syndrome (MetS). Previous studies have shown that men have higher incidence of MetS, while women with MetS have a higher risk for cardiovascular diseases, and that components of MetS (abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure) were unequally distributed between men and women. These previous findings were established on the use of the sex category variable (i.e. man/woman), mostly assuming that observed disparities were attributable to biological- and genetic-related mechanisms. Aligning with a *gender medicine* approach, Alipour, Azizi, *et al* have investigated the role of sociocultural gender, beyond the sex category variable, using data from a Swiss prospective cohort study. Because indicators of gender position or roles were not specifically collected in the cohort study, they used demographic and socioeconomic variables – such as employment status, income, education, domestic status – that are gendered in their distribution to capture their “gender-related” effects on MetS. Their main findings are that the reduced risk of MetS in women was attenuated if they had a low educational level, low income and if they were older. The effect of smoking was different whereby men who smoked had increased risk of developing MetS while women had a decreased risk.

Why is the inclusion of sex and gender crucial in health research?

What Alipour, Azizi, *et al* highlight is that women and men are not at equal risk of developing MetS, and this is due to biological (sex) and social (gender) factors. When using the sex category variable, data from the Swiss cohort showed a protective effect of being female. However, when looking into the interacting effect of age and sex, it appeared that women above menopause age were largely more at risk compared to men in the same age group. Hypothesis was set that the hormonal levels change at menopause may explain this trend. This calls for a better inclusion of the sex dimension in research (4), namely for precise measures of hormonal levels when assumption is made that hormones are at play. Further, the sex category effect appeared to be nuanced and to vary upon the gendered social positions that individuals occupied. Not all women were less at risk of developing MetS, and not all individuals with lower education were at higher risk of developing MetS. In fact, the deleterious effect of low education on developing MetS was stronger in women compared to men. The same phenomenon applied to income. This calls for the inclusion of variables that can capture gendered social dimensions. Encompassing such dimensions is crucial to understanding mechanisms and pathways that lead to the

distribution of health and disease between women and men, beyond biological or genetic considerations (2).

Can sex and gender effects be disentangled? Scholars have proposed methodological strategies to disentangle biological from social effects in women's and men's health (5, 6). Applying such strategy is however limited because biological and social effects are dynamically interacting throughout the life-course. As developed by Fausto-Sterling studying bone density, social gendered systems that influence diet and exercise habits, occupation, broader living conditions and exposure to health risks likely shape bones throughout a person's life phases (7). In other words, the social gets under the skin and marks biology.

The approach that Alipour, Azizi *et al* have applied can be named an intersectional approach. The concept of intersectionality, first coined by Kimberlé Crenshaw in the late 1980s, asserts that "individual identities and social positions, such as gender, race, and class, intersect" leading to "distinct experiences that are often overlooked when one identity is emphasized over another" (8). It is in this sense that narrowing research to the binary sex category variable could be limiting when it comes to health distribution in a population. It is crucial to recognize that demographic and socioeconomic factors are intricately intertwined in their modulation of health-related behaviours, especially when dealing with lifestyle-related chronic diseases such as MetS. One finding that Alipour, Azizi *et al* have put forward is the intersecting effect of gender and education. As described, education does not bring the same benefits or privileges in men and women. Intersectionality is about acknowledging and examining "the intersecting nature of power and privilege, whether due to patriarchy, colonialism, capitalism, neoliberalism, or the many other endemic hierarchies, and reveal(ing) health disparities and gender-related barriers to health information and quality services" (9). Applied to health research, this intersectional approach enables the consideration of gender in its different dimensions – including gender roles, interpersonal dynamics, and institutionalized gender norms –, as well as other axes of inequalities – race/descent, (dis)ability, migration status, age and socioeconomic status – that shape individuals' lives and the distribution of health in a given population.

Isn't it too complex?

Considering the substantial disease burden associated with the components of MetS – global prevalence of 12.5% to 31.4% in adult population (10) – leading to high cardiovascular morbidity and mortality, and other significant impacts on healthcare systems, an urgent and comprehensive response is necessary. This is especially crucial in regions undergoing an epidemiological transition, where the prevalence of MetS is rapidly increasing. Aligning with Alipour, Azizi *et al*, we emphasize the importance of considering the complex interplay between sex, gender and other socioeconomic factors not only to produce context-relevant evidence, but also to better guide the formulation of prevention strategies and screening policies, especially in the context of lifestyle-related chronic diseases. Taking the multifaceted aspects of gender into consideration when evaluating epidemiological risk factors appears to be one promising approach for gaining a deeper understanding of complex chronic conditions that require

complex clinical responses, and ultimately that may enhance the quality and equity of healthcare, including for at-risk or underserved population groups (2). Context-specific data can, in turn, have a significant impact on clinical practice, particularly in terms of diagnosis (with pre-test probabilities more closely reflecting individual realities), treatment strategies (enhanced understanding of adherence factors and treatment responses), and secondary prevention, all for the same compelling reason. Last, encompassing social factors and understanding their influence on health and disease provide further evidence on the need to support the Health in All Policies approach, namely that all sectors should work together to improve health (11). In the case of MetS, the education, employment and social sectors are concerned among others.

Call for an intersectional feminist approach in biomedical research

As noted by Alipour, Azizi *et al*, a limitation of their findings is that “more diverse populations are warranted to assess the intersectionality of race/culture/country with gender and sex”. In fact, the cohort study used for their research included a sample of over 90% individuals who identified as Caucasian, while the study population is composed of 43% non-Swiss residents, of whom not all would identify as Caucasian (12). The process of constructing this sample based on access and language practicality as well as a genetic homogeneity for scientific purpose – situated in 2003 when the cohort was started – is politically and socially grounded just as any other scientific process of production. Knowledge produced with this cohort on cardiovascular disease and mental illnesses is applicable to the sampled population, and not to specific groups such as residents with a migration background from the South who are nevertheless using the Swiss healthcare system. A call for an intersectional feminist approach in biomedical research is thus a call for a critical reflection on the influence of socially constructed (and often implicit and unconscious) frameworks that shape all research processes, from study designs to sampling strategy and to data interpretation and dissemination. In other words, “decisions about what needs to be measured and how, and the evidence that is constructed based on the analyses and interpretations of large scale data, are inevitably subjective and political” (9).

The social determinants of health have been known to influence the development of diseases since the 1960s. Beyond being a social determinant of health, gender intersects with other determinants, and these interactions need to be taken into account to produce knowledge on specific social intersections that create compounding living conditions, health-related behaviours and risk factors for the development of diseases such as MetS. Frameworks and methods for intersectional approaches are awaiting to be adopted by health researchers (13-15) – they may appear complex, but wouldn't that reflect reality?

Conflict of interests

The authors of this commentary regularly collaborate with co-authors of the commented paper on other projects (i.e., Profs. C. Clair, M. Preisig, and P. Vollenweider).

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