Editorial: Epidemiologic Approaches to Women’s Health

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Abbreviations: ER, estrogen receptor; ORWH, Office of Research on Women’s Health; PR, progesterone receptor.

Since 1991 when the Office of Research on Women’s Health (ORWH) of the National Institutes of Health published the first US women’s health research agenda, the science of women’s health has developed rapidly. Contributors to the first research agenda on women’s health provided a definition demarcating the field: “Women’s health research” referred to studies of health conditions that are specific to women or more common or more serious in women and that have distinct causes, manifestations, outcomes, or treatments in women. Moreover, determinants of health, including biological, psychological, environmental, and sociocultural factors that affect women disproportionately or uniquely, were included in the scope of women’s health research (1, 2). Sex and gender were differentiated in an Institute of Medicine study published after the second women’s health research agenda in 1999 (3): “Sex” refers to the classification of living things as male or female according to their reproductive organs and functions assigned by chromosomal complement, and “gender” refers to a person’s self-representation as male or female or how that person is responded to by social institutions on the basis of that presentation (4).

In 2010, the ORWH of the National Institutes of Health and the Institute of Medicine both published new reports that promise to shape women’s health research in years to come (4, 5). Results of the ORWH review, Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women’s Health Research, build on the original 1991 agenda and the 1999 update, Agenda for Research on Women’s Health for the 21st Century (3). Six goals for the future were specified in the vision for 2020:

1. Increase sex differences research in basic science studies
2. Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs
3. Actualize personalized prevention, diagnostics, and therapeutics for girls and women
4. Create strategic alliances and partnerships to maximize the domestic and global impact of women’s health research
5. Develop and implement new communication and social networking technologies to increase understanding and appreciation of women’s health and wellness research
6. Employ innovative strategies to build a well-trained, diverse, and vigorous women’s health research workforce.

The Institute of Medicine report, Women’s Health Research: Progress, Pitfalls, and Promise (4), identified areas in which research has contributed to major progress, including studies of breast cancer, cardiovascular disease, and cervical cancer. The authors concluded that research has contributed to some progress in depression, human immunodeficiency virus/ acquired immunodeficiency syndrome, and osteoporosis. They also concluded that there were several conditions for which there had been little progress: unintended pregnancy, maternal morbidity and mortality, autoimmune diseases, alcohol and drug addictions, lung cancer, gynecological cancers other than cervical cancer, nonmalignant gynecological disorders, and Alzheimer’s disease.

Global attention has been focused since 1994 on reproductive health and since 2000 on maternal health, as one of the Millennium Development Goals. As the countdown to reporting on Millennium Development Goal achievements now approaches, attention is increasingly shifting to women’s health as a potential goal for the post-2015 agenda (6). A recent issue of the Bulletin of the World Health Organization (7) encourages further examination of national and international policy related to women’s health. In particular, sexual and gender differentials in health and wellbeing, rising risks for noncommunicable diseases (such as cardiovascular disease; breast, cervical, and other reproductive organ cancers; obesity; and diabetes), and osteoporosis and mental depression are highlighted. Protection of vulnerable female populations, such as elderly women, women in poverty, and women without health-care access, is additionally singled out as a priority. As the epidemiologic transition advances through low-resource countries and completes itself, the women’s health agenda for screening, diagnosis, care, and treatment and for research initiatives will lose its underlying geographical...
distinctions, and solutions will become more a matter of resources, equitable allocations, and political will. Universal health coverage through social or private insurance schemes has been implemented in a number of economically challenged settings, such as Burundi, Cambodia, Ghana, and Rwanda. Addressing women’s health needs does warrant some special considerations in health-care financing, because women’s earnings capacity and poverty tend to be worse than those of men. Coverage of women’s health needs should also begin early in the life course and be framed beyond reproduction.

The contents of this volume include an appraisal of research done in several areas that advance the field of women’s health. Taken together, these reviews enrich our understanding of the intricate relationships among sex, gender, and health, as well as of the ecology of women’s health and therapies to promote it. A comprehensive view of women’s health necessitates consideration of the interrelationship of the reproductive and nonreproductive dimensions of women’s health. In this issue, authors appraise the evidence pertaining to the relationship of the menstrual cycle and its endocrine dynamics to cardiometabolic biomarkers (9), pregnancy and cardiovascular health (10), and ovulatory function and bone mineral density (11).

Cardiovascular disease is the leading cause of death for women and responsible for significant morbidity. As biomarkers for heart disease development and progression are used in caring for women, their utility rests on accurate interpretation of test results. An examination of effects of the menstrual cycle phase on cardiometabolic biomarkers, such as oxidative lipids, insulin sensitivity, and systematic inflammation, revealed significant differences and implies a need to base timing of measures on menstrual cycle phase (9). Conclusions of this review imply a need to synchronize timing of testing to menstrual cycle phase and to develop norms for women who are cycling based on the menstrual cycle phase of measurement.

A review of commonly experienced pregnancy complications on women’s future cardiovascular health examined associations of fetal growth restriction, preterm delivery, hypertensive disorders, and gestational diabetes and parity with women’s cardiovascular mortality and morbidity. In another review, consistent and strong associations were found between pregnancy complications and latent and future cardiovascular disease (10). Subclinical vascular and metabolic dysfunction preceded pregnancy complications and may be useful markers of latent cardiovascular disease. Implications for screening, prevention, and treatment of cardiovascular disease in women await replication of these studies of cohorts of women across the lifespan. Pregnancy may serve as a perturbation that unmask subclinical cardiovascular disease.

Progesterone, as well as estrogen, plays an important role in osteoblast function, promoting formation of bone. Subclinical ovulatory disturbances, resulting in anovulation and a short luteal phase, lower levels of progesterone, thus potentially affecting bone mineral density. Spinal bone mineral density loss in regularly menstruating women with more prevalent subclinical ovulatory disturbances was evident in this review (11). Despite the heterogeneity of many studies, results of this review warrant consideration of treatment of ovulatory disturbances, such as anovulation, in premenopausal women.

Interrelationships of a woman’s health and that of her offspring include physical as well as mental characteristics of both, as seen in the infrequently explored relationship between anorexia nervosa and low birth weight (12). The authors’ meta-analysis of 14 eligible studies found a lower standardized mean difference in birth weight of −0.181 g (95% confidence interval: −0.249, −0.113; P < 0.0001) among mothers with anorexia nervosa compared with nonexposed mothers. Publication bias cannot be ruled out because the number of studies is few, although the difference in birth weight is small. The authors recommend that antenatal care providers give consideration to mothers with anorexia nervosa as having elevated risk for poor pregnancy outcomes.

Health problems specific to women are exemplified by a review of the prevalence and risk factors for dysmenorrhea, a prevalent health problem among women (13). Dysmenorrhea is a painful menstrual condition that, when severe, can limit women’s ability to carry out daily activities. The authors’ review of 14 primary studies meeting their inclusion criteria found dysmenorrhea’s incidence to be 16% over 1 month and 28% over 12 months of follow-up. Although dysmenorrhea is common for a large proportion of women of reproductive age, severe symptoms are less common, and the review confirms improvement with age, parity, and use of oral contraceptives. Effect sizes were modest to moderate; odds ratios ranged from 1 to 4. Evidence regarding effects from modifiable factors, such as obesity, socioeconomic status, employment, smoking, and alcohol, was inconclusive.

A set of reviews addresses the ecology of women’s health (14–16). The influence of macrosocial policies to eliminate gender disparities in health is assessed by Borrell et al. (14) across 19 selected studies. Reproductive health policies, followed by family and welfare state policies and US state comparisons, are the most common focus in this set. Parental leave policies are secondarily reviewed, particularly in the Nordic countries’ social welfare regimes, and found to promote women’s health, specifically longer durations of leave, reducing maternal depressive symptoms. Longer paid maternity leave was also generally associated with better mental health in US settings.

The impact of environmental factors on human fecundity and pregnancy-related outcomes is not easy to isolate for a range of research design issues, including assessment methods and statistical approaches. Slama et al. (15) outline how study design, outcome assessment, medical intervention, exposure assessment, and type of statistical analysis can affect findings from investigations of environmental links to time to pregnancy (conception), fetal loss, congenital anomalies, gestational duration, and preterm delivery, and they suggest possible ways to limit bias. They caution against misinterpretation of findings in the absence of appropriate and timely measurement and encourage careful analysis before drawing conclusions about environmental effects on human reproduction.

Gender differences in the experience of postdeployment post-traumatic stress disorder reflect the environmental influence of war on women’s mental health (16). Deployment of troops to Iraq and Afghanistan resulted in an unprecedented
mobilization of women, including to direct combat roles (owing to erasure of clear battle lines) with their exposure to a variety of traumatic events. Seven of 18 studies revealed that women were at higher risk for postdeployment post-traumatic stress disorder than were men. In Veterans Affairs, treatment-seeking samples showed lower risk in 4 studies. Design of future studies should evaluate gender differences carefully, including evaluation of combat experiences, women’s vulnerability related to histories of childhood sexual abuse and intimate partner violence, and the type of traumatic events to which they were exposed, including military sexual trauma in the field, unique stressors of handling human remains common to health-care providers, and lack of support from their unit members and the broader society. Results of this review support use of predeployment history taking, focusing on past trauma in the care of military personnel and tracked among veterans.

A final important topic focuses on the therapeutics for women. Although evidence of the association between preconception risk factors and adverse pregnancy outcomes is extensive, evidence of the effectiveness of lifestyle interventions directed at reducing these risks and improved health is not as robust, as reported by Temel et al. (17). Munsell et al. (18) review 44 selected studies out of a large research literature regarding the effectiveness of interventions targeting alcohol, smoking, weight, diet/nutrition, physical activity, and folic acid (fortification and supplementation). Evidence is lacking regarding interventions that reduce alcohol-exposed pregnancies, although there is evidence for nutrition interventions for preconception dietary intake and birth weight. Smoking interventions help reduce smoking, and both individual and collective interventions to increase folic acid use improve pregnancy outcomes. Evidence regarding integration of single interventions is not found.

The complex interrelationships of postmenopausal hormone therapy and obesity and their association with breast cancer risk also were examined by Munsell et al. (18). Despite claims that obesity is associated with postmenopausal breast cancer, it is uncertain whether obesity is related to all types of breast cancer, such as estrogen receptor–positive (ER+) and triple negative types. Moreover, use of hormone therapy and the type of hormone therapy used should be considered. In this review, having a body mass index (defined as weight (kg)/height (m)²) greater than 30 was associated with a lower relative risk of breast cancer among premenopausal women. Having a higher body mass index was associated with ER+/progesterone receptor–positive (PR+) breast cancer but not estrogen receptor–negative (ER−)/progesterone receptor–negative (PR−) breast cancer among premenopausal women. The relationship between body mass index and breast cancer differed for postmenopausal women in whom greater body mass index was associated with an increased incidence of ER+/PR+ but not ER−/PR− breast cancer. Estrogen and progesterone therapy use was associated with increased risk of breast cancer among current users but not among past users and for ER+/PR+ type. The majority of data pertain to white women with a need for additional studies of Latinas, African Americans, and other American ethnic groups. Premenopausal obese women experience ovulatory dysfunction consistent with lower serum estrogen levels, and postmenopausal obese women metabolize estrogen in adipose tissue, thus contributing to increased serum levels of estrogen, likely influential in the association with ER+/PR+ breast cancers.

The relationship between postmenopausal hormone therapy and risk of dementia has been a source of controversy following the publication of results of the Women’s Health Initiative Memory Study (WHIMS) (19). A review of the effects of hormone therapy on all-cause dementia and Alzheimer’s disease from prospective studies and clinical trials revealed no association between ever and never use of hormone therapy and risk of Alzheimer’s disease. Limited studies of timing of use (early vs. later and varying durations) did not yield consistent results. Authors of this review conclude that their findings do not support use of hormone therapy for prevention of dementia. Future studies should explore newer hormone therapy regimens and timing and duration of use.

Taken together, the papers in the issue systematically and comprehensively review the evidence of a range of gender and behavioral factors and clinical and biomedical interventions affecting a number of women’s health conditions. Spanning across a broad spectrum of the women’s health research literature, the reviews are sometimes definitive in the existence and size of effects and sometimes appropriately circumvent when the methodological rigor is insufficient. They point to challenges facing the elimination of health disparities in relation to gender, economic status, and effective policies and interventions. Several papers address special issues, such as postconflict mental wellbeing, dementia and Alzheimer’s disease risks, or maternal anorexia nervosa. Nearly all papers cited the importance of study design, longitudinal data, community-based assessments, strong measurement, and adequate analyses, and many called for continued high-quality research efforts to properly assess the relative influences of biological, cognitive, emotional, and social factors on women’s health outcomes. Such efforts are requisite if the design, development, and implementation of effective behavioral and clinical interventions are to be evidence based and well informed. In the United States, 22 years after its inception, the federally funded Women’s Health Initiative has demonstrated its enormous value as a rigorous research effort, validating the need to include women and minorities as subjects and generating medical and clinical findings connecting hormonal exposure levels with risks for breast cancer, cardiovascular disease, diabetes, osteoporosis, and cognitive impairment, among other things, and transforming menopausal hormone therapy guidelines and practices (20).

Collectively, the papers in this volume showcase the wide ranging health consequences of the multiple personal, familial, occupational, and societal roles women occupy across the life course. Representing half of the world’s population, women help steward the epigenetic legacy of future generations through healthy pregnancies. As individuals, women merit enjoying full health, as a fundamental human right, as much as men, and being duly protected by universal health coverage programs, whether under the Affordable Care Act in the United States, welfare state policies in European countries, or national health insurance schemes in Ghana, Cambodia, Chile, or elsewhere.
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REFERENCES


