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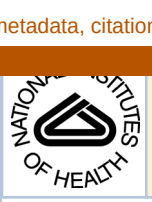

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Am J Public Health. Author manuscript; available in PMC 2014 October 01.

Published in final edited form as:
Am J Public Health. 2013 October ; 103(0 1): . doi:10.2105/AJPH.2013.301229.

Sex, Gender, Genetics, and Health

Susan E. Short, PhD,
Department of Sociology and the Population Studies Training Center, Brown University, Providence, RI

Yang Claire Yang, PhD, and
Department of Sociology, Lineberger Comprehensive Cancer Center, and Carolina Population Center at the University of North Carolina-Chapel Hill

Tania M. Jenkins, MA
Department of Sociology, Brown University

Abstract

This article addresses 2 questions. First, to what extent are sex and gender incorporated into research on genetics and health? Second, how might social science understandings of sex and gender, and gender differences in health, become more integrated into scholarship in this area? We review articles on genetics and health published in selected peer-reviewed journals. Although sex is included frequently as a control or stratifying variable, few articles articulate a conceptual frame or methodological justification for conducting research in this way, and most are not motivated by sex or gender differences in health. Gender differences in health are persistent, unexplained, and shaped by multilevel social factors. Future scholarship on genetics and health needs to incorporate more systematic attention to sex and gender, gender as an environment, and the intertwining of social and biological variation over the life course. Such integration will advance understandings of gender differences in health, and may yield insight regarding the processes and circumstances that make genomic variation relevant for health and well-being.

The last decade has seen an explosion in research on genetic contributions to health and well-being. With the emergence of affordable genotyping technologies, researchers from many fields collect and process genomic bio-markers as part of new and ongoing studies of human health and behavior. The information about individual-level differences provided by such biomarkers offers potential for enhancing understanding of patterns of health and well-being. Not all individuals respond in the same way to similar health risks and exposures. Physiological variation, including genomic variation, plausibly contributes to individual response.

Coincidentally, just as health researchers embraced the opportunity to examine genetic differences, they also responded to the call to examine contextual differences, or variation at the societal level, and its contribution to health. Social epidemiology, as described in the influential volume by Berkman and Kawachi,[1] brought renewed attention to social context, and the value of locating an individual within this context, for deeper understandings of

Correspondence should be sent to Susan E. Short, Box 1916 Maxcy Hall, Brown University, 112 George Street, Providence, RI 02912 (susan_short@brown.edu). Reprints can be ordered at http://www.ajph.org by clicking the “Reprints” link.

Contributors
S. E. Short proposed and outlined the original article. S. E. Short and Y. C. Yang developed the conceptual ideas, designed analyses, and drafted the article. T. M. Jenkins contributed to data collection, analysis, and revisions to the article.

Human Participant Protection
Institutional review board approval was not needed because human participants were not directly involved.

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health risks and exposures. As a consequence of these developments, contemporary health researchers look both deeper within the body itself, and further upstream to environments, thus "situating" the body.

One advantage of an approach that incorporates genomic and contextual variation—individually and in their intersection—is the opportunity to deepen understanding of sex and gender differences in health. Men and women have different susceptibilities to disease, and these differences are not well understood.[2,3] Sex-specific biological variation, including genomic variation, may play a role.[4] Although sex-specific variation in the human genome is understood to be small, and its functional relevance is the subject of ongoing research investigation, dyadic processes support the production of male and female gametes, which, in turn, are associated with morphological variation.[5] In a parallel fashion, gendered social and cultural institutions suggest that individuals experience and create gender-differentiated environments.[6,7] They interact on a daily basis within social, economic, and institutional environments, including family, school, and work settings that are highly gendered. These observations lead naturally to the question: How does the interplay of gender-specific variation in environments and sex-specific variation in biology yield differences from birth to death in health trajectories and outcomes for men and women?

We seek to bring attention to the intersection of sex, gender, genetics, and health. Although this intersection yields considerable terrain worthy of investigation, we explore 2 specific questions. First, to what extent are sex and gender incorporated into research on genetics and health? Does this literature examine the interplay between social experiences and biological pathways in an attempt to explain systematic differences in men's and women's health? Second, how might social science understandings of sex and gender, and gender differences in health, be more fully integrated into scholarship in this area?

The remainder of this article is divided into 5 sections. The first section reviews the terms sex and gender. The second summarizes typical practices with regard to sex and gender in research on genetics and health based on a review of articles published over the past 5 years in 4 leading peer-reviewed journals. The third section describes persistent and unexplained gender differences in health, and reviews biological and social explanations. The fourth section presents 2 brief examples of the interplay of biological and social factors over the life course in shaping differences in men's and women's health. Finally, the article concludes by considering possible future directions for research.

NATURE AND NURTURE, SEX AND GENDER

The terms "sex" and "gender" merit clarification because both are used inconsistently and interchangeably in research on health. Sex refers to the biological distinctions between males and females, most often in connection with reproductive functions.[8] Gender, by contrast, emphasizes the socially constructed differences between men and women that give rise to masculinity and femininity.[9] The term gender can be applied to individual difference, as well as to cultural, institutional, and structural difference. In the 1970s, feminist scholars promoted use of the term gender to draw attention to the reality that not all differences between men and women could be explained by biology. This distinction allowed scholars to counter academic and popular portrayals of the differences between men and women as natural, and by extension, immutable.

Sex, with its emphasis on sex-specific variation in biology, includes sex-specific variation in chromosomes. In addition to 22 pairs of autosomal chromosomes, humans have an additional pair of what have come to be known as the sex chromosomes. Most females have 2 X chromosomes and most males have an X and Y chromosome. With males and females sharing all 22 autosomal chromosome pairs and an X chromosome, sex-specific variation

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among the roughly 20 000 protein-coding genes is small. Relatively few genes, estimated around 75, are located on the Y chromosome, including those linked to the development of the testes.[10,11] Although a quick reading of such numbers might suggest sex-specific variation in genes of about 0.5%, estimating functionally relevant variation is complex. Recent estimates suggest that protein-coding genes account for only about 3% of the human genome.[12] Not all genes code for unique proteins; noncoding DNA is relevant to biological function and phenotypic expression, and methylation patterns, expression levels, and other factors may shape meaningful sex-specific genomic variation.[10,12,13]

Furthermore, despite the binary that is suggested by human reproduction, both sex and gender are fluid. Variations in chromosomes, hormone levels, and reproductive organs result in more than 2 sexes, reflecting complex processes of sex development across multiple levels, and suggesting that sex itself is culturally constructed.[14,15] Likewise, individuals transgress normative gender boundaries in everyday life, recasting gender as more than a simple dichotomy of men and women.[16] Gender is created and recreated through social interaction that takes place in dynamic cultural and institutional contexts.[7]

Much as there is not a neat dichotomy represented within sex or gender, the supposed dichotomy between sex-as-biology (within the body) and gender-as-society (outside the body) masks considerable complexity. More recent scholarship recognizes that gender is not disembodied, and that physiological differences, including sex differences, can contribute to gendered realities. The observation that gender contributes to biological expression is much less prevalent, but is emerging, especially with regard to health and disease.[17] In a study of bones, biologist Fausto-Sterling illustrates the myriad pathways through which culture and lived experience can affect biology. For example, Fausto-Sterling explains how culture, which might include gender-specific ideas and opportunities regarding diet or physical activity, can interweave with biology to shape group differences in bone characteristics.[18] Others suggest that gender structures in society can constrain individual choices, which can, in turn, have an effect on health, including longevity.[19] Moreover, gender contexts in society can shape our very understanding of sex differences, as illustrated by Jordan-Young using the example of brain organization.[20]

Thus, as our science recognizes that individual attributes reflect the combination of biological and social factors that work in concert over time to shape one another, and that physiological difference can reflect social experience, scholars have called both for greater precision in use of the terms sex and gender, and for abandonment of the false sex and gender dichotomy.[18,21,22] Just as the over-simplification represented in a nature---nurture distinction is inadequate, so too is the over-simplification reproduced in the sex---gender distinction. These issues come to the fore in the arena of gender, genetics, and health.

We use the phrase “gender differences in health” to refer to differences between men and women. Because health itself refers to the body, we understand that gender differences in health reflect social and biological factors. We use the terms sex and “sex differences” when referring more narrowly to physiological differences associated with male and female bodies, and reporting on literatures that primarily use the term sex. Although we recognize that these differences also reflect social factors, and the very argument of this article is to more fully represent this integration, we adopt what we understand to be the conventional interpretation of sex in public health and medical research for the purposes of this article, rather than the term “sex/gender” as is sometimes used by gender scholars and social scientists.[23]

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SEX AND GENDER IN RESEARCH ON GENETICS AND HEALTH

To gain insight into how sex and gender are incorporated into research on genetics and health, we reviewed studies published in 4 top peer-reviewed journals. We reviewed articles published in the *American Journal of Public Health*, the flagship journal of the American Public Health Association and among the most influential journals in the field of public health.[24,25] In addition, we reviewed articles published in *Epidemiology* and the *American Journal of Epidemiology*, 2 leading general interest epidemiology journals. Both are also among the most highly ranked public health journals.[24,25] We selected epidemiology journals because this field has embraced genetic analysis, as reflected in the subspecialty referred to as genetic epidemiology or molecular epidemiology. As such, we expect articles on genetics and health published in epidemiology journals to reflect scholarship that blends the perspectives and approaches of public health and genetics. In addition to these 3 leading public health journals, we reviewed research articles published in *Nature Genetics*. This is the top-ranked general interest journal in the field of genetics, and includes articles on genetics and human health.[25]

Our review was based on a comprehensive search of this small set of journals rather than a keyword search in PubMed. A primary reason was that we were interested in reviewing whether and how articles referenced sex and gender in studies on genetics and health, a goal that required the inclusion of articles that did not emphasize sex or gender. By contrast, Patsopoulos et al.[26] evaluated claims of sex differences in genetic associations and reviewed articles that featured sex differences. Accordingly, they searched PubMed for all articles published through a target date that used the term “polymorphism*” together with either “sex” or “gender,” in the title, a search that yielded a manageable set of 215 articles, and further limited this group to 77 articles based on inclusion criteria. If our highest priority was a random selection of articles, we might have begun by searching on a term such as “polymorphism*” alone or with other keywords, but given the large number of articles such a search would retrieve, a sampling of this set would be required. This strategy would have resulted in articles from hundreds of journals in many fields, yielding a summary that might have been of limited use to readers of this journal or to scholars in any 1 field. We emphasize that in selecting these 4 journals it was not our intention to represent research on genetics and human health in a generalizable way. Rather, we selected 4 leading general interest journals that span public health and genetics as examples, and searched them systematically to inform our understanding regarding current practices. Notably, all of these journals are based in the United States.

Full-length research articles published between 2007 and 2011 were eligible for inclusion. We chose this time period because we are interested in current practices. We included only articles that met the following criteria: (1) the analysis was based on a sample of humans and focused on a health outcome, and (2) the conclusions about genetic susceptibilities were based on empirical analyses contained in the study itself. Articles that addressed genetics but were not primarily about a health outcome, such as articles about methodology, were excluded. Similarly, commentary pieces, reports, and systematic reviews (not including meta-analyses) were excluded because they did not include new empirical analyses. Eligibility was assessed by 2 separate reviewers. In the rare event of a disagreement, a third coder assessed eligibility and made the final determination. The final set of articles included 198 articles, 139 of which were published in one of the 3 public health journals. Figure 1 summarizes the process that yielded this set of articles. The number of articles that met the inclusion criteria over this 5-year period differed substantially across journals, with the *American Journal of Public Health* and *Epidemiology* publishing a combined total of 13 articles, and the *American Journal of Epidemiology* and *Nature Genetics* publishing 126 and 59 articles, respectively.

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For each article, we determined whether sex or gender was used in the title or abstract, and then coded for all of the following terms: sex, gender, male, female, men, women, maternal, paternal, and X chromosome throughout the article. We ascertained whether the analysis focused on a single sex or gender, and if so, whether the health outcome under study was a reproductive or sex-specific health outcome. Among those articles that were not single sex or gender studies, we reviewed the context in which all of the terms were used, and developed codes to summarize how sex or gender was used in analysis. Findings, which are presented for all journals as well as for the public health journals only, are shown in Table 1, and discussed further in the following.

Of the 198 articles, 35 included empirical analyses based on data specific to either men or women. Of these 35, 12 featured reproductive or sex-specific outcomes (e.g., endometrial cancer). Another 23 articles limited analyses to either men or women, but studied a health outcome that was not specific to a single sex (e.g., atherosclerosis). Of the articles that included both men and women, very few featured the terms sex or gender prominently in the title or abstract, which is suggestive of the relative (un)importance of these 2 concepts in the analyses themselves. One study of non-genital cancers published in the *American Journal of Epidemiology* was motivated by sex differences in health, and examined, but did not find support for, X-chromosome linked factors.[27] Another *American Journal of Epidemiology* study of blood pressure and serum insulin investigated sex-specific distributions of the outcomes.[28] Overall, the general motivation for taking sex into account, if stated, included both sex-specific variation in physiological differences and sex or gender specific differences in health outcomes. Notably, in 20 articles (16 of which were published in public health journals), discussion of sex or gender was absent because of the case-control design approach, which led researchers only to remark in their data section that cases and controls were matched on sex and other factors. About 10% of studies including men and women relied on a twin design and often same-sex pairs.

By and large, the treatment of sex took the form of a control variable, or a term included in regression analyses to account for—but not necessarily explain—differences between men and women. Of all articles based on data from males and females, 57% adjusted for sex. Other studies, 21% of all articles not limited to a single sex, stratified by sex. In research that entailed investigation of genome-wide genetic associations, analyses sometimes included the X chromosome. One study, an association analysis of 249 796 individuals in search of loci associated with body mass index, was an example of an article with detailed attention to sex; analyses were adjusted for sex, stratified by sex, and included testing for sex-by-gene interactions.[29] Still others tested for substantively plausible interactions by sex, and notably, half of the articles that did so were published in *Nature Genetics*. Finally, in roughly 15% of articles that included men and women, sex and gender were not discussed and were not used in analysis.

In reviewing these articles, we offer 3 observations. First, established sex and gender differences in health and longevity motivate very little research on genetics and health in these journals. Second, sex, when incorporated, is most often treated as a confounding factor, or a source of variation that needs to be controlled, to make room for substantive conclusions about other factors. Third, the conceptual reasoning behind the incorporation of sex as a control is rarely articulated. Does it derive from observed differences in gender and health, observed sex or gender differences in relevant genetic or biological pathways, assumptions about relevant sex difference in physiological “environment,” or some combination? The lack of systematic attention to sex differences in health is curious, given that such differences are persistent, largely unexplained, and presumed to be, to some extent, a function of biology.

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SEX AND GENDER DIFFERENCES IN HEALTH

Despite the rather modest attention paid to sex and gender in recent publications, as discussed in the preceding section, men and women continue to have different patterns of illness and life expectancies. Although sex and gender differentials have narrowed in recent years, they remain substantial.[30] Questions about the origins and mechanisms for these disparities have long intrigued scientists from many disciplines. In particular, how and why sex and gender differentials unfold in aging over the life course are not well understood.[21]

Overall, sex and gender differences in health and longevity are pervasive and persistent. Lower survival rates and life expectancy for males than for females have been found across time, place, and even species.[4,31] Among humans, the "sex health paradox," or the observation that females have higher rates of morbidity but lower rates of mortality, motivated a series of analyses with national health statistics in the United States.[32–34] This research found the following patterns: (1) sex differences in the distribution of illness conditions; namely, women have higher rates of acute illnesses and most nonfatal daily symptoms and chronic conditions, whereas men have higher rates of the leading fatal conditions; (2) sex differences in age-related patterns of disease, such that men die from more life-threatening chronic diseases (cardiovascular disease and cancer) at younger ages; and (3) that controlling for a broad array of social behavioral factors reduces female excess in morbidity and reveals consistent greater male vulnerability to illness and death. These findings may have reconciled the discrepancy in trends in sex differences in morbidity and mortality, but they beg a further question: why are there sex gaps in health at all?

Because of sex-specific variation in biology, several theories propose a biological basis for sex differences in health and survival. First, such differences are consistent with marked sexual dimorphism across the species in major physiological functions such as immune competence related to reproductive biology and regulated by sex gonadal hormones. Second, aging research suggests sex differences in insulin-like growth factor 1, signaling, and oxidative stress production. A review of related hypotheses is available in Austad.[4] Third, sex determination is asserted to be the major genetic determinant of longevity differences within human populations, fueling the idea that the biological differences between males and females may stem ultimately from the genes on the X and Y chromosomes themselves and in X inactivation.[35]

One line of reasoning is that the female advantage can be explained by the heterogametic sex hypothesis, which posits that the sex with 2 different sex chromosomes (in mammals, that would be the XY male) is shorter lived.[4,36] The logic is that a single copy of genes on the X chromosome exposes males to more risk because any deleterious alleles on the X chromosome will have no compensatory allele. By contrast, cell mosaicism, uniquely owned by females, is advantageous because it ameliorates the deleterious effects of X-linked mutations and contributes to physiological diversity and robustness.[37] Because one or the other female X chromosome is inactivated randomly throughout the tissues, cells with one of the 2 X chromosomes that have fewer deleterious alleles—the better one—will survive better and gradually predominate in all the cells in a specific tissue as aging progresses. About 15% of the genes on the "inactivated" X chromosome are not fully inactivated, which may also provide a survival advantage.[38] In addition, it has been suggested that telomere length in humans may be longer in women than men.[4] Although telomere length was first thought to be negatively related to cell aging, a recent review of the evidence on the telomere-aging link calls this assumption into question.[39]

In a parallel way, because of gender differences in society, social and epidemiological research has advanced explanations that emphasize social structural, behavioral, or

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psychosocial factors, such as social class, smoking, and stress, as factors that contribute to sex and gender differences in health and longevity. For instance, women's lower socioeconomic status (in terms of educational attainment, participation in paid employment, income) and fewer job hours have been shown to compromise their health.[34] By contrast, men are disproportionately disadvantaged by occupational hazards, gender role socialization, and health behaviors, including higher levels of cigarette smoking, alcohol consumption, meat and fat consumption, and aggressive behavior and violence.[40–43] Nonetheless, men benefit relative to women from more physical activity and healthier body weight, as well as beneficial psychosocial risk factors, such as a higher sense of mastery and self-esteem.[34,44] Furthermore, psychosocial stress, which has been positively associated with cardiovascular disease, may result from gendered processes, such as uneven family responsibilities, gender-specific harassment or discrimination, and unequal levels of poverty.[23] In addition, women's poorer health may reflect constrained choices.[3,19] In sum, social behavioral models have demonstrated considerable power in explaining gender differences in morbidity and mortality. The discovery of a male health disadvantage after controlling for social factors is in line with biological theories about persistent male excess in mortality, and offers some resolution to the sex health paradox. Nonetheless, our knowledge is far from complete about why such a sex difference exists in the first place.

One major deficiency in extant research is that few studies simultaneously consider biological and social forces as explanations of sex and gender differentials in health and longevity. Thus, we know little about the multifaceted interconnections between social and biological processes or how social conditions can shape sex- and gender-specific patterns of health. Furthermore, research to date tends to ignore age and changing social contexts in the investigation of health. Gender inequalities in health over the life course vary.[45,46] The gender gap can grow with age, consistent with cumulative advantage theory, or converge with age, consistent with an age-as-leveler or selective survival process. In addition, these age-related changes can be further conditioned or modified by contextual factors specific to birth cohort, factors that represent social historical changes exogenous to individual trajectories of physical and mental states. For example, the longitudinal study by Yang and Lee, based on a nationally representative sample of close to 4000 US respondents, found that the male-female gap in depressive symptoms converges with age, but with less convergence in more recent cohorts, and hence, a potentially weakening age-as-leveler process over time.[46] This pattern not only affirms the need for a developmental approach to understanding the interplay between social and biological factors, but also an approach that features changing contextual variation.

Age variations in sex differences in health contribute to the complexity of explanations for sex differences in health but have not been systematically examined from a biological and developmental perspective nor rigorously modeled. One reason is that prospective longitudinal data are less common in the biological sciences than in the social sciences. Analysis of change over the life course may offer considerable leverage in understanding the nature of differences in health by sex. Specific patterns of age variation may provide important clues to the underlying biological mechanisms that contribute to sex and gender differences, once these variations are put in the context of development and aging. Recent population research using explicit measures of biological robustness shows strong evidence for post-reproductive change in sex differentials in physiological functions such as systemic inflammation, metabolic syndrome, and the allostatic load that are consistent with and partly account for the reduction of sex differences in overall and cardiovascular disease mortality in old age.[47,48]

In terms of genetic research on health, sex and gender differences, when they are considered, are often implicitly represented as biologically based, as discussed previously. An

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alternative approach may start with gender as an environment and explore the ways in which gendered experiences are embodied and reflected in physiological processes, and how and when genomic factors enable, constrain, or shape this process, or are, in turn, reshaped by it. An integrated research agenda could begin to tease out the nature of these interactions, and in so doing, elucidate pathways that move us toward explanation. Such an approach would not focus on sex-linked genes as genetically relevant variants. Instead, it would recognize that genetic variants similar in men and women may have different health implications when expressed in "contexts" or "environments" that are gendered.

SOCIAL AND BIOLOGICAL FACTORS OVER THE LIFE COURSE

We present 2 examples of social and biological factors affecting health over the life course with applications to gender differences in health. These examples extend previous studies by Yang and Kozloski and illustrate the importance of addressing some of the under-explored issues we have outlined above.[47,48] Based on data from about 38 000 adults in the National Health and Nutrition Examination Survey (NHANES) conducted between 1988–1994 (III) and 1999–2006, we estimated multivariate regression models to assess the parametric relationships of sex and age with various biological functions and assess how social behavioral factors may account for such relationships.

Figure 2 shows the age curves of the inflammation burden by sex and smoking status predicted from the best fitting model that adjusts for other covariates. The curves indicate that the female excess in inflammation decreases with age ($P < .001$ for the sex by age interaction). Interestingly, the patterns of age variations in sex differentials depend on smoking behaviors. Cigarette smoking is associated with elevated risks of inflammation for both sexes, but the association is significantly larger for men than women ($P < .001$ for the sex by smoking interaction), such that the sex gap before old age is much smaller, converges much earlier, and even reverses later in life for current smokers compared with never or past smokers.

The second example further shows how differential exposures and vulnerabilities to social behavioral risk factors can contribute to sex differences in physiological determinants of health and longevity and their age variations. Using the NHANES III data, we found that the associations between social integration and physiological dysregulation differ by sex and age. Figure 3 shows that lack of religious attendance, in particular, is associated with more inflammation and higher probabilities of metabolic syndrome in men than women and in the older than the younger age group. It is also associated with higher allostatic load or more cumulative physiological dysregulation in older adults. These results are largely consistent with the observation that socially isolated older men are particularly more vulnerable to disease and mortality, and hence, suggest specific biophysiological mechanisms by which social relations are associated with health and sex and age heterogeneity therein.[49] These examples suggest the interconnections between measures of 2 domains of explanatory factors, social and biological, that have been commonly examined in studies of health. They also show the value of considering age. The next step is to reveal the precise mechanisms, including the role of relevant gene activities or possible epigenetic changes, through which such interconnections translate into gender differences in health over the life course.

IMPLICATIONS FOR FUTURE RESEARCH

To conclude, we return to our initial questions. First, to what extent are sex and gender incorporated into research on genetics and health? Second, how might social science understandings of sex and gender, and gender differences in health be more fully integrated into scholarship in this area? Our systematic review suggests that although sex is frequently included as a control or stratifying variable, few articles articulate a conceptual frame or

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methodological justification for conducting research in this way. Most studies are not motivated by sex or gender differences in health; sex, when it is considered, is secondary, and gender (as a concept reflecting social variation) is most often ignored.

We argue that making the connection between sex-linked biological variation and gender differences in health outcomes will benefit from greater attention to the intertwining of social and biological variation over the life course. We also suggest that gender differences in health can result when genetic variants are expressed in different contexts, biological or social, including "gendered" or "sexed" environments. Growing evidence suggests that the relationship between genetic factors and health outcomes are conditioned by environments. We argue that gender needs to be recognized as a dynamic social, cultural, and institutional environment. In an investigation of the heritability of resilience, results are suggestive that such a direction may be productive; resiliency, which is overall equally heritable in men and women, manifests more in men, which the authors suggest could be based in group-level differences in environmental mastery.[50]

Research to date suggests not only that biological factors are key pathways linking sex or gender and health, but also that they operate in concert with social behavioral factors to produce sex- and gender-specific variation in disease and mortality patterns. Future studies will benefit from adopting a multisystems approach to explicate the complex processes underlying such differences across levels of organization, including the biology at the cellular, organ, developmental, behavioral, and contextual levels.[14] Such a change is necessary for understanding the multiple forces that shape sex differences in both physiology and behavior in particular and that are essential for understanding and finding solutions to problems arising from reciprocal interactions between a person's social and physical worlds in general. Genetic factors are an integral component of this system and understanding how genetic activities contribute to these reciprocal interactions between a person's social and physical world is essential.

In addition, future research would benefit from adopting a life course perspective with an emphasis on age variations.[51] Studies of complex age dynamics of sex-mortality differentials in nonhuman species such as medflies, savannah baboons, and other mammalian and nonmammalian species contribute knowledge of biological and genetic explanations to sex-specific variation in specific animal populations and might inform studies of sex-specific variation in health in humans.[52–54] The recent explosion of new biological information, including samples that can be used to study the cellular and molecular mechanisms of human biology in large population-based surveys, offers opportunities for epidemiologists and other population scientists.[55] Likewise, the recent interest and movement in the genetics community toward collecting longitudinal data from large cohorts, and developing standard measures of phenotypes, and a host of environmental factors, presents complementary opportunities for biologists, geneticists, and other natural scientists.[56] Taken together, these developments reflect broad interest in an integrated science of human health.

In this context, the leading questions for a new era of integrative social and biodemographic research on sex and gender differentials in health and longevity include: What are the major markers of intrinsic biological robustness that relate to sex-specific disease and aging processes? How do social exposures and aging processes operate independently and together to alter such robustness? How can we deepen our understanding of sex and gender differentials in health by better situating genetic processes in their dynamic, multilevel social and biological contexts? Answers to these questions will have important scientific and policy implications for reducing social disparities in health and mortality. At the same time, approaching them will require an integrative explanatory framework that bridges the social

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and biomedical sciences. This framework should allow us to first identify sex-specific variation in major aspects of biological structures and functions as well as social factors, model how these differences contribute to sex and gender differentials in health, and more importantly, elucidate the interconnections of biological parameters and social factors in these models. This integrative framework can further address the gap in previous research by adopting a life course perspective. It should allow us to transform knowledge on the additive and interactive social, biological, genetic, and behavioral pathways that lead to disease by linking sex- and gender-specific risk to physical and social exposures that occur over time, during gestation, childhood, adulthood, and old age. Such integration promises to advance understandings of gender differences in health, and may well yield insight regarding the processes and circumstances that make genetic variation relevant for health and well-being.

Acknowledgments

This research was supported in part by the Population Studies and Training Center at Brown University (5R24HD041020, 5T32HD007338), as well as by the Carolina Population Center (R24 HD050924). We gratefully acknowledge additional support from the Andrew W. Mellon Foundation, the National Institutes of Health (K01AG036745-01), and the Social Sciences and Humanities Research Council of Canada (Doctoral Fellowship 752-2010-0219).

We thank Michael Kozloski and Sara Harris for assistance with data preparation.

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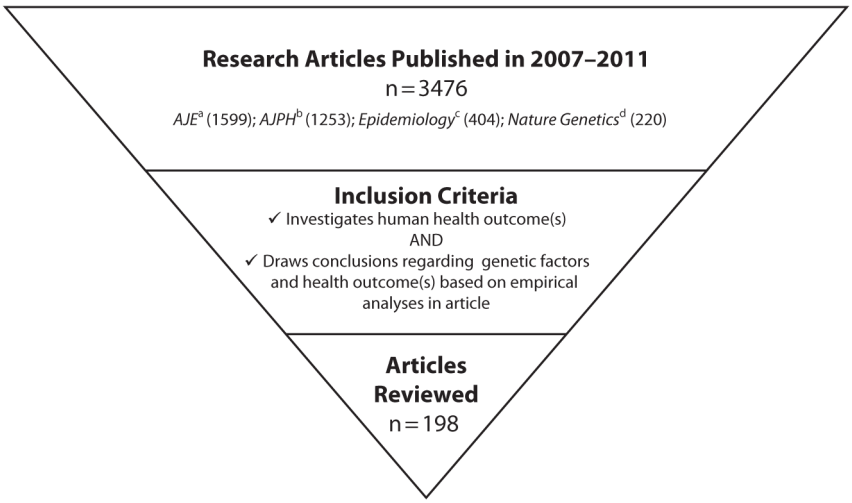

[a]*American Journal of Epidemiology* (*AJE*) publishes 2 issues/month, for 12 months (24 issues/year).
[b]*American Journal of Public Health* (*AJPH*) publishes 1 issue/month, for 12 months (12 issues/year).
[c]*Epidemiology* publishes 1 issue every 2 months (6 issues/year).
[d]*Nature Genetics* publishes 1 issue/month, for 12 months (12 issues/year).

FIGURE 1.
Selection process of articles reviewed, 2007–2011.

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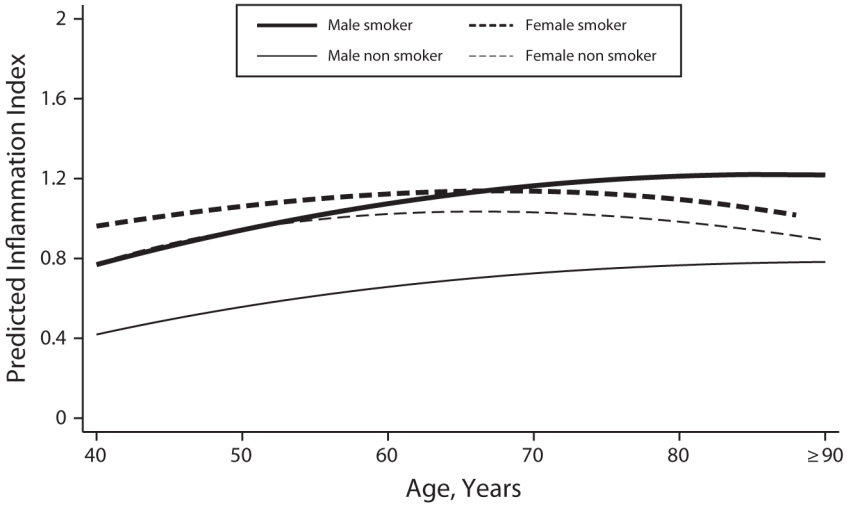

Note. Inflammation index is the sum of the positive indicators of systemic inflammation including high C-reactive protein (> 3.0 mg/dL), high fibrinogen (highest quartile), and low urinary albumin (≤ 3.5 μg/mL) and ranges 0–3.[47] Predicted values from an ordinal logistic model are presented, adjusting for race, education, family income, marital status, obesity, alcohol use, chronic illnesses, and metabolic syndromes.

FIGURE 2.
Sex difference and age variation in inflammation by smoking status.

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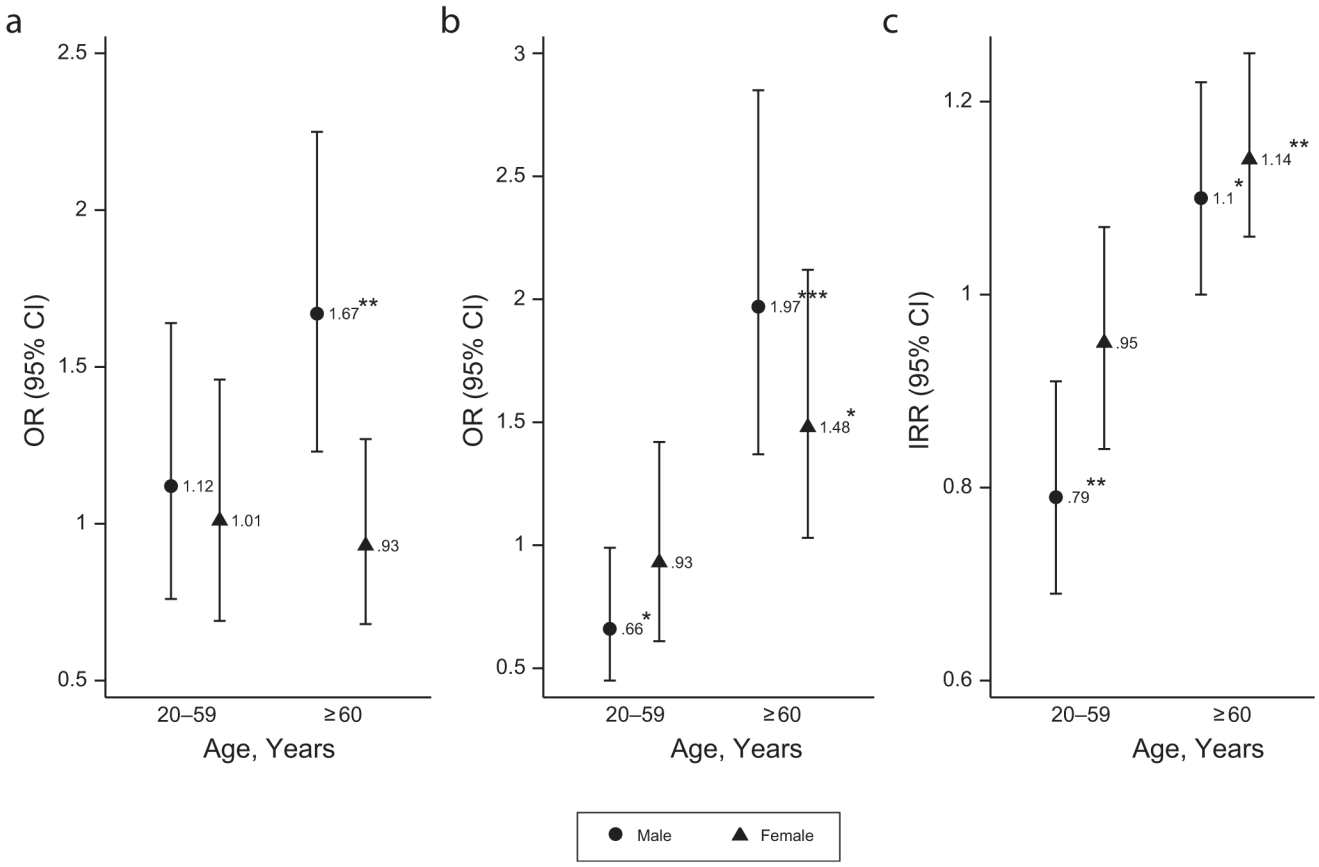

Note. CI = confidence interval. No religious attendance is defined as answering "never" to the question that "How often do you attend church or religious service per year?" (reference = 1 or more times); metabolic syndrome is defined based on the National Cholesterol Education Program/ATP III criteria as positive (= 1) for those having ≥ 3 of 5 metabolic disorders: abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women; high blood pressure: systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg; and hypertriglyceridemia (≥ 150 mg/dL), low high-density lipoprotein cholesterol (< 40 mg/dL), and high fasting glucose (≥ 110 mg/dL). Allostatic load is the sum of positive indicators of 14 markers of physiological disorder, including inflammation, metabolic syndrome, and others.[47] Odds ratios (ORs) of inflammation and metabolic syndrome are presented, as well as incidence rate ratios (IRRs) of allostatic load, adjusting for race, education, family income, marital status, obesity, alcohol use, and chronic illnesses (and hypertension and cholesterol medications for metabolic syndrome and allostatic load).
*P < .05; **P < .01; ***P < .001; P values were determined by 2-sided test.

FIGURE 3.
Social integration, as determined by no religious attendance, and physiological dysregulation, as determined by (a) inflammation index, (b) metabolic syndrome, and (c) allostatic load.

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TABLE 1

Summary of Incorporation of Sex or Gender in Research Articles on Genetics and Health

Variable	All Journals,[a] No. (Proportion)	Public Health Journals,[b] No. (Proportion)
Total number of articles	198	139
Single sex/gender analysis sample		
Total	35	32
Reproductive or sex-specific outcome[c]	12 (0.34)	10 (0.31)
Non–sex-specific health outcome	23 (0.66)	22 (0.69)
Multiple sex/gender analysis sample		
Total	163	107
Level of inclusion		
Sex/gender in title	2 (0.01)	0 (0.00)
Sex/gender in abstract	19 (0.12)	18 (0.13)
Type of inclusion		
Match on sex in sampling	20 (0.12)	14 (0.10)
Control/adjust for sex in analysis	93 (0.57)	62 (0.45)
Incorporate sex with twin design	16 (0.10)	15 (0.11)
Stratify analysis by sex	34 (0.21)	22 (0.16)
Interact sex with genetic variant	12 (0.07)	6 (0.04)
No mention of treatment of sex/gender in analysis	28 (0.17)	10 (0.07)

Note. All articles were published between 2007 and 2011. Ten studies did not clearly indicate which sex(es) or gender(s) they included and are presumed not to be single sex or gender studies.

[a] All Journals includes *American Journal of Epidemiology, American Journal of Public Health, Epidemiology* and *Nature Genetics.*

[b] Public Health Journals excludes *Nature Genetics.*

[c] Breast cancer was coded as non–sex-specific health outcome.