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# Gendered innovation in health and medicine

Zusammenfassung

Gendered Innovation in Gesundheit und Medizin

„Gendered Innovations" integriert eine Sex- und Genderanalyse in alle Phasen der biomedizinischen und Gesundheitsforschung, um Exzellenz und Qualität auf Ergebnisseite zu sichern. Der Beitrag stellt die interdisziplinären internationalen Kooperationsbemühungen dar, in deren Rahmen sowohl zeitgemäße Methoden der geschlechterfokussierten Analyse im Bereich von Gesundheit und Medizin entwickelt als auch Fallstudien durchgeführt wurden: zur Osteoporoseforschung bei Männern, zu genetischen Faktoren der Geschlechtsbestimmung, Herzerkrankungen bei Frauen, Stammzellenforschung, Tierversuchen, Nutrigenomik und zum „Degendering" bei Knieimplantaten. Der Beitrag schließt mit einem kurzen Blick auf kanadische, US-amerikanische und europäische Gesundheitsinstitute, medizinische Curricula und den Umgang peer-reviewter Zeitschriften mit Forschungsberichten über Sex-/Genderanalysen.

*Schlüsselwörter*
Gendered Innovations, Sex-/Genderanalyse, Biomedizin, Gesundheitsforschung

Summary

"Gendered Innovations" integrates sex and gender analysis into all phases of biomedical and health research to assure excellence and quality in outcomes. This article reports on the interdisciplinary, international collaboration that produced: 1) state-of-the-art methods of sex and gender analysis for health and medicine; and 2) case studies to illustrate how gender analysis leads to discovery in biomedicine and better outcomes in health research: osteoporosis research in men, the genetics of sex determination, heart disease in women, stem cell research, animal research, nutrigenomics and degendering knee implants. The article concludes with a short review of policy at the Canadian, US, and European institutes of health, medical curricula, and policies for peer-reviewed journals in relation to reporting sex/gender analysis in research.

*Keywords*
Gendered Innovations, sex and gender analysis, biomedicine, health research

## 1 Introduction

Since 1993, the U.S. National Institutes of Health (NIH) has required that women and minorities be included in phase III clinical trials. Interestingly, this policy was legislated in the U.S. Congress through a political process rather than emerging from notions of excellent science. Congress required that NIH grantees include women and minority groups in human subjects research to "ensure that the [clinical] trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial" (National Institutes of Health 1993: c). Cost was not allowed as an acceptable reason for exclusion. This requirement applied only to phase III trials, meaning that sex was not considered in preclinical research.

In many instances, females were not tested until late in the process. The result is that researchers did not see anything unique to females in the discovery phase; they also did not see important sex differences that might influence outcomes.

One measure of the failure of these policies is failed drugs. Between 1997 and 2000, for example, ten drugs were withdrawn from the US market because of life-threatening health effects. Eight of these posed "greater health risks for women than for men" (United States General Accounting Office 2001: 1). Not only does developing a drug in the current market cost billions, but when drugs failed they caused human suffering and death. Currently, only about five per cent of drug candidates come to market (Arrowsmith 2011; Herper 2013).

In 2010, all 13 institutes of which the Canadian Institutes of Health Research (CIHR) is composed required applicants to consider sex and gender in their research. The CIHR states that "the purpose of this tool is to give health researchers a framework for thinking through how gender and/or sex might be integrated into their research designs" (Canadian Institutes of Health Research 2012: para. 2). In December 2013, to better meet its grand societal challenges, the European Commission implemented policies to integrate sex and/or gender analysis in research and innovation (R&I). In the proposal template, under "concept and approach", applicants are asked "[w]here relevant, describe how sex and/or gender analysis is taken into account in the project's content" (European Commission 2011: 19; 2013: 2; 2014: 7). And since 2014 the NIH has implemented policies that "require applicants to report their plans for the balance of male and female cells and animals in preclinical studies unless sex-specific inclusion is unwarranted, based on rigorously defined exceptions" (Clayton/Collins 2014: 283).

Now researchers need to be trained to do sex and gender research in basic and applied sciences. Interestingly, the European Commission has been the global leader in policy related to sex and gender in research. In 2001, the Commission already sought to integrate "the gender dimension" into research by requiring that researchers question "systematically whether, and in what sense, sex and gender are relevant in the objectives and in the methodology of projects" (European Commission 2003: 8). This policy was not overtly successful, and reasons put forward in "Stocktaking 10 years of 'Women in Science' policy by the European Commission 1999–2009", among other arguments, pointed to confusion about the meaning of "the gender dimension" and a need for more guidance for researchers (European Commission 2010: 218ff.). Few institutions of higher education have integrated sex and gender analysis into science, health and medicine, and engineering curricula. The Erasmus project European Gender in Medicine (EUGiM) brought together seven European universities to develop a flexible Master programme ready to be incorporated into local curricula,[1] and the Charité – Universitätsmedizin Berlin has mainstreamed gender medicine across its core curriculum (Ludwig et al., forthcoming).

Few researchers, then, are prepared to carry out sophisticated sex and gender analysis. This is the problem Gendered Innovations set out to solve. Gendered Innovations began at Stanford University in 2005 with a major conference (Schiebinger 2008). The European Commission supported the project in January 2011 and the U.S. National Science Foundation joined in January 2012. The project has consisted of an international,

1 See http://gender.charite.de/en/education/eugim/.

interdisciplinary collaboration of over 60 experts from across Europe, the United States, and Canada. The Republic of Korea has recently joined the effort.

This project: 1) develops state-of-the-art methods of sex and gender analysis for scientists (including health and biomedical researchers) and engineers; and 2) provides case studies to illustrate concretely how sex and gender analysis leads to innovation.

What is important in this project is understanding how sex and gender should be considered in each step of the research process, from strategic considerations for establishing priorities and theory to more routine tasks of formulating questions, designing methodologies, and interpreting data. Each of the seven methods listed in Figure 1 helps researchers pose questions, for example when setting research priorities or developing basic conceptual frameworks for a project, in order to integrate sex or gender considerations into that step of the research process.

Sex and gender analysis is not just one thing researchers do – it is not one question. Sex and gender analysis informs each step within the research process. State-of-the-art methods of sex and gender analysis work alongside other methodologies in a particular field to provide yet further "controls" (or filters for bias), enhancing excellence in science, medicine, and engineering research, policy, and practice. The methods of sex and gender analysis are one set of methods among many that researchers will bring to a project. As with any set of methods, new ones will be fashioned and others discarded as circumstances change. The value of their implementation depends on the creativity of the research team. Some of these methods plus their practical application in case studies are summarized below.

*Figure 1:* Methods of sex and gender analysis

1. Rethinking research priorities and outcomes
2. Rethinking concepts and theories
3. Formulating research questions
4. Analyzing sex
5. Analyzing gender
6. Analyzing how sex and gender interact
7. Analyzing factors intersecting with sex and gender

Source: authors' figure.

Gender researchers from the humanities and social sciences will recognize that our methods are based on 40 years of gender studies of science, medicine, and technology. Gender theory has done much to transform the humanities and social sciences, yet it has had little success in the natural sciences and engineering. Health and medical sciences represent a middle ground between the two. Humanistic gender theory has been deeply influenced by feminist biologists and medical research, especially in formulating new understandings of sex. Anne Fausto-Sterling's work on sex and race in osteoporosis, for example, drove home the point that sex (the very bones that support the human frame) are formed by cultural norms related to exercise, diet, customs, and modes of life (Fausto-Sterling 2005 and 2008). Suzanne Kessler's work on intersex further drove home the point that even "sex" is not a given, but varies with medical, psychological, and parenting practices (Kessler 1998). Further, the complications of (trans)gender have led to further scrutiny of efforts to analytically distinguish sex/gender (Rippon et al. 2014).

## 2 Methods and case studies

Evidence shows that integrating sex and gender analysis into basic and applied research enhances excellence in science, health and medicine, and engineering research, policy, and practice (Klinge 2008; Wajcman 2007; Schraudner 2010). Historically, feminists have critiqued science and technology after the fact. A rich and important literature has critiqued science and technology from multiple gender points of view (reviewed in Schiebinger 2014a). Gender experts are now turning critique toward a positive research program that – from the beginning – integrates gender analysis into basic and applied research. This is the goal of the Gendered Innovations projects. Again, the novelty of our approach is showing how sex and/or gender can be integrated as one aspect into each step of the research process (see Figure 2). The proximate goal is to avoid gender-blind research, gender critique, and retrofitting research to include sex or gender. The ultimate goal is to harness the creative power of sex and gender analysis to make new discoveries. The owl of sex and gender analysis must fly at dawn.

*Figure 2:* Phases of sex and gender analysis




Source: authors' figure.

### Method 1: Rethinking research priorities and outcomes
*Case study: Osteoporosis research in men*

Gendered Innovations has developed 25 case studies through a series of collaborative international workshops. In what follows here, we present seven of our twelve methods and the associated practical application (or case studies) related to health and biomedi-

cal research. (Case studies related to technology, basic science, and environment can be found on our website.) These materials are drawn from the Gendered Innovations website, where readers can find the full methods and case study plus all references to original research and a list of contributors who assisted in developing these materials (Schiebinger et al. 2011–2015). Each short example here highlights a problem, a method of sex or gender analysis, and solutions or Gendered Innovations.

The first method (rethinking research priorities and outcomes) poses questions to researchers to assist them in considering sex or gender when setting research priorities and outcomes. Governments, industries, funding agencies, and scientists themselves set priorities for future research. Research priorities respond to numerous social imperatives and background assumptions, such as intended markets, funding levels, lobbies, and notions about gender. Questions related to gender include: How do gender norms, behaviours, and attitudes influence research priorities? Do established practices and priorities of funding agencies enforce gender bias or encourage gender equality and innovation?

Every research project begins by setting priorities, i.e. choosing how to invest limited social and intellectual resources, and what questions to pursue. Discussing research priorities and outcomes is complex; here space allows for one example from osteoporosis research.

A number of our case studies examine problems that arise when the male is taken as the norm (see, for example, the "genetics of sex determination" and "heart disease in women" case studies below). "Osteoporosis research in men", by contrast, reveals how assuming a female default can be detrimental to men. One gendered innovation is setting men as a priority in osteoporosis research.

Osteoporosis has long been defined as a disease primarily of post-menopausal women, an assumption that has shaped its screening, diagnosis, and treatment. Why is this a problem? It is true that women suffer more from osteoporosis than men and at an earlier age. Men over the age of 75, however, account for a third of hip fractures, and when men break their hips, they die more often than women (Burge et al. 2007). Men, too, need to be factored into osteoporosis research.

Despite the relatively high numbers of men who suffer from osteoporosis, the basic diagnostics for the disease were developed using young, white women (aged 20–29 years; Centre for Disease Control and Prevention 2002). A key gendered innovation in this particular case study came in 1997 when a reference population of young men was established to diagnose osteoporosis in men. Although reference populations for men have been developed, in men the disease is still identified using the female diagnostic cut-off. More research is needed to determine whether or not this cut-off applies to men (Szulc et al. 2012).

Research projects typically employ a number of methods of sex and gender research. In this case, the discerning reader will have zeroed in on the fact that reference populations discussed above are white. Method 7 (analyzing factors intersecting with sex and gender) pushes researchers to go beyond looking only at sex and gender to consider differences among men with different lifestyles. Bones respond to biological preconditions as well as to lifestyle (diet, smoking, exercise; Fausto-Sterling 2005, 2008). Lifestyles can differ dramatically across cultures, ethnicities, and socio-economic class.

Current studies are analyzing cohorts of men from China and Sweden, for example, to understand these types of differences. The goal is to maintain healthy bones in diverse populations.

### Method 2: Rethinking concepts and theories

*Case study: Genetics of sex determination*

Our second method (rethinking concepts and theories) is applied in the case study on the genetics of sex determination. Theories provide frameworks for explaining and predicting phenomena; concepts relate to how data are described and interpreted, including how particular phenomena are categorized. Theories and concepts frame how research is conducted within a particular field or topic area, influencing: what constitutes an interesting research topic; what requires explanation; what counts as evidence; how evidence is interpreted; and what methods are considered appropriate. The case study on the genetics of sex determination provides an example of how questioning a basic concept from a gender perspective (in this case the notion of the female developmental pathway as a "default") opened new areas to research.

Until about 2010, research on sex determination (the differentiation of the embryonic bipotential gonad into a testis or an ovary) focused primarily on testis development (Uhlenhaut et al. 2009; Richardson 2013). Andrew Sinclair's 1990 Nature paper famously identified a Y-chromosome gene as the Sex-Determining Region Y (SRY; Sinclair et al. 1990). SRY and its downstream targets, such as SOX9, became the focus of research. Female sexual development, by contrast, was thought to proceed by "default" in the absence of SRY.

"Default" means "failure to act; neglect" or "a preselected option adopted […] when no alternative is specified". In the case of sex determination, "default" became the prevailing concept framing research into female pathways, i.e. it was assumed that an ovary results in the absence of other action. In the case of the genetics of sex determination, biologists failed to question the "default" model for ovarian development inherited from the 1950s and 1960s. The notion of a "passive" female fits with current scientific theories and gender assumptions in broader society. The active processes controlling ovarian development remained unexplored.

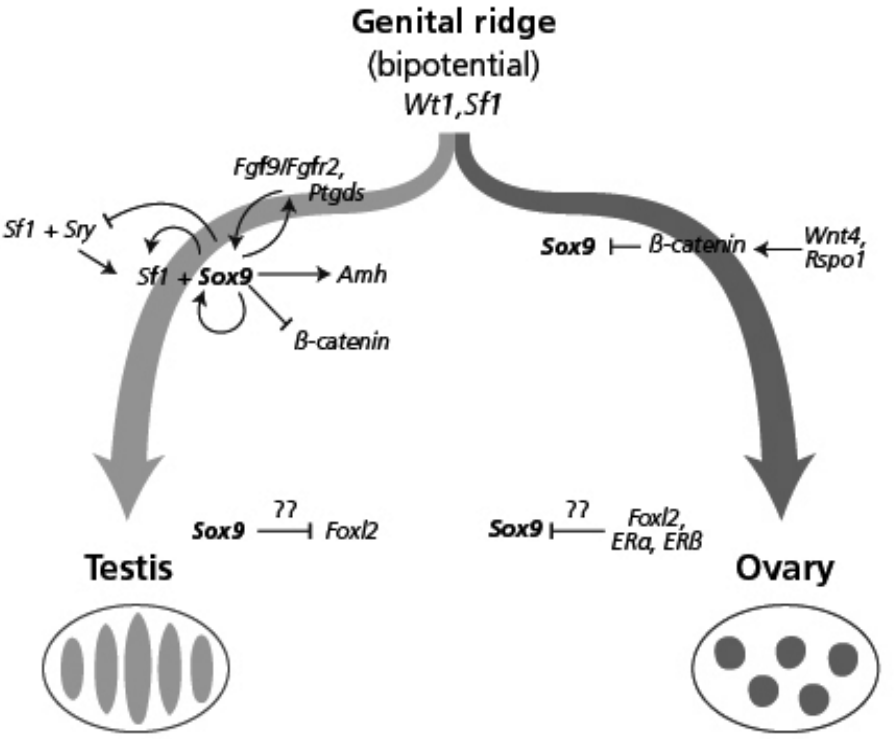
Rethinking foundational concepts, questioning the notion of "default", led to new questions about ovarian development and the discovery of a cohort of genes required for ovarian function (see Figure 3). Gender analysis led to three innovations in this field:

1. The recognition of ovarian determination as an active process (Veitia 2010). These investigations have also enhanced knowledge about testis development, and how the ovarian and testicular pathways interact.
2. The discovery of ongoing ovarian and testis maintenance. Research into the ovarian pathway revealed that the transcriptional regulator FOXL2 must be expressed in adult ovarian follicles to prevent "transdifferentiation of an adult ovary to a testis" (Uhlenhaut et al. 2009). Subsequently, researchers found that the transcription factor DMRT1 is needed to prevent the reprogramming of testicular Sertoli cells into granulosa cells (Matson et al. 2011).

3. New language to describe gonadal differentiation. Researchers have dismissed the concept of "default" and emphasize that, while female and male developmental pathways are divergent, the construction of an ovary (like the construction of a testis or any other organ) is an active process. Each pathway requires complex cascades of gene products in proper dosages and at precise times.

*Figure 3:* Sex determination

Molecular and Genetic Events in Mammalian Sex Determinaltion
Genes in the female pathway repress *Sox9*; genes in the male patheway express it.




"The bipotential genital ridge is established by genes including *Wt1* and *SF1*, the early expression of which might also initiate that of *Sox9* in both sexes. *ß-catenin* can begin to accumulate as a response to Rspo1-Wrt4 signaling at this stage. In XX supporting cell precursors, *ß-catenin* levels could accumulate sufficiently to repress SOX9 activity, either through direct protein interactions leading to mutual destruction, as seen during cartilage development, or by a direct effect on *Sox9* transcription. However, in XY supporting cell precursors, increasing levels of SF1 activate *Sry* expression and then SRY, together with SF1, boosts *Sox9* expression. Once SOX9 levels reach a critical threshold, several positive regulatory loops are initiated, including autoregulation of its own expression and formation of feed-forward loops via FGF9 or PGD2 signaling. If SRY activity is weak, low or late, it fails to boost *Sox9* expression before *ß-catenin* levels accumulate sufficientlty to shut it down. At later stages, FOXL2 increases, which might help, perhaps in concert with ERs, to maintain granulose (follicle) cell differentiation by repressing *Sox9* expression. In the testis, SOX9 promotes the testis pathway, including *Amh* activation, and it also probably represses ovarian genes, including *Wnt4* and *Foxl2*. However, any mechanism that increases *Sox9* expression sufficiently will trigger Sertoli cell development, even in the absence of SRY" (Sekido et al., 2009).

Source: Adapted with permission from Sekido & Lovell-Badge (2009).

Method 3: Formulating research questions

*Case study: Heart disease in women*

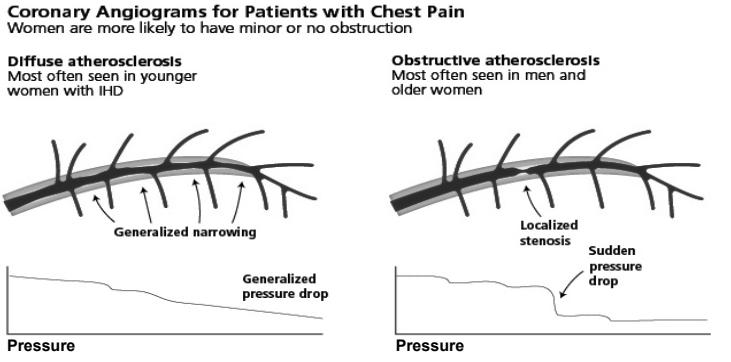
Our third method (formulating research questions) is applied in our case study on heart disease in women. Research questions typically flow from priorities and from the theories and concepts that frame research (see above). Research priorities (along with concepts and theories) function to: 1) delimit questions asked (and, by implication, questions not asked), and 2) frame research design and choice of methods. The choice of questions asked is often underpinned by assumptions – both implicit and explicit – about sex and gender. Formulating new research questions constitutes Method 3.

Heart disease research in women offers one of the most developed examples of gendered innovations. Although heart disease is a major killer of women in developed countries, it has been defined primarily as a male disease, and "evidence-based" clinical standards have been created based on male pathophysiology and outcomes. As a result, women are often mis- and under-diagnosed (Oertelt-Prigione et al. 2012).

Improving women's healthcare has required new social, medical, and political judgments about women's social worth, and a new willingness to support women's health and well-being. Analyzing sex and gender in heart disease has also required formulating new research questions about disease definitions, symptoms, diagnosis, prevention strategies, and treatments. Once sex and gender were factored into the equation, knowledge about heart disease increased dramatically. As is often the case, including women subjects – of diverse social and ethnic backgrounds – in research has led to a better understanding of disease.

To take just one example, consider how underlying pathophysiology may differ between women and men (Bairey Merz et al. 2010). Coronary angiography, the "gold standard" for diagnosing patients with chest pain, typically results in a diagnosis of obstructive coronary artery disease (CAD) in men (see Figure 4, right) but frequently fails to identify the cause in a large proportion of women (Bugiardini/Bairey Merz 2005). As a result, many women with chest pain but "normal" angiograms (see Figure 4, left) may be told that they have no significant disease and sent home.

*Figure 4:* Coronary angiograms for patients with ischemic heart disease (IHD)




Source: Adapted with permission from Gould (1999).

New studies show, however, that the prognosis for these women is not benign: Women with a primary diagnosis of "non-specific chest pain" may suffer heart attack or stroke shortly after being discharged from hospital (Robinson et al. 2008). This may also be true for some men. Large-scale randomized trials are needed to better understand the pathophysiology and optimal therapies for women and men with angina and "normal" angiograms.

After 20 years of research, sex and gender analysis has prompted policy changes, increased the representation of women subjects in heart disease research, and enhanced knowledge about diagnosis and treatment in women and men alike. In addition, robust prevention campaigns have utilized understandings of gender to promote heart-healthy behaviours, such as exercise and tobacco and smoking cessation.

### Method 4: Analyzing sex
*Case study: Stem cells*

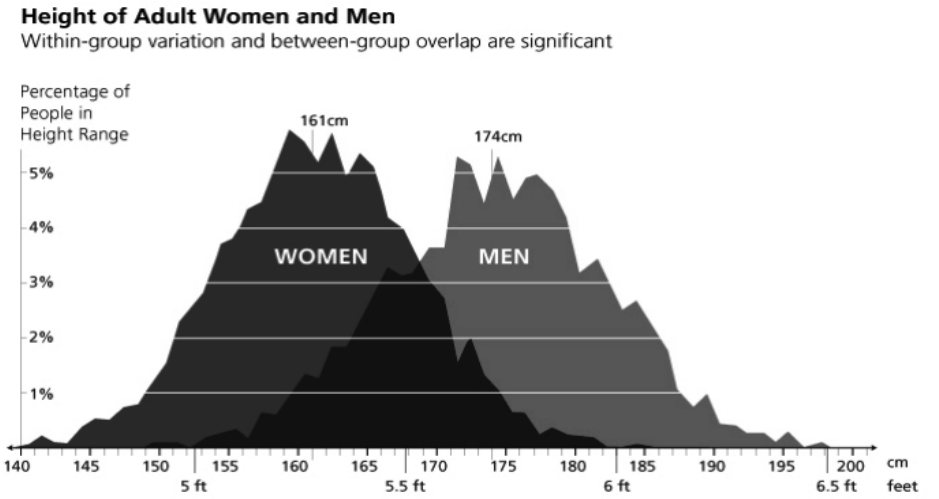
Our fourth method (analyzing sex) is applied in our case study on stem cells. Sex (referring to biological qualities, as discussed above) is an important variable to consider when setting research priorities, developing hypotheses, and formulating study designs. In biomedical research, sex may need to be analyzed in humans, animals, organs, tissues, cells, and their components (Institute of Medicine 2012; Wizemann/Pardue 2001). In engineering, sex may need to be analyzed at the levels of user physiology and biomechanics in both product and systems design.

Analyzing sex involves at least five steps: 1) reporting the sex of research subjects or users; 2) recognizing differences that exist between but also within groups of females and males, and identifying potential overlap between groups (see Figure 5); 3) collecting and reporting data on factors intersecting with sex in study subjects or users/consumers, such as age, socio-economic status, and ethnicity; 4) analyzing and reporting results by sex; and 5) reporting null findings. This final step is important: Researchers should report when sex differences (main or interaction effects) are not detected in their analyses to reduce publication bias and improve meta-analyses.

Method 4 (analyzing sex) is basic and commonly used in Gendered Innovations case studies, including animal research, environmental chemicals, nutrigenomics, and pregnant crash test dummies. Here we take an example from stem cell research. Stem cell therapies hold great promise for treatments for debilitating diseases, such as Parkinson's disease and muscular dystrophy, although few are currently in use.

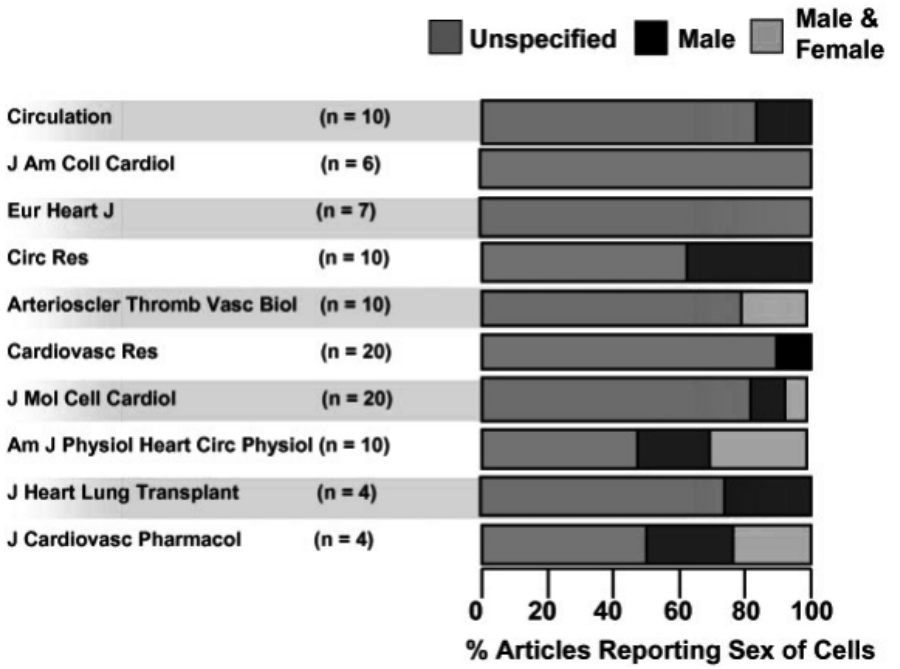
Oddly enough, most research today is still done in males (Beery/Zucker 2011). A 2011 Mayo Clinic study showed that for the most part the sex of the cell is not reported (Taylor et al. 2011; see Figure 6). This is money wasted, research that is lost to future meta-analysis.

*Figure 5:* Within-group variation and between-group overlap




Adults ages 18–86 in 2007. Source: U.S. Centers for Disease Control (CDC) (2007).

*Figure 6:* Percentage of articles reporting the sex of cells




Source: Taylor et al. (2011).

Not taking the sex of the cell into account can lead to life-threatening consequences and leave researchers with unsolved puzzles. For example, an international collaboration between labs in Norway and Australia encountered problems working with bone marrow stem cells in mice. Researchers in the labs appropriately used both male and female mice (excellent research design), but they used all female stem cells without considering why. This was an unconscious decision that does not reflect best scientific practice. The result was that their male mice died – and they did not understand why.

Taking sex into account will be important when it comes to advancing basic knowledge. Research has documented potential sex differences in the therapeutic capacity of stem cells. Muscle-derived stem cells, for example, show variability in proliferation and differentiation. Researchers found that XX cells showed a higher regenerative capacity than XY cells. This may constitute an important clinical finding, but requires further investigation. Researchers should consider all combinations of donor/recipient sex interaction before ruling out sex as a variable. This type of donor/recipient analysis has also been important in human organ transplant (Kaczmarek et al. 2013).

The effects of sex, however, may also vary by type of stem cell used, type of disease treated, and hormonal and environmental factors, plus their intersections. It is complicated, but research that takes these factors into account leads to better outcomes.

### Method 5: Analyzing gender
*Case study: Animal research*

Our fifth method (analyzing gender) is applied in our case study on animal research. While many Gendered Innovations methods integrate gender in various phases of the research process, this method provides the techniques for analyzing gender, a major tool for identifying unconscious bias. Gender is a primary linguistic, cognitive, and analytical category in science, health and medicine, and engineering. Yet gender assumptions often go unquestioned and hence remain invisible to scientific communities. These background assumptions unconsciously influence scientific priorities, research questions, and choices of methods, as we have seen. Gender comes into play when cultural attitudes shape and are shaped by: 1) researchers' gender assumptions and behaviours as these relate to the proposed research, 2) research subjects' and users' gender needs, assumptions, and behaviours as these relate to the proposed research, 3) the interaction between numbers 1 and 2.

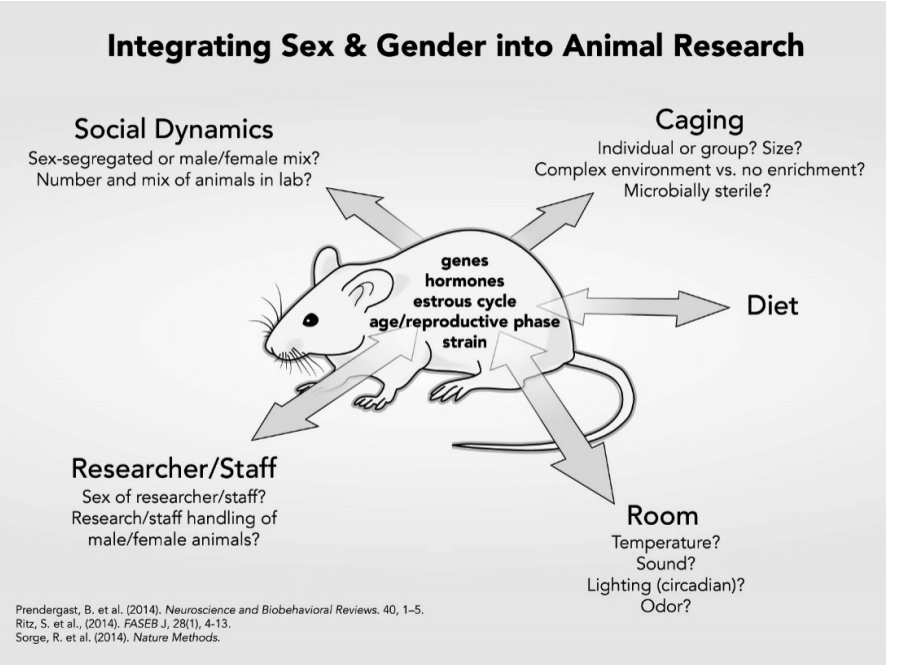
The case study on animal research investigates how gender, by which we mean key "socio-cultural" (environmental) factors, influence biomedical experiments with animals. Understanding how to take into account "gender-based" confounders and how to study the influence of "gender" on biology may increase the translational value of research in animals to humans.

What is gender, and can we discuss it in relation to animals? Definitions of gender abound. Here we highlight three approaches:

- Gender norms refer to researchers' differing attitudes toward male or female animals. Researchers may act on gender stereotypes concerning expected behaviours of male and of female animals.

- Gender relations refer to social interactions between female and male animals, on the one hand, and between animals (of differing sex) and men and women researchers (with potential differing gender expectations), on the other.
- Gender identities refer to how individuals perceive and present themselves, and how they are perceived by others. There is no evidence that rodents develop conscious gender identities.

*Figure 7:* Animal research includes analyzing sex and gender




Animal research includes analyzing sex (biological characteristics, such as genes, hormones, age, reproductive phase, strain etc.) and gender (socio-cultural or environmental process, such as caging practices, attitudes and behaviours of researchers, room temperature, diet etc.). The double-ended arrows represent interactions between sex and gender. Source: authors' figure.

As a first example of "gender" in relation to animals, we will look at caging practices. Male rodents are often caged in small groups or alone (because they fight). Rodents housed alone "expend more energy maintaining body temperature, which can cause differences in parameters such as caloric intake, muscle activity, metabolic rate, fat distribution, or body size, with a plethora of potential downstream effects on bodily and cellular activity" (Ritz et al. 2014: 8). In other words, animals caged individually use more energy to maintain body temperature. This can impact basic metabolism. Animals housed together tend to sleep clustered together and, as a result, expend less energy to keep warm. Importantly, differences in caging practices between male and female animals should not be mistaken for biological sex differences.

The solution may not be as simple as housing females and males in the same conditions. The same sized group may create different stressors for females and males, and being caged alone may itself cause stress (Ritz et al. 2014). It is crucial that all researchers describe housing conditions, specifying the number of animals per cage (Prendergast et al. 2014).

A second example of where gender matters in animal research has to do with gender relations, i.e. the dynamic between the sex of the research staff and the animal's reaction. Interestingly, experimenter sex may be a confounding variable in rodent research where stress is a significant factor. Sorge et al. (2014) found that rats and mice demonstrated a reduced pain response in the presence of a male experimenter, as compared with an empty room, whereas the presence of a female experimenter produced no difference. Both male and female rodents showed this response, but females had a greater effect. T-shirts worn by men for a night and bedding from other male mammals, including predator and nonpredator species, produced the same analgesic effect. The researchers identified this "'male observer' effect" (Sorge et al. 2014) as a stress response to androstenone and androstadienone, axillary secretions found in higher concentrations in males than in females.

In this example, the sex of the experimenter matters. Standard laboratory practice will need to account for experimenter sex when this is shown to have an effect. All too often "sex differences" in research animals are reported where more complex interactions that involve gender or, in this case, lab conditions may be at work.

### Method 6: Analyzing how sex and gender interact

*Case study: Nutrigenomics*

Our sixth method (analyzing how sex and gender interact) is applied in our case study on nutrigenomics. "Sex" and "gender" are distinguished for analytical purposes. In reality, sex and gender interact (i.e. mutually shape one another) to form individual bodies, cognitive abilities, and disease patterns, for example. And, as we shall see in Method 7 (analyzing factors intersecting with sex and gender), sex and gender intersect in important ways with a variety of other social factors, including age, educational background, socio-economic status, ethnicity, geographical location, etc.

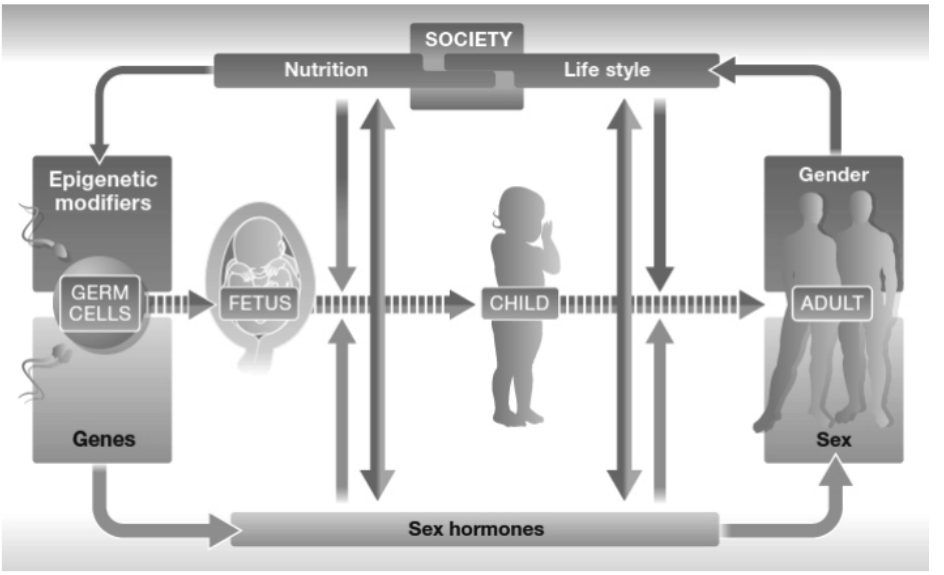
The image from Vera Regitz-Zagrosek below (Figure 8) suggests how sex and gender interact to create individual behaviours, health outcomes, and attitudes etc. across the life span. Although women and men are fundamentally alike, sex and gender can work together to produce different outcomes.

How sex and gender interact can be illustrated in the case study on nutrigenomics. It examines the epidemic of non-communicable diseases (e.g. heart disease, diabetes, and cancers) that are on the rise across Europe and North America.

Figure 9 shows the hypothetical relative influences of sex- and gender-related factors determining a person's disease risk over her or his lifetime. Importantly, gender-related social factors (such as obesity, lack of exercise etc.) interact with sex-related biological factors (such as genetic predispositions and hormones) to determine how a person ages. For instance, to understand differences in women's and men's obesity rates, we need to analyze gender differences in lifestyle. Perhaps gender norms in society lead men to exercise more than women; this can lead to greater disease among women. Or

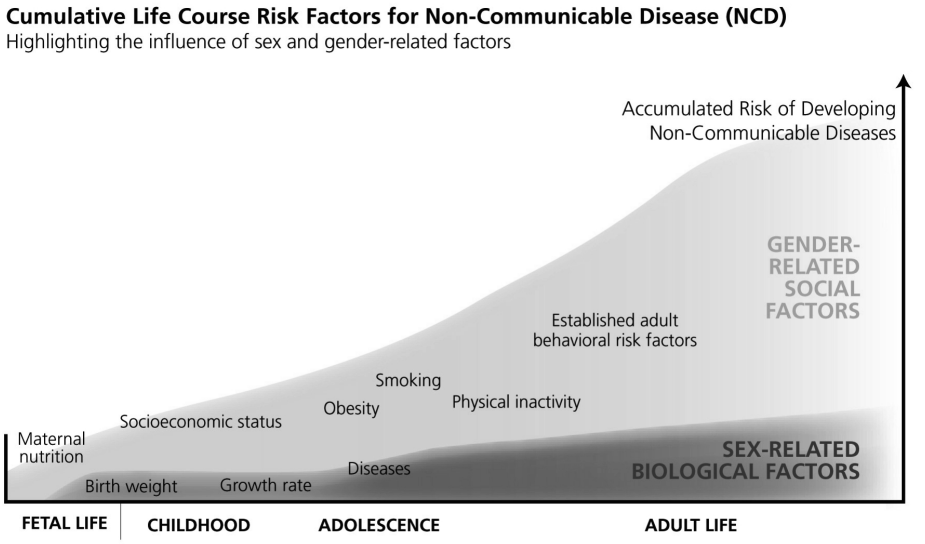
perhaps gender norms in society lead men to eat less healthy food than women. This gendered behaviour can lead to greater disease among men.

*Figure 8:* Complex interdependency of sex and gender throughout the human life cycle




Source: Regitz-Zagrosek (2012).

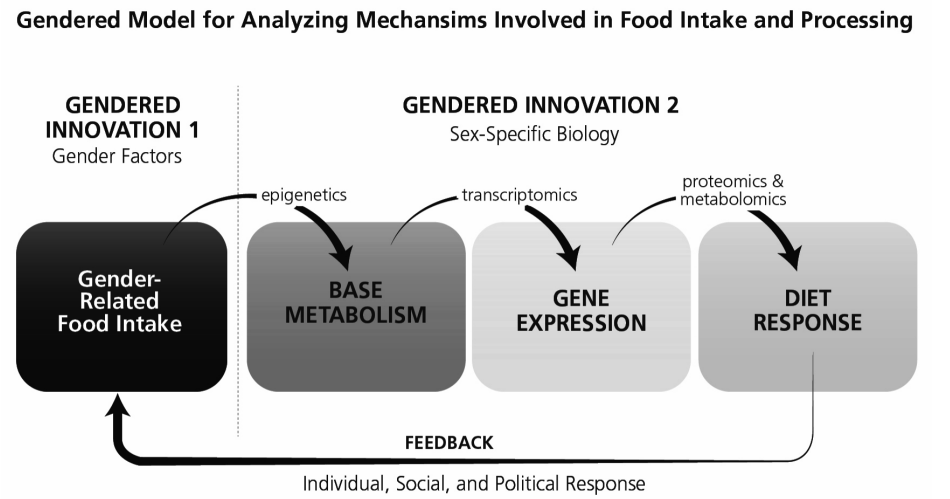
*Figure 9:* Cumulative life risk factors for non-communicable diseases




Source: Adapted from Darnton-Hill/Nishida/James (2004).

In Figure 10 we see how gender-related food intake can be translated into sex-specific basic metabolism and gene expression, and, finally, into sex-specific responses to dietary interventions. Nutritionists have used sex analysis to explore – at the functional, mechanistic level – how nutrients affect gene expression and cell function in women and men. In one study, they examined vitamin E/gene interactions affecting the incidence of respiratory tract infections in the elderly. The main finding suggested that the effect of vitamin E differed by sex: only in women (with a certain genotype) did vitamin E reduce respiratory tract infections.

*Figure 10:* Gendered model for analyzing mechanisms involved in food intake and processing




The diagram above illustrates how researches might analyze a three-way interaction between gender-related factors, sex-specific biology, and various biological mechanisms involved in human food intake and processing. Gender-related food intake is translated into different sex-specific base metabolism, gene expressions, and dietary responses, thereby making nutrigenomics a pervasive Gendered Innovation.

Source: authors' figure (by courtesy of Bart Penders).

## Method 7: Analyzing factors intersecting with sex and gender

*Case study: Degendering the knee*

Our seventh method (analyzing factors intersecting with sex and gender) is applied in our case study on degendering the knee. This method applies to nearly every research project – and it is often a game changer. Intersecting factors, such as ethnicity or socio-economic background, may reveal sub-group differences among women and among men that are obscured when analyzing only gender or only sex. Researchers can investigate how sex and/or gender intersect with other significant factors by: 1) identifying all relevant factors, 2) defining those factors, and 3) identifying intersections between those variables. These factors can be biological, socio-cultural, or psychological, and may include genetics, age, sex hormones, reproductive status, body composition, comorbidi-

ties, body size, disabilities, ethnicity, nationality, geographical location, socio-economic status, educational background, sexual orientation, religion, lifestyle, language, family configuration, environment etc.

The case study on degendering the knee provides a cautionary tale. As we have seen, it is crucial to test for sex and gender differences before ruling them out. However, sex differences should not be overemphasized or studied to the exclusion of other intersecting factors. Researchers often overemphasize differences and neglect the overlap or sameness between the sexes (for a discussion of this applied to gender, see Hyde 2014). Overemphasizing sex differences can lead to three types of errors : First, sex differences may be asserted without sufficient evidence or documentation. As noted above, the bias against reporting negative or null results means that findings of sex differences are reported more often than findings of no sex difference (Institute of Medicine 2012). Second, differences between men and women may be improperly attributed to sex (a biological quality) when in fact cultural factors, such as socio-economic factors, come into play. Third, sex may be emphasized to the exclusion of other important variables, as illustrated in the case study on degendering the knee.

This case study treats knee replacements, i.e. the prostheses that are implanted to replace worn-out knees. In 2007, an estimated 500,000 total knee arthroplasty (TKA) procedures were performed worldwide, about two thirds in women. In the 1990s, with increased attention to women's health research, manufacturers, such as Zimmer Inc., began producing "gender-specific" knees and marketing them directly to women. Did this lead to better healthcare quality?

Sex may appear to be the most important variable in choosing a knee implant until height is considered. Specifically, research shows that two anatomical sex differences (greater Q-angle and lesser anterior condylar height in women) disappear when corrected for standing height. This suggests that height may be more important than sex in determining the knee implant a patient should receive.

It is important to analyze sex differences before ruling them out. Many additional factors, however, influence outcomes in TKA, including age, body composition, comorbidities, preoperative knee mobility, ethnicity, and surgeon or hospital volume.

This case study demonstrates the importance of reporting null results. Finding no sex effect is as important as finding a sex effect. To reduce publication bias, researchers should report when sex differences (main or interaction effects) are not detected or when data regarding sex differences are statistically inconclusive (Wizemann, 2012). Publishers often do not report negative findings. Publishing only positive sex differences, however, runs the risk of overemphasizing sex difference and underplaying sameness. With respect to sex, reporting negative results is crucial for meta-analysis.

## 3 Conclusions and policy recommendations

Gendered Innovations has moved gender studies beyond identifying gender bias to prioritizing sex and gender analysis as a resource to create new knowledge and technology. The key step is – from the beginning – to incorporate sex and gender analysis

into each step of the research process. This move from being reactive to being proactive means that researchers have a better chance of getting it right the first time. Discoveries, pharmaceuticals, technologies, and the like will no longer need to be retrofit to the neglected sex. Incorporating sex and gender as robust variables into research (as described in the seven methods discussed here) can fuel life-saving research and protect public resources.

Such research thrives on interdisciplinary work. Interdisciplinarity requires shared conceptual frameworks and vocabularies. It also thrives on a willingness to meet partners half way. The Gendered Innovations project has hopefully developed methods that are beginning to facilitate this type of interdisciplinary, global research.

We close with a few policy recommendations. Policy is one driver of research and discovery and it can encourage scientists to integrate sex and gender analysis into their research. Interlocking policies need to address gate keepers, i.e. granting agencies, hiring committees, editors of peer-reviewed journals, industry leaders, and educators.

## 3.1 Granting agencies

As discussed above, granting agencies implemented policies in the 1990s to support women's health research and in the 2010s to support sex and gender analysis in research. A new study has evaluated the overall return on public funding to society of one study, the U.S. National Institutes of Health Women's Health Initiative oestrogen plus progestin clinical trial. This large, government-funded trial was done in the 1990s and cost $260 million. The study found that the return for every $1 spent was $140. Overall, the net economic return of the research returned $37.1 billion.

More than money, the study also saved lives in the form of 76,000 fewer cases of cardiovascular disease, 126,000 fewer breast cancers, and 145,000 more quality-adjusted life years. While most of the results were positive, the analysis did find 263,000 more osteoporotic fractures (Roth et al. 2014). While we know that research done wrong can cost money and lives, this evaluation shows that research done right can save money and lives.

Another study evaluated the impact of the CIHR policy implemented in 2010 that required applicants to indicate whether their research designs accounted for sex or gender. The study showed that the mandatory questions led to an overall increase in the proportion of funded research that incorporated sex and gender in their research designs. Results varied by discipline, with biomedical researchers being least likely to account for sex and gender, clinical researchers being most likely to account for sex, and population health researchers being most likely to account for gender. Interestingly, women principal investigators were more likely to incorporate sex and gender than their male counterparts. A qualitative portion of the study found that research requires more guidance on how to do this research. Many, for example, conflated sex and gender; a number assumed that studying women was equivalent to studying sex and gender (Johnson et al. 2014).

More granting agencies are requiring sex and gender analysis in order to fund research. We expect the European Research Council and the U.S. National Science Foundation to implement such requirements for the life sciences and engineering, or any

field with human endpoints. The Korean National Research Foundation is considering similar measures.

### 3.2 Editorial boards of peer-reviewed journals

Editorial policies of peer-reviewed journals can contribute to regulating excellence in research by requiring sophisticated sex- or gender-based analysis when selecting papers for publication. A number of journals have implemented this policy. Clinical Orthopaedic and Related Research has recommended that studies be sufficiently powered to analyze sex (Leopold et al. 2014). In 2012, each of the American Physiological Society's 14 journals required that authors report and analyze sex (Miller 2010). Science and Nature are considering such policies.

### 3.3 Universities

Universities have two important jobs that urgently need to be undertaken: 1) Large "methods and techniques" workshops need to be implemented so that researchers can exchange strategies for efficiently and effectively integrating sex and gender into research. Norway's University of Tromsø has developed an excellent model of hosting such a workshop plus offering funding supplements to researchers for incorporating sex or gender. The idea was to ready their researchers to apply for Horizon 2020 monies. Stanford's Gendered Innovations along with Stanford's Women and Sex Differences in Medicine Center have hosted such workshops. The NIH's Office of Women's Health and Research also hosted a national a workshop on methods in biomedical science in October 2014. It is crucial that universities and national organizations take the lead when it comes to training the current generation of researchers in sex and gender analysis. 2) Universities must immediately integrate the results of Gendered Innovations into their curricula. In medicine and public health in particular teaching new materials that incorporate sex and gender can be a matter of life or death. Sweden's Karolinska Institute and Germany's Charité – Universitätsmedizin Berlin have both created centres for gender medicine that promote sex and gender analysis in research and medical education (Klinge 2008: 10). The next step is to reform the curriculum to incorporate sex and gender.

Sex and gender analysis adds value to research by ensuring excellence and quality in outcomes and enhancing sustainability. Sex and gender analysis adds value to society by making research more responsive to social needs, and it adds value to business by developing new ideas, patents, and technology. The goal is to stimulate gender-responsible science and technology, thereby enhancing quality of life for both women and men worldwide. Can we afford to ignore such opportunities?

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